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SPECIALTY BOARD REVIEW

Dermatology
A Pictorial Review
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CONTRIBUTORS

Sumaira Aasi

Chapter 12

Asra Ali, MD
Assistant Professor, Department of Dermatology, University of Texas at Houston, Houston, Texas
Chapters 4, 9, 10, 13, 16, 18, 19, 22, 23, 26, 29, 32, 33

Nishath Ali, MD
Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas
Chapter 5

Syed Azhar, MD
Associate Professor, Department of Family Medicine, University of Texas, Medical Branch, Galveston, Texas
Chapter 2

Carolyn A. Bangert, MD
Assistant Professor, Department of Dermatology, University of Texas Medical Center at Houston, Houston, Texas
Chapter 22

Brenda L. Bartlett, MD
Clinical Research Fellow, Center for Clinical Studies, Houston, Texas
Chapter 17

Melissa A. Bogle, MD
Clinical Assistant Professor, Department of Dermatology, University of Texas M. D. Anderson Cancer Center, Houston, Texas
Chapters 1, 2, 6, 16, 19, 24, 32

John C. Browning, MD
Fellow, Pediatric Dermatology, Baylor College of Medicine, Houston, Texas
Chapter 13, 15

Kamal Busaidy

Chapter 4

John J. Cangelosi, MD
Resident, Department of Pathology, University of Texas Medical Branch, Galveston, Texas
Chapter 11

Samantha Carter

Chapter 34

T. Minsue Chen, MD
Mohs Research in Advanced Dermatologic Surgery and Education Fellow, Department of Dermatology, University of Texas M. D. Anderson Cancer Center, Houston, Texas
Chapters 25, 26, 32, 33

Brenda Chrastil-LaTowsky, MD
Texas Health Science Center, University of Texas M. D. Anderson Cancer Center, Houston, Texas
Chapter 2

Alice Chuang

Chapter 29

Katherine M. Cox, MD
Chapters 8, 12

Hafeez Diwan, MD, PhD
Assistant Professor of Dermatology, Division of Pathology and Laboratory Medicine, University of Texas M. D. Anderson Cancer Center, Houston, Texas
Chapter 30

Dirk M. Elston, MD
Director, Department of Dermatology, Geisinger Medical Center, Danville, Pennsylvania
Chapter 16

Adrienne M. Feasel, MD
Ladera Park Dermatology, Austin, Texas
Chapters 14, 15

Aron J. Gewirtzman, MD
Center for Clinical Studies, Houston, Texas
Chapter 17

Angela A. Giancola, MD
Resident, Department of Dermatology, University of Texas at Houston Medical School, Houston, Texas
Chapter 24
Sarah Goel, BA
Medical Student (MSIII), Western University of Health Sciences, Pomona, California
Chapter 17

Adelaide A. Hebert, MD
Professor of Dermatology and Pathology, Director of Pediatric Dermatology, University of Texas Medical School at Houston, Houston, Texas
Chapter 14

Kelly L. Herne, MD
Advanced Dermatology, Houston, Texas
Chapter 7

Whitney High

Chapter 7

Doina Ivan, MD
Assistant Professor of Pathology and Dermatology, Section of Dermatopathology, University of Texas M. D. Anderson Cancer Center, Houston, Texas
Chapter 11

Robert H. Johr, MD

Chapter 31

Jennifer L. Jones, MD
Instructor in Dermatology, Harvard Medical School, Boston, Massachusetts
Chapter 34

Robert E. Jordon, MD
Professor, Department of Dermatology, University of Texas at Houston Medical School, Houston, Texas
Chapter 7

Jennifer Krejci-Manwaring, MD
Assistant Professor of Dermatology, University of Texas Health Science Center, San Antonio, Texas
Chapters 5, 10

Joy H. Kunishighe, MD
Department of Dermatology, University of Texas Health Science Center; Department of Dermatology, M. D. Anderson Cancer Center, Houston, Texas
Chapter 14

Mark LaRocco, PhD
Adjunct Associate Professor, Department of Pathology and Laboratory Medicine, University of Texas at Houston Medical School, Houston, Texas
Chapter 19

Alexander J. Lazar, MD, PhD
Assistant Professor of Pathology and Dermatology, University of Texas M. D. Anderson Cancer Center, Sections of Dermatopathology and Soft Tissue/Sarcoma Pathology, Sarcoma Research Center, Houston, Texas
Chapter 11

Kurt Q. Lu

Chapters 27, 28

Steven Marcet, MD
Dermatologist, Newnan Dermatology, Newnan, Georgia
Chapter 18

Natalia Mendoza, MD
Assistant Professor, Research Division, Center for Clinical Studies, Universidad El Bosque, Colombia
Chapter 17

Denise W. Metry, MD
Associate Professor, Department of Dermatology and Pediatrics, Bayor College of Medicine, Houston, Texas; Chief of Service, Dermatology Service, Texas Children’s Hospital, Houston, Texas
Chapters 13, 15

Giuseppe Militello, MD
Assistant Professor of Clinical Dermatology, Columbia University, New York, New York
Chapter 6

Jason H. Miller, MD
Resident Physician, Department of Dermatology, University of Texas at Houston Health Science Center, M. D. Anderson Cancer Center, Houston, Texas
Chapters 9, 23

Paradi Mirmirani, MD
Permanente Medical Group, Vallejo, California; University of California, San Francisco, California; Case Western Reserve University, Cleveland, Ohio
Chapter 1
Tri H. Nguyen, MD
Associate Professor Dermatology and Otolaryngology, Department of Dermatology, Division of Medicine, University of Texas M. D. Anderson Cancer Center, Houston, Texas
Chapter 25

Victoria G. Ortiz, MD
Department of Dermatology, University of Texas Health Science Center, Houston, Texas
Chapter 8

Clare Pipkin, MD
Instructor, Department of Dermatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Chapters 19, 34

Victor G. Prieto, MD, PhD
Professor, Departments of Pathology and Dermatology, University of Texas M. D. Anderson Cancer Center, Houston, Texas
Chapter 30

Ronald P. Rapini, MD
Professor and Chairman, Department of Dermatology, University of Texas Medical School, M. D. Anderson Cancer Center, Houston, Texas
Chapter 21

Aly Raza, MPH, PhD
Professor, Department of Dermatology, University of California at San Francisco, UCSF Medical Center, San Francisco, California
Chapter 19

Bryan Selkin, MD
Instructor of Dermatology, Department of Dermatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Chapter 34

Benjamin Solky, MD
Winchester, Massachusetts
Chapter 34

Tahniat S. Syed, MD, MPH
Assistant Professor of Pediatrics, Division of Adolescent Medicine, Department of Pediatrics, St. Christopher’s Hospital for Children, Philadelphia, Pennsylvania
Chapter 29

Rakhshandra Talpur, MD
Chapter 8

Marziah Thurber, MD
Mount Sinai Medical Center, Miami, Florida
Chapter 14

Anne Marie Tremaine
Chapter 17

Stephen K. Tyring, MD, PhD
Clinical Professor, Department of Dermatology, University of Texas Health Science Center and Center for Clinical Studies, Houston, Texas
Chapter 17

Ravi Ubriani, MD
Department of Dermatology, Columbia University, New York, New York
Chapter 3

Genevieve Wallace, MD
University of Texas Health Science Center, Houston, Texas
Chapter 27

Rungsima Wanitphakdeedecha, MD
Instructor, Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
Chapters 25, 26

Stephen E. Wolverton, MD
Professor of Clinical Dermatology, Department of Dermatology, Indiana State University, Indianapolis, Indiana
Chapter 24
Dermatology is a specialty that addresses both medical diseases and cosmetic problems of the skin, scalp, hair, and nails. It is a specialty that oftentimes allows the practitioner to make a diagnosis based solely on physical examination and history. Because skin symptoms and signs account for 10% of all symptoms and signs, understanding of dermatology is required of many medical specialties, particularly internal medicine, family practice, pediatrics, neurology, and rheumatology.

Initially, this book was designed to prepare dermatology residents and practicing dermatologists for the dermatology boards and dermatology recertification exam. However, as the book has developed, it has become a comprehensive source of information on dermatologic presentations, diseases, and cosmetic and surgical procedures. Therefore, the book will not only be helpful to dermatology residents and practicing dermatologists, but also to physicians in other fields of medicine.

The second edition has been updated to keep the review current. Questions and answers were also added in order to make the learning process more interactive. I hope you will find this review as useful and informative and learn as much from it as I did while making it.
CHAPTER 1

HAIR FINDINGS

PARADI MIRMIRANI

DEVELOPMENT

- Follicles form during 3rd month of gestation; form first on head
- Lining of follicle = ectodermal origin
- Dermal papilla = mesodermal origin
- Epidermal invaginations occur at an angle to the surface and over sites of mesenchymal cell collections
- Eventually these epidermal cells form a column that surrounds the mesenchymal dermal papilla to form the bulb
- The dermal papilla (along with “stem” cells in the bulge) induce hair follicle formation by the overlying epithelium
- Additionally, two or three other collections of cells form along the follicle
  - Upper collection becomes the mantle from which the sebaceous gland will develop
  - Lower swelling becomes the attachment for the arrector pili muscle and where follicle germinal cells reside in telogen phase
- If a third collection of cells exists, it is found opposite and superior to the sebaceous gland and develops into the apocrine gland

STRUCTURE (FIG. 1-1)

- Longitudinal structure: (superior to inferior)
  - Permanent portion of the hair follicle
    - Infundibulum
    - Area of the sebaceous gland
    - Isthmus: begins at sebaceous gland and ends at the bulge (site of insertion of arrector pili muscle)
  - Area of the bulge: location of follicular stem cells
  - Transient portion of the hair follicle
    - Lower hair follicle
  - Hair bulb: contains the matrix, melanocytes; envelopes the dermal papilla; critical line of Auber is at the widest diameter; below this line is the bulk of mitotic activity

MICROSCOPIC STRUCTURE (FIG. 1-2)

- The hair follicle is arranged in concentric circles (from outer to inner)
  - Basement membrane (glassy membrane): PAS-positive, acellular; thin during anagen and thickens during catagen
  - Outer root sheath (ORS): present the length of the follicle; never keratinizes; stays fixed in place
  - Inner root sheath (IRS): grows toward cell surface and separates from the hair shaft at the level of the sebaceous gland
    - Henle’s layer: one cell thick and first to cornify
    - Huxley’s layer: two cells thick; eosinophilic-staining trichohyalin granules
  - Cuticle
  - Hair shaft: grows toward cell surface; cornifies without trichohyalin or keratohyalin granules
  - Cuticle: shingle-like hair cells that interlock with cuticle cells of IRS
  - Cortex: arises from cells in center of hair bulb; disulfide bonds in this region give hair its tensile strength; keratinizes to form shaft; contains pigment of hair
  - Medulla: contains melanosomes; found only in terminal hairs
  - Hair cycle: follicles (Fig. 1-1) cycle in a mosaic pattern (adjacent hairs in different stages)
    - Anagen: growth phase, stages I–VI
      - 84% of hair follicles at any one time; last a few months to 7 years
      - Cells in the hair bulb are actively dividing
    - Catagen: transitional or degenerative stage
      - 2% of hair follicles at any one time
Last a few days to weeks
- Matrix cells have stopped dividing
- Incomplete keratinization
- Thickened basement membrane (glassy layer)
- Transient, lower portion of follicle is broken down

- Telogen: resting phase
  - 14% of hair follicles at any one time
  - Last about 3 months
  - “Club hair”; no inner root sheath
  - Dermal papilla retracted to higher position in dermis

- Hair pigmentation
  - Pigment comes from melanocytes located in the matrix, above the dermal papilla
  - Eumelanin: pigment of brown-black hair
  - Pheomelanin: pigment of blonde-red hair

- Loss of melanocytes causes graying of hair—poliosis (can be seen in regrowth of hair after alopecia areata)

- Hair growth
  - Hair grows approximately 0.35–0.37 mm/day
  - Longer anagen phase = longer hair

HAIR DISORDERS

Alopecia, Nonscarring

1. Androgenetic alopecia
   - Hereditary thinning in genetically susceptible men and women
   - Circulating testosterone (T) is converted to dihydrotestosterone (DHT) by 5-alpha-reductase enzyme at the target tissue
DHT is the active androgen causing miniaturization of hairs in androgen sensitive areas of scalp. Anagen is shorter; number of follicles remains the same. Paradoxically DHT enlarges hair in androgen sensitive areas (beard, chest)

Male pattern: potential areas of hair loss are the frontal, temporal, midscalp and vertex regions (Hamilton-Norwood classification) (Fig. 1-3)

Female pattern: diffuse thinning in the midscalp, vertex, and temporal areas; frontal hairline is retained (Ludwig classification)

Histology: miniaturization increased vellus-to-terminal-hair ratio, preserved sebaceous glands

Medical treatment:
- Finasteride: 5-alpha-reductase type II inhibited
- Minoxidil: increases the number of follicles in anagen, enlarges miniaturized hairs

Surgical treatment: hair transplantation with minigrafts and micrografts

2. Alopecia areata (Fig. 1-4)
- Abrupt onset
- Patchy non-scarring hair loss
- Exclamation-point hairs which are broken hairs that are tapered at the scalp (Fig. 1-5)
- Pigmented hair affected first, subsequently grey hair may also be targeted
- Peach or salmon colored scalp
- Hair pull test positive for telogen hairs when disease is active
- Follicular damage in anagen; then rapid transformation into telogen
- Alopecia totalis: total scalp hair loss
- Alopecia universalis: total scalp and body hair loss
- Ophiasis: localized hair loss along the periphery of the scalp
- Nails: pitting, mottled lunula, trachyonychia, or onychomadesis
- Histology: peribulbar infiltrate of T cells and macrophages (“swarm of bees”)
Chapter 1    HAIR FINDINGS

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Telogen hairs move back to anagen in 3–4 months following the inciting event; hair density may take 6–12 months to return to baseline. The percentage of hairs in telogen rarely goes beyond 50%. Positive pull test: more than 6 telogen hairs. Telogen hairs on hair mount (Fig. 1-6). Histology: increased number of telogen hairs. Prognosis: Recovery is spontaneous and occurs within 6 months if inciting cause is reversed. Regrowing hairs with tapered or pointed hairs can be seen in the recovery phase.

• Associations: In the patient: atopic disorders, thyroid disease, vitiligo. In the family: atopic disorders, thyroid disease, vitiligo, diabetes mellitus, pernicious anemia, systemic lupus erythematosus (other autoimmune conditions)
• Treatment: Patchy, or < 50%: intralesional steroids, minoxidil 5% solution, anthralin, topical steroids. Unresponsive or extensive: topical immunotherapy [squaric acid dibutylester (SADBE) or diphencyprone (DPCP)], psoralen plus ultraviolet A (UV-A), prednisone, cyclosporine

3. Telogen effluvium
• Hair shedding, often with an acute onset
• Reactive process response to a physical event (surgery, pregnancy, thyroid disease, iron deficiency, high fever), medications (Table 1-1), or severe mental or emotional stress
• A large number of hairs shift from anagen to telogen at one time

4. Loose anagen syndrome
• Fair-haired children with thin, sparse, hair; no need for haircuts; easily dislodgable hair

FIGURE 1-3 Androgenetic alopecia, typical male pattern.

FIGURE 1-4 Alopecia areata. (Courtesy of Dr. Asra Ali.)

FIGURE 1-5 Exclamation point hairs in alopecia areata. (Courtesy of Dr. Paradi Mirmirani.)
Examination reveals sparse growth of thin, fine hair and diffuse or patchy alopecia. Anagen hairs are easily and painlessly pulled from scalp. Diagnosis: Epilated hairs are predominantly in anagen phase; hair mount shows distorted anagen bulb, ruffled cuticle (Fig. 1-7).

Histology: premature and abnormal keratinization of the inner root sheath.

Improves with age.

5. Anagen effluvium (aka anagen arrest)

- Hair broken off and not shed
- Radiation therapy and chemotherapy agents
- Hair shafts are abruptly thinned (Pohl-Pinkus constrictions) and break off at skin surface
- Other causes: mercury intoxication, boric acid intoxication, thallium poisoning, colchicine, severe protein deficiency
- Histology: normal follicles

6. Trichotillomania

- Impulse-control disorder
- Repeated plucking or pulling of hairs
- Confluence of short sparse hairs within an otherwise normal area of the scalp
- Varying lengths of regrowth, “friar tuck” distribution of hair loss (Fig. 1-8)
- Regrowing hair is blunt-tipped instead of pointed
- Eyebrows and upper eyelashes may be affected
- Often have other habits: nail biting, skin picking
- Histology: pigment casts, increased catagen hairs, trichomalacia
- Treatment: psychological intervention and/or psychiatric medication to modify behavior

7. Pityriasis amiantacea (Fig. 1-9)

- Thick scale, matted hair
- May mimic severe seborrheic dermatitis or psoriasis; however, hair that is involved is easily dislodged on attempts to physically remove the scale
- Scarring alopecia can result
- Treatment: keratolytics, corticosteroids, oil, improves with age

**TABLE 1-1 Common Medications Causing Telogen Effluvium**

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<td>Anticoagulation</td>
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<td>Anticonvulsant</td>
<td>(sodium valproate, carbamazepine)</td>
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<td>Tricyclic antidepresants and other psychiatric (amitriptyline, doxepin, haloperidol, lithium, haloperidol)</td>
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<td>Antigout</td>
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<td>Antithyroid</td>
<td>(methimazole, propylthiouracil)</td>
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<tr>
<td>Beta-blockers</td>
<td>(propranolol, timolol)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>(nitrofurantoin, sulfasalazine)</td>
</tr>
<tr>
<td>Other</td>
<td>(indomethacin, vitamin A)</td>
</tr>
</tbody>
</table>
6. Traction alopecia (Fig. 1-10)
   - Prolonged traction on the scalp by physical pressure: tight braids, foam rollers, tight ponytail, hair extensions
   - Hair loss may be persistent if the traction is unrelenting
9. Triangular (temporal) alopecia (Fig. 1-11)
   - Triangular patch of vellus hairs or complete hair loss—usually appears early in life
   - Frontal-temporal region
   - Histology: vellus hairs
   - No treatment, usually persistent
10. Hair loss secondary to oral contraceptives
    - Hair loss while taking oral contraceptive:
      - In women predisposed to androgenetic alopecia
      - Usually from androgenic progestins
      - Treatment: substitute oral contraceptive with less androgenic progestin
    - Hair loss after stopping oral contraceptive:
      - Onset 2 to 3 months after oral contraceptive stopped
      - May occur after stopping any of the oral contraceptives
      - Similar to postpartum effluvium, self-limited

**Alopecia, Scarring**

Current classification is based on histology of predominant infiltrate seen on scalp biopsy. If there is no significant infiltrate the hair loss is classified as end-stage scarring alopecia

- Predominantly neutrophilic: folliculitis decalvans, dissecting cellulitis
- Mixed infiltrate: Acne keloidalis

1. Pseudopelade (of Brocq; Fig. 1-12)
   - Oval or irregularly shaped atrophic patches which may be mistaken for alopecia areata with patches of hair growth, “footprints in the snow.”
   - No scalp redness or perifollicular scale
   - Histology: atrophy, perifollicular inflammation at the level of the infundibulum, fibrosis that extends into the subcutis

2. Lichen planopilaris (LPP) (Fig. 1-13)
   - Perifollicular erythema and scale at the periphery of the patch of alopecia
   - > 50% associated with cutaneous or oral lichen planus
HAIR DISORDERS

• Involves scalp alone or scalp and other hair-bearing areas (Graham Little syndrome)
• Frontal fibrosing alopecia: frontotemporal hairline recession and eyebrow loss in postmenopausal women that is associated with perifollicular erythema and scaling, in a bandlike distribution along the fronto-temporal hairline
• Histology: typically same as LPP, may see lichenoid interface dermatitis of the superficial follicular epithelium

3. Lupus erythematous

• Chronic cutaneous (discoid) lupus erythematosus (Fig. 1-14): scarring alopecia erythema, hypo and hyperpigmentation of the scalp, dilated follicles ± keratin plugs, scaling at the center of the patch of alopecia
• Systemic lupus erythematosus: diffuse, nonscarring alopecia; broken hairs in frontal region (“lupus hairs”)
• Diagnostic biopsy and direct immunofluorescence
• Treatment: topical, intralesional, or oral steroids; systemic retinoids; antimalarials

4. Central centrifugal cicatricial alopecia (CCCA) (Fig. 1-15)

• Previously called follicular degeneration syndrome; hot-comb alopecia
• Follicular loss mainly on the crown of the scalp
• Possibly secondary to hair care practices
• Histology: premature desquamation of the inner root sheath, mononuclear infiltrate at the isthmus, loss of the follicular epithelium with fibrosis

5. Alopecia mucinosa (follicular mucinosis)

• Erythematous plaques or flat patches without hair
• Children: head and neck, benign, self-resolving

• Adults: more widespread distribution; may be associated with cutaneous T-cell lymphoma
• Histology: mucin in the outer root sheath and sebaceous glands, perifollicular lymphohistiocytic infiltrate

6. Dissecting cellulitis: Perifolliculitis capitis abscedens et suffodiens (Fig. 1-16)

• May be part of the follicular occlusion triad (cystic acne, hidradenitis, dissecting cellulitis)
• Fluctuant nodules on vertex, occiput, sterile pus
• Histology: sinus tracts, sterile abscesses
• Treatment: systemic steroids, systemic antibiotics, dapsone, retinoids, surgical excision

7. Folliculitis decalvans (Fig. 1-17)

• Scarring alopecia with crusting, pustules and erosions
• Staphylococcus aureus usually cultured
8. Acne keloidalis (Fig. 1-18)
- Follicular pustules and papules that progress to firm, keloidal papules
- Commonly on occiput of patients with coarse and/or curly hair
- Foreign-body reaction to trapped hair shaft fragments
- Often bacterial superinfection

Histology: acute suppurative folliculitis with neutrophils and eosinophils; later mixed with lymphocytes and histiocytes
- Loss of sebaceous epithelium and perifollicular fibrosis
- Treatment: staphylococcal eradication: systemic antibiotics with or without rifampin, systemic and/or topical steroids

FIGURE 1-15  Central centrifugal cicatricial alopecia. (Courtesy of Dr. Paradi Mirmirani.)

FIGURE 1-16  Dissecting cellulitis. (Courtesy of Dr. Paradi Mirmirani.)

FIGURE 1-17  Folliculitis decalvans. (Courtesy of Dr. Paradi Mirmirani.)

FIGURE 1-18  Acne keloidalis. (Courtesy of Dr. Adelaide Hebert.)
- Histology: follicular dilatation and mixed periinfundibular infiltrate with follicular rupture and foreign-body granulomas
- Treatment: systemic antibiotics, topical and/or intralesional steroids

**Genetic Syndromes (Table 1-2)**
1. Anhidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome)

**TABLE 1-2 Hair Shaft Disorders**

<table>
<thead>
<tr>
<th>Hair Finding</th>
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<th>Associations</th>
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</thead>
<tbody>
<tr>
<td>Trichorrhexis nodosa (Fig. 1-19)</td>
<td>Frayed nodes spaced along hair (brooms stuck end to end)</td>
<td>Most common hair shaft dystrophy</td>
</tr>
<tr>
<td></td>
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<td>Congenital or acquired:</td>
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<td></td>
<td>Arginosuccinic aciduria, Menkes’ kinky hair syndrome, citrullinemia, trichothiodystrophy</td>
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<tr>
<td></td>
<td></td>
<td>Acquired disease:</td>
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<tr>
<td></td>
<td></td>
<td>Proximal: common in black female hair after chemical or hot comb straightening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distal: excessive brushing</td>
</tr>
<tr>
<td>Pili trianguli et cannaliculi</td>
<td>Hair has triangular cross section with longitudinal groove on electron microscopy</td>
<td>Uncombable hair syndrome</td>
</tr>
<tr>
<td>Flag sign</td>
<td>Intermittent reddish discoloration of hair</td>
<td>Kwashiorkor, anorexia nervosa</td>
</tr>
<tr>
<td>Trichorrhexis invaginata</td>
<td>“Bamboo hair” with intussusception of the hair shaft (ball and socket)</td>
<td>Netherton’s syndrome; abnormal keratinization of hair shaft in the keratogenous zone</td>
</tr>
<tr>
<td>Pili torti (Fig. 1-20)</td>
<td>Hair flattened and twisted from 90–360 degrees, multiple irregular intervals</td>
<td>Björnstad syndrome, citrullinemia, Menkes’ kinky hair syndrome, Crandall’s syndrome, Bazex’s syndrome, Salamon’s syndrome, Beare’s syndrome, trichothiodystrophy, isotretinoin therapy</td>
</tr>
<tr>
<td>Monilithrix</td>
<td>Elliptical nodes with a regular periodicity of 0.7–1 mm between nodes, hair shaft is constricted (fractures common)</td>
<td>Autosomal dominant variable expressivity; short, brittle hairs emerging from keratotic follicular papules</td>
</tr>
<tr>
<td>Pili annulati</td>
<td>“Zebra-striped hair” with alternating segments of light and dark color due to air cavities</td>
<td>Pili annulati</td>
</tr>
<tr>
<td>Trichoschisis</td>
<td>Clean transverse break along hair shaft where a local absence of cuticle is present</td>
<td>Tichothiodystrophy</td>
</tr>
<tr>
<td>Tiger tail</td>
<td>Zigzag alternating light and dark transverse bands on polarized microscopy</td>
<td>Tichothiodystrophy</td>
</tr>
</tbody>
</table>
• Abnormal facies: saddle nose, frontal bossing, thick lips, and peg teeth
• Hair has longitudinal groove on electron microscopy
• Female carriers must be watched for hyperpyrexia

2. Argininosuccinic aciduria
• Autosomal recessive
• Decrease in argininosuccinase
• Most common urea cycle defect
• Hyperammonemia, failure to thrive, hepatomegaly, seizures, ataxia, mental retardation
• Trichorrhexis nodosa
• Low-protein diet and arginine supplementation may reverse hair anomalies

3. Björnstad syndrome
• Missense mutations in the BCS1L gene on chromosome 2q34–36. Abnormal mitochondrial function, leads to the production of reactive oxygen species
• Pili torti (spares eyelashes)
• Bilateral sensorineural deafness correlates with the severity of hair defects
• Crandall syndrome is pili torti and deafness with hypogonadism

4. Hidrotic ectodermal dysplasia (Clouston’s syndrome)
• Autosomal dominant defect in gap junction protein (connexin 30)

5. KID syndrome
• Autosomal dominant mutation in gap junction protein GJP2 (connexin 26)
• Keratitis (± blindness), ichthyosis, and deafness
• Scarring alopecia, dystrophic nails

6. Menkes kinky hair syndrome
• XLR defect in MKHD gene (copper transport ATPase 7A)
• Decreased serum copper and ceruloplasmin with increased copper in all organs except the liver
• Sparse, light-colored, “steel wool” hair; pili torti (most common), trichorrhexis nodosa
• Skin is pale with laxity and a “doughy” consistency
• Progressive cerebral degeneration
• Radiologic findings: wormian bones in cranial sutures, metaphyseal widening, spurs in long bones
• Tortuous arteries, genitourinary anomalies

7. Monilohtrix
• Autosomal dominant defect in keratins 1 and 6
• See Table 1-2

8. Netherton’s syndrome
• Autosomal recessive defect in SPINK5
HAIR DISORDERS

- Ichthyosis linearis circumflexa, atopic dermatitis
- Trichorrhexis invaginata (bamboo hair) is the most common hair abnormality, but trichorrhexis invaginata is the most characteristic

9. Piebaldism
   - Autosomal dominant defect in C-KIT
   - White forelock, depigmented patches on ventral midline

10. Trichothiodystrophy
    - Autosomal recessive defect in XPB/ERCC3 DNA repair transcription gene (analogous to xeroderma pigmentosum group D)
    - Ataxia but no freckling or UV-induced skin cancers
    - Trichoschisis, banding with polarized microscopy (“tiger tail”)
    - Hairs have 50% reduction in sulfur (cysteine) content
    - PIBIDS: photosensitivity, intellectual impairment, brittle hair, ichthyosis, decreased fertility and short stature

11. Uncombable hair syndrome
    - Autosomal dominant or sporadic
    - Defect: an abnormal configuration of inner root sheath that keratinizes before the hair shaft
    - Blond, shiny, “spun glass” hair
    - Electron microscopy: pili trianguli et canaliculi, longitudinal groove, triangular shape on cross section
    - Lashes and brows are not affected
    - Biotin may help symptoms

12. Wooly hair
    - Autosomal dominant
    - Negroid hair on the scalp of person of non-Negroid background
    - Involves only scalp hair
    - Microscopy: hair shaft tightly coiled
    - Improves with age

13. Cronkhite-Canada syndrome
    - Sporadic
    - Extensive alopecia
    - Melanotic macules on the fingers, gastrointestinal polyposis, generalized hyperpigmentation, onychodystrophy, malabsorption/diarrhea

14. Aplasia cutis congenita
    - Congenital absence of skin and subcutaneous tissue; may involve cranium
    - Coin-sized defect or larger
    - Often midline scalp vertex
    - Hair collar sign: ring of dark hair encircling aplasia lesion; suggests neural tube defect
    - Adams-Oliver syndrome: severe aplasia cutis congenita, cutis marmorata telangiectatica congenita, limb defects, and atrial septal defect

Infectious Disorders

1. Tinea capitis (Table 1-3; Fig. 1-21; Fig. 1-22).
   - Treatment: Griseofulvin; terbinafine, itraconazole, may add oral prednisone in case of kerion

2. Piedra
   - Gritty nodules on the hair in temperate climates
   - White piedra is caused by Trichosporon beigelii
   - Black piedra is caused by Piedraea hortai

3. Syphilis (Fig. 1-23)
   - “Moth-eaten” alopecia

4. Trichomycosis nodosa
   - Granular sheath around hair shaft
   - Axilla or pubic area
   - Corynebacterium tenuis, due to poor hygiene

<table>
<thead>
<tr>
<th>TABLE 1-3 Presentations of Tinea Capitis</th>
</tr>
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<tbody>
<tr>
<td>Tinea</td>
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<tr>
<td>-------</td>
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<tr>
<td>“Black dot” tinea: alopecia with pinpoint black dots (infected hairs that have broken off) (see Fig. 1-21)</td>
</tr>
<tr>
<td>Kerion: boggy lesions with crust, severe inflammatory reaction (Fig. 1-22)</td>
</tr>
<tr>
<td>Favus: large crust of matted hyphae (scutula)</td>
</tr>
</tbody>
</table>

Hypertrichosis
- Overgrowth of hair not localized to androgen-dependent areas
- Local congenital or acquired hypertrichosis: melanocytic nevi, Becker’s nevus (smooth muscle hamartoma), menigioma, porphyria, spinal dysraphism
- Generalized congenital hypertrichosis: X-linked dominant congenital hypertrichosis lanuginosa, fetal hydantoin syndrome, fetal alcohol syndrome
- Generalized acquired hypertrichosis: acquired hypertrichosis lanuginosa, internal malignancy, Rubenstein-Taybi, Cornelia de Lange, minoxidil, cyclosporine, phenytoin, anorexia nervosa
- Eyelash trichomegaly-HIV

Hirsuitism
- Excessive terminal hair growth in androgen-dependent areas.
- Hypertrichosis is excessive hair growth in non-androgen dependent areas
- Usually related to hyperandrogenism
• Polycystic ovarian syndrome: hirsuitism, acne, abnormal periods, obesity
• Ovarian, adrenal, pituitary tumors
• Medications: androgens, high-progesterone oral contraceptives, minoxidil
• Treatment: waxing, plucking, shaving, bleaching, cream hair removal, electrolysis, laser, spironolactone, efuornithine cream

Miscellaneous
1. Pseudofolliculitis (Fig. 1-24)
   • Occurs at any site where hair is shaved, most common on beard
   • Ingrown hairs, foreign-body reaction
2. Green hair
   • Reaction to copper in pools
   • Treat with chelating agents
3. Bubble hair (Fig. 1-25)
   • Brittle, fragile hair from excessive heat
   • Hairdryers, straightening irons
4. Acquired progressive kinking
   • Kinking and twisting of hair shaft at irregular intervals
   • Most common in young men in frontotemporal or vertex scalp as a precursor of androgenetic alopecia
   • Rarely occurs in women or prepubertal men without progression to alopecia
   • Widespread kinking of the hair: AIDS, drugs (retinoids)

Questions
1. A 34-year-old Caucasian female patient complains of bothersome excess facial hair which she has been plucking for many years. She has a normal body mass index and has regular menses. On exam she has a clear complexion with terminal hair growth on the chin and neck, but no excess body hair. The most likely diagnosis is:
   A. Hypertrichosis
   B. Hyperandrogenism
   C. Polycystic ovary syndrome
   D. Hirsutism
   E. Pseudofolliculitis

2. A 24-year-old woman is seen with gradual hair thinning over the past few years. On exam her frontal hairline is retained but the central part is widened and there are many hairs of varied length and caliber. The follicular markings are intact and there is no scaling or erythema of the scalp. A pull test is negative. A scalp biopsy will likely show:
   A. Peribulbar lymphocytic inflammation
   B. An increased catagen/telogen ratio
   C. Premature desquamation of the inner root sheath
   D. Miniaturized hair follicles with preserved sebaceous glands

3. In a normal hair follicle the inner root sheath and the hair shaft have the following relationship:
   A. The inner root sheath is present the length of the hair shaft
   B. The inner root sheath separates from the hair shaft at the level of the sebaceous gland
   C. The inner root sheath is present only in pigmented hair shafts
   D. The inner root sheath is attached to the hair shaft via strong disulfide bonds

4. A 6-year-old girl is brought in by her mother who is concerned that she has never needed a haircut. There is no family history of similar hair problems. Her daughter does not complain of any scalp itching. The blond girl has fine textured hair that covers her scalp well but is barely past her ears in length. She has no patchy or diffuse hair loss. A hair pull is done and many hairs are easily extracted. A hair mount is done. The most likely finding:
   A. Exclamation point hairs
   B. A telogen club hair
   C. Dystrophic anagen hair with a ruffled cuticle
   D. Trichorrhexis nodosa

5. Match the syndrome on the right with most common hair findings on the left:
   A. Pili torti
   B. Trichorrhexis invaginata
   C. Pili trianguli et canaliculi
   D. Trichoschisis
   E. Trichorrhexis nodosa
   i. Trichothiodystrophy
   ii. Menkes kinky hair syndrome
   iii. Netherton syndrome
   iv. Uncombable hair syndrome
   v. Argininosuccinic aciduria

6. The following hormone is responsible for hair miniaturization in androgen sensitive areas of the scalp:
   A. 5-Alpha reductase type II
   B. Testosterone
   C. Prolactin
   D. Dihydrotestosterone
   E. Finasteride
7. A 60-year-old woman with previously “salt-and-peper” hair comes in to the office complaining that her hair “turned white overnight.” Exam shows diffuse hair loss but the follicular markings are intact. There is no scaling or erythema of the scalp. A pull test is positive. A hair mount shows telogen club hairs. Your diagnosis is:

A. Alopecia areata  
B. Telogen effluvium  
C. Anagen effluvium  
D. Androgenetic alopecia

8. A 54-year-old post-menopausal woman is seen with a complaint of a “receding hairline.” Her scalp is itchy. On exam there is a band of alopecia at the frontal hairline and extending to the temporal hairline. Where the hairline used to be, the skin is atrophic and white with loss of follicular markings. Along the current hairline there is perifollicular scaling and erythema. A scalp biopsy is done showing a dense lymphocytic infiltrate at the level of the isthmus. Your diagnosis:

A. Hair loss due to excess androgens  
B. Folliculitis decalvans  
C. Alopecia areata in an ophiasis pattern  
D. Frontal fibrosing alopecia

9. The following is/are part of the permanent portion of the hair follicle:

A. Follicular melanocytes  
B. Dermal papilla  
C. Stem cells  
D. All of the above

10. The following hair shaft disorders are associated with increased hair fragility and breakage:

i. Trichorrhexis nodosa  
ii. Trichorrhexis invaginata  
iii. Pili annulati  
iv. Pili trianguli et canaliculi  
v. Monilethrix

A. i and ii  
B. all of the above  
C. iii and iv  
D. i, ii, v

**Answers**

1. D. The clinical scenario fits best with a diagnosis of idiopathic hirsutism. Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas (beard, chest, axilla, pubic area). Hypertrichosis is excess hair growth in non-androgen dependent areas.

2. D. The description of hair loss fits best with a clinical diagnosis of androgenetic alopecia. The histologic findings seen in androgenetic alopecia are miniaturized follicles with retained sebaceous glands.

3. B. The inner root sheath resembles a hard mold surrounding the newly forming hair shaft. The inner root sheath moves upward with the hair shaft but separates at the level of the sebaceous gland. The inner root sheath is present in all types of hair shafts. Disulfide bonds crosslink are found in the hair cortex providing tensile strength to the hair shaft.

4. C. The clinical scenario is that of a patient with loose anagen syndrome. There is no alopecia, but the hair is somewhat sparse and fails to grow long. Hairs that are easily extracted show a hook-shaped appearance (dystrophic anagen) with a ruffled cuticle.

5. A-ii; B-iii, C-iv, D-i, E-v.

6. D. Circulating testosterone is converted to dihydrotestosterone by 5-alpha-reductase at the genetically susceptible target tissue (scalp). It is the dihydrotestosterone that is the active hormone leading to scalp hair miniaturization.

7. A. The clinical scenario describes a patient with alopecia areata. Alopecia areata not uncommonly will affect pigmented hair first, thus giving the appearance of “going white overnight.” In active alopecia areata telogen hairs or broken hairs may be seen on hair mount.

8. D. Frontal fibrosing alopecia is a primary cicatricial alopecia, lymphocytic type, thought to be a variant of lichen planopilaris. The typical patient is a post-menopausal woman with a band-like area of hair loss along the fronto-temporal rim; loss of eyebrows is variably seen. At the active border of hair loss there is perifollicular erythema and scaling.

9. C. The permanent portion of the hair follicle includes the infundibulum and isthmus. The follicular stem cells are located at the level of the bulge (insertion of the arrector pili muscle) located near at the isthmus.
10. D. Hair shaft disorders are typically divided into those that cause increased fragility/breakage and those that do not. Patients with trichorrhexis nodosa, trichorrhexis invaginata, and monilethrix typically present with short, broken hair.

REFERENCES


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CHAPTER 2
EYE FINDINGS
BRENDA CHRASTIL-LATOWSKY
SYED AZHAR

EYELID ANATOMY (FIG. 2-1)

Eyelids
- Superficial to deep
  - Skin: epidermis appears atrophic, few vellus hair follicles, no subcutaneous fat
  - Ocularis oculi: Closes the eyelid, innervated by facial nerve
  - Areolar tissue: communicates with subaponeurotic layer of scalp
  - Tarsal plates: fibrous tissue responsible for structural integrity of eyelid; connected to orbital margin by lateral and medial palpebral ligaments
  - Palpebral conjunctiva: mucosal membrane
  - Sensory innervation: Terminal branches of the trigeminal nerve [cranial nerve V (CNV)]: ophthalmic (V1) and maxillary (V2) divisions

Upper Eyelid
- Extends superiorly to the eyebrow
- Upper lid retractors
  - Levator palpebrae superioris (LPS) elevates anterior portion, innervated by oculomotor nerve (CN III)
  - Müller’s muscle (deeper fibers of LPS) elevates posterior portion

Lower Lid
- Extends below the inferior orbital rim to join the cheek
- Lower eyelid retractors
  - Inferior rectus is the main retractor, innervated by oculomotor nerve (CN III)
  - Inferior oblique is innervated by CNIII
    - Ptosis caused by CN III palsy and Horner’s syndrome

Interpalpebral Fissure
- Fusiform space between the eyelid margins (usually 10–11 mm in youth; decreases with age to 8–10 mm)

Eyelashes
- Lid margins have horizontal row of irregularly-arranged eye lashes anteriorly and approximately 25 openings of Meibomian glands posteriorly
- More eyelashes on top lid margin
- Trichiasis
  - Misdirected eyelashes that rub on the cornea
  - Very common acquired condition
  - Results in ocular irritation made worse on blinking
  - Caused by chronic blepharitis, herpes zoster ophthalmicus (see below), trauma, or chemical injuries to eyes
- Distichiasis
  - Eyelashes grow abnormally from meibomein gland openings, resulting in 2nd row of eyelashes
  - Results from intense inflammation of eyelids, such as from cicatricial pemphigoid or Stevens-Johnson syndrome, or may be congenital (see below)
- Lymphedema-Distichiasis syndrome
  - Autosomal dominant with high penetrance, variable expressivity
  - Mutation in the FOXC2 gene, a transcription regulator
  - Epithelial germs cells destined to develop into Meibomian glands instead differentiate into complete pilosebaceous units
  - Second row of posteriorly-directed eyelashes
  - Lymphedema of the legs
- Trichomegaly (Table 2-1)
- Entropion
  - Inward turning of the eyelid margin from infection, scarring, mechanical trauma
  - Causes irritation, redness, and stringy white mucoid discharge
- Ectropion
  - Outward turning of the eyelid margin from lower eyelid laxity, mechanical (collodion membrane)
TABLE 2-1 Causes of Trichomegaly

<table>
<thead>
<tr>
<th>Acquired</th>
<th></th>
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<tbody>
<tr>
<td>Drug-induced: phenytoin, cyclosporine, topical prostaglandin analogues, interferon α 2a, epidermal growth factor inhibitors, systemic tacrolimus</td>
<td></td>
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<tr>
<td>Malnutrition</td>
<td></td>
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<tr>
<td>Acquired immunodeficiency syndrome (AIDS)</td>
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<tr>
<td>Porphyria</td>
<td></td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Familial</td>
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<table>
<thead>
<tr>
<th>Congenital</th>
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</tr>
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<tbody>
<tr>
<td>Cornelia de Lange syndrome: synophrys, low hairline, developmental and musculoskeletal abnormalities</td>
<td></td>
</tr>
<tr>
<td>Hermansky-Pudlak syndrome: albinism and bleeding diathesis</td>
<td></td>
</tr>
<tr>
<td>Oculocutaneous albinism type I</td>
<td></td>
</tr>
<tr>
<td>Oliver-MacFarlane syndrome: retinitis pigmentosa, short stature (GH deficiency), trichomegaly, and hair anomalies</td>
<td></td>
</tr>
</tbody>
</table>

EVIDI ANATOMY

- Causes tearing, corneal irritation and conjunctival redness, dry eyes
- Lower eyelid is involved most commonly

**Dermatochalasis (Fig. 2-2)**
- Redundant eyelid skin and fat
- May result in functional loss of superior vision if the tissue hangs over the eyelid margin

**Blepharoptosis (Fig. 2-3)**
- Drooping of the margin of the eyelid, may cause functional vision loss
- Etiology includes age-related dehiscence of the levator muscle, Horner’s syndrome, third cranial nerve palsy, myasthenia gravis, and trauma


**Glands of the Eyelid**

- **Zeis glands**
  - Small, modified sebaceous glands
  - Open into the hair follicles at the base of the eyelashes
  - External hordeolum (stye): Staph infection of lash follicle and associated gland of Zeis

- **Meibomian glands**
  - Sebaceous glands, present within the tarsus; secrete lipid layer of tear film
  - Chalazion (Meibomian cyst) (Fig. 2-4): granulomatous reaction to sebaceous secretion into surrounding stroma
    - Nontender, firm nodule located deeply within the tarsal plate about 5 mm from the lid margins
    - Eversion of the lid may reveal the inflamed meibomian gland
  - Internal hordeolum: chalazion superinfected with Staph
    - Both internal and external hordeolum can arise as a secondary complication of blepharitis

- **Glands of Moll**
  - Apocrine glands
  - Located anterior to the meibomian glands within the distal eyelid margin
  - Apocrine hidrocystoma (cyst of Moll) – translucent, bluish cyst on anterior margin of eyelid. Eccrine hidrocystoma usually located medially or laterally and does not involve the lid margin

- **Schopf-Schulz-Passarge syndrome**
  - Autosomal recessive
  - Hidrocystomas of eyelids
  - Hypotrichosis, hypodontia, nail abnormalities
  - Palmarplantar eccrine syringofibroadenosis

CONGENITAL ABNORMALITIES

Albinism (See Chapter 29)
- Oculocutaneous albinism
  - Involves both the skin and eyes
- Ocular albinism
  - Mainly affects the eyes with minimal to no skin involvement
  - Sex-linked or autosomal recessive disease: reduction in the number of melanosomes
- Color of the iris usually is blue for tyrosinase-negative albinism, blue to yellow-brown for tyrosinase-positive albinism

Ataxia-Telangiectasia (Louis-Bar Syndrome) (Fig. 2-5) (See Chapter 32)
- Autosomal recessive, defect in ATM gene on 11q22-23
- Telangiectasia of the bulbar conjunctiva (first appears at 3–5 years)
- Accelerated aging of skin and vessel changes on eyelids (rare)
- Strabismus and nystagmus
- Poor ability to initiate rapid eye movements
- Visual acuity, pupillary reflex responses, and fundi are normal

Juvenile Xanthogranuloma (JXG)
- Non-Langerhans cell histiocytosis with Touton giant cells (under age 2 years)
- Ocular involvement is the most common extracutaneous site
- Orbital masses, unilateral glaucoma, yellowish brown iris lesions resulting in iris heterochromia and spontaneous hyphema, uveitis
- JXG in a patient with neurofibromatosis type 1 signals a 20-fold to 32-fold increased risk for juvenile chronic myelogenous leukemia

Nevus of Ota (Ocular Melanocytosis or Melanosis Oculi) (See Fig. 8-2)
- Unilateral congenital pigmented lesion of sclera (bluish or slate gray)
- May involve eyelid or adjacent skin with dermal hyperplasia (commonly seen in Asians)
- Higher incidence of glaucoma and possibly malignant melanoma

Down’s Syndrome (See Chapter 32)
- Trisomy 21
- Brushfield’s spots (white spots indicative of hyperplasia of iris) present in 90% of patients
- Prominent epicanthal folds
- Amblyopia
- High refractive errors
- Glaucoma during infancy
- Cataracts, early or late

Cockayne’s Syndrome (CS) (See Chapter 32)
- Autosomal recessive
- CS type 1 is caused by a defect in the Cockayne syndrome type A gene (CSA or ERCC8) located on chromosome 5
- Mutations in the DNA excision repair gene ERCC6 located on band 10q11 cause CS type 2
- In some patients there is an overlap with xeroderma pigmentosa complementation group B, D or G
- Retinitis pigmentosa (“salt and pepper retina”)
- Cataracts in children younger than 3 years
- Optic atrophy or optic disk pallor

Gardner Syndrome (Familial Adenomatous Polyposis) (See Chapter 32)
- Autosomal dominant
- Mutations in the tumor suppressor adenomatous polyposis coli gene (APC) on 5q21-22
- Mutations on the APC gene that correlate with congenital hypertrophy of the retinal pigment epithelium (CHRPE) are between codon 311 on exon 9 and codon 1444 on exon 15
- Benign hyperpigmented lesion of the retinal pigment epithelium
- Typically smaller, multiple, and bilateral in Gardner syndrome (50–80%)

Hypomelanosis of Ito (Incontinentia Pigmenti Achromians)
- Mosaicism of the X chromosome
- Retinal pigment abnormalities: radial hypopigmented streaks
- Unilateral heterochromic iris

CONGENITAL ABNORMALITIES

- Hypopigmentation of the cornea, strabismus, and hypertelorism
- Cataracts and retinal detachment

**Goldenhar Syndrome (Oculo-Auriculo-Vertebral Dysplasia)**
- Sporadic
- Upper lid coloboma
- Microphthalmos (presence indicates increased risk of mental retardation)
- Epibulbar tumors
- Microtia
- Preauricular acrochordons
- Hypoplasia of malar, maxillary and mandibular regions
- Macrostomia

**Epidermal Nevus Syndrome (See Chapter 11)**
- Mosaicism
- Epidermal nevi, which may involve eyelid and bulbar conjunctiva
- Lipodermoid tumors
- Coloboma
- Corneal opacities

**Incontinentia Pigmenti (Bloch-Sulzberger Syndrome) (See Chapter 8)**
- X-linked dominant defect in NEMO
- Retina with mottled, diffuse hypopigmentation (nearly pathognomonic)
- Abnormal peripheral retinal vessels with areas of nonperfusion (very common), retrolental membrane formation (pseudoglioma), cataracts, glaucoma, microphthalmos, nystagmus, and strabismus
- Optic atrophy or foveal hypoplasia
- 1/3 of children have retinal detachment in the first year of life, resulting in white pupillary reflex (leukocoria)

**Leopard Syndrome (Moynahan Syndrome)**
- Autosomal dominant
- Defect in PTPN11, encoding the tyrosine phosphatase SHP-2 located on 12q24.1
- Mutation results in loss-of-function
- Lentigines (spares the mucous membranes), electrocardiographic (ECG) conduction defects, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, deafness

**Nail Patella Syndrome (See Chapter 11)**
- Also known as hereditary osteoonychodysplasia (HOOD)
- Autosomal dominant
- Defect in transcription factor gene LMX1B
- Lester iris: hyperpigmentation of the pupillary margin of the iris (45% of patients)
- Heterochromia of the iris with cloverleaf deformity, cataracts, microcornea, and glaucoma

**Xeroderma Pigmentosum (See Chapter 32)**
- Autosomal recessive
- Progressive photophobia, conjunctivitis, pigmentation of eyelids and conjunctivae
- Ectropion
- Benign lid papillomas and malignant tumors: BCC, SCC, melanoma

**Treacher Collins Syndrome**
- Defect in first and second branchial arch structures
- Autosomal dominant
- Lower lid coloboma (77%)
- Downward slanting of the palpebral fissures ( antimongoloid)
- Cataracts
- Normal intelligence in most
- Malformation of the pinnas and conductive hearing loss
- Hypoplastic mid-face: bilateral and symmetric mandibular and zygomatic hypoplasia
- Micrognathia

**Apert Syndrome (Alpert’s Syndrome)**
- Premature fusion of all cranial sutures
- Autosomal dominant and sporadic (associated with increased paternal age)
- Major criteria: craniosynostosis and syndactyly
- Flattened occiput and prominent forehead
- Mid-facial hypoplasia and beaked nose
- Acneiform eruption of trunk and extremities, moderate-severe acne at adolescence in 70%
- Downward slanting palpebral fissures
- Amblyopia and strabismus

**Crouzon Syndrome**
- Autosomal dominant
- Most common mutation: FGFR2 on chromosome 10
- Mutation in the FGFR3 gene associated with acanthosis nigricans
- Hypoplastic midface
- Mandibular prognathism
- Proptosis secondary to shallow orbits
- Hypertelorism
- Blue sclerae reported less commonly

**Riley-Day Syndrome (Familial Dysautonomia)**
- Autosomal recessive
- Hyperhidrosis
- Generalized lack of response to pain
- Lack of tears
• Decreased corneal sensaation
• Miosis of the pupil in response to 2.5% methacholine (no response in normal subjects)

CONNECTIVE TISSUE DISORDERS

Ehlers-Danlos Syndrome (See Chapter 32)
• Abnormalities in the synthesis and metabolism of collagen
• Most ocular abnormalities occur in the kyphoscoliosis type (previously known as type VI)
• Autosomal recessive
• Mutations in the PLOD gene
• Defect in lysyl hydroxylase
• Retinal detachments, microcornea, myopia, blue sclera, angioid streaks, keratoconus, myopia, lens subluxation, and ocular fragility can lead to a ruptured globe/blindness

Marfan’s Syndrome (See Chapter 32)
• Autosomal dominant
• Defect mutations in the fibrillin-1 (FBN1) gene located on chromosome 15q21.1
• Fibrillin needed to form microfibrils
• Structural component of the suspensory ligament of the lens
• Lens subluxation (50–80%)
  • Lense tends to displace superotemporally
  • Typically present at birth and is nonprogressive
  • Can result in hyperopic or myopic shift, astigmatism
• Slit-lamp exam
  • Displaced crystalline lens
  • Appears as a black crescent at the edge of the lens against a red reflux from the fundus
• Other ocular anomalies
  • Flat cornea
  • Increased axial length of the globe resulting in myopia (nearsightedness) and retinal detachment
  • Glaucoma and cataracts in patients younger than 50 years
  • Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

Osteogenesis Imperfecta (Table 2-2) (See Chapter 32)
• Autosomal dominant
• Blue sclera is caused by thinness and transparency of the collagen fibers of the sclera allowing visualization of underlying uvea
• Also may present with keratoconus, megalocornea, anterior embryotoxon, congenital glaucoma, zonular cataract, dislocated lens, choroidal sclerosis, retinal hemorrhage

Pseudoxanthoma Elasticum (PXE) (See Chapter 32)
• Autosomal recessive

<table>
<thead>
<tr>
<th>Type</th>
<th>Ocular Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Premature arcus senilis, blue sclera</td>
</tr>
<tr>
<td>II</td>
<td>Dark-blue sclera</td>
</tr>
<tr>
<td>III</td>
<td>Sclera of variable hue</td>
</tr>
<tr>
<td>IV</td>
<td>Normal sclera</td>
</tr>
</tbody>
</table>

• Defect in ABCC6 gene
• Cutaneous and ocular findings of PXE are referred to as Grönblad-Strandberg syndrome
• Increased amounts of elastic tissue that become calcified
• Angiod streaks
  • Dark-red to brown bands that are breaks in the thickened and calcified Bruch membrane
  • Radiate from the optic nerve
  • Bruch’s membrane is a collagen- and elastin-containing membrane between the retina and the choroid
• Macular degeneration, retinal hemorrhage, choroidal ruptures

Waardenburg Syndrome (Table 2-3) (See Chapter 29)
• Autosomal dominant
• Defect of neural crest cell migration and differentiation
• Dystopia canthorum (most common)
• Distance between the inner angles of the eyelids is accompanied by increased distance between the inferior lacrimal points
• Heterochromic irides, bilateral isohypochromia iridis (pale-blue eyes)
• Strabismus
• Albinotic fundus: generalized decrease in retinal pigment

Werner Syndrome (Progeria Adultorum) (See Chapter 32)
• Autosomal recessive
• Defect in the WRN gene (DNA helicase)
• Posterior subcapsular cataracts (20–40 years)

Focal Dermal Hypoplasia (Goltz Syndrome) (See Chapter 32)
• X-linked dominant, Xp22
• Heterochromia, irregularity of the pupils, aniridia, lens subluxation
• Colobomas of the iris, choroid, retina, or optic disc
• Corneal defects, cloudiness of the vitreous, widely spaced eyes
VASCULAR DISORDERS

KERATOTIC DISEASES (TABLE 2-4)

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>PAX3</td>
<td>Dystopia canthorum, convergent strabismus (blepharophimosis), and reduced visibility of the medial sclera</td>
</tr>
<tr>
<td>II</td>
<td>MITF</td>
<td>Heterochromia iridium, no dystopia canthorum</td>
</tr>
<tr>
<td>III</td>
<td>PAX3</td>
<td>Dystopia canthorum</td>
</tr>
<tr>
<td>IV</td>
<td>SOX10</td>
<td>Hirschsprung’s disease</td>
</tr>
</tbody>
</table>

CHIME Syndrome
- Colobomas of the eye, heart defects, ichthyosiform dermatosis, mental retardation, and ear defects

Vogt-Koyanagi-Harada Syndrome (See Chapter 29)
- Pathogenesis targets melanocytes
- HLA-DR1 and 4
- Granulomatous uveitis/iridocyclitis, swollen optic disc, chorioiditis, vitreous opacities, and serous retinal detachments
- The above findings are followed several weeks later by poliosis of eyelashes and brows and vitiligo, depigmented fundus and limbic lesions

VASCULAR DISORDERS

Osler-Weber-Rendu (Hereditary Hemorrhagic Telangiectasia) Syndrome (See Chapter 32)
- Autosomal dominant
- Defects in endoglin and activin receptor-like kinase type I (ALK-1) genes, which encode for TGF-β receptor
- Conjunctival telangiectasias by 3 to 6 years of age

Capillary Hemangiomas
- One of the most common benign orbital tumors of infancy (females 2:1)
- Benign endothelial cell and vascular channel neoplasms that are typically absent at birth and characteristically have rapid growth in infancy
- Ocular morbidity related to space-occupying effects
- Amblyopia (43–60%), astigmatism, strabismus with eyelid involvement
- Presentation: unilateral, superionasal, eyelid, or brow lesion

Sturge-Weber Syndrome
- Disease characterized by facial capillary malformation with underlying soft tissue and skeletal hypertrophy, ipsilateral arteriovenous (AV) malformation, cerebral calcification, hemiparesis, hemianopia, contralateral seizures, and some mental deficiency
- Glaucomas: 60% at birth or early infancy and 30% presenting during childhood, almost always unilateral and ipsilateral to the port-wine stain
- “Tomato catsup” fundus with a bright-red or red-orange color
- Tortuous conjunctival and episcleral vascular plexuses
- Choroidal angiomas (indirect binocular ophthalmoscopy)
- Anisometric amblyopia

Lipoid Proteinosis (Urbach-Wiethe Disease) (See Chapter 27)
- Autosomal recessive
- Mutation in extracellular matrix protein 1
- Eyelid “string of pearls”

Naegeli-Franceschetti-Jadassohn Syndrome
- Rare autosomal dominant form of ectodermal dysplasia
- Hyphidrosis and palmarplantar keratoderma
- Lack of dermatoglyphics
- Dermatoocular syndrome (starting at age 2)
- Reticular pigmentation of the neck, chest, and abdomen, improving with age
- Spotlike pigmentation may be present around the mouth and eyes

Hay-Wells Syndrome
- Ankylolobharon-ectodermal dysplasia-clefting (AEC) syndrome
- Autosomal dominant
- Sparse eyelashes
- Cleft palate and cleft lip
- Ankylolobharon filiforme adnatum

CHANDS Syndrome
- Autosomal recessive with pseudodominance
- Curly hair
- Ankylolobharon
- Nail Dysplasia (hypoplastic nails)
Chapter 2  EYE FINDINGS

TUMORS

**Basal Cell Carcinoma (BCC) (Fig. 2-6)**
- Most common epithelial tumor of the eyelid
- Most common location is the lower eyelid (48.9–72.1%)
- Highest recurrence in lesions arising from the medial canthus (60%)
- Nodular BCC most common type

**Squamous Cell Carcinoma (SCC) (Fig. 2-7)**
- Approximately 5% of malignant eyelid tumors
- Incidence of metastasis is 0.23–2.4% of cases
- Location of lesion most common on lower eyelid, then lid margin

**Sebaceous Cell Carcinoma**
- Female predilection
- May mimic either a chalazion or chronic blepharitis
-Invades locally and can spread to regional lymph nodes
- It arises generally from the meibomian glands and glands of Zeis
- Predilection for the upper lid
- Yellowish, firm, painless, indurated papule or ulceration
- May arise from meibomian glands (most common), Zeis glands, or glands associated with the caruncle
- Large anaplastic cells with open vesicular nuclei and prominent nuclei set in foamy or frothy cytoplasm, pagetoid spread
- Overall mortality rate 5–10%
- Associated with Muir-Torre syndrome

**Nevus (Fig. 2-8)**
- Nevi are well-demarcated, flat or elevated, pigmented or nonpigmented lesions
- May become more pigmented, more elevated, or cystic during adolescence or young adulthood
- Pigmented lesions that have changed in appearance should be excised

**TABLE 2–4 Keratotic Diseases: Inheritance, Gene Defects and Ocular Findings**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Enzyme defect</th>
<th>Ocular Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked ichthyosis</td>
<td>X-linked recessive</td>
<td>Steroid sulfatase</td>
<td>Comma-shaped corneal deposits</td>
</tr>
<tr>
<td>Lamellar ichthyosis</td>
<td>Autosomal recessive</td>
<td>Transglutaminase 1</td>
<td>Ectropion, megalocornea</td>
</tr>
<tr>
<td>Refsum syndrome</td>
<td>Autosomal recessive</td>
<td>Phytanic acid oxidase deficiency</td>
<td>“Salt-and-pepper retina,” cataracts, nystagmus, night blindness</td>
</tr>
<tr>
<td>Sjögren-Larsson syndrome</td>
<td>Autosomal recessive</td>
<td>Fatty alcohol oxidoreductase deficiency</td>
<td>“Glistening dots,” pigmentary retinopathy</td>
</tr>
<tr>
<td>Conradi-Hunermann syndrome</td>
<td>X-linked dominant</td>
<td>PEX7/EBP</td>
<td>Asymmetric focal cataracts, optic nerve hypoplasia</td>
</tr>
<tr>
<td>KID (keratitis, ichthyosis, deafness) syndrome</td>
<td>Autosomal dominant and autosomal recessive reported</td>
<td>GJP2/Connexin26</td>
<td>Keratitis, blindness, photophobia</td>
</tr>
</tbody>
</table>

**FIGURE 2-6** Basal cell carcinoma in “danger” zone
A. Smooth, glistening, pearly tumor with telangiectasia. Basal cell carcinomas arising in the central area of the face, in the nasolabial folds, around the eye, and in the sulcus behind the ear (“danger zones”) must be removed with Moh’s surgery to prevent unmanageable recurrences, as these tumors move deeply along the fascial planes. (Reproduced with permission from Wolff K et al. Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 5th Ed. New York: McGraw-Hill; 2005.)
Melanoma (Fig. 2-9)
- Rare pigmented eyelid tumor
- Must be differentiated from nevi and BCC
- Change in the appearance of a pigmented lesion warrants excisional biopsy of the lesion

Merkel Cell Carcinoma (Fig. 2-10)
- Rarely suspected clinically
- 2/3 of all patients with Merkel cell carcinoma have lymph node metastases within 18 months of diagnosis, 1/3 develop hematogenous spread
- Affects the elderly
- Upper eyelid most commonly affected
- Violaceous, well demarcated nodule with little epidermal change

SYSTEMIC HAMARATOMA SYNDROMES

Tuberous Sclerosis (See Chapter 32)
- Autosomal dominant and spontaneous mutations (66%)
- Hamartin and tuberin found on chromosomes 9 and 16, respectively
- Hypopigmented macule in the iris, seizures
- Retinal hamartomas (phakomas), astrocytic hamartomas: whitish gray nodular lumps with a mulberry appearance, glial cell in origin and may calcify, some lesions are flat and smooth
- Retinal hamartomas are usually benign, but there are reports of aggressive growth, resulting in retinal detachment and glaucoma (some cases have require enucleation of the eye)
- Nystagmus and angioid streaks

Neurofibromatosis I (See Chapter 32)
- Autosomal dominant, nearly half are sporadic
- NF-1 encodes Neurofibromin, and is found on 17q11.2
- Congenital glaucoma
- Lisch nodules (iris hamartomas) (Fig. 2-11), tan, asymptomatic nodules that develop in the first to third decades (usually before 6 years of age)
  - Present in 95% of patients
  - Found on slit-lamp examination
- Optic nerve glioma occurs in 15% and may involve other brain structures
- Plexiform neurofibroma of the orbit or eyelid leading to glaucoma and ptosis, ectropion uveae, retinal hamartoma, prominent corneal nerves
- Choroidal nevi
  - May have increased risk of developing into melanoma
Sjögren Syndrome (See Chapter 25)
- Autoimmune condition (SSA (Ro) and SSB (La) antigens) of lacrimal and salivary glands
- Human leukocyte antigen B8 (HLA-B8), DR3, DQw2 and DRw52 antigens
- Xerophthalmia: foreign body sensation is an early sign
- Repeated blinking and rubbing results in minor corneal abrasions, which may produce photophobia
- Keratoconjunctivitis sicca, punctate keratopathy, uveitis, optic neuritis, scleritis
- Rarely, Adie pupil (tonic pupil) – response to light and accommodation is sluggish
- One of the few conditions to produce bilateral enlargement of lacrimal (and salivary) glands
- Rapid enlargement, however, warrants a workup for B-cell lymphoma

Relapsing Polychondritis (RP)
- Episodic inflammatory condition involving cartilaginous structures
- Antibodies to collagen type II
- HLA-DR4
- Inflammation of almost every part of the eye: conjunctivitis, episcleritis, scleritis, uveitis, retinopathy, diplopia, and eyelid swelling

Polyarteritis Nodosa (PAN)
- Disease with necrotizing inflammation of medium- or small-sized arteries
- Hypertensive and ischemic retinopathy, central nervous system (CNS) lesions resulting in visual loss,
CN palsies, scleritis, marginal corneal ulceration, interstitial keratitis, occlusive retinal periarteritis

**Dermatomyositis (DM) (See Chapter 25)**
- Heliotrope rash: violaceous to dusky erythematous rash, most prominent on upper eyelids
- With or without edema in a symmetric distribution involving the periorbital skin
- Rare ophthalmoplegia owing to myositis of extraocular muscles
- Retinopathy may occur in juvenile dermatomyositis

**Wegener Granulomatosis (WG)**
- Autoimmune inflammatory process with necrotizing granulomas
- Antineutrophil cytoplasmic antibodies (c-ANCA) directed at neutrophil proteinase 3 (PR-3)
- Ocular involvement in 29–58%; can be localized to the orbit
- Orbital pseudotumors causing refractile proptosis, pain and loss of vision
- Nasolacrimal duct stenosis
- Uveitis
- Nodular scleritis, peripheral keratitis, and retinal vasculitis

**Sarcoidosis (Fig. 2-12) (See Chapter 30)**
- Multisystem granulomatous disease of unknown etiology; ocular or lacrimal involvement in 25%
- Lacrimal gland and ductal involvement
- Conjunctival granulomatous nodules
- Interstitial keratitis
- Cataract and glaucoma: complication of uveitis and/or the corticosteroid treatment
- Anterior uveitis: most common ocular manifestation of sarcoidosis with mutton fat keratic precipitates, iris nodules (Busacca and Koepppe), iris synechae
- Glaucoma: both open-angle and angle-closure
- Retinal neovascularization, periphlebitis, perivascular cuffing and exudates
- Vitreous cavity inflammation (pars planitis), choroidal lesions
- Rarely neurosarcoid: granulomas of the optic nerve (CN II) along with oculomotor nerves (CNs III, IV, and VI)
- May cause diplopia, ptosis, or paresis of extraocular muscles
- Heerfordt syndrome (uveoparotid fever)
  - Fever, uveitis, which may precede the parotid enlargement, and facial nerve palsy
- Löfgren syndrome
  - Fever, erythema nodosum, bilateral hilar adenopathy, and arthralgias
  - Associated with anterior uveitis in 6% of patients
- Mikulicz syndrome

**Ocular Cicatricial Pemphigoid (OCP) (See Chapter 10)**
- Autoantibodies directed against
  - Bullous pemphigoid antigen 2 at a site near the lamina densa (explains the scarring)
    - Autoantibodies bind the epidermal side of salt-split skin
  - β4 subunit of α6β4-integrin (205-kDa protein, also known as CD104)
    - Epiligrin (laminin 5, α subunit) ligand for α6β4-integrin
    - Autoantibodies bind to the dermal side of salt-split skin
    - Autoantibodies cross-react with the alpha subunit of laminin-6
- Mouth most common site affected in cicatricial pemphigoid
- Ocular anomalies in older individuals (70 years mean age)
- Ocular involvement more common in patients with oral involvement (75%) versus skin without oral involvement (25%)
- Involvement is bilateral, but disease may initially present unilaterally; signs and symptoms may be asymmetrical
- Early disease is subtle: irritation, dry eye, discharge
  - Can detect disease involvement by slit-lamp exam
- Chronic conjunctivitis may lead to scarring, blindness if untreated
- Scarring leads to conjunctival shrinkage, symblepharon, fibrotic bands, trichiasis
• Differential diagnosis includes cicatrizng conjunctivitis resulting from use of pilocarpine, guanethidine, ephedrine or idoxuridine
• There are reports of ocular cicatricial pemphigoid that began after severe ocular injury resulting from Stevens-Johnson syndrome

**Stevens-Johnson Syndrome**
• Delayed hypersensitivity reaction to drugs, usually acute (HLA-B12, –A29, DR7)
• Other causes: infection, vaccination, systemic diseases, physical agents
• Incidence in HIV patients is 3 times higher than that of the general population
• Conjunctivitis, chemosis, vesicles, bullae, membranes, ulceration
• Bilateral lacrimation
• Swollen and ulcerated eyelids leading to entropion, dry eyes
• Subepithelial fibrosis, lagophthalmos, corneal ulceration, vascularization, opacification, and rarely, perforation
• Scarring manifests as conjunctival shrinkage, shortening of fornices resulting in symblepharon, ankyloblepharon, trichiasis

**METABOLIC DISORDERS (TABLE 2-5)**

**Alkaptonuria (Fig. 2-13) (See Chapters 11, 27)**
• Autosomal recessive
• Deficiency of homogentisic acid oxidase, encoded on chromosome 3
• Causes ochronosis

**TABLE 2–5  Metabolic Disorders**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Gene Defect</th>
<th>Characteristic Ocular Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaptonuria</td>
<td>Autosomal recessive</td>
<td>Homogentisic acid oxidase</td>
<td>Blue-black sclerae (Osler sign)</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>X-linked recessive</td>
<td>α-galactosidase</td>
<td>Whorled corneal opacities</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Autosomal recessive</td>
<td>Copper transporter ATP7B</td>
<td>Keyser-Fleisher rings</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Autosomal recessive</td>
<td>Cystathionine-beta-synthetase</td>
<td>Downward ectopia lentis</td>
</tr>
<tr>
<td>Richner-Hanhart syndrome</td>
<td>Autosomal recessive</td>
<td>Hepatic tyrosine aminotransferase</td>
<td>Corneal cluring, pseudoherptic corneal ulcers</td>
</tr>
<tr>
<td>(Tyrosinemia II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucopolysaccharidoses</td>
<td>AR (Hunter’s XLR)</td>
<td>Varies</td>
<td>Corneal cluring, pigmented retinopathy in some</td>
</tr>
</tbody>
</table>

• Incidence higher in Slovakian population
• Bluish black discoloration of sclerae
• Osler sign: blue-black pigment in sclera near insertion of rectus muscles
  • Usually triangular, with base facing site of muscle insertion
  • First ocular manifestation to appear
• Oil-droplet opacities in cornea
• Pigmented pinguecula in the shape of rings

**Fabry Disease (See Chapters 9, 27)**
• X-linked recessive
• Defect in α-galactosidase
• Characteristic corneal opacities: cornea verticillata (whorled corneal deposits)
  - Amiodarone and chloroquine produce deposits that appear identical
  - “Fabry cataract”: spokelike lens deposits of posterior lens
    - Unique to Fabry’s and found in males and female carriers
    - First ocular manifestation
• Conjunctival and retinal vascular lesions: early in life there is tortuosity, aneurysms of venules and sausage-like dilation of veins
  - Later, systemic hypertension produces retinal changes
• Oculomotor abnormalities

**Hepatolenticular Degeneration (Wilson Disease) (Fig. 2-14) (See Chapter 27)**
• Autosomal recessive
• Disorder of copper metabolism
• Keyser-Fleiser ring: greenish brown ring of copper in Descemet membrane
Homocystinuria (See Chapter 27)
- Autosomal dominant
- Deficiency of cystathionine-beta-synthetase (CBS)
- Downward lens dislocation (ectopia lentis)
  - Within first decade of life
- Myopia
- Rupture of the sclera and retinal detachment

Primary Amyloidosis (Myeloma-Associated) (Fig. 27-4)
- Amyloid protein (AL) derived from immunoglobulin light chains
- Periorbital purpuric plaques (“pinch purpura”)
- Amyloid deposition in the corneal stroma, conjunctiva and eyelid nodules
- Lattice corneal dystrophy

Richner-Hanhart Syndrome (Tyrosinemia II) (See Chapters 27, 30)
- Autosomal recessive
- Deficiency of hepatic tyrosine aminotransferase
- Eye lesions occur before skin lesions (2 weeks of age to 8 years of age)
- Corneal clouding and opacities, progressing to dendritic ulcers (pseudoherpetic)

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**FIGURE 2-13** Alkaptonuria has pathognomonic ocular signs. The first to appear is grayish black scleral pigmentation anterior to the tendon insertions of the horizontal recti muscles. At times, pigmentation of the elastic tissue in piaqueula may stain a dark brown or black, and it usually has the configuration of small, dark rings. In advanced cases of ochronosis, Bowman’s membrane, adjacent to the limbus, may have areas of black pigmentation. (*Reproduced with permission from Wolff K et al., Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill, 2008.*)

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Chapter 2    EYE FINDINGS

**Generalized Sialidosis (Cherry-Red Spot-Myoclonus Syndrome)**
- Lysosomal storage disease
- Color blindness or night blindness
- Cherry red spots
- Corneal or lens opacities

**Xanthelasma Palpebrarum (Fig. 2-15)**
- Asymptomatic bilateral and symmetric, yellow, flat, polygonal papules around the eyelids
- Most common in the upper eyelid near the inner canthus
- May be associated with isolated hyperlipidemia or familial syndromes
  - Familial hypercholesterolemia, familial defective Apo B, Familial dysbeta lipoproteinemia
- Patients may be normolipemic
- Lesions characterized by accumulations of lipid-laden macrophages

**Thyroid-Associated Ophthalmopathy (TAO) (See Chapter 27)**
- Also known as Graves’ ophthalmopathy
- Autoimmune-mediated inflammation of the extraocular muscle and periorbital connective tissue
- Dalrymple sign: upper lid retraction
- Eyelid retraction (can see sclerae superior to the iris), proptosis, chemosis, periorbital edema, and altered ocular motility (restrictive myopathy, usually of inferior rectus and medial rectus, resulting in hypotropia and esotropia and defective elevation and abduction), diplopia, congestion of orbit
- Exposure keratopathy is common and should be prevented
- Optic nerve damage with visual field loss can be gauged by relative afferent pupillary defects

**ACNEIFORM CONDITIONS**

**Acne Rosacea**
- Eyelid telangiectasias, blepharitis, recurrent chalazia, conjunctivitis, corneal scarring

**VIRAL INFECTIONS**

**Varicella and Herpes Zoster Ophthalmicus (See Chapter 17)**
- Varicella-zoster virus (VZV) (Fig. 2-16): Human herpes virus 3 (HHV3) that causes both varicella (chicken pox) and herpes zoster (shingles) Herpes zoster ophthalmicus occurs in later life and causes ocular complications and severe neuralgic pain
- More common in immunosuppressed individuals
- Ophthalmic branch of the trigeminal nerve is commonly involved


- Nasociliary branch involvement results in conjunctivitis, punctate keratitis, episcleritis and uveitis
- Hutchinson’s sign: involvement of nasal tip or nasal sidewall, innervated by the external nasal nerve; signifies potential ocular involvement
- Prodrome of pain over the affected dermatome
- Eruption may present as maculopapular, vesiculopapular, ulcerative, and may form a crust with possible scarring
- No correlation between severity of skin eruption and severity of ocular involvement
- Ocular complications such as keratitis and uveitis occur in 50% of patients with cutaneous eruption and appear within 3 weeks of developing rash
Anterior uveitis is treated with topical steroids and cycloplegics
Acute retinal necrosis has been reported following chicken pox and herpes zoster infection in healthy patients
Cranial nerve palsies may occur; oculomotor (CNIII) nerve most commonly affected

**Herpes Simplex Keratitis (See Chapter 17)**
- Primary ocular herpes occurs as a follicular conjunctivitis, regional lymphadenitis, and ulcerative blepharitis
- Recurrent episodes of keratitis are common
- Dendritic corneal ulcers are pathognomonic
- Recurrent stromal keratitis causes structural damage to cornea resulting in corneal opacities often requiring corneal transplant
- Most common cause of corneal blindness in the United States

**Molluscum Contagiosum (See Chapters 8 and 17)**
- Small, waxy nodules have a central umbilication
- If present on the eyelids, they may produce a follicular conjunctivitis

**Rubella (See Chapter 17)**
- When congenital, cataracts may develop (bilateral in 75% of patients)

**Measles (Rubeola) (See Chapter 17)**
- Conjunctivitis (part of the 3 C's: cough, coryza, conjunctivitis and Koplik spots)
- Koplik spots may be seen on the conjunctiva

**Mumps**
- Dacryoadenitis (inflammation of lacrimal glands)

**Vaccination**
- Optic neuritis may occur following certain vaccinations
- MMR vaccination most common
- Onset within 2 weeks
- Bilateral vision loss; pain with eye movement can also occur
- Treatment is oral corticosteroids
- Prognosis: complete recovery

**Actinomyces (See Chapter 28)**
- *Actinomyces israelii* is a gram-positive anaerobic bacillus; found in soil, brackish water
- *Actinomyces keratitis* (keratoactinomycosis)
- In the US, keratitis associated with contact lens use, especially when tap water used to cleanse lenses
- Dry ulceration with central necrosis surrounded by a gutter of demarcation
- Conjunctivitis, blepharitis
- Primary chronic canaliculitis of tear drainage apparatus
- 30% have negative cultures; culture of contact lens case may reveal organism

**Hordeolum (See also above text)**
- External hordeolum (stye)
- Arises from a blockage and infection of Zeiss or Moll sebaceous glands
- Abscess points at the lid margin
- Internal hordeolum
• Secondary infection of meibomian glands in the tarsal plate
• *Staphylococcus aureus* is the infectious agent in 90–95% of cases

**FUNGAL DISEASES**

**Candidiasis (See Chapters 4 and 22)**
- 2/3 patients with systemic candidiasis have ocular involvement
- White exudative lesions in the vitreous signifying necrotizing granulomatous retinitis
- “String of pearls” on exam signifies spread to vitreous cavity
- Requires intravitreal therapy

**Mucormycosis (See Chapter 4)**
- Occurs in immunocompromised patients, especially poorly controlled diabetics
- Rhizopus, Mucor, Absidia
- Pathognomonic black hemipalate, proptosis
- Blindness may occur from ophthalmic artery occlusion

**INFESTATIONS, BITES, PARASITIC DISEASES**

**Onchocerciasis (River Blindness) (See Chapter 5)**
- Onchocerca volvulus
- Simulium black fly vector
- Microfilariae in the anterior chamber
- Sclerosing keratitis, chorioretinitis, glaucoma, blindness

**Loaíasis (See Chapter 5)**
- Filarial nematode: *Loa loa*
- Bite from *Chrysops*
- Calabar swellings: localized areas of angioedema
- Migration of adult worm across conjunctiva

**Pediculosis Pubis (See Chapters 5 and 22)**
- Occasionally, infestation may be present in the eyebrows and eyelashes

**Toxoplasmosis**
- Congenital
- 1/3 of exposed infants are affected
- Chorioretinitis

**DERMATOUVEITIDES**

**Behçet Disease**
- HLA-B5, -B51

**VITAMIN-RELATED DISORDERS**

**Vitamin A Deficiency (See Chapter 19)**
- Night blindness, dryness, corneal ulceration/keratomalacia, HSV infection
- Bitot’s spots: foamy areas on conjunctiva from accumulation of keratin or bacteria

**Vitamin B Deficiency (See Chapter 19)**
- B1 (Beriberi)
  - Thiamin deficiency
  - 70% have ocular abnormalities: dry eyes, vision loss from optic nerve atrophy
- B2
  - Riboflavin deficiency
  - Rosacea keratitis, seborrheic blepharitis, secondary conjunctivitis

**Vitamin C Deficiency (See Chapter 19)**
- Scurvy
- Ocular features include those of Sjögren syndrome, as well as subconjunctival hemorrhage and hemorrhage within the optic nerve sheath
1. What syndrome has angiod streaks (and what does this finding represent)?

2. In what syndromes can blue sclerae be found?

3. Glaucoma is associated with:
   A. Neurofibromatosis 1
   B. Neurofibromatosis 2
   C. Sturge-Weber syndrome
   D. PHACES syndrome
   E. Biotinase deficiency

4. Which syndrome has downward ectopia lentis?
   A. Homocystinuria
   B. Marfan’s syndrome
   C. Nail patella syndrome
   D. Focal dermal hypoplasia (coloboma)

5. Matching:
   i. Phakoma
   ii. Retinal hemangioblastoma
   iii. Comma-shaped corneal opacity
   iv. Lester iris
   v. Lisch nodule
   A. Neurofibromatosis 1
   B. Hyperpigmentation of papillary margin
   C. Von-Hippel-Lindau syndrome
   D. X-linked ichthyosis
   E. Astrocytic hamartomas of optic nerve

6. In what two syndromes can a “salt-and-pepper” retina be seen?

7. What is the most common epithelial tumor of the eyelid?
   A. Basal cell carcinoma
   B. Squamous cell carcinoma
   C. Sebaceous cell carcinoma
   D. Melanoma
   E. Merkel cell carcinoma

8. A young patient presents with brittle bones resulting in easy fractures with minor trauma as well as easy bruising. A common eye finding is:
   A. Comma-shaped corneal deposits
   B. Ectropion
   C. Blue sclera
   D. Cataracts
   E. Lisch nodules

9. An elderly female patient presents with a painless subcutaneous module on the right upper eyelid. She was treated with warm compresses and topical antibiotics for several weeks without any improvement. The biopsy showed sebaceous differentiation, prominent atypia, with pagetoid spread. What is your diagnosis?
   A. Merkel cell carcinoma
   B. Sebaceous adenoma
   C. Melanoma
   D. Sebaceous cell carcinoma
   E. Basal cell carcinoma

10. Apocrine glands along the eyelid are called:
    A. Zeis glands
    B. Meibomian glands
    C. Glands of Moll
    D. Montgomery glands
    E. Fordyce spots

Answers
1. Pseudoxanthoma elasticum; represents rupture of Bruch’s membrane.
2. Osteogenesis imperfecta, types 1, 2, 3; Ehlers-Danlos syndrome, type 6 (other findings are retinal detachment, ruptured globe, keratoconus); reported in Crouzon syndrome.
3. A and C.
4. A. Marfan’s syndrome associated with upward ectopia lentis, nail patella syndrome associated with Lester iris, focal dermal hyperplasia associated with coloboma.
5. i-E. Phalcoma. Astrocytic hamartomas of the retina or optic disc are typical lesions in patients with tuberous sclerosis. They are detected by angiography. They are usually benign and appear as white/gray nodular lumps.
   ii-C. Von Hippel-Lindau (VHL) syndrome is characterized by hemangioblastomas of the brain, spinal cord, and retina. VHL syndrome is autosomal dominant and is due to a mutation in the VHL tumor suppressor gene.
   iii-D. X-linked ichthyosis is associated with comma-shaped corneal opacities that may be evident with slit lamp examination. X-linked ichthyosis most typically appears in infancy with scaling on the posterior neck, upper trunk and extensor surfaces of the extremities.
   iv-B. Hyperpigmentation of the papillary margin is the description of Lester iris. Nail patella syndrome (hereditary osteonchydysplasia) is an autosomal dominant disorder with a mutation in the gene encoding transcription factor LMXIB. The main clinical findings include fingernail dysplasia, absent or hypoplastic patellae, the presence
of posterior conical iliac horns, and deformation of the radial heads. Lester iris occurs in 45% of patients with nail patella syndrome.

v-A. Neurofibromatosis 1 (NF-1). NF-1 is diagnosed if two or more of the following are present:
1. Six or more café-au-lait spots, 15-mm or larger in an adult; six or more café-au-lait spots, 5-mm or larger in a prepubertal child
2. Two or more neurofibromas or one plexiform neurofibroma
3. Freckling of the axillary or inguinal region, an optic pathway glioma, two or more Lisch nodules
4. Characteristic osseous lesions, such as sphenoid wing dysplasia
5. A first degree relative with NF-1

Lisch nodules are the most common type of ocular involvement in NF-1. They are melanocytic hamartomas, usually clear yellow or brown elevations that project from the surface of the iris. Slit lamp is the ideal method to evaluate them.


7. A. Basal cell carcinoma is the most common tumor of the eyelid. The most common location is the lower eyelid (48.9–72.1%). Sebaceous cell carcinoma has a predilection for the upper eyelid. Melanoma is a rare pigmented eyelid tumor. Merkel cell carcinoma usually affects the upper eyelid. Squamous cell carcinoma occurs in 5% of malignant eyelid tumors.

8. C. Blue sclera. The patient has osteogenesis imperfecta. Type 1 collagen is the defective protein. Mutations of COL1A1 and COL1A2 causes defects in pro-alpha 1 and pro-alpha 2 chains that impose type 1 collagen. Blue sclera is also found in the following disorders: progeria, cleidocranial dysplasia, Menkes syndrome, cutis laxa, Cheney syndrome and pyknody sostosis.

9. D. Sebaceous carcinoma (SC). Sebaceous carcinoma occurs most commonly in a periocular (75%) location. The most frequent clinical presentation is a painless subcutaneous nodule; it is often misdiagnosed as a chalazion or chronic blepharitis. Histologically, SCs may be classified as well, moderately, or poorly differentiated. They show sebaceous differentiation, prominent atypia with pagetoid spread. The tumors have high rates of recurrence and metastasis. Mortality ranges from 9% to 50%. The tumors are associated with Muir-Torre syndrome.

10. C. Glands of Moll. Glands of Moll are apocrine glands located anterior to the meibomian glands within the distal eyelid margin. Zeis glands and meibomian glands are both sebaceous glands of the eyelid. Montgomery’s glands are sebaceous glands in the areola. Fordyce spots are ectopic sebaceous glands found on the vermillion lip and/or genital area.

REFERENCES


NAIL ANATOMY (FIG. 3-1)

- **Nail plate**
  - Forms from keratinization of the nail matrix epithelium and is firmly attached to the nail bed
  - Dorsal nail plate is produced by the nail matrix
  - Ventral portion is produced by the nail bed
  - Nail thickness depends on the length of the nail matrix and nail bed
  - Pink color owing to underlying nail bed blood vessels
  - Onychocorneal band: most distal portion of firm attachment of the nail plate to the nail bed
  - Onychodermal band: pink band that lies between the onychocorneal band and the nail plate white free edge
- **Proximal nail fold**
  - Dorsal portion: thinner than skin of the digit, devoid of pilosebaceous units
  - Ventral portion: in continuity with the matrix, adheres to the nail plate surface, and keratinizes with a granular layer
  - Horny layer forms the cuticle and prevents the separation of the plate from the nail fold
  - Dermis contains numerous capillaries that run parallel to the surface of the skin; morphology can be altered in connective tissue diseases
- **Nail matrix**
  - Lies above the midportion of the distal phalanx
  - Keratinization of the proximal nail matrix cells produces the dorsal nail plate
  - Keratinization of the distal nail matrix cells produces the ventral nail plate
  - Lunula: where the distal matrix is not completely covered by the proximal nail fold but is visible through the normal nail plate as a white half-moon-shaped area
- **Cells are able to synthesize both “soft,” or skin-type, and “hard,” or hair-type, keratins – the matrix expresses keratins Ha1, K1, K10
- **Alteration in the color of lunula can be an indication of either a cutaneous or systemic disorder or a systemic drug side effect
- **Nail bed**
  - Extends from the distal margin of the lunula to the onychodermal band
  - Completely visible through the nail plate
  - Epithelium is adherent to the nail plate, two to five cell layers
  - Nail bed keratinization produces a thin horny layer that attaches to the ventral nail plate
  - The bed expresses keratins K6, K16, K17
  - No granular layer is present
- **Hyponychium**
  - Anatomic area between the nail bed and the distal groove, where the nail plate detaches from the dorsal digit
- **Dermis**
  - No subcutaneous tissue, no pilosebaceous units
  - Condensed connective tissue that forms a tendon-like structure connecting the matrix to the periosteum of the phalangeal bone
- **Blood and nerve supply**
  - Blood supply provided by the lateral digital arteries, arches supply the matrix and nail bed
  - Sensory nerves: originate from the dorsal branches of the paired digital nerves, run parallel to the digital vessels
- **Nail growth**
  - Fingernails: 3 mm/month, 0.1 mm/day, take 5–6 months to regrow
  - Toenails: 1 mm/month, 0.03 mm/day, take 12–18 months to regrow
  - After nail plate is avulsed, it takes 40 days before new fingernail will first emerge
NAIL DISORDERS

**Chromonychia**
- Abnormality in color of the substance and/or the surface of the nail plate and/or subungal tissue
- Systemic cause: all digits are usually involved
- Endogenous cause: edge of color corresponds to shape of lunula (concave)
- External contact: edge of color follows the shape of the proximal nail fold (convex)

1. **Blue lunula**
   - Causes of this condition include
     - Wilson’s disease
     - Argyria, silver nitrate
     - Drugs: azidothymidine (AZT), quinacrine, busulfan, phenolpthalein

2. **Red lunula** (Fig. 3-2)
   - Causes of this condition include
     - Cardiac failure
     - Rheumatoid arthritis
     - Alopecia areata
     - Lupus
     - Polycythemia vera
     - Carbon monoxide poisoning

3. **Leukonychia**
   - Can be caused by defective keratinization of the distal matrix with persistent parakeratosis in the ventral nail plate
   - White color of nail in five patterns: total leukonychia (inherited usually), distal portion still appears pink, transverse leukonychia (systemic disorder), punctate (from minor trauma), longitudinal (associated with Darier’s disease)
   - One hereditary form is autosomal dominant and may be associated with epithelial cysts and renal calculi. There are also reported families with leukonychia and acquired sensorineural deafness

4. **Longitudinal melanonychia** (Fig. 3-3)
   - Presence of a pigmented stripe, usually brown or black
   - Deposition of melanin in the nail plate from a variety of causes
     - Melanotic macule is the most common cause
     - Bands of nevocellular nevi
     - Nevi, pigmented fungal infections, or melanoma
     - Drugs
       - azidothymidine (AZT): develops between 8 weeks to 1 year
       - antimalarials
     - Laugier-Huntziker syndrome (findings include longitudinal melanonychia, and macular pigmentation of the lips, mouth, and anogenital area)
     - Trauma
     - Pregnancy
     - Radiation-induced
     - Inflammatory nail disorders (lichen planus, onychomycosis, chronic radiation dermatitis, pustular psoriasis, or Hallopeau’s disease)
     - Systemic diseases: Acquired immune deficiency syndrome (pigmentation unrelated to AZT treatment), Addison’s disease, Cushing’s
NAIL DISORDERS

syndrome, hyperthyroidism, hemosiderosis, hyperbilirubinemia, alkaptonuria, systemic lupus erythematosus, scleroderma and porphyria

• Nutritional disorders
  – vitamin B12 or folate deficiency
  – bluish-black pigmentation
  – pigmentation is completely reversible after correction of the vitamin deficiency

5. Subungual melanoma
  • Broad band, dark brown to black in color with indistinct lateral borders
  • 0.7–3.5% of cutaneous melanomas. Most common type of melanoma in Asian and African-American populations – the rate is the same as in Caucasian populations, but is overrepresented because the frequency of other types of melanoma is low
  • Longitudinal black or brown bands with different hues
  • Commonly affects thumbs and great toes
  • Hutchinson’s sign: spread of pigmentation onto the nail folds
  • Pigmentation in a single digit, especially the index finger, thumb or great toe
  • Usually occurs at age 50 or older

6. Subungual hemorrhage (Fig. 3-4)
  • Reddish to reddish-black pigment depending on the age of the bleed
  • Progressively grows out distally as the nail plate grows
  • Can be due to trauma
  • Nail tumors can be preceded by or first recognized after trauma and may bleed

• May need to be biopsied to rule out subungual melanoma if hemorrhage does not grow out with the nail or if it recurs at the same place

External Factors Causing Nail Disorders

1. Habit-tic deformity (Fig. 3-5)
  • Multiple transverse grooves (Christmas-tree pattern) with a central depression
  • Usually affects thumbnails
  • Chronic mechanical injury to the cuticle and underlying matrix

2. Onychogryphosis (Fig. 3-6)
  • Curved, thickened nail plate without attachment to the nail bed
  • Opaque, yellow-brown with an oyster shell appearance
  • Nail keratin is produced by the nail matrix at uneven rates, with the faster-growing side determining the direction of the deformity
  • Ill-fitting footwear, self-neglect, trauma, age, occasionally inherited as an autosomal dominant trait
  • Hemionychogryphosis with lateral deviation of the nail plate results from congenital malalignment of the big toenail

3. Onycholyis
  • Separation of the nail plate from the bed
  • Yeast and bacteria usually colonize underlying space
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- Primary causes
  - Trauma
  - Idiopathic
- Secondary
  - Dermatologic and systemic conditions: onychomycosis, diabetes mellitus, thyroid disorders, pregnancy, porphyria, pellagra, scurvy, psoriasis, scleroderma, lupus, hidrotic ectodermal dysplasia, chronic contact dermatitis, pompholyx, herpes simplex, sarcoidosis, amyloidosis
  - Photo-induced onycholysis: tetracyclines (demecycline highest, doxycycline next, minocycline least), psoralens, 8-MOP, fluoroquinolones, chloramphenicol
  - Nail bed tumors
    - Congenital
      - Treatment: Remove underlying cause. If traumatic, emphasize non-traumatic nail practices and reduce wetwork. Concurrent use of topical anti-yeast medications can reduce colonization and hasten reattachment. There is not a role for oral antifungals. In cases of single resistant onycholysis, examination of the underlying nailbed with biopsy may be necessary to rule out underlying malignancy

4. Onychoschizia/brittle nails
- Splitting of the free edge and distal portion of the nail plate impairment of intercellular adhesive factors of the nail plate
- May also include breaking of the lateral edges, causing transverse splitting
- Causes of onychoschizia consist of external factors that dissolve or break the coherence between corneocytes: immersion/desiccation, chemicals, trauma, fungi
- Treatment: in some cases, reduction in use of nail cosmetics may be helpful. Oral supplementation with biotin or silicone may be helpful as well

5. Splinter hemorrhages
- Red to black small thin longitudinal lines under the nail plate
- Most commonly located in the distal nail plate
- Disruption of longitudinal blood vessels in the nail bed
- Caused by injury to the nail (most common cause) or by certain drugs, and/or inflammatory nail disorders
- Resolves spontaneously
- Treatment: if no underlying cause, reassurance as to benign nature of condition. Otherwise, treat underlying condition

6. Ingrown nails
- Great toenails are particularly vulnerable
- Improper nail trimming, tight shoes, or poor posture can cause a corner of the nail to curve downward into the skin
- Can lead to inflammation, granulation tissue formation, and infection
- Treatment: non-surgical treatments try to separate the lateral nail fold from the nailplate with barriers or by taping the lateral nail fold away from the plate. Surgical treatment includes phenol destruction of the lateral part of the nail plate leading to a narrowed nail. In acute cases, antibiotics and/or drainage of purulent collection may be necessary

7. Transverse overcurvature (Pincer or Trumpet nail)
- Nail displays an increase in curvature along the nail bed
- May be associated with subungual exostosis
- Overcurvature may extend to the point of encompassing a cone of nail bed soft tissue
NAIL DISORDERS

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Can be a side effect of epidermal growth factor receptor inhibitors
• Treatment: acute cases: (see nail infection section below); chronic cases: reduction of wetwork and contact with irritants and discontinuation of traumatic nail practices is necessary. Short-term use of high-potency topical steroids. Topical anti-yeast medications have become less favored, but can be used in addition. Oral antifungal medications should not be used as single therapy, but have not been disproven as adjuncts to above therapy

8. Chronic paronychia (Fig. 3-7)
• Inflammation of the proximal nail fold with painful periungual erythema
• Nail detaches from the distal portion of the proximal nail fold, which has lost its cuticle
• May result in Candida invasion with discolored nail plate and cross-ridged lateral edges
• Can be acute or chronic
• Acute: usually caused by infection (see nail infection section below)
• Chronic: Occurs in patients whose hands are subjected to moist local environments or in patients who damage the cuticle through traumatic nail practices. Thought to be an irritant or allergic contact dermatitis of the proximal nail fold due to entry of irritants or allergens under the proximal nail fold after loss of the cuticle

9. Onychomadesis (nail shedding)
• Spontaneous separation of the nail plate from the nail bed beginning from the proximal nail end
• Associated with: systemic lupus erythematosus, pemphigus vulgaris, mycosis fungoides, alopecia areata universalis, epidermolysis bullosa, keratosis punctata palmaris et plantaris, thrombocytopenia, neurologic disease, peritoneal dialysis, penicillin anaphylaxis, chemotherapy, retinoids (dose related nail matrix damage), lead intoxication, and carbamazepine
• When associated with systemic illness, generalized skin disease, or drug therapy the condition may be considered a severe form of Beau’s lines. (temporary slowing or cessation of nail plate production)
• Nail plate shows a transverse split but continues growing for some time
• Eventually the nail is cast off after losing the connection to the underlying nailbed
• Treatment: Reassurance as to eventual resolution if related to a one-time event. Treat underlying cause if still active or related to an underlying disease

Genetic Syndromes

1. Keratosis follicularis (Darier’s disease) (Fig. 3-8)
• Autosomal dominant
• Defect in ATPase 2A2, which encodes sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2), a calcium pump
• Nails: red and white longitudinal streaks, wedge-shaped nicking of the distal nail plate, subungual hyperkeratosis
• May be related to acrokeratosis verruciformis of Hopf (acral Darier’s disease): multiple warty lesions resembling plane warts typically observed on the dorsum of the hands and feet

2. Nail-patella syndrome
• Also known as HOOD or Fong syndrome
• Autosomal dominant
Chapter 3  NAIL FINDINGS

Abnormalities of the nail matrix and nail bed associated with the pathologic genetic alterations of the dermal-epidermal junction

7. Pachyonychia congenita (PC)
   - Autosomal dominant
   - Nail changes: Severe nail thickening, yellow-gray color, transversely overcurved with subungual hyperkeratosis mainly at the distal portion of the nails
   - Two main clinical subtypes, PC-1 and PC-2, and other rare variants
     - Type I PC: Jadassohn-Lewandowsky (more common)
       ▶ Keratins 6a and 16 defects
       ▶ Palmoplantar and follicular hyperkeratosis, benign oral leukoplakia
     - Type II PC: Jackson-Lawler
       ▶ Keratins 6b and K17 defects
       ▶ Type I PC symptoms plus bullae on palms and soles, early dentition/natal teeth, steatocystoma multiplex
     - Type III: Shafer-Branauer
       ▶ Type I symptoms plus corneal dystrophy, cataracts
     - Type IV: pachyonychia congenita tarda
       ▶ Late onset, hyperpigmentation around the neck, waist, and flexures

Infections of the Nails

1. Onychomycosis (Fig. 3-9)
   - Clinical features depend on type of infection present
     - Distal subungual onychomycosis: Trichophyton rubrum, Trichophyton interdigitale
       ▶ Distal onycholysis with subungual hyperkeratosis, and yellow discoloration
     - Proximal subungual onychomycosis:
       T. rubrum, Fusarium sp., Aspergillus sp., Scopulariopsis sp.
       ▶ Proximal leukonychia with normal nail plate surface
       ▶ Associated with AIDS
     - Superficial white onychomycosis: Trichophyton interdigitale, Fusarium sp., Aspergillus sp.
       ▶ Superficial areas of friable opaque leukonychia
       ▶ More common in children and HIV-positive individuals
   - Treatment: oral antifungals or topical antifungal nail lacquer should be used if no contraindications with appropriate laboratory monitoring

2. Green nails (Pseudomonas nail infection) (Fig. 3-10)
   - Pseudomonas aeruginosa (gram negative bacteria) can infect the dorsal or ventral nail plate of the nail

3. Dyskeratosis congenita
   - X-linked form associated with DKC1 gene, located at Xq28, encodes for dyskerin protein (essential in ribosome biogenesis and telomerase assembly)
   - Autosomal dominant form associated with hTERC gene
   - Classical tetrad of progressive bone marrow failure, reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia
   - Nails: ridging, longitudinal fissuring, thin and dystrophic – first component of syndrome to appear

4. Congenital malalignment
   - Lateral deviation of the long axis of nail growth relative to the distal phalanx
   - Subsequent ingrowing and possible hemionychogryphosis if untreated
   - Acquired traumatic malposition may follow acute trauma

5. Hereditary ectodermal dysplasia
   - Primary epidermal disorders in which one of the following signs occur: hypotrichosis, hypodontia, onychodysplasia, and anhidrosis
   - Nails are most commonly short, thickened, and hypoplastic

6. Epidermolysis bullosa (EB)
   - Junctional and dystrophic forms may produce anonychia

- Defect in LMX1B gene
- Nails: triangular lunula, hypoplasia of nails, may involve all fingernails (thumbs are the most severely affected)
- Hypoplastic or absent patella, bilateral posterior iliac horns, radial head subluxation, scoliosis, palmoplantar hyperhidrosis
- Glomerulonephritis ± renal failure
- Eyes: heterochromic irides, Lester iris, cataract

FIGURE 3-8  Darier nail. (Courtesy of Dr. Adelaide Hebert.)
NAIL DISORDERS

Presents with green (pyocyanin) or yellow (fluorescein) nail pigmentation
Can happen more frequently to patients with underlying onycholysis or onychomycosis
Treatment: topical vinegar soaks, floxacin, or gentamicin can be used to treat the infection. Treat underlying condition if onycholysis or onychomycosis is present

3. Acute paronychia (Fig. 3-11)
- Associated with direct or indirect trauma to the cuticle or nail fold
- May start in the paronychium (lateral nail fold) at the side of the nail with local redness, swelling, and pain
- Most common causative pathogen is *Staphylococcus aureus*, less commonly *Streptococcus pyogenes*, *Pseudomonas pyocyanea*, *Proteus vulgaris*, or herpes simplex virus
- Treatment: incision and drainage with culture and appropriate antibiotics for staph and strep infection. Consideration should be given to diagnostic procedures for HSV as acute paronychia can be caused by HSV

Nail Signs of Systemic Disease

1. Nail pitting
- Depressions in the nail plate that vary in morphology and distribution
- Characteristic of psoriasis, alopecia areata, and eczema
- Easily detachable parakeratotic cells in the superficial layers of the nail plate, as the nail plate grows outwards, these parakeratotic foci are exposed to the surrounding environment and there is a gradual sloughing of these cells, leaving a distinct depression within the nail plate

- Indicates a disturbance in the maturation and keratinization of the proximal nail matrix
  - Alopecia areata (Fig. 3-12)
    - Nail findings are seen in 20% of adults and 50% of children
    - Geometric nail pitting (most common); pits are small and regularly distributed along longitudinal and transverse lines
    - Twenty nail dystrophy or trachyonychia (generalized nail roughness) seen mainly in patients with alopecia totalis or alopecia universalis
Chapter 3  NAIL FINDINGS

Psoriasis
- Deep and irregularly distributed pits

Atopic dermatitis
- Deep and irregularly distributed pits

Treatment: topical psoriasis medications applied to the proximal nail fold or injection of steroid into the proximal matrix may be helpful, but side effects may limit use to only the most motivated patients

2. Koilonychia
- Nail plate is concave with raised edges (spoon nails)
- Iron-deficiency anemia associated with Plummer-Vinson syndrome
- Normal finding in childhood
- Can be seen in patients with Mal de Maleda (keratoderma palmoplantaris transgrediens): painful glove-and-stocking keratoderma, psoriasiform hyperkeratotic plaques, koilonychia, onychogryphosis, fissured tongue/lingua plicata

3. Lichen planus (Fig. 3-13)
- Affects one or more nails in 10% of cases
- Nail changes include: ridging, distal splitting, thinning, subungual hyperkeratosis, pterygium formation (adhesion of the proximal nail fold to the proximal nail bed), and possible loss of the nail
- Treatment: injections of steroid or systemic prednisone may be necessary to prevent development of pterygium, but side effects must be balanced on an individual basis

Histology mirrors that of lichen planus in the skin, demonstrating a lichenoid infiltrate with apoptosis of keratinocytes. Spongiosis, focal parakeratosis, and scarring are more common in lichen planus of the nails

4. Lindsey’s nail (half-and-half nail)
- Distal nail bed: brown to pink; proximal nail bed (40–80%) white
- Associated with the following conditions: Azotemia, chronic renal failure with uremia

5. Mees’ lines
- Transverse white bands
- Grow out with nail
- Appear after an episode of poisoning with arsenic, thallium or other heavy metals

6. Muehrcke’s lines
- Nonspecific finding that may be associated with periods of metabolic stress, which transiently impairs the ability of the body (and particularly of the liver) to synthesize proteins
- Paired white bands parallel to the lunula, and do not grow out with nail
- Associated with: hypoalbuminuria, nephritic syndrome, chemotherapy, malnutrition, cirrhosis

7. Nail fold telangiectasias (nailfold capillary loops)
- Can be visualized by nailfold capillaromicroscopy or dermoscopy
- Dermatomyositis: enlargement of capillary loops, loss of capillaries, disorganization of the normal distribution of capillaries, ‘budding’ (‘bushy’) capillaries, twisted enlarged capillaries and capillary hemorrhages
- Scleroderma (SSc): architectural disorganization, giant capillaries, hemorrhages, loss of capillaries, angiogenesis and avascular areas found in > 95% of patients
- Systemic lupus erythematosus: morphological alterations of capillary loops, venular visibility and sludging of blood with variability of capillary loop length
- Anti-phospholipid syndrome: symmetrical microhemorrhages
- Sjogren’s syndrome: abnormalities range from non-specific findings (crossed capillaries) to more specific findings (confluent hemorrhages and pericapillary hemorrhages) or SSc-type findings

8. Terry’s nail
- 1- to 2-mm distal pink band, proximal nail is opaque (white, ground-glass-like opacity)
- Lunula is obliterated
- Associated with hepatic failure, hyperthyroidism, malnutrition, liver cirrhosis, hypoalbuminemia congestive heart failure, diabetes mellitus

9. Twenty-nail dystrophy (trachonychia)
- Term used to describe nail plate roughness, pitting, and ridging that may affect 1 to 20 nails
- Autosomal dominant inherited form: present at birth and gets worse with age
- Alopecia areata, psoriasis, lichen planus, atopic dermatitis, ichthyosis vulgaris, immunoglobulin A deficiency, or idiopathic
- Histology demonstrates spongiosis most often

10. Yellow-nail syndrome (YNS) (Fig. 3-14)
- Pathogenesis unknown, lymphatic vessel alterations may play a role in some cases
- Spontaneous partial or total remission in 7–30% of cases, however, relapse often occurs
- Nail improvement is often concomitant with improvement of the respiratory pathology
- Characterized by the triad of characteristic nail changes, chronic respiratory disorders

 FIGURE 3-14 Yellow nails. (Courtesy of Dr. Ravi Ubriani.)

- Bronchiectasis, pleural effusion, bronchial hyperresponsiveness, bronchiectasis, chronic bronchitis) and primary lymphedema
- Total or distal yellow discoloration, with slow growth and loss of the cuticle and lunula. Other characteristics include: thickening, hardening, longitudinal over-curvature, transverse ridging associated with variations in the ungual growth rate, and onycholysis that may lead to shedding
- Erythema and edema of the proximal nail fold or chronic paronychia may occur
- Most cases reported are idiopathic, however the syndrome has been described in association with malignancy
- Familial occurrence of YNS has been reported
- Treatment: case reports have suggested itraconazole or high-dose vitamin E as treatments, but these must be balanced against side effects on an individual basis

11. Psoriasis
- Affects 10–55% of adults
- Nail matrix disease: pitting (most common nail finding), leukonychia, red spots in lunula, nail plate crumbling, Beau’s lines (occurs in lesions of the matrix of short duration, often caused by intermittent inflammation), onychorrhexis (occurs in lesions of the matrix of long duration)
- Acrodermatitis continua of Hallopeau (ACH): rare pustular eruption on the distal portions of the fingers and less often, on the toes. Classified as a form of acropustular psoriasis that tends to be resistant to treatment
- Histology mirrors that of psoriasis in the skin, except that hypergranulosis is more often a feature

12. Beau’s lines (Fig. 3-15)
- Interruption of growth in the nail matrix will produce transverse linear depressions in the nail plate separated by areas of normal nail
- Can be seen in the following conditions: chronic paronychia, chemotherapy, use of systemic retinoids, fever, illness, Raynaud’s disease, pemphigus, trauma

13. Median canaliform dystrophy of Heller (Fig. 3-16)
- Midline split with backward-angled ridges (“fir tree”)
Chapter 3  NAIL FINDINGS

14. Pterygium (“angel-wing” deformity)
   - Has been described on both dorsal and ventral aspects of the nail plate
   - Dorsal nail plate: gradual progressive thinning of the nail plate and secondary fissuring caused by the fusion of the proximal nail fold to the matrix and then to the nail bed
     - Portions of the divided nail plate progressively decrease in size as the pterygium widens
     - Total loss of the nail with permanent atrophy
     - Associated with: lichen planus, bullous disorders, radiotherapy, digital ischemia, trauma, congenital
   - Ventral nail plate: distal extension of the hyponychial tissue that is anchored to the undersurface of the nail, thereby obliterating the distal groove. Also known as pterygium inversum unguis
     - Associated with: scleroderma, Raynaud’s disease, median nerve causalgia (sympathetic maintained pain), formaldehyde/nail polish, trauma, congenital

15. Brachyonychia/racquet nail
   - Short nails, the width of nail plate and nail bed is greater than length, occurs with a congenitally short distal phalanx
   - Thumb involvement is common, may be bilateral
   - Autosomal dominant trait secondary to obliteration of the epiphyseal line

16. Onychorrhexis
   - Longitudinal nail ridging (aged nails)
   - Abnormalities in epidermal growth and keratinization of the proximal nail matrix
   - Associated with the following disorders: lichen planus, alopecia areata, rheumatoid arthritis, graft-versus-host disease, drugs: isotretinoin, thallium poisoning

17. Clubbing (Fig. 3-17)
   - Increased transverse and longitudinal nail curvature
   - Hypertrophy of the soft tissue components of the digit’s pulp
   - Hyperplasia of the fibrovascular tissue at the base of the nail
   - Early clubbing obliterates the normal diamond-shaped window formed at the base of the nail beds when there is opposition of the dorsum of two fingers from opposite hands. The angle that the proximal nail fold makes with the proximal nail plate is called Lovibond’s angle. Normally this is about 160 degrees. In clubbing, it exceeds 180 degrees
   - Associated with: inflammatory bowel disease, pulmonary malignancy, asbestos, chronic bronchitis, chronic obstructive pulmonary

FIGURE 3-15 Beau’s lines. (Courtesy of Dr. Sharon Hymes.)

FIGURE 3-16 Median canaliform dystrophy. (Courtesy of Dr. Ravi Ubriani.)
NAIL DISORDERS

18. Anonychia
- Absence of all or part of one or several nails
- May be congenital (with underlying bone abnormalities) or acquired (usually associated with lichen planus)
- Occurs sporadically or may have a dominant or recessive inheritance pattern

19. Acrokeratosis paraneoplastica (Bazex syndrome)
- Multiple, well-defined, psoriasiform, scaly, erythematous patches and plaques, distributed symmetrically over dorsa of hands and feet, helices of ears with similar lesions
- Palms and soles with keratoderma-like lesions
- Nail changes: ridging, thickening, yellow discoloration, onycholysis, paronychia
- Clinical course: acrokeratosis on the hands, feet, ears and nose that spreads progressively to the arms, legs and trunk as the tumor grows
- More than half of acrokeratosis paraneoplastica associated malignancies are found in the upper aerodigestive tract (upper parts of the respiratory and gastrointestinal tracts)
- Regional lymphadenopathy is often present
- In nearly two-thirds of cases, cutaneous lesions precede the symptoms or diagnosis of malignancy
- Cutaneous manifestations disappear during the treatment of the tumor

**Tumors of the Nail Area**

1. Periungual and subungual warts (Fig. 3-18)
   - Hyperkeratotic papules with a rough surface: caused by human papilloma virus, most frequently types 1, 2, and 4
   - Most common nail tumor that affect fingernails more often than toenails
   - Direct trauma usually causes inoculation of the virus and initiates the localized viral infection, penetration of papilloma viruses into the skin is favored by skin abrasion or maceration
   - Clinical development of warts occurs a few weeks to more than 1 year after inoculation
   - Subungual warts may appear as a nodule under the nail plate and may result in onycholysis; it may present as a linear growth under the nail plate causing a longitudinal band of onycholysis with splinter hemorrhages
   - Warts may produce slight matrix damage due to compression, resulting in nail plate ridging and grooving
   - Periungual warts are asymptomatic, however, there may be pain associated with subungual warts
   - Located around the nailfold, usually extend under the nail plate and may lie adjacent to the nail matrix
   - Histology: hyperkeratosis with columns of parakeratosis overlying elongated papillae, hypergranulosis, and koilocytic changes
   - Bowen’s disease and squamous cell carcinoma have been reported to occur in long-standing periungual warts

2. Epidermal inclusion cyst
   - Occur secondary to traumatic impregnation of the dermis with epidermal cells
   - Cyst is lined with epidermis and filled with keratin
   - Occasionally observed under the nail following trauma (such as a complication of nail surgery)
   - Can erode adjacent structures, including bone
   - Often asymptomatic, however, rupture of the cyst wall can elicit a foreign-body giant-cell reaction
Chapter 3  NAIL FINDINGS

• May appear as a subungual tumor raising the nail plate or causing a bulbous enlargement of the terminal phalanx
• X-ray will show a sharply demarcated, round defect
• Treatment by surgical removal of the cyst contents and the wall of the cyst

3. Onychomatricoma
• Uncommon benign tumor of the nail matrix
• Longitudinal band of yellow thickening of the nail plate with longitudinal ridging
• Increased transverse curvature of the nail, splinter hemorrhages of the proximal nail plate
• Villous tumor projections in the nail plate, MRI shows tumoral core in the matrix area and invagination of the lesion into the funnel-shaped nail plate
• Fibroepithelial tumor that consists of nail matrix epithelium over a connective tissue core
• Epithelium may show clear cell change
• Treatment
  – Simple retraction of the proximal nail fold allows superficial removal of the tumor from the matrix

4. Subungual and periungual keratoacanthoma
• May occur as solitary or multiple tumors
• Rare, benign, rapidly growing, and locally aggressive
• Usually situated below the edge of the nail plate or in the most distal portion of the nail bed
• Lesion may start as a small and painful keratotic nodule visible beneath the free edge of the nail plate, occasionally it occurs under the proximal nail fold
• Rapid growth to a 1- to 2-cm lesion within 4 to 8 weeks
• The tumor can erode the bone, radiographically; it appears as a well-defined, crescent-shaped lytic defect (MRI is superior to radiographic studies in detecting an erosion of the distal phalanx)
• Treatment: removal of the entire tumor with histologic control of the resection margins. The patient should be followed to rule out a recurrence

5. Acquired periungual fibrokeratoma
• Asymptomatic nodule with a hyperkeratotic tip, narrow base
• Possibly caused by trauma
• Variant of acquired digital fibrokeratoma
• Emerges from beneath the proximal nail fold, grows on the nail and causes sharp longitudinal depressions
• Some of these lesions originate from within the matrix and thus grow in the nail plate, eventually to emerge in the middle of the nail. (also called “dissecting ungual fibrokeratoma”)
• Histology demonstrates a hyperkeratotic and acanthotic epithelium with prominence of the granular layer overlying a dense and hypocellular collagenous tissue core
• Immunohistochemistry shows that the fibroblasts are vimentin positive, and many of them stain with HHF35 (monoclonal antibody, specific for muscle actin)
• Treatment: excision

6. Koenen’s tumor
• Periungual fibroma
• Develops in about 50% of the cases of tuberous sclerosis (epiloia or Bourneville-Pringle disease)
• Usually appear between the ages of 12 and 14 years and increase progressively in size and number with age
• Small, round, smooth, flesh-colored, asymptomatic, more frequent on toes than on fingers
• Tumors grow out of the nail fold, overgrow the nail bed and destroy the nail plate. May cause longitudinal depressions in the nail plate
• Sometimes tumors also grow in the nail plate
• Histology: similar to that of fibrokeratoma as described above with atypical stellate myofibroblasts in the tissue core
• Treatment: Excessively large tumors often are painful and should be excised at their base

7. Infantile digital fibromatosis
• (1- to 2-cm) Round, smooth, dome-shaped, shiny, firm red dermal nodules
• Dorsal and axial surfaces of the fingers and toes
• Not painful but can lead to functional deformity of a joint or cause limited mobility
• It may be present at the time of birth or develop within the first year of life
• Slow growth in the first month, followed by a rapid phase of growth (10–14 months), then be spontaneous involution
• Conservative approach unless IDF causes a problem with mobility
• Histology: scattered cells with eosinophilic cytoplasmic inclusions on routine hematoxylin and eosin staining. Inclusions are typically juxtanuclear and may even indent the adjacent nucleus
• Treatment: Excessively large tumors often are painful and should be excised at their base

8. Bowen’s disease (in situ epidermoid carcinoma)
• Carcinoma in situ of the nail that differs from other variants. squamous cell carcinoma
• Etiology linked to HPV-16, -34, and -35; arsenic also may play a role (also think about association with genital warts), exposure to x-ray
• Presents as a circumscribed plaque with a warty surface extending from the nail groove both under
and around the nail, periungual swelling due to deep tumor proliferation.

- Commonly presents with subungual involvement with extensive hyperkeratosis of the nail bed, associated with partial or total nail loss.
- Less common presentations: longitudinal melanonychia, lifting of the nail plate by subungual pseudofibrokeratoma.
- Nail dystrophy develops when the matrix is affected.
- Carcinoma cuniculatum: rare variant of squamous cell carcinoma with low biologic malignancy.
- Treatment: imiquimod, photodynamic therapy, methotrexate, radiation therapy, Mohs’ micrographic surgery, excisional therapy, bone involvement requires amputation of the distal phalanx.

9. Myxoid cyst (digital mucoid cyst) (Fig. 3-19)
   - Asymptomatic, smooth nodule that enlarges slowly.
   - Typically located at the distal interphalangeal (DIP) joints or in the proximal nail fold.
   - A split or groove in the nail develops distally.
   - Incision of the cyst results in extrusion of clear jelly-like material.

10. Subungual exostosis and osteochondroma
    - Subungual exostoses are not true tumors but rather are outgrowths of normal bone or calcified cartilaginous remains.

- Location: commonly in the dorso-medial aspect of the tip of the great toe, although subungual exostoses may also occur in lesser toes or, less commonly, thumb, or index fingers.
- Triad of pain (the leading symptom), nail deformation, and radiographic features is usually diagnostic.
- Trauma is the main cause.
- Begin as small elevations on the dorsal aspect of the distal phalanx and may eventually emerge from under the nail edge or destroy the nail plate.

11. Osteochondroma
    - Bone-hard tumor, confirmed by x-ray.
    - History of trauma, growth rate is slow.
    - Radiographic studies show a well-defined, circumscribed, pedunculated or sessile bone growth projecting from the dorsum of the distal phalanx near the epiphyseal line.
    - Therapy of subungual exostosis and osteochondroma consists of local curettage or excision.

12. Giant cell tumor of the tendon sheath
    - Solitary, often lobulated, slow-growing, skin colored, and smooth-surfaced nodule that tends to feel firm and rubbery.
    - Usually occurs on the dorsum of the distal interphalangeal joint, rarely it can present in the region of the lateral nail fold and may interfere with nail growth.
    - Periodic inflammation and drainage may occur.
    - Histopathology shows a cellular tumor composed of histiocytic and fibroblastic cells with a variable number of giant cells and some foam cells in a hyalin stroma with siderophages.
    - Treatment is surgical excision.

**Vascular Tumors**

1. Pyogenic granuloma
   - Eruptive hemangioma usually seen following trauma.
   - Small, benign, eruptive bluish/red nodule develops rapidly on the periungual skin, may develop distally in the hyponychium region or in the nail bed, especially associated with onycholysis of the toe.
   - Tenderness and a tendency to bleed are characteristic features.
   - Lesion becomes necrotic and forms a collarette of macerated white epithelium.
   - Granulation tissue can be secondary to systemic retinoids, antiretroviral medications, cyclosporine, or epidermal growth factor receptor inhibitors. These medications can
Vitamins and Nail Disease

- There is circumstantial evidence that vitamin and mineral supplementation can be beneficial in nail disease. A review from August 2007 suggests that there is no role for vitamin or mineral supplementation in healthy nails. Clinical cases such as nail changes in hemodialysis, anorexia, bulimia, and genodermatoses provide the circumstantial evidence of the role of vitamins and minerals in nail health
  - Biotin: shown in multiple well-designed studies to be an effective treatment for brittle nail syndrome, but takes two to three months to have an effect
  - Vitamin E: case reports have shown success in yellow nail syndrome, but the supplementation was in conjunction with other treatments
  - Retinoids and Vitamin A: Deficiency can be associated with eggshell nails. Overdosage or systemic retinoid therapy can result in numerous nail problems, including acute paronychia, pyogenic granulomas, plate fragility and thinning, onychorrhexis, onychoschizia, onychomadesis, median canaliform dystrophy, transverse leukonychia, and a desquamative erythroderma with complete destruction of the nails. Topical retinoids are beneficial in nail psoriasis and can have a role in pachyonychia congenita
  - Vitamin D: Topical use is beneficial in nail psoriasis
  - Vitamin B12: Deficiency can result in hyperpigmentation of the nail
  - Calcium: severe deficiency can lead to a transverse leukonychia
  - Iron: deficiency can result in koilonychia, as in Plummer-Vinson syndrome. Supplementation can reduce brittleness of the nails, even when laboratory evaluation reveals no iron deficiency
  - Zinc: supplementation improves nail changes in acrodermatitis enteropathica. Acute onset deficiency can lead to a transverse leukonychia or Beau’s lines
  - Selenium: Super-therapeutic selenium administration can lead to multiple nail problems, including brittle nails, transverse yellowish-white or red streaks, or longitudinal streaks
  - Silicon: supplementation has been shown to decrease nail brittleness in well-designed studies
  - Claims have been made regarding benefits from gelatin, L-methionine, ceratin, collagen, panthothenic acid, salt, chromium, rhodanates, pyridoxine, vitamin C, or primrose oil, but the review did not find enough evidence to support a role for any of these supplements

Drug Reactions Affecting the Nails

- Many drug reactions can cause problems with the nails. Drug reactions in the nails can differ from

FIGURE 3-20 Glomus tumor. (Courtesy of Dr. Ravi Ubriani.)
other cutaneous drug reactions because the kinetics of nail formation can result in delayed or prolonged abnormalities

- Teratogenesis: nail hypoplasia and anonychia may result from drugs taken during pregnancy. Anticonvulsants and anticoagulants are the most common causes
- Beau’s lines and onychomadesis: result from acute severe toxicity to the nail matrix keratinization. Is clinically noted weeks after administration of the drug because of the slow growth of the nail. The most common causes are chemotherapy and radiation but these have been described with many different medications
- Nail fragility: chemotherapy, retinoids, antiretroviral agents
- Slowed nail growth: cyclosporine, heparin, lithium, methotrexate, and zidovudine
- Increased nail growth: fluconazole, itraconazole, levodopa, oral contraceptives
- Transverse leukonychia: results from retention of nuclei in the nail plate due to transient impairment of keratinization in the matrix. When they present as bands along the entire width of the nail plate, they are known as Mees’ lines. This finding has been reported with many medications including chemotherapy, cyclosporine, and retinoids, and can be seen in arsenic or thallium poisoning. Apparent leukonychia that does not migrate with nail growth and fades with compression is called Muehrcke’s lines. It is associated with low albumin and can be seen in patients treated with chemotherapy even with normal albumin levels
- Onycholysis and photo-onycholysis: Result from acute toxicity to the nail bed epithelium. Onycholysis with subungual abscess has been reported most frequently with taxane chemotherapy, but has also been reported with methotrexate, retinoids, and infliximab. Photo-onycholysis is seen with PUVA, tetracyclines, fluoroquinolones, OCPs, thiazide diuretics, and captopril
- Acute paronychia: can be seen with methotrexate, antiretrovirals (indinavir and lamivudine), retinoids (especially isotretinoin), and epidermal growth factor receptor inhibitors (gefitinib, erlotinib, and cetuximab)
- Pyogenic granulomas: causes are similar to acute paronychia. Can be caused by cyclosporine, indinavir, and epidermal growth factor receptor inhibitors
- Ischemic changes: Beta-blockers (especially propanolol) and bleomycin can produce ischemic and Raynaud’s phenomenon. Bleomycin effects can be seen several months after treatment
- Subungual hemorrhages: antithrombotics, anticoagulants, taxanes, tetracyclines, and ganciclovir
- Nail atrophy: prolonged application of high-potency topical steroids
- Melanonychia: zidovudine, chemotherapy, hydoxyurea, psoralens all can cause activation of melanocytes and appearance of melanonychia. Radiation therapy can cause melanonychia even when used remote from the affected area
- Pigmentation: deposition of agents in the nails and subungual tissue can produce pigmentary changes. Tetracycline (yellow), gold salts (yellow), and clofazimine (dark-brown) deposit in the nails – these deposits will grow out with the nails and will be parallel to the lunula. Minocycline (blue-gray) and antimalarials (blue-brown) can deposit in the subungual tissues – these deposits will not grow out with nail growth. Tar and anthralin can stain the superficial layers of the nail plate and have a proximal border parallel to the cuticle as they are not dependent on endogenous deposition

**Questions**

1. A 56-year-old woman presents with a split nail on her left second finger. There is a bluish subungual discoloration proximal to the split. She complains of tenderness and temperature sensitivity in the affected digit. The most likely cause is:
   A. Blue nevus
   B. Glomus tumor
   C. Myxoid cyst
   D. Pyogenic granuloma
   E. Squamous cell carcinoma

2. Epidermal growth factor receptor inhibitors can cause which of the following side effects?
   A. Onycholysis
   B. Paronychia
   C. Yellow nails
   D. Clubbing
   E. Splinter hemorrhages

3. Pterygium inversum unguis is associated with which of the following diseases?
   A. Psoriasis
   B. Lichen planus
   C. Scleroderma
   D. Alopecia areata
   E. Congestive heart failure
4. Which of the following disorders can result in loss of both the cuticle and lunula?
   A. Chronic paronychia
   B. Yellow-nail syndrome
   C. Psoriasis
   D. Rubenstein-Taybi syndrome
   E. Alopecia areata

5. A 60-year-old man develops transverse white bands in all of his nails that blanch with pressure. The most appropriate initial test would be:
   A. Arsenic level
   B. Albumin
   C. Liver function
   D. Chest x-ray
   E. Fasting glucose

6. What is the approximate growth rate of normal fingernails?
   A. 0.1 mm/day
   B. 0.2 mm/day
   C. 0.3 mm/day
   D. 0.4 mm/day
   E. 0.5 mm/day

7. What medicine has the lowest rate of photo-induced onycholysis?
   A. Demecycline
   B. Doxycycline
   C. Minocycline
   D. Oxpsoralen
   E. Tetracycline

8. A 40-year-old man has long-standing abnormalities of his fingernails. On exam, red and white longitudinal streaks with wedge-shaped distal nicking and subungual hyperkeratosis are noted. The most likely diagnosis is:
   A. Anhidrotic ectodermal dysplasia
   B. Dyskeratosis congenita
   C. Keratosis follicularis
   D. Pachydermoperiostosis
   E. Pachyonychia congenita

9. A 5-year-old boy has congenital nail dystrophy with triangular lunulae in all his nails. He should be referred to which of the following clinical specialists?
   A. Audiologist
   B. Cardiologist
   C. Dentist
   D. Gastroenterologist
   E. Nephrologist

10. Match the following nail findings with the most likely causative clinical scenario
    i. Non-blanching transverse white bands that grow out with the nail
       A. Cirrhosis
    ii. Blanchable paired transverse white bands that do not grow out with the nail
        B. Renal failure
    iii. Opaque proximal nail with 1-2 mm distal pink band
         C. Congestive heart failure
    iv. Proximal pallor with brown/pink distal half of nail
        D. Hypoalbuminemia
    v. Increased transverse and longitudinal nail curvature with obliteration of Lovibond’s angle
        E. Arsenic poisoning

**Answers**

1. B (glomus tumor). The triad of glomus tumor is pain, tenderness, and temperature sensitivity. A single affected digit in a middle-aged woman is the correct demographic. A bluish subungual discoloration with a distal split is a typical appearance of a glomus tumor. While some of the other diagnoses could present with some of the symptoms, all three are distinctive for glomus tumor.

2. B (paronychia). Paronychia, periungual pyogenic granulomas, and xerosis are associated with epidermal growth factor receptor inhibitors.

3. C (scleroderma). Pterygium inversum unguis is associated with scleroderma and lupus. Dorsal pterygium is associated with lichen planus.

4. B (yellow-nail syndrome). Yellow-nail syndrome is associated with loss of both the cuticle and the lunula. Chronic paronychia can result in loss of the cuticle but not of the lunula. Rubenstein-Taybi syndrome is associated with broad thumbs.

5. B (albumin). The description is that of Muehrcke’s nails. This is classically associated with low albumin. Arsenic level should be checked with Mees’ lines, which do not blanch with pressure.

6. A (0.1 mm/day). Fingernails grow at 3 mm/month (0.1 mm/day) and take 5–6 months to regrow. Toenails grow at 1 mm/month (0.03 mm/day) and take 12–18 months to regrow.

7. C (minocycline). The rate of photo-onycholysis for tetracyclines is as follows: demecycline > doxycycline > tetracycline > minocycline.
8. C (keratosis follicularis). These nail changes are specific for Darier’s disease, also known as keratosis follicularis.

9. E (nephrologist). The clinical scenario describes nail-patella syndrome, also known as HOOD syndrome or Fong syndrome. This genodermatosis is associated with hypoplastic or absent patella, bilateral posterior iliac horns, radial head subluxation, scoliosis, palmar/planter hyperhidrosis, glomerulonephritis ± renal failure, heterochromic irides, Lester iris, and cataract. Of the doctors listed, the nephrologist is the only suitable choice because of the risk of glomerulonephritis and renal failure.

10. i-E; ii-D; iii-A; iv-B; v-C.
   i. Non-blanching transverse white bands that grow out with the nail = Mees lines, classically associated with arsenic poisoning
   ii. Blanchable paired transverse white bands that do not grow out with the nail = Muehrcke’s nails, classically associated with hypoalbuminemia
   iii. Opaque proximal nail with 1–2 mm distal pink band = Terry’s nails, associated with cirrhosis
   iv. Proximal pallor with brown/pink distal half of nail = Lindsay’s nails or half-and-half nails, associated with renal failure
   v. Increased transverse and longitudinal nail curvature with obliteration of Lovibond’s angle = clubbing, associated with congestive heart failure

REFERENCES


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BLACK HAIRY TONGUE (FIG. 4-1)

- Inadequate hygiene or microbial overgrowth stimulates elongation of filiform papillae (covers entire anterior dorsal tongue)
- Also associated with smoking, antibiotic therapy and poor general health status
- Clinical: black or brown hairlike projections on dorsal tongue
- Histology: elongation of filiform papillae; many microbial colonies between them
- Treatment: Eliminate smoking. Advise tongue brushing/scraping: aids in desquamation

ACTINIC CHEILOSIS/CHELITIS (FIG. 4-2)

- Due to long-term exposure to ultraviolet (UV) light (actinic radiation)
- Clinical findings
  - Thinned pale areas, especially lower lip. Later may develop areas of crusting
  - May progress to overt invasive squamous cell carcinoma
- Histology: hyperkeratosis usually is accompanied by dysplasia and superficial invasion
- Treatment: liquid nitrogen, imiquimod cream 5%, 5-fluorouracil, surgical excision

APHTHOUS STOMATITIS (FIG. 4-3)

- Clinical findings
  - One to several painful ulcers on the lining mucosa
  - Ulcers heal in 7 to 10 days without scarring
  - Recurrent aphthous ulcers (RAU)
  - Three clinical forms
    - RAU minor
      - Accounts for 80% of all RAUs
    - RAU major
      - Oval-shaped ulcers that are 1 to 3 cm in diameter
      - Severe form, 1 to 10 major aphthae may be present
      - Herpetiform RAU: tends to occur in clusters that may consist of tens or hundreds of minute ulcers
  - Causes difficult to pinpoint
    - Genetic
    - Vitamin deficiency: iron, folic acid, or vitamin B12
    - Immune dysregulation
    - Stress
    - Environmental factors
    - Local, chemical, or physical trauma (pathergy)
    - Contact allergy
    - HIV infection (associated with lesions)
    - Behçet syndrome (associated with lesions)
- Histology: non specific ulceration
- Treatment
  - Topical corticosteroids are the mainstay of treatment
  - Systemic agents
    - Systemic steroids for refractory cases
    - Colchicine (0.6 mg tid) if associated with arthralgias
    - Cimetidine (200 mg bid/qid)
    - Azathioprine (50 mg qd) if ocular lesions
    - Thalidomide

CICATRICIAL PEMPHIGOID (FIG. 4-4)

- Clinical findings
  - Muco-cutaneous vesiculobullous eruptions
  - Rupture leaving a slough covering a shallow ulcer that heals with scarring
  - Also may affect the eyes, mucous membranes of the genitalia and occasionally the skin
SQUAMOUS CARCINOMA IN SITU (FIG. 4-5)

- Associated with tobacco use
- Can lead to invasive squamous cell carcinoma
- Clinical finding: white and/or red patch or soft ulcer
- Histology: anaplasia with or without hyperkeratosis; no invasion beyond basement membrane

Bullous pemphigoid affects oral mucosa less than cicatricial form and is more self limiting, but otherwise histologically similar

- Histology: Subepidermal separation with eosinophilic infiltrate. Direct immunofluorescence of normal appearing mucosa shows immune deposits at the basement membrane
- Treatment: corticosteroid therapy: oral and/or topical; immunosuppressive therapy
FOCAL MELANOSIS

Buccal mucosa (often bilateral), the vermilion upper lip
Histology: ectopic sebaceous glands
Treatment: none

FOCAL MELANOSIS (FIG. 4-8)

Clinical findings: isolated macules, usually brown. Small (1–6mm diameter)
Histology: increased melanin in basal layer
Otherwise normal appearance
Treatment: none

FISSURED TONGUE (SCROTAL TONGUE, LINGUA PLICATA) (FIG. 4-6)

Developmental etiology
Seen in
- Melkersson-Rosenthal’s syndrome
- Down’s syndrome
Frequently associated with benign migratory glossitis (geographic tongue)
Clinical findings
- Irregular clefts are observed in the dorsum tongue
- Food debris and Candida albicans colonies may form in the fissures
- May be associated with burning tongue
Treatment: maintain good oral hygiene

FIGURE 4-6 Fissured tongue. (Courtesy of Dr. Nadarajah Vigneswaran.)

FIGURE 4-7 Fordyce spots. (Courtesy of Dr. Nadarajah Vigneswaran.)

• Buccal mucosa (often bilateral), the vermilion upper lip
• Histology: ectopic sebaceous glands
• Treatment: none

FORDYCE’S SPOTS (FIG. 4-7)

Clinical findings
- Yellow papules

FIGURE 4-5 Carcinoma in situ. (Courtesy of Dr. Kamal Busaidy.)
Chapter 4  ORAL PATHOLOGY

MELANOACANTHOMA, MELANOACANTHOSIS (FIG. 4-9)

- Clinical findings: brown/black pigmentation of gingiva, tongue, palate. Macules can be several centimeters in diameter
- Histology: melanocytes scattered in epithelial layer. Acanthosis of epithelium
- Treatment: none

GEOGRAPHIC TONGUE (BENIGN MIGRATORY GLOSSITIS) (FIG. 4-10)

- Clinical findings
  - Atrophy of the filiform papillae of the tongue
  - Atrophic area surrounded by a serpiginous, white, hyperkeratotic border
  - Heals and develops again elsewhere (“migration”)
  - Burning sensation or an irritation of the tongue noted with hot or spicy foods
  - In patients with psoriasis, geographic tongue occurs in 10% of patients
- Histology: psoriasiform mucositis; elongation of the rete ridges is noted with associated hyperparakeratosis and acanthosis; absence of filiform papillae in center; clustering of neutrophils within the epithelium (Munro microabscesses)
- Treatment: none
- Prognosis: excellent; often self-limited

GRANULAR CELL TUMOR (GCT) (FIG. 4-11)

- Cells are of neural derivation (Schwann cells)
- Tongue is affected in approximately 25% of cases
- Gastrointestinal tract harbors approximately 5% of all GCTs
- Malignant GCTs are present if cells show cytologic features of malignancy
- Clinical findings: submucosal nodule covered with normal mucosa
- Histology
  - Tumor cells with abundant granular eosinophilic cytoplasm with centrally located vesicular or pyknotic nuclei and markedly enlarged lysosomes
  - Periodic acid–Schiff (PAS) staining; Sudan black B. trichrome preparations
ORAL LICHEN PLANUS (OLP)

Histology
- Hyperkeratosis, parakeratosis, acanthosis, and sawtooth rete pegs
- Chronic inflammation; bandlike subepithelial mononuclear infiltrate consisting of T cells and histiocytes
- Basal cell liquefaction, degenerating basal keratinocytes that form colloid (Civatte, hyaline, cytoid) bodies

Treatment
- Eliminate factors that exacerbate soreness
- Topical steroids, topical tacrolimus or cyclosporine

Immunohistochemical stains: S-100 protein, neuron-specific enolase, and NK1-C3, myelin-associated P0 and P2 proteins, myelin basic protein, and Leu-7

Treatment: surgical excision

Prognosis
- Benign lesions; recurrence rates are 2% to 8%
- Ki-67 immunoreactivity of 10% or more tumor cells is an adverse prognostic factor

ORAL LICHEN PLANUS (OLP) (FIGS. 4-12, 4-13)

Clinical findings
- Affects buccal, vestibular, lingual mucosa. 15% of patients with OLP have coincident skin lesions, (purple pruritic polygonal papules)
- Reticular form: intersecting white lines in a netlike pattern; irregular white plaques (Wickham’s Sriae)
- Erosive form: ulceration and sloughing; potential for cancer formation (fewer than 1% of patients). Patients may have desquamative gingivitis in addition
- OLP related to
  - Medications (Nonsteroidal anti-inflammatory drugs (NSAIDs), sulfonylureas, antimalarials, beta-blockers, and some angiotensin-converting enzyme (ACE) inhibitors)
  - Dentures, amalgams; allergy to metals or components of dental appliances
  - Hepatic causes: hepatitis C virus (HCV) infection, autoimmune chronic active hepatitis, and primary biliary cirrhosis

Histology
- Hyperkeratosis, parakeratosis, acanthosis, and sawtooth rete pegs
- Chronic inflammation; bandlike subepithelial mononuclear infiltrate consisting of T cells and histiocytes
- Basal cell liquefaction, degenerating basal keratinocytes that form colloid (Civatte, hyaline, cytoid) bodies

Treatment
- Eliminate factors that exacerbate soreness
- Topical steroids, topical tacrolimus or cyclosporine
LYMPHANGIOMA (FIG. 4-14)

- Benign
- 70% to 80% involve the mandible
- May grow to significant size before causing bony expansion or other symptoms
- Radiologic findings: Usually incidental finding on routine dental screening x-rays. Well-demarcated radiolucency with a scalloped, radiopaque margin
- Histology
  - Cyst derived from the remnants of the dental lamina
  - Distinctive lining of 6 to 10 cells in thickness
  - Exhibits a basal cell layer of palisaded cells and a surface of corrugated parakeratin
- Treatment: enucleation versus resection

MEDIAN RHOMBOID GLOSSITIS (FIG. 4-15)

- Inflammatory lesion of the tongue secondary to candidiasis
- Clinical findings
  - Papillary atrophy on dorsal surface of the tongue along the midline, anterior to the foramen cecum
  - 1- to 3-cm rhomboid or oval, red, smooth
- Treatment: topical or systemic antifungal drugs

ODONTOGENIC KERATOCYST (OKC) (FIG. 4-16)

- Clinical findings
  - May be associated with nevoid basal cell carcinoma syndrome
OSTEOMA

LEUKOPLAKIA (LEUKOKERATOSIS, ERYTHROLEUKOPLAKIA) (FIG. 4-18)

- Clinical term describes mucosal conditions that produce a whiter than normal coloration of the mucous membranes
- Potentially precancerous especially if located in the floor of the mouth. Red patches have higher premalignant potential
- Clinical findings: White or red patch varies from flat, smooth, and slightly translucent macular areas to thick, firm, rough-surfaced, and fissured raised plaques
- Etiology: tobacco, alcohol, ultraviolet radiation, microorganisms, trauma
- Histology: thickened surface; keratin layer; a thickened spinous layer of chronic inflammatory cells in the connective tissue
- Treatment: Excision for small lesions. Close surveillance for malignant change

OSTEOMA (FIG. 4-19)

- Clinical findings
  - Usually solitary exophytic nodular growth of dense cortical bone on or within the mandible or maxilla
  - Multiple jaw osteomas may be associated with Gardner syndrome; autosomal dominant (gastrointestinal polyps, multiple osteomas,

XEROSTOMIA (DRY MOUTH)

- Clinical findings: dry, glossy atrophic mucosa
- Causes
  - Medications (secondary to anticholinergic effects): diuretics, sedatives, hypnotics, antihistamines, antihypertensives, antipsychotics, antidepressants, anticholinergics, and appetite suppressants
  - Radiation therapy to head and neck
  - Salivary gland surgery
  - Autoimmune disorders: human immunodeficiency virus (HIV) infections, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren’s syndrome
  - Endocrine disorders: diabetes and hyperthyroidism
- Treatment
  - Discontinue offending medication
  - Commercial saliva substitute
  - Fluoride supplementation

DRUG-INDUCED GINGIVAL HYPERPLASIA (FIG. 4-17)

- Clinical findings
  - Increase in the fibrous component of the gingiva
  - Long-term phenytoin (Dilantin), cyclosporine, and nifedipine
- Treatment
  - Good oral hygiene with regular dental cleanings
  - Discontinuation of precipitating drugs when possible
  - Surgical or laser resection of tissue for severe cases

FIGURE 4-17 Drug-induced gingival hyperplasia. (Courtesy of Dr. Mark Wong.)

FIGURE 4-18 Leukoplakia. (Courtesy of Dr. Bela Toth.)
Initiated by irritation from rough buccal cusps, bruxism, or habitual clenching of teeth

Histology: parakeratosis of tissue

Treatment: no treatment necessary

**Supernumerary Teeth and Epidermoid Cysts/Fibromas**

- Radiographic features: well-delineated or spherical calcifications
- Treatment: none. May require excision if severely deforming or interfere with function

**Kaposi’s Sarcoma**

- Related to human herpes virus 8 and HIV
- Clinical findings
  - Hard palate with hyperpigmented macular lesions are most common and may include the gingiva, tongue, uvula, tonsils, pharynx, and trachea
  - Larger nodular lesions may become exophytic and ulcerated
- Histology
  - Spindle cells
  - Slit-like vascular spaces containing erythrocytes
  - Inflammatory cell infiltrate
- Treatment: excision. Systemic or intalesional chemotherapy

**Hutchinson’s Incisors (Fig. 4-20)**

- Screwdriver-shaped central incisors seen in congenital syphilis

**Mulberry Molars**

- Berry-like molars seen in congenital syphilis

**Linea Alba (Fig. 4-21)**

- Clinical findings
  - Linear white streak on the buccal mucosa at the occlusal line
- Initiated by irritation from rough buccal cusps, bruxism, or habitual clenching of teeth
- Histology: parakeratosis of tissue
- Treatment: no treatment necessary
VERRUCOUS CARCINOMA

ORAL-FACIAL-DIGITAL SYNDROME

- X-linked dominant
- Malformations of the face, oral cavity, and digits
- Clinical findings: oral anomalies: lobed tongue, hamartomas or lipomas of the tongue, cleft of the hard or soft palate, accessory gingival ferrule, hypodontia

PAPILLON-LEFÈVRE SYNDROME

- Autosomal recessive disorder
- Clinical findings
  - Aggressive periodontal disease. Palmar/plantar keratosis
  - Affects both primary and permanent dentitions
- Radiographic findings: Teeth appear to float in the soft tissue
- Treatment: periodontal therapy and antibiotics

PYOGENIC GRANULOMA (FIG. 4-22)

- Clinical findings
  - Smooth or lobulated red to purple masses that may be either pedunculated or sessile; commonly on the gingiva but can occur anywhere in the mouth
  - In response to chronic irritation (e.g., from rough surface of tooth)
- Histology: proliferating vascular channels and a mixed inflammatory infiltrate
- Treatment: surgical excision, laser excision. Removal of underlying irritant

SQUAMOUS CELL CARCINOMA

- Malignant neoplasm of stratified squamous epithelium
- Clinical findings
  - Early lesion: leukoplakias and erythroplakias
  - Late lesion: painless ulcer, tumorous mass, or verrucous (papillary growth)
  - Associated with tobacco smoking and alcohol use
- Histology
  - Keratin pearls (abnormal keratinization) invading lamina propria
  - Increased mitotic activity
  - Nuclear pleomorphism
  - Chronic inflammation
- Treatment: surgical excision, radiation therapy

VERUCOUS CARCINOMA (FIG. 4-24)

- Papillary, superficial form of well-differentiated squamous cell carcinoma
- Rarely metastasizes
- Clinical findings: broad-based, exophytic, indurated lesion
- Histology: well-differentiated; basement membrane intact; marked epithelial hyperplasia and hyperparakeratosis
- Treatment: excision, radiation

FIGURE 4-22 Pyogenic granuloma. (Courtesy of Dr. Nadarajah Vigneswaran.)

FIGURE 4-23 Squamous cell carcinoma. (Courtesy of Dr. Bela Toth.)
Symmetric, thickened, white, corrugated or velvety, diffuse plaques
• Buccal mucosa, ventral tongue, labial mucosa, soft palate, alveolar mucosa, or floor of the mouth
• Histology: acanthosis, spongiosis, hyperkeratosis
• Treatment: No treatment necessary

MUCOCELE (FIGS. 4-27, 4-28)
• Caused by traumatic injury to a minor salivary gland
• Clinical findings: dome shaped, soft, painless, translucent bluish lesion
ORAL CANDIDIASIS (THRUSH)

Located mainly on the sides of the tongue.

Clinical findings:
- White thickening or coating of the lining of the mouth; does not scrape off.
- Typically affects immunosuppressed individuals.
- 40% of patients with HIV may develop this.

Treatment: No treatment typically required. May respond to acyclovir or ganciclovir, topical retinoids.

TORI AND EXOSTOSES (FIGS. 4-29, 4-30)

- Overgrowth of mature bone
- Clinical findings:
  - Elevated bony hard lesions extending out from the jaws
  - Tori are specifically in midline hard palate, or lingual of mandible
- Treatment: no treatment required unless interferes with denture wearing or oral hygiene; may be surgically removed.

ORAL HAIRY LEUKOPLAKIA (FIG. 4-31)

- Secondary to Epstein-Barr virus (EBV)

FIGURE 4-28  Mucocoele – tongue. (Courtesy of Dr. Kamal Busaidy.)

FIGURE 4-29  Mandibular tori. (Courtesy of Dr. Bela Toth.)

FIGURE 4-30  Palatal torus. (Courtesy of Dr. Kamal Busaidy.)

ORAL CANDIDIASIS (THRUSH) (FIG. 4-32)

- Caused by Candida albicans
Clinical findings
- Velvety white plaques in the mouth and on the tongue
- Lesions may be rubbed off to leave behind an inflamed base that may be painful and may bleed
- Usually a mild and self-limited illness

Predisposing factors
- Underlying immunodeficiency
- Antibiotics, steroids
- Dry mouth
- Medication-induced: antidepressants, antipsychotics, chemotherapy, radiotherapy, or Sjögren’s syndrome
- Diabetes mellitus
- Vitamin deficiency: iron, folate
- Treatment: oral antifungal agents

ACTINOMYCOSIS (FIG. 4-33)
- Facultatively or strictly anaerobic gram-positive bacilli
- Bacteria with fungi-like structures
- Normal flora of the upper respiratory, gastrointestinal and female genital tracts
- Causes opportunistic disease following disruption of mucosal barriers by trauma, surgery, or infection

Clinical findings
- Multiple abscesses and interconnecting sinus tracts: contain granules of microcolonies
  - Imbedded in tissue elements
- Macroscopic masses of filamentous bacterial cells that are “cemented” together by calcium phosphate
- Known as sulfur granules owing to their yellow or orange appearance
- Chronic suppuration results in granuloma formation and a fibrotic “walling off” of the lesion
- Cervicofacial actinomycosis
HEMANGIOMA

- Most common form
- Associated with poor oral hygiene, an invasive dental procedure, or oral trauma
- Tissue swelling with fibrosis and draining sinus tracts along the jawline

- Laboratory studies
  - Difficult to culture and identify because the numbers of organisms are limited in affected tissues and are sequestered in sulfur granules
  - Fastidious and slow growth (up to 2 weeks or more)

- Treatment
  - Surgical debridement
  - Long-term antibiotic therapy (susceptible to penicillin)
  - Maintain good oral hygiene
  - Prophylactic antibiotics prior to invasive oral or abdominal surgical procedures

CHEMOTHERAPY-INDUCED ORAL MUCOSITIS

- Clinical findings
  - Localized areas of full-thickness erosions occur
  - Can become covered by a fibrinous pseudomembrane
  - May become colonized by mixed flora
  - Dose-limiting toxicity for antimetabolites
  - Fluorouracil, methotrexate, and purine antagonists
  - Chemotherapeutic insult
  - Causes release of inflammatory cytokines, resulting in local tissue damage and increased vascularity
  - Decrease rates of cell division in the oral basal epithelium
  - Leads to reduced cell renewal, atrophy, and ulceration

- Treatment
  - Analgesics and nutritional support
  - Antimicrobial treatment for secondary infection
  - Tocopherol (vitamin E) accelerates mucosal healing
  - Ice chips
  - Induce local vasoconstriction; reduce amount of fluorouracil delivered to oral mucosal cells
  - Reduces the severity and duration of mucositis by 50%
  - Palifermin-synthetic keratinocyte growth factor

ANKYLOGLOSSIA (FIG. 4-34)

- Clinical findings: Attachment of the tongue to the floor of the mouth or anterior lingual gingivae limits tongue movement

FIGURE 4-34 Ankyloglossia. (Courtesy of Dr. Kamal Busaidy.)

- May be associated with speech defects or periodontal disease
- Treatment: surgical release of attachment

HEMANGIOMA (FIG. 4-35)

- Usually occurs in childhood
- Capillary type also known as strawberry hemangioma. Purple exophytic mass

FIGURE 4-35 Hemangioma. (Courtesy of Dr. Kamal Busaidy.)
• Cavernous type are deeper with larger blood filled spaces
• Treatment: Capillary type commonly involute in time. Cavernous type do not involute, and require excision if causing functional or cosmetic disturbances

CENTRAL GIANT CELL GRANULOMA (FIG. 4-36)

• Clinical findings
  • Painless expansion of alveolar bone
  • Most commonly in mandible; in 2nd to 4th decade
  • Displacement and loosening of teeth
  • Benign but may exhibit aggressive local growth
• Radiologic findings
  • Multilocular radiolucency. Radiographically indistinguishable from odontogenic keratocyst or ameloblastoma
• Histology: abundant multinucleated giant cells on background of mesenchymal cells
• Treatment: surgical excision. Intralesional steroids. Intralesional interferon. Systemic calcitonin

PERIPHERAL GIANT CELL GRANULOMA (FIG. 4-37)

• Clinical findings
  • Similar appearance to pyogenic granuloma
  • Location limited to gingivae
  • Commonly a response to local irritation or trauma
• Histology: Similar to central giant cell granuloma with multinucleated giant cells on a background of

ERYTHEMA MULTIFORME (FIG. 4-38)

• Associated with recent viral infection (herpes) or drugs (NSAIDs, sulphonamides, penicillamine)
• Clinical findings

spindle shaped mesenchymal cells, and with occasional dystrophic calcifications
• Treatment: excision and removal of underlying irritant
PERIPHERAL OSSIFYING FIBROMA

- Shallow oral ulcerations, crusted bleeding lips, often erythematous skin lesions ("target lesions")
- Steven-Johnson syndrome is more severe form of EM that also causes conjunctivitis and genital ulceration
- Histology: subepithelial edema and mixed inflammatory infiltrate
- Treatment: systemic corticosteroids; hydration; analgesia; self-limiting usually

NATAL TEETH (FIG. 4-39)

- Teeth are present at or around time of birth
- Usually mandibular incisors
- May exhibit significant mobility
- Treatment: removal if tooth mobility poses a risk of aspiration

BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAWS (FIG. 4-40)

- Clinical findings
  - Chronic exposure of bone in the mouth in a patient who has taken bisphosphonate drugs in the past
  - Often a history of recent dental extraction
  - Hypovascular, hypocellular, hypermineralized bone. Often superimposed bacterial colonization
- Treatment: conservative debridement. Oral hygiene. Antibiotics if superinfected

PERIPHERAL OSSIFYING FIBROMA (FIG. 4-41)

- Clinical findings
  - Firm, often ulcerated mass occurring exclusively on the gingivae. May look similar to pyogenic granuloma except for consistency
  - Commonly in the incisor region
  - May represent a pyogenic granuloma that has matured and become fibrosed/calcified
- Histology: fibrous proliferation with variable amounts of calcification
- Treatment: excision down to and including periosteum

FIGURE 4-39 Natal teeth. (Courtesy of Dr. Kamal Busaidy.)

FIGURE 4-40 Bisphosphonate-related osteonecrosis of the jaws. (Courtesy of Dr. Kamal Busaidy.)

FIGURE 4-41 Peripheral ossifying fibroma traumatic fibroma. (Courtesy of Dr. Kamal Busaidy.)
**TRAUMATIC FIBROMA (FIG. 4-42)**

- Clinical findings
  - Sessile or pedunculated, firm mass, most commonly on the buccal mucosa along occlusal line
  - Response to chronic trauma (e.g., cheek biting). Not true neoplasm
- Histology: dense mass of connective tissue covered by hyperkeratinized epithelium
- Treatment: excision

**QUIZ**

Questions

1. A white lesion is present on the buccal mucosa. It cannot be rubbed off, and exhibits a lace-like pattern of striations. The striations do not disappear when the mucosa is stretched. The lesion most likely represents
   A. Leukoedema
   B. Leukoplakia
   C. Lichen planus
   D. Hairy leukoplakia

2. A 9-mm diameter purple soft ulcerated somewhat sessile mass is present on the marginal gingivae adjacent to the lower left incisor. It bleeds readily. Histologic examination reveals the presence of fibrous connective tissue, chronic mixed inflammatory infiltrate, and occasional areas of dystrophic calcification. The lesion most likely represents
   A. Peripheral giant cell granuloma
   B. Pyogenic granuloma
   C. Peripheral ossifying fibroma
   D. Epulis fissuratum

3. A 52-year-old patient with COPD and hypertension presents with diffuse gingival enlargement around all his teeth which has become progressively worse over the last year. He takes Singulair and verapamil. The most likely cause of the gingival condition is
   A. Peripheral ossifying fibroma of the gingivae
   B. Drug induced gingival hyperplasia
   C. Hereditary gingival fibromatosis
   D. Papillon-Lefèvre syndrome

4. Which of the following carries the most unfavorable prognosis?
   A. 3-cm diameter verrucous carcinoma of the lip
   B. 2-cm squamous cell carcinoma of the lateral tongue
   C. 6-cm central giant cell granuloma of the mandible
   D. 2-cm squamous cell carcinoma of the lower lip

5. Direct immunofluorescence demonstrates immune complex deposition along the basement membrane of a specimen of oral mucosa. The finding is most indicative of
   A. Erythema multiforme
   B. Reiter’s syndrome
   C. Pemphigus
   D. Cicatricial pemphigoid

6. A 20-year-old male complains of soreness of his tongue. On examination the tongue exhibits two areas of erythema surrounded by a ragged whitish border, one on the left lateral surface, and the other on the tip of the tongue. The patient reports they arose within the last week and that a similar lesion had occurred on the right side of the tongue and healed spontaneously a month ago. The condition most likely represents
   A. Erythroplakia
   B. Geographic tongue
   C. Median rhomboid glossitis
   D. Lichen planus

**FIGURE 4-42** Traumatic fibroma. (Courtesy of Dr. Kamal Busaidy.)
7. Black hairy tongue
   A. Is a bacterial infection that should be treated with penicillin
   B. Is the inevitable result of full thickness skin grafting to the tongue
   C. Is a premalignant condition
   D. Should be managed with periodic tongue brushing/scraping

8. Which of the following conditions may be seen in a patient with an accentuated linea alba?
   A. Candidal infection of the mouth
   B. Worn occlusal surfaces of teeth
   C. Psoriatic skin lesions
   D. Restricted mouth opening

9. A 25-year-old male with multiple jaw osteomas, epidermoid cysts and multiple supernumerary teeth should undergo which of the following:
   A. CT examination of the head
   B. Ultrasound examination of the abdomen
   C. Colonoscopy
   D. Blood test for parathyroid hormone level

10. Hypodontia is associated with which of the following?
    A. Ectodermal dysplasia
    B. Gardner’s syndrome
    C. Cleidocranial dysostosis
    D. Down’s syndrome

Answers
1. B. None of the lesions listed can be rubbed off. All appear white. Leukoedema appears grayish white, typically affecting the buccal mucosa bilaterally. There may be wrinkles or striations present, but these disappear when the mucosa is stretched. Leuoplakia does not typically have associated striations. Hairy leukoplakia appears as a shaggy white covering of the mucosa, typically on the lateral aspect of the tongue. The lace-like striae of the reticular form of lichen planus are termed Wickham’s striae, and do not disappear with stretching of the mucosa either.
2. C. The first three lesions may appear remarkably similar on inspection, and may only be distinguishable histologically. Pyogenic granulomas are not restricted to the gingivae as are PGCG and POFs. Epulis fissuratum typically appears at the margin of an ill-fitting denture, and may be grooved by it. Histologically a PGCG demonstrates multinucleated giant cells. A POF demonstrates mineralized components that are not present in a pyogenic granuloma or an epulis fissuratum. The POF may in fact represent the mature form of a pyogenic granuloma that has undergone fibrosis and maturation.
3. B. Peripheral ossifying fibroma is a localized condition. Gingival fibromatoses may be idiopathic or hereditary. Hereditary gingival fibromatosis typically appears in the first two decades of life. Papillon-Lefèvre syndrome involves aggressive periodontal disease affecting both the deciduous and permanent dentitions, palmar/plantar keratoses and dry keratotic skin lesions, beginning within the first decade of life. Drugs associated with gingival hyperplasia include cyclosporine, phenytoin, and calcium channel blockers such as nifedipine, verapamil, diltiazem.
4. B. Verrucous carcinoma rarely metastasizes. Central giant cell granuloma can exhibit extremely aggressive local growth but does not metastasize. Squamous cell carcinoma metastasizes early. Lesions 2 cm in diameter on the tongue will have already invaded muscle, and therefore constitute T4 lesions. Squamous cell carcinoma lesions in the anterior part of the mouth and lips have a better prognosis than those in the posterior of the oral cavity.
5. D. Reiter’s syndrome does not have any associated findings on direct immunofluorescence. Direct immunofluorescence of mucosa affected by erythema multiforme may demonstrate perivascular C3 deposits. Pemphigus demonstrates immune complex deposits on the intercellular surfaces within the epithelial layer. A finding of immune complex deposits along the basement membrane is characteristic of pemphigoid.
6. B. Erythroplakia is a red patch, often located within an area of leukoplakia, that does not resolve spontaneously, and is associated with a significant risk of progression to squamous cell carcinoma. Median rhomboid glossitis is an oval-shaped area of atrophy of surface papilla in the center of the dorsal surface of the tongue, and is usually asymptomatic. Lichen planus may present as smooth plaques on the tongue, and may come and go, giving a picture similar to erythema migrans (geographic tongue). However lesions of geographic tongue are typically well defined and bordered by a distinct irregular white line. The lesions heal spontaneously over a few weeks only to reappear in other areas of the tongue, hence giving the impression that they are migrating.
7. D. Overgrowth and subsequent staining of filiform papillae on the dorsal surface of the tongue results in black hairy tongue. While microbial deposits are common in the rough surface, treatment with antibiotics does not resolve the condition. The condition is not premalignant, and usually responds to good
oral hygiene measures, including periodic tongue brushing or scraping.

8. B. A linea alba is a common finding. It represents the region of friction on the buccal mucosa corresponding to the occlusal line of the teeth. However, a markedly accentuated line may be seen in patients who habitually clench or grind their teeth. In such a circumstance there will commonly also be excessive wear of the teeth.

9. C. The findings are consistent with Gardner’s syndrome. Intestinal polyps are extremely common in such patients, and colonoscopy is warranted to screen for malignancy since their rate of malignant transformation is so high.

10. A. Gardner’s syndrome and cleidocranial dysostosis are associated with supernumerary teeth (extra teeth). Down’s syndrome may be associated with cleft palate and macroglossia, but does not typically cause hypodontia. Ectodermal dysplasia affects multiple ectodermally derived elements, often resulting in hypohidrosis, sparse hair and reduced number of teeth (hypodontia).

REFERENCES


LICHEN SCLEROSUS ET ATROPHICUS (LS) (FIG. 5-1)

- Atrophic white papules or plaques, most commonly affects the anogenital area in females (85% to 98% of patients) with extragenital involvement in 15% to 20%
- Figure-of-eight lesion when perineum and anus involved
- Females affected more often than males
- Secondary problems: candidiasis or atrophic vaginitis
- Severe cases can lead to scarring of vaginal vault and introitus with fusion of the labia minora and narrowing of the introitus, leading to a buried clitoris
- Penile LS (balanitis xerotica obliterans)
  - Common in middle age
  - Glans and inner aspect of the prepuce or circumferentially around the urethral meatus (can cause phimosis in uncircumcised males)
- Squamous cell carcinoma can arise in lesions in males and females
- Etiology is unknown: possible immune dysregulation with organ specific antibodies; infective agents have been linked with LS: pleiomorphic and, variably, acid fast bacilli and spirochetes
- Histology: orthokeratosis, hyperkeratosis, atrophy, basal cell layer vacuolation, edema and homogenization of collagen in the upper dermis; a focal perivascular or bandlike mononuclear cell infiltrate containing plasma cells is seen beneath the edema
- Treatment: high-potency topical glucocorticoids, topical antibiotics, circumcision for phimosis

PYRONIE’S DISEASE (PENILE FIBROMATOSIS)

- Idiopathic disorder
- Angulation of erect penis in middle age
- Caused by fibrosis of tunica albuginea, covers the corpora cavernosa

VULVODYNIA

- Diagnosis of exclusion
  - The cause has not yet been established; increased intraepithelial innervation in skin biopsies and an increase in the number of C-afferent nociceptors on special histopathological staining (S-100); an increase has also been found in the number of mast cells
  - Vulvar discomfort, usually burning pain
  - International Society for the Study of Vulvovaginal Disease (ISSVD) classified the disease according to the localization of the pain in the vulva, whether it is generalized or localized and to whether it arises on provocation of the area or is unprovoked
  - Q-tip test may localize pain
  - Treatment: tricyclicantidepressant, topical corticosteroids/antifungals, gabapentin, biofeedback, low oxalate diet, oral calcium citrate, acupuncture, local botox injections

PEARLY PENILE PAPULES (FIG. 5-2)

- Normal variant
- Small pearly papules along the coronal rim; may extend to the frenulum and urethral meatus
Chapter 5  GENITAL DERMATOLOGY

Histology: angiofibromas with dense connective tissue and a rich vascular complex
No treatment is indicated

SCROTAL CYSTS

- Common
- Diagnosis includes
  - Epidermal inclusion cyst
  - Steatocystoma simplex
  - Median raphe cyst lined with epithelium of combined epidermal and urothelial origin; congenital alterations in embryologic development, typically found on ventral penile shaft

SCROTAL CALCINOSIS

- May arise from dystrophic calcification of epidermal or follicular cysts
- Cysts with white chalky material seen after incision
- Treatment: surgical excision

FOURNIER’S GANGRENE

- Necrotizing soft tissue infection of the genital and anorectal regions
- Tissue necrosis: cellulitis, fasciitis, and myositis
- Involves scrotum and penis with edema, erythema, skin necrosis, crepitus, and bulla formation
- Progression is rapid
- Etiologic factors: diabetes mellitus, periurethritis with urinary extravasation, indwelling catheter placement, traumatic injury
- Treatment: surgical debridement, prolonged antibiotics

DIAPER DERMATITIS (FIG. 5-3)

- Related to the irritant substances found in stool and superinfection with *Candida albicans*
- Presents with a bright red acute dermatitis confined to the genital and buttock areas with occasional extensions onto the abdomen or inner thighs and usually spares skin folds
- Treatment: barrier emollients, frequent diaper changes, topical antibacterial creams, topical antifungals

ANGIOKERATOMA OF FORDYCE (FIG. 5-4)

- Purple 1- to 5-mm papules
- Found on the scrotum, penis, and vulva
- Asymptomatic, occasionally bleed spontaneously or following trauma to or friction of skin
- Histology: dilated dermal blood vessels surrounded by a thin epidermis

FIGURE 5-1  Lichen sclerosus et atrophicus. (Courtesy of Dr. Libby Edwards.)

FIGURE 5-2  Pearly penile papules. (Reprinted with permission from Wolff K et al. Fitzpatrick’s Dermatology in General Medicine, 7th ed. New York: McGraw-Hill; 2008.)
MALIGNANT CONDITIONS

Genital Bowen’s Disease (GBD)/Erythroplasia of Queyrat (EQ)/Vulvar Intraepithelial Neoplasia

- Clinical presentations of high-grade penile intraepithelial neoplasia (PIN)
- Most common etiologic factor: prevalence of human papilloma virus infection (HPV) in PIN is (60–100%)
  - HPV 16 is the most common type found
  - Other risk factors include: lack of circumcision, phimosis, balanitis, or any chronic inflammation of the penile skin
  - Progression into penile cancer is more common in EQ, occurring in around 30% of the cases
- Erythroplasia of Queyrat
  - Squamous cell carcinoma (SCC) in situ confined to the mucosa of the glans penis
  - One or more red, moist plaques on the mucosal surfaces of the glans, which may spread to the inner aspect of the prepuce
- Genital Bowen’s disease
  - SCC in situ that presents as a single, scaly plaque, located on keratinized genital skin
  - Vulvar intraepithelial neoplasia (VIN) (Fig. 5-5) develops within a mature stratified squamous epithelium of vulvar epidermis or squamous mucosa
  - Classified from VIN I-III depending on depth in epithelium
  - HPV is consistently present in a high percentage of VIN
- Histology: full thickness dysplasia of the squamous epithelium. Epidermis and

keratinocytes show disorderly maturation, parakeratosis and loss of granular layer with mitotic figures, multinucleated cells and dyskeratotic cells

Treatment: None needed; bleeding lesions can be ablated easily by electrocoagulation, laser
Chapter 5    GENITAL DERMATOLOGY

Associated with cutaneous, adnexal-structure adenocarcinomas and with internal malignancies

Occurs either as: primary disease—a primary intraepidermal neoplasm of the epidermis (apocrine adenocarcinoma in situ, derived from the Toker cells in apocrine glands) or secondary disease—less common, resulting from disease spread from an underlying internal malignancy (associated with adenocarcinoma arising in the rectum, cervix, ovary, or transitional cells)

Eroded macular, slightly raised plaque with well-demarcated borders, pink, red, tan or brown, lesions can be pruritic

Histology: epidermal acanthosis and elongated rete ridges. Paget’s cells are large intraepidermal cells with a large nucleous and abundant pale cytoplasm

Immunohistiochemistry: cytokeratin 7, cytokeratin 20, gross cystic disease fluid protein

Cutaneous EMPD is characteristically positive for cytokeratin (CK)7, negative for CK20, and positive for gross cystic disease fluid protein (GCDFP)15+, whereas endodermal EMPD shows a CK7 + CK20 + GCDFP15- phenotype

Treatment: surgery: wide surgical excision or Mohs’ micrographic surgery

INFLAMMATORY CONDITIONS

**Inverse Psoriasis (Fig. 5-7)**

- Occurs in intertriginous areas
- Genital psoriasis is frequently accompanied by perianal and intergluteal cleft psoriasis
- Vulvar psoriasis affects fully keratinized skin, sparing the modified mucous membrane
- Dusky red, well-demarcated plaques; with moist, fine scale or a glazed, shiny surface texture
- Frequently complicated by *Candida* infection
- Treatment: hydrocortisone or other mild topical glucocorticoids, calcinuerin inhibitors, calcipotriene

**Lichen Planus (Fig. 5-8)**

- Violaceous, flat-topped, polygonal papules with Wickham’s striae (fine, whitish puncta or reticulated networks)
- Commonly affects oral mucosa, glans penis, wrists
- Severe scarring erosive variant more common in women
- Squamous cell carcinoma may occur in patients with genital lichen planus
- Associated with hepatitis C
- Histology: lichenoid infiltrate with basal cell vacuolarization, sawtooth rete ridges, Max-Joseph spaces
- Treatment: topical or intralesional steroids, calcinuerin inhibitors
INFLAMMATORY CONDITIONS

Results from chronic rubbing and scratching
Areas of hypo- and hyperpigmentation may result
Treatment: Castellani’s paint, intralesional or topical mild- to moderate-strength glucocorticoid, and oral antipruritic agents

Hidradenitis Suppurativa (Fig. 5-11)
- Chronic, inflammatory, scarring disease of apocrine gland-bearing skin (axillae, buttocks, inguinal region, breasts)
- Follicular-occlusion triad: acne conglobata, hidradenitis suppurativa, dissecting cellulitis of the scalp

Lichen Nitidus
- Small skin-colored papules with a glistening appearance
- Often on the penis, abdomen, and arms
- Histology: clawlike extension of rete ridges around a focal mixed dermal infiltrate
- Resolves spontaneously after months to years

Plasma Cell Balanitis (Balanitis Circumscripta Plasmacellularis, Zoon’s Balanitis)
- Solitary, glistening, red or cayenne pepper-colored plaque on the glans penis and/or prepuce of uncircumcised men
- Female equivalent is plasma cell vulvitis (Fig. 5-9); oral mucosal equivalent is plasma cell orificial mucositis
- Histology: dense bandlike or lichenoid infiltrate with a predominance of plasma cells
- Treatment: low-potency topical steroids, circumcision, calcinuerin inhibitors

Lichen Simplex Chronicus (Fig. 5-10)
- Scrotum and/or penis, vulva: symmetrical lichenified plaques

Lichen Planus

Inverse psoriasis. (Courtesy of Dr. Libby Edwards.)

Plasma cell vulvitis. (Courtesy of Dr. Libby Edwards.)

Lichen Nitidus

FIGURE 5-7 Inverse psoriasis. (Courtesy of Dr. Libby Edwards.)

FIGURE 5-8 Lichen planus. (Courtesy of Dr. Libby Edwards.)

FIGURE 5-9 Plasma cell vulvitis. (Courtesy of Dr. Libby Edwards.)
Chapter 5  GENITAL DERMATOLOGY

Common on glans and distal shaft of the penis, vulva, labia
• Other presentations:
  • Generalized or multiple fixed drug eruptions: multiple to numerous and are disseminated, shows polysensitivity, in which there is more than one causative drug and the drugs may be chemically unrelated
  • Erythema multiforme-like fixed drug eruptions: clinical manifestations are similar to those of erythema multiforme
  • Bullous fixed drug eruptions: subepidermal bullae, heal without scarring

Early lesion is a tender dermal abscess; recurrent episodes cause scarring and sinus tract formation
• Rectal, urethral, and vaginal fistulas may develop rarely
• Staging
  • Stage I: solitary or multiple isolated abscess formation without scarring or sinus tracts
  • Stage II: recurrent abscesses, single or multiple widely separated lesions with sinus tract formation and cicatrizaton
  • Stage III: diffuse or broad involvement across a regional area with multiple interconnected sinus tracts and abscesses
• Staphylococcus, Streptococcus, and E. coli are most commonly cultured
• Histology: follicular plugging with various degrees of inflammation and fibrosis, dermal abscess
• Treatment: intralesional steroids, antibiotics, incision and drainage, isotretinoin; wide local excision may be performed in recalcitrant cases, liposuction with gland removal

Fixed Drug Eruption (Fig. 5-12)
• Follows ingestion of a sensitizing hapten: barbiturates, carbamazepine, dapsone, griseofulvin, nonsteroidal anti-inflammatory drugs, phenazones, sulfonamides, tetracycline, Oxyphenbutazone was also reported as a frequent causative drug of mucosal fixed drug eruption
• Sharply demarcated, dusky, erythematous macules or erosions
• Heals with postinflammatory hyperpigmentation
• Recurs in the same location with rechallenge

• Common on glans and distal shaft of the penis, vulva, labia
• Other presentations:
  • Generalized or multiple fixed drug eruptions: multiple to numerous and are disseminated, shows polysensitivity, in which there is more than one causative drug and the drugs may be chemically unrelated
  • Erythema multiforme-like fixed drug eruptions: clinical manifestations are similar to those of erythema multiforme
  • Bullous fixed drug eruptions: subepidermal bullae, heal without scarring
INFECTIONS AND INFESTATIONS

- Treatment: fixed eruption heals in 2 to 3 weeks, drugs should be discontinued, desensitization can be tried, if necessary

Kawasaki’s Disease (Mucocutaneous Lymph Node Syndrome)
- Thought to be mediated by bacterial toxins but etiology still elusive
- 80% of cases occur before 4 years of age
- Perineal erythema may be presenting feature
- Strawberry tongue, fissured lips, fever, cervical lymphadenopathy, non-purulent conjunctivitis, erythema/edema of hands and feet. Later, dequamation
- Risk for coronary artery aneurysm. Mortality approximately 1% in the United States
- Treatment: high dose aspirin, IVIg

Langerhan’s Cell Histiocytosis (Histiocytosis X)
- Classified clinically into 4 types
  - Lettere-Siwe disease: acute diffuse form with visceral and bone lesions
  - Hand-Schuller-Christian disease: classic triad of diabetes insipidus, bone lesions, exophthalmos, chronic progressive course
  - Eosinophilis granuloma: localized variant with solitary bone lesions
  - Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease): benign variant with single or widespread lesions that spontaneously resolves
- Acute variant onset < 2 years of age. Other variants: onset in early childhood
- Non-healing groin rash common: papules, pustules, vesicles become crusted and impetigenized. Often confused with diaper dermatitis or seborrheic dermatitis
- Treatment: dependent on number of body systems involved but may include: chemotherapy, radiation or curettage (bone), topical corticosteroids, antibacterial agents, PUVA, nitrogen mustard (skin)

- It can present with a groin rash similar to acrodermatitis enteropathica

Acrodermatitis Enteropathica
- Autosomal recessive
- Inability to absorb sufficient zinc from the diet
- Triad: acral dermatitis, alopecia, and diarrhea
- Distribution: face, hands, feet, anogenital area
- Dry, scaly, eczematous plaques, perlèche
- Progresses to vesicobullous, pustular, and erosive lesions
- Alopecia worsens with time
- Diarrhea is variable: intermittent or totally absent
- Treatment: supplementation with zinc salts

Hailey-Hailey (Familial Benign Pemphigus) (Fig. 5-13)
- Autosomal dominant, chromosome 3q
- Axillae, groin, intertriginous areas; mucosal surfaces are rarely involved
- Flaccid vesicles and blisters on an erythematous background
- Friction breaks blisters, resulting in erosions
- Frequent exacerbations, precipitated by friction and infection
- Histology: suprabasal cleavage, acantholysis, and intercellular edema (“dilapidated brick wall”)
- Treatment: tetracyclines, fusidic acid, imidazoles, topical or systemic glucocorticoids

INHERITED DISEASES

Cystic Fibrosis
- Autosomal recessive
- Exocrine glands affected: involves the tracheobronchial tree, pancreas, and gastrointestinal tract
- Mucous plugs may cause fecal impaction, intussusception, and rectal prolapse in infancy
- Pancreatic insufficiency
- Progressive lung disease with chronic bronchitis, emphysema, and cor pulmonale
- Cutaneous features: increased amounts of electrolytes in the sweat lead to excessive skin wrinkling when the palms and soles are immersed in water

INFECTIONS AND INFESTATIONS

Candidiasis
- Usually caused by C. albicans
- Vaginal and vulvovaginal candidiasis

FIGURE 5-13 Hailey-Hailey disease. (Courtesy of Dr. Libby Edwards.)
• Thick vaginal discharge associated with burning, itching, and dysuria
• Whitish plaques on the vaginal wall with underlying erythema and surrounding edema; can extend to labia and perineum
• Balanitis or balanoposthitis
• Small papules on glans or coronal sulcus
• Erythematous erosions with a collarette of whitish scale
• Infection may spread to the scrotum and inguinal areas
• Confluent and discrete erythematous areas with pustular and erosive satellite lesions
• Treatment: oral or topical azoles

**Crab Louse (Pediculosis Pubis)**
• Parasite Phthirus pubis, the pubic louse
• Transmitted sexually; mites cling to pubic and facial hair/eyelashes
• Nits (egg casings) of head and crab lice are firmly cemented to the hairs of the host
• Main symptom is pruritus; bites are painless, rarely detected
• Maculae ceruleae: blue macules
• Treatment
  • Permethrin 1% cream rinse
  • Lindane 1% shampoo (potential for central nervous system toxicity; not recommended for use on infants, young children, or pregnant or nursing women)
  • Sexual contacts should be treated simultaneously

**Tinea Cruris**
• Dermatophytosis involving the groin area
• Causative dermatophytes: Epidermophyton floccosum, Trichophyton rubrum
• Dermatophytoses elsewhere on the body provide a reservoir for autoinfection in tinea cruris
• Clinical: multiple, erythematous papulovesicles with a well-marginated, raised border
• Scrotum usually appears completely normal (Candida may spread to the scrotum)
• Treatment: decrease occlusion and moisture in the involved area; tolnaftate, and topical imidazoles, powder or minimally occlusive cream base

**Erythrasma**
• Pigmented or erythematous patches, can have fine scale
• Inguinal folds
• Coral red fluorescence under Wood’s lamp due to coproporphyrin III
• Caused by Corynebacterium minutissimum
• Treated with topical erythromycin or clindamycin

**Peri-anal Streptococcus Disease**
• Group A – hemolytic streptococcus
• Sharply demarcated bright erythema or crusting in perianal area
• Usually children under 4 years of age
• May have constipation because of pain with defecation
• Associated with guttate psoriasis. Oral and rectal swabs for bacterial culture in children with outbreak
• Treatment: penicillin or erythromycin

**BULLOUS DISEASES CAUSING GENITAL ULCERATION (COVERED IN OTHER CHAPTERS)**
• Bullous pemphigoid
• Cicatricial pemphigus
• Linear IgA bullous dermatosis
• Pemphigus vulgaris
• Erythema multiforme
• Stevens-Johnson syndrome
• Behçet’s syndrome

**SEXUALLY TRANSMITTED DISEASES (DESCRIBED IN OTHER CHAPTERS)**
• Bacterial vaginosis
• Chancroid
• Gonorrhea
• Granuloma inguinale
• Human immunodeficiency virus infection
• Syphilis
• Donovonosis
• Lymphogranuloma venereum
• Genital herpes
• Molluscum contagiosum
• Nongonococcal urethritis
• Pubic lice
• Trichomoniasis
• Human papilloma virus infection

**QUIZ**

**Questions**
1. A mother brings her 3-month-old infant to your office for evaluation of a rash in the diaper area. On exam there is erythema on the vulva and peri-anal area with sparing of the skin folds. What is the most likely cause?
   A. Psoriasis
   B. Zinc deficiency
   C. Strep pyogenes
   D. Irritation from urine and stool
2. A 55-year-old female with lichen sclerosis of the vagina and perineum has been well-controlled with topical clobetasol propionate ointment intermittently for the last 10 years. She now complains of an area that has increased pain, erythema, occasionally bleeds and does not heal. What are you worried about?
   A. Squamous cell carcinoma
   B. Atrophy from topical corticosteroids
   C. Herpes genitalis
   D. Contact dermatitis to clobetasol

3. A 40-year-old man presents with multiple, small, red-brown papules with a flat-to-verrucous surface on the shaft of his penis. The most common HPV serotype for this presentation is:
   A. 6, 11
   B. 7
   C. 13
   D. 16, 18

4. A 25-year-old medical student comes to your office because he notes an area of hyperpigmentation on the glans penis. The lesion will start out more erythematous but seems to wax and wane and at times is almost completely resolved. He is otherwise healthy except for seasonal allergies for which he takes an over-the-counter medicine to treat as needed. What do you suspect?
   A. Recurrent herpes genitalis
   B. Fixed drug reaction
   C. Lichen planus
   D. Zoon’s balanitis

5. A 17-year-old female presents to your office with a new pruritic rash involving her axillae, inguinal area, and posterior neck. It is scaly and erythematous with crusting. Her father has a similar rash. What do you expect to see on histology?
   A. Suprabasal cleavage, acantholysis, and serum scale crust
   B. A lichenoid infiltrate in a band-like distribution which obscures the dermoeopidermal junction
   C. Parakeratosis and increased granular layer
   D. Atypical cells with pale-staining cytoplasm and atypical nuclei, mitoses distributed singly or in clusters in the epithelium

6. Erythrasma is caused by:
   A. Kytococcus sedentarius
   B. Corynebacterium tenuis
   C. Corynebacterium minutissimus
   D. Pseudomonas

7. What is the best treatment for pubis pediculosis?
   A. Malathion
   B. Lindane
   C. Permethrin
   D. Shaving the pubic hair

8. You are called as a consult on an 8-month-old female who has a diaper rash that is unresponsive to treatment with topical antifungals and emollients. On biopsy you see large mononuclear cells with reniform nuclei scattered in the dermis. You expect what immunohistochemical stain to be positive?
   A. CD7
   B. CD1a
   C. CD30
   D. CD56

9. A 3-year-old child presents to the ER with fever, conjunctivitis, swelling of the hands and feet and peri-anal erythema. You recommend treatment with:
   A. Low-dose aspirin
   B. High-dose aspirin
   C. Prednisone
   D. High-dose aspirin and IVIg

10. A 29-year-old man complains of small blue/violet papules on his scrotum. He sometimes notices blood on his underwear that he attributes to scratching these lesions. They are otherwise asymptomatic and he has no medical problems. What is your next step?
    A. Biopsy
    B. Check HIV
    C. Check alpha-galactosidase levels
    D. Reassurance

Answers

1. C. This is a description of diaper dermatitis caused by the urine and stool in areas of contact. Psoriasis and peri-anal strop will also cause erythema in this area but does not have the classic sparing of the skin folds. Zinc deficiency is found in infants fed cow’s milk or in acrodermatitis enteropathica once they are weaned from breast milk.

2. A. Squamous cell carcinoma is a rare complication of long-standing LS. Any area that becomes eroded, bleeds, and does not heal warrants a biopsy. Long-term use of topical super-potent steroids could lead to atrophy and cause skin breakdown but the question stated she used them intermittently.
3. D. This is a description of Bowenoid papulosis, which is caused most commonly by HPV types 16 and 18. It is considered malignant but has a low rate of transformation (2.9%). Types 6 and 11 are responsible for most genital warts. Type 7 causes butcher’s warts. Type 13 is associated with Heck’s disease (focal epithelial hyperplasia).

4. B. This is a typical scenario for a fixed drug reaction related to pseudoephedrine, a common ingredient in cold and allergy medicine. HSV would have vesicles but could wax and wane with frequent recurrences. Lichen planus may be on the genitals in both the papular and erosive form but does not wax and wane. Zoon’s balanitis also tends to be persistent unless treated and typically presents as a glistening patch on the glans in an uncircumcised male.

5. A. This is Hailey-Hailey. It is autosomal dominant and on pathology is described as the “dilapidated brick wall.” Choice B refers to lichen planus. Choice C refers to axillary granular parakeratosis. Choice D refers to Paget’s disease.


7. C. Pubic lice is best treated with permethrin cream (1% Nix® or 5% Elimite®). Shaving is the treatment of choice for trichomycosis axillaris which can affect the pubic hair.

8. B. This is Langerhan’s cell histiocytosis. Langerhan’s cells stain with S-100 and CD1a. CD7 stains T-cells and is sometimes lost in MF. CD30 is positive in lymphomatoid papulosis. CD56 is found in NK cell lymphoma.

9. D. This is Kawasaki’s disease. Initial treatment includes high dose aspirin (80–100 mg/kg/d PO divided qid for 2 wk initial) plus IVIG.

10. D. This is angiolkeratoma of Fordyce. It is a benign condition and you can reassure the patient. Fabry’s disease has low levels of alpha-galactosidase but is associated with angiolkeratoma corporis diffusum. Kaposi’s could look similar clinically but typically are larger and more nodular. This would be a reason to check HIV.

REFERENCES


CONTACT DERMATITIS

• Inflammatory response of the skin to an antigen or irritant
• Allergic contact dermatitis (ACD)
  • Delayed type hypersensitivity reaction (type IV)
    – Langerhans’ cells play a central role in processing and presenting antigen complexes
  • Individuals previously sensitized to the allergen will develop lesions. Subsequent exposure to the allergen will result in incrementally more severe reactions
  • Common allergens include: plants from the *Toxicodendron* genus (e.g., poison ivy), nickel sulfate, formaldehyde
  • Acute ACD: lesions appear within 24 to 96 hours of exposure to the allergen
• Irritant contact dermatitis (ICD)
  • Irritants produce various effects: cytotoxicity of the keratinocyte, disruption of lipid architecture, initiation of immunologic cascade
  • ICD will only occur in areas of the skin that has been in direct contact with the offending agent
  • Subsequent inflammatory response in the dermis
  • Caused mostly by chemicals
    • Two types
      – Mild irritants: require prolonged or repeated exposure before inflammation is noted
      – Strong irritants: strong acids, alkalis, can produce immediate reactions similar to thermal burns
  • Clinical changes
    • Acute contact dermatitis: clear fluid–filled vesicles or bullae that appear on bright red edematous skin, pruritic
    • Subacute contact dermatitis: less edema and formation of papules, pruritic
    • Chronic contact dermatitis: minimal edema, scaling, skin fissuring, and lichenification
• Histology
  • Dermis with perivascular lymphocytes and other mononuclear cells, epidermal spongiosis, cytotoxicity more commonly seen in irritant contact dermatitis
  • Chronic ACD: acanthosis with hyperkeratosis and parakeratosis
  • Difficult to distinguish, clinically and histologically, allergic contact from irritant contact dermatitis

CONTACT URTICARIA

• An immunoglobulin E (IgE)–mediated immediate hypersensitivity reaction (type I)
• Immediate release of inflammatory mediators, resulting in a wheal-and-flare reaction
• Rubber latex currently is the most important source of allergic contact urticaria

PHOTOSENSITIVITY INDUCED BY EXOGENOUS AGENTS

• Photodermatitis
  • Diagnosed by the presence of lesions limited to sun-exposed body areas; certain substances transform into allergens (photoallergic) or irritants (phototoxic) by ultraviolet light
• Photoallergic reaction
  • Delayed-type hypersensitivity reaction (type IV)
Onset delayed as long as 24 to 72 hours after exposure to the drug and light
- Amount of drug required to elicit photoallergic reactions is considerably smaller than that required for phototoxic reaction
- Irradiation of certain substances by ultraviolet light results in the transformation of the substance into allergens
- Reactions resemble allergic contact dermatitis, with a distribution limited to sun-exposed areas of the body (see above)
- Usually spares the lower eyelids, and the postauricular and submental areas
- When the reactions are severe or prolonged, they may extend into covered areas of skin
- Examples of agents that can cause a photoallergic reaction (Tables 6-1 and 6-2)
- Phototoxic reaction (Tables 6-3 and 6-4)
  - Often occur within minutes or hours of light exposure
  - Chemically induced nonimmunologic acute skin irritation
  - Does not require prior sensitization
  - Active chemical may enter the skin via topical administration or via ingestion, inhalation, or parenteral administration
  - Damaging effects of light-activated compounds on cell membranes
  - Most compounds are activated by wavelengths within the ultraviolet A (UV-A) (320–400 nm) range
  - Clinical appearance: an exaggerated sunburn reaction
- Photopatch test
  - Used to find causative agent of photoallergic reaction
  - Photopatch testing protocol
    - Day 1: Determine minimal erythema doses (MEDs), and apply two sets of patches
    - Day 2: Read MEDs
    - Day 2: Remove patches, read, and irradiate one set (10 J/cm² UV-A)
    - Day 4: First reading
    - Days 5–9: Second reading

FRAGRANCE-RELATED ALLERGENS

1. Balsam of Peru (also referred to as *Myroxylon pereirae*)
   - Wood extract derived from *Myroxolon balsamum* tree
   - Contains
     - Cinnamoid (cinnamic acid, cinnamyl cinnamate, benzyl benzoate, benzoic acid and vanillin)
   - Polymers of coniferyl alcohol with benzoic acid and cinnamic acid
   - Found in the following products: fragrances, flavorings/spices (cola), pharmaceuticals (antifungal and antibacterial products), diaper powders and ointments, cough medicines, aperitifs
   - Cross-reacts with colophony, turpentine, benzoin, wood tar
2. Bergamot
   - Berloque dermatitis (see “Plant-Related Allergens”)
3. Cinnamic aldehyde
   - Fragrance and flavor agent; constituent of cinnamon oil
   - When found in toothpaste, mouthwash, gum, patients may experience perioral dermatitis, tongue swelling, mouth ulceration
   - Flavoring in beverages (cola)
   - Spices: causes hand dermatitis in bakers
   - Essential oils: balsam of Peru, hyacinth, myrrh, patchouli, ceylon, cassia oil
4. Lily of the valley
   - Allergen: hydroxycitronellal (synthetic)
   - Found in perfumes, soaps, cosmetics, eye cream, aftershaves
   - Also used in insecticides and antiseptics
5. Musk ambrette
   - Fixative in perfumes
   - Photocallergen
6. Oak moss absolute
   - *Evernia prunastri*: lichen oak moss
   - Main allergen: atranorin
   - Essential oil from lichens can contain the following other allergens: evernic acid and fumarprotocetaric acid
   - “Masculine” odor in aftershaves
7. Geraniol
   - *Sweet floral* odor of rose
   - Constitutes a large portion of rose and palmarose oil, geranium oil, lavender oil, jasmine oil, and citronella oil
   - Most widely used fragrance in perfumes, colognes, facial makeup, and skin-care products
8. Eugenol
   - Powerful spicy odor of clove with a pungent taste
   - Found in oils of clove and cinnamon leaf
   - Also found in roses, carnations, hyacinths, and violets
   - Fragrance in perfume, cosmetics; flavoring in toothpaste, mouthwash; and food flavorings, dental cement, insecticidal and fungicidal properties—used to preserve meats and other foods
9. Fragrance Mix I
   - Used as a screening tool for detecting fragrance allergy
## TABLE 6-1  Topical Photoallergens

<table>
<thead>
<tr>
<th>Group</th>
<th>INCI Name/Chemical Name/Trade Name*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunscreens</td>
<td><strong>UVB absorbers:</strong></td>
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<tr>
<td></td>
<td><em>para-Aminobenzoic acids (PABA):</em></td>
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<tr>
<td></td>
<td>Amyl dimethyl PABA (<em>Padimate A; Escalol 506)</em>†</td>
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<td></td>
<td>PABA (<em>Pabanol)</em>†</td>
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<tr>
<td></td>
<td>Ethylhexyl dimethyl PABA (octyl dimethyl PABA; <em>Padimate O; Escalol 507)</em>†</td>
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<td><strong>Cinnamates:</strong></td>
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<td></td>
<td>Cinoxate (2-ethoxyethyl-p-methoxycinnamate; <em>Phiasol</em>)</td>
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<td></td>
<td>Ethylhexyl methoxycinnamate (octyl methoxycinnamate; <em>Parsol MCX; Escalol 557</em>)</td>
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<td><strong>Salicylate:</strong></td>
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<td>Homosalate (metahomomenthyl salicylate; <em>Eusolex HMS</em>)</td>
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<td><strong>UVA absorbers:</strong></td>
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<td></td>
<td><strong>Anthranilate:</strong></td>
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<td>Menthyll anthranilate (cyclohexanol; <em>Trivent MA</em>)</td>
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<td></td>
<td><strong>Benzophenones (partial UVB absorption):</strong></td>
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<td></td>
<td>Benzophenone-3 (oxybenzone; <em>Escalol 567)</em>†</td>
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<td>Benzophenone-4 (sulisobenzone; <em>Escalol 577)</em>†</td>
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<td><strong>Dibenzoylmethane:</strong></td>
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<td>Butyl methoxydibenzoylmethane (avobenzone; <em>Parsol 1789)</em>†</td>
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<td>Fragrances</td>
<td>6-Methylcoumarin†</td>
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<td></td>
<td>Musk ambrette†</td>
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<td>Sandalwood oil</td>
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<td>Antibacterials</td>
<td>Dibromosalicylanilide (dibromsalan; DBS)†</td>
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<tr>
<td></td>
<td>Tetrochlorosalicylanilide (TCSA; <em>Impregon; Irgasan BS200)</em>†</td>
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<td>Tribromosalicylanilide (tribromsalan; TBS)*</td>
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<td>Chlorhexidene (<em>Hibiclens</em>)</td>
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<td>Dimethylol-dimethyl hydantoin</td>
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<td></td>
<td>Hexachlorophene (<em>pHisHex</em>)</td>
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<td></td>
<td>Bithionol (thiobisdichlorophenol; bisphenol; <em>Actamar)</em>†</td>
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<td>Dichlorophene (G4)</td>
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<td>Triclosan (<em>Irgasan DP300</em>)</td>
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<tr>
<td>Antifungals</td>
<td>Fentichlor (thiobischlorophenol)*</td>
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<tr>
<td></td>
<td>Jadit (butylchlorosalicylamide; buclozamide)</td>
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<td></td>
<td>Multifungin (bromochlorosalicylanilide; BCSA)</td>
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<tr>
<td>Others</td>
<td>Chlorpromazine (<em>Thorazine)</em></td>
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<td></td>
<td>Clioquinol</td>
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<tr>
<td></td>
<td>Ketoprofen (<em>Orudis</em>)</td>
</tr>
<tr>
<td></td>
<td>Olaquindox</td>
</tr>
<tr>
<td></td>
<td>Promethazine (<em>Phenergan)</em></td>
</tr>
<tr>
<td></td>
<td>Quinidine (<em>Cardioquin; Quinidex)</em></td>
</tr>
<tr>
<td></td>
<td>Thiourea (thiocarbamide)</td>
</tr>
</tbody>
</table>

*INCI: International Nomenclature of Cosmetic Ingredients.
†Commonly reported photoallergens.
### TABLE 6-2  Systemic Photoallergens

<table>
<thead>
<tr>
<th>Property</th>
<th>Generic Name (U.S. Trade Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal</td>
<td>Griseofulvin (Fulvicin-U/F)</td>
</tr>
<tr>
<td>Antimalarial</td>
<td>Quinine</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Quinolone: Enoxacin (Penetrex), sulfonamides</td>
</tr>
<tr>
<td>Cardiac medication</td>
<td>Quinidine (Quinaglute, Quinidex)</td>
</tr>
<tr>
<td>Nonsteroidal</td>
<td>Ketoprofen (Orudis, Oruvall)</td>
</tr>
<tr>
<td></td>
<td>Piroxicam (Feldene)</td>
</tr>
<tr>
<td>Vitamin</td>
<td>Pyridoxine hydrochloride (vitamin B6)</td>
</tr>
</tbody>
</table>


### TABLE 6-3  Topical Phototoxic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose bengal</td>
<td>Ophthalmologic examination</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Occur naturally in plants, fruits and vegetables (lime, lemon, celery, fig, parsley, and parsnip); used in perfumes and cosmetics; used for topical photochemotherapy</td>
</tr>
<tr>
<td>Tar</td>
<td>Topical therapeutic agent; roofing materials</td>
</tr>
</tbody>
</table>


- Constituents: α-amylcinnamic alcohol, cinnamic alcohol, cinnamic aldehyde, eugenol, geraniol, hydroxycitronellal, isoeugenol, oak moss absolute
- Along with balsam of Peru, Fragrance Mix I detects the majority of patients with a fragrance allergy

**HAIR-RELATED ALLERGENS**

1. Paraphenylenediamine (PPD)
   - Blue-black aniline dye
   - Dark permanent hair dye: hand dermatitis in hairdressers, scalp/hairline dermatitis in clients

2. Glycerol thioglycolate (GTG)
   - Acidic (salon) permanent wave solutions and hair straighteners
   - Chemical remains in hair shaft for months: chronic dermatitis in hairdressers and clients
   - Note: Alkaline (home) permanent solutions contain ammonium thioglycolate (ATG) and are also irritating

- Dyed furs, photographic developers, photocopy, printing ink, dark cosmetics, black rubber (rubber antioxidant), leather processing
- Cross-reacts with PABA, ester anesthetics, sulfamedications, azo dyes (textile dermatitis)
- Synthetic henna: formulations are available that contain PPD and sometimes lead to an allergic reaction (Type IV hypersensitivity)
- Natural henna is derived from the *Lawsonia alba* plant and does not usually lead to ACD
- Patch test with PPD
<table>
<thead>
<tr>
<th>Property</th>
<th>Generic Name (U.S. Trade Name)</th>
<th>Property</th>
<th>Generic Name (U.S. Trade Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antianxiety drugs</td>
<td>Alprazolam (<em>Xanax</em>)</td>
<td>Antipsychotic drugs</td>
<td>Prochlorperazine (<em>Compazine)</em></td>
</tr>
<tr>
<td></td>
<td>Chlordiazepoxide (<em>Librium; Limbitrol</em>)</td>
<td></td>
<td>Thioridazine (<em>Mellaril</em>)</td>
</tr>
<tr>
<td>Anticancer drugs</td>
<td>Dacarbazine (<em>DTIC-Dome</em>)</td>
<td></td>
<td>Trifluoperazine (<em>Stelazine</em>)</td>
</tr>
<tr>
<td></td>
<td>Fluorouracil (<em>Adrucil</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate (<em>Rheumatrex</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinblastine (<em>Velban</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Tricyclics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amitriptyline (<em>Elavil; Limbitrol; Triavil</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desipramine (<em>Norpramin</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipramine (<em>Tofranil</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungal</td>
<td>Griseofulvin (<em>Fulvicin; Grifulvin V; Gris-PEG</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Chloroquine (<em>Aralen</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Quinolones:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin (<em>Cipro</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enoxacin (<em>Penetrex</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gemifloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lomefloxacin (<em>Maxaquin</em>)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin (<em>Avelox</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nalidixic acid (<em>NegGram</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Norfloxacin (<em>Chibroxin; Noroxin</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ofloxacin (<em>Flinox; Ocufox</em>)</td>
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</tr>
<tr>
<td></td>
<td>Sparfloxacin (<em>Zagam</em>)</td>
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<tr>
<td></td>
<td>Sufoxamides</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetracyclines:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Demeclocycline (<em>Declomycin</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline (<em>Monodox; Periostat; Vibramycin</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minocycline (<em>Dynacin; Minocin</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetracycline (<em>Helidac; Sumycin</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trimethoprim (<em>Bactrim; Polymixin; Primsal; Septra</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>Phenothiazines:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine (<em>Thorazine</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perphenazine (<em>Triavil; Trilafon</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dye

Fluorescein (*AK-Fluor; Fluor; Fluor-I-Strip Fluorescite*)
Methylene blue (*Urised*)

Furocoumarins

Psoralens:
5-Methoxypsoralen*
8-Methoxypsoralen (Oxpsoralen-Ultra 4,5',8-Trimethoxypsoralen*)

Hypoglycemics

Sulfonylureas:
Acetohexamide
Chlorpropamide (*Diabinese*)
Glipizide (*Glucotrol*)
Glyburide (*DiaBeta; Glucovance*
Glyclamide *Pres Tab; Micronase*)
Tolazamide (*Tolinase*)
Tolbutamide (*Orinase*)*

NSAIDs

Acetic acid derivative:
Diclofenac (*Arthrotec; Cataplan Voltaren*)
Anthraniolic acid derivative:
Mefenamic acid (*Ponstel*)
Enolic acid derivative:
Piroxicam (*Feldene*)*

(Continued)
TABLE 6-4 (Continued)

<table>
<thead>
<tr>
<th>Property</th>
<th>Generic Name (U.S. Trade Name)</th>
<th>Property</th>
<th>Generic Name (U.S. Trade Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs (cont.)</strong></td>
<td>Propionic acid derivatives:</td>
<td>Photodynamic therapy agents</td>
<td>Porfimer (Photofrin)*</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen (Advil; Motrin;</td>
<td></td>
<td>Verteporfin (Visudyne)*</td>
</tr>
<tr>
<td></td>
<td>Nuprin Vicoprofen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketoprofen (Orudis; Oruvail)</td>
<td>Retinoids</td>
<td>Acitretin (Soriatane)</td>
</tr>
<tr>
<td></td>
<td>Naproxen (Aleve; Naprelan;</td>
<td></td>
<td>Isotretinoin (Accutane)</td>
</tr>
<tr>
<td></td>
<td>Naprosyn)*</td>
<td></td>
<td>Etretinate</td>
</tr>
<tr>
<td></td>
<td>Oxaprozin (Daypro)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tiaprofenic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salicyclic acid derivative:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dolobid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td>Celecoxib (Celebrex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nabumetone (Relafen)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEDICINE-RELATED ALLERGENS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Tixocortol pivalate</td>
<td>Used to test for allergy to</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>group A steroids (e.g.,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>prednisone, hydrocortisone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Short-chain esters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Budesonide</td>
<td>Screening agent for allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>to groups B (e.g., triamcinolone) and D2 (e.g., HC-17 butyrate) steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cross reactions may be seen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>between Groups A and D2, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>between Groups B and D2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long-chain steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Ethylenediamine dichloride</td>
<td>Stabilizer in topical creams,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>medicines, dyes, rubber, resin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>waxes, insecticides, asphalt,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fungicides</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previously found in nystatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cream</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cross-reacts with aminophylline,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>antihistamines (hydroxyzine),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>meclizine (antivert)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Glutaraldehyde (Fig. 6-1)</td>
<td>Cold sterilizing solution (medical/dental equipment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Embalming fluid, electron</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>microscopy, cosmetics, waterless hand cleansers, wallpaper, liquid fabric softener, leather tanning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Wool alcohols</td>
<td>Lanolin and lanolin alchol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>From the sebum of sheep</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lanolin consists of 95% wool esters: alcohols (52%) and acids (48%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Ammonia persulfate
   - Peroxide hair bleaches
   - Bleached baking flour
   - Contact urticaria and anaphylactoid reactions

4. Cocamidopropyl betaine
   - Allergen may be dimethylaminopropylamine or amidoamine (residues from synthesis)
   - Surfactant
   - Shampoo (dermatitis in hair dressers), liquid soaps

5. Wool alcohols
   - Lanolin and lanolin alchol
   - From the sebum of sheep
   - Lanolin consists of 95% wool esters: alcohols (52%) and acids (48%)

**FIGURE 6-1** Chronic fingertip dermatitis due to glutaraldehyde allergy in an assistant sterilizing colonoscopy equipment. (Courtesy of Dr. Giuseppe Militello.)
PLANT-RELATED ALLERGENS

1. Ethyl cyanoacrylate
   - Instant glue (“Super Glue”), artificial nail glue
   - Liquid bandages, sealant for ileostomy appliances
   - Electronic circuit boards, aircrafts, automobiles
2. Methyl methacrylate
   - Clear, rigid plastic (artificial nails, hard contact lenses, hearing aids, dentures, dental fillings/sealants)
   - Glue for surgical prostheses/artificial joints: dermatitis in orthopedic surgeons
   - Cross-reacts with ethyl methacrylate
3. Toluene-sulfonamide (tosylamide) formaldehyde resin
   - Used in nail polishes
   - Nail polish: eyelid, face, neck, finger dermatitis
   - Cross-reacts with balsam of Peru
   - Source of turpentine, oleoresin also contains irritants, such as alpha-pinene, and allergens, such as delta-3-carene

PLANT-RELATED ALLERGENS

1. Pinaceae
   - Pine trees (i.e., Pinus species) and spruce trees
   - Source of colophony (or wood rosin)
     - Main allergens of colophony are oxidation products of abietic acid and its isomer primaric acid
     - Found in medical adhesives, cosmetics, athletic grip aids, dental cement, violin bow rosin, newsprint/magazine paper, soldering materials, nail coating (construction workers)
   - Cross-reacts with balsam of Peru
   - Source of turpentine, oleoresin also contains irritants, such as alpha-pinene, and allergens, such as delta-3-carene

2. Alliaceae
   - Genus Allium
     - Includes onions, garlic, and chives
     - Allergens: diallyldisulfide, allylpropyl disulfide, and allicin
     - Fresh garlic is both an allergen and a potent irritant
     - Causes second- and third-degree burns when applied to injured skin
     - Most common cause of fingertip dermatitis in housewives and caterers

3. Lichens
   - Allergens: usnic acid, atranorin, evernic acid, fumarprotocetraric acid
   - Forest workers, gardeners, woodcutters
   - Lichen extracts (oak moss, tree moss): dermatitis from aftershave products

4. Primulaceae (Fig. 6-2)
   - Primula obconica: primrose
   - Allergen is primin
   - Highly allergenic petals and sepals
   - May cross-react with other quinones: orchids or tropical woods, such as teak, rosewood

NAIL-RELATED ALLERGENS

- Wool alcohols are used to test for lanolin allergy
- Topical creams (e.g., Eucerin), cosmetics, adhesives, topical steroids
- Propylene glycol
  - A dimer alcohol used to make drugs more soluble
  - Vehicle base in pharmaceuticals (Valium, ECG and lubricant jelly), cosmetics, food, and topical medications (corticosteroid creams, ointments, foams, gels, and solutions)
  - Brake fluid, tobacco formulations, antifreeze
- Mercury-containing organic compound (an organomercurial)
  - Made from the combination of ethyl mercuric chloride, thiosalicylic acid, sodium hydroxide, and ethanol
  - Preservative in vaccines: influenza (flu) vaccines and tetanus and diphtheria vaccines (Td and DT) are not available without thimerosal
  - Also found in antitoxins, immunoglobulins
  - False-positive intradermal testing (e.g., to tuberculosis) can occur if material is preserved with thimerosal
  - Eye/ear drops, nasal sprays, contact lens solutions: conjunctivitis, eyelid dermatitis
  - Cosmetics, liquid soap, oral hygiene products, pesticides
  - Cross-reacts with piroxicam, mercury
  - Most reactions seen with patch testing are not relevant and are indicative of prior exposure (e.g., vaccines)
- Neomycin sulfate
  - Antibiotic in the aminoglycoside group
  - Used topically in ointments, creams, ear drops, and eye drops
  - Cross-reacts with gentamycin, tobramycin, streptomycin, or any systemic aminoglycoside
  - Often cosensitivity to bacitracin
- Triclosan
  - Antibacterial agent
  - Soap, shampoo, mouthwash
- Benzocaine
  - Topical anesthetic (remedies for hemorrhoids, sunburn, toothaches, sore throats, athlete’s foot)
  - Cross-reacts with ester anesthetics, PABA, paraphenylenediamine, sulfa medications
  - Patch test with caine mix: benzocaine, dibucaine hydrochloride, and tetracaine hydrochloride
- Contact dermatitis to nail allergens may present as chronic paronychia, onychodystrophy, fingertip dermatitis, or face and neck dermatitis (ectopic dermatitis)
- Ethyl cyanoacrylate
  - Instant glue (“Super Glue”), artificial nail glue
  - Liquid bandages, sealant for ileostomy appliances
  - Electronic circuit boards, aircrafts, automobiles
5. Family Asteraceae (previously Compositae family) (Fig. 6-3)
   - Ragweed, chrysanthemum, feverfew and carrot weed, daisy, sunflower, dandelion, artichoke, lettuce, and endives
   - Gardeners, florists, farmers, cooks: airborne or summer-exacerbated dermatitis
   - Allergen: Sesquiterpene lactone (SQL)
     - Found in the leaves, stems, flowers, and some pollen
     - Cross-reactivity occurs randomly
     - SQL mix (i.e., alantolactone, dehydrocostus lactone, costunolide) is not very sensitive
     - Compositae mix (arnica, yarrow, tansy, German chamomile and feverfew) may be a more sensitive mix
   - Ragweeds (Ambrosia species)
     - Oleoresin is thought to cause airborne contact dermatitis
     - Typically occurs in atopic patients
   - Feverfew and carrot weed (Parthenium hysterophores)
   - Chrysanthemum (Dendranthema grandiflorum cv.): most common Asteraceae plants that cause occupational contact dermatitis
   - Sunflower (Helianthus annuus)
     - 1-0-methyl 1-4,5-dihydroneveisin A
     - Trichomes, or small hairs, on the surfaces of the leaf secrete the allergen
     - Windblown trichomes from dry plants can cause airborne contact dermatitis
   - Dandelion (Taraxacum officinale)
     - Airborne allergic contact dermatitis
     - Allergen is taraxinic acid (1-0-b-glucopyranoside)

6. Toxicodendron
   - Species (Rhus); family (Anacardiaceae)

   - Allergens are pentadecylcatechols, found in the plant sap
     - Urushiol (milky secretion)
     - Oleoresin (dry resin)
     - Cathecols are soluble in rubber
     - Particles suspended in smoke can carry urushiol
     - Blister fluid does not contain urushiol
     - Nonleaf portions of the plant can induce dermatitis
   - Most common cause of contact dermatitis in children
   - Poison ivy
     - T. radicans: climbing vine, eastern United States
     - T. rydbergii: nonclimbing dwarf shrub, the northwestern United States (Fig. 6-4)
   - Poison oak
     - T. diversilobum, western United States
     - T. toxicarium, eastern United States (Fig. 6-5)
   - Poison sumac: T. vernix
   - Identification
     - Poison ivy and poison oak: 3 to 5 leaflets per compound leaf
     - Poison sumac, 7 to 13 leaflets per leaf; have smooth edges
   - Cross-reacting substances
     - Cashew nut tree: entire tree except for the cashew nut
     - Indian marking tree: black juice (used as a laundry marker, causes Dhobi itch)
     - Japanese laquer tree: viscous sap that is used for varnishing wood; polymerized urushiol persists in the lacquer
     - Brazilian pepper tree: sap and crushed berries

FIGURE 6-2 Primulaceae. (Courtesy of Dr. Kiyoshi Isono.)

FIGURE 6-3 Family asteraceae.
PLANT-RELATED ALLERGENS

- Mango tree: skin of the fruit and the leaves, bark, and stems of the plant contain sensitizing resorcinols; pulp of the fruit is nonallergenic
- Ginkgo tree: anacardic acid, which is present in the seed pulp

7. Liliaceae
- Tulips, hyacinths, and asparagus
- Tulip fingers
- Combined allergic and irritant contact dermatitis
- Allergen: tuliposide A is converted to tulipalin A, the allergen, by means of acidic hydrolysis

8. Alstroemeriaceae family (Peruvian lily)
- Tuliposide A and B are found in virtually all portions of the plant
- Flowers contain more allergen than the stems; the leaves have the smallest amount of allergen
- Most common cause of allergic hand dermatitis in florists

9. Phytophotodermatitis
- Phytophotodermatitis results in hyperpigmentation (Fig. 6-6)
- Berloque dermatitis is due to bergamot oil; UV light reacts with bergapten (a furocoumarin) and induces melanogenesis
- Most common plant families Umbiliferae (most common), Rutaceae, and Moraceae
  - Umbiliferae: cow parsley, parsley, celery, carrot, fennel, cow parsnip, hogweed, parsnip
  - Rutaceae: lime, lemon, grapefruit, mokihana (Hawaiian leis), rue
  - Moraceae: fig
• Allergens can be found in perfumes and fragrances, cosmetics, toiletries, soap, household cleaners, detergents, air fresheners

10. Contact urticaria from plants
• Roasted chili peppers contain capsaicin
• Urticaceae family: stinging nettle (Urtica dioica)
• Irritant chemicals, which include acetylcholine, histamine, and 5-hydroxytryptamine

11. Chemical irritant dermatitis
• Most common dermatitis in florists
• Dieffenbachia picta (Araceae), also known as dumb cane: calcium oxalate
• Daffodil itch: calcium oxalate in the sap

Rubber Allergens

1. Latex
• Milky fluid derived from rubber tree Hevea brasiliensis
• Composed primarily of cis-1,4-polyisoprene
• Reaction can involve irritant dermatitis, immediate (type I) hypersensitivity; rarely may cause delayed (type IV) hypersensitivity
• Multiple episodes of contact urticaria with scratching can lead to clinical appearance of chronic dermatitis
• Gloves, condoms, balloons, rubber adhesives
• Corn starch powder—with which gloves are dusted—is a potent carrier of latex proteins
• Health care workers, rubber industry workers, children with spina bifida or urogenital abnormalities
• In vitro tests: radioimmunoassay tests (RAST) for IgE
• Cross-reaction
  − Food: bananas, avocados, chestnuts, kiwis
  − Shared IgE epitopes: ragweed, grasses, and Ficus trees

2. Rubber accelerators and other rubber related allergens
• Rubber accelerators are chemicals used to speed up the manufacturing process of rubber (vulcanization); sulfur cross-links the polymer chains in the latex
• Carbamates (carba mix)
  − Rubber accelerator
  − Rubber dermatitis in bleached fabrics (waistbands, bra straps)
• Consumer rubber products (condoms, swimwear, makeup sponges, eyelash curlers, gloves, shoes)
  − Cross-reacts with thiurams
• Mercaptobenzothiazole (MBT, mercapto mix)
  − Rubber accelerator
  − Most common cause of allergic shoe dermatitis (Fig. 6-7)

FIGURE 6-7 Typical distribution of an allergic shoe dermatitis. (Courtesy of Dr. Giuseppe Militello.)

  − Rubber products: gloves, makeup sponges, rubber in undergarments/clothing, swimwear
  − Also in tires, condoms, antifreeze, fungicides, flea and tick powders, photographic film emulsions, adhesives, bactericides, and is an anticorrosive agent in cutting oils and greases
• Thiuram mix
  − Most common rubber additives to cause a type IV reaction
  − Found in almost all rubber products, shoes, gloves, condoms, elastic bands, and ingredients of pesticides, insect repellents, antiscabies medication, fungicides, wood preservatives, paint additives, lubricating oils, and the drug disulfiram (Antabuse)
• Thiourea
  − commonly tested with a dialkyl thiourea mix
  − common source is neoprene rubber

Antioxidants

• Added to decrease the rate of rubber degradation
• Substituted phenols are used for latex gloves

PRESERVATIVES

1. Formaldehyde
• Released from the proallergen N-hydroxymethyl succinimide
• Cleaved into succinimide and formaldehyde when it comes in contact with the transepidermal water on the surface of the skin
2. Formaldehyde is the active allergenic compound
   - Textile resins
     - Permanent press or wrinkle-resistant textiles (urea-formaldehyde, melamine formaldehyde)
   - Cosmetics, household products, ink, latex paint, pathology fixatives, fertilizer, embalming solution, insulation
   - Formaldehyde resins
     - p-tert-butylphenol formaldehyde resin (common shoe allergen)
       ▲ Leather adhesive
       ▲ Other uses: waterproof glues and finishes
   - Formaldehyde-releasing preservatives
     - Quaternium-15 (most common): cosmetics, lotions, creams, shampoos and soaps, polishes, cleaners, cutting fluids, and paints
     - Imidazolidinyl urea (Germall 115, Euxyl K200)
     - Diazolidinyl urea (Germall II)
     - DMDM hydantoin
     - 2-Bromo-2-nitropane-1,3-diol (Bronopol)
3. Non-formaldehyde-releasing preservatives
   - Methyl dibromo glutaronitrile (MDBGN)
   - Parabens
     - Most used topical preservatives worldwide
     - Paraben Paradox: some sensitized patients only react to parabens when applied to dermatitic skin (e.g., leg ulcer patients)
     - Medical creams, lotions, pastes, and several cosmetics and skin care products; food preservatives; industrially in oils, fats, and glues
   - Isothiazolinones
     - Kathon CG: combination of methylchloroisothiazolinone and methylisothiazolinone
     - Cosmetics and commercial household products such as shampoos, creams, lotions, cleaners, and washing materials; it is also a widely used industrial preservative for cutting fluids

COLORS AND DYE ALLERGENS

Tattoos
- Ink particles are found within large phagosomes in the cytoplasm of both keratinocytes and phagocytic cells
- Allergic reactions to red tattoo pigments are the most common (Table 6-5)
- Photoaggravated reactions: most commonly yellow dye
- Foreign-body reaction: most commonly red (mercury)
- Tattoo-induced pseudolymphoma: most commonly red

Dyes
- Disperse Blue 106 and 124 are the most common dye allergens in textile dermatitis

METAL ALLERGENS

1. Nickel
   - Most common cause of patch test reactions
   - Jewelry, clothing (snaps, zippers, and buttons), coins, keys, other metals; gold less than 18 carats can contain nickel
   - Also used for nickel plating, to color ceramics, to make some batteries
   - Foods naturally high in nickel include chocolate, soybeans, nuts, and oatmeal
   - Dimethylglyoxime test is used to detect nickel
     - Rub on the item; if solution turns color (pink to reddish), it indicates a positive reaction
     - Indicates the presence of nickel in a concentration of at least 1:10,000

2. Potassium dichromate
   - Chromates (chrome)
   - Usually found as chrome salts
   - Cement, leather tannin, ceramics, paint, match heads, suture, bleach/detergents, numerous industrial chemicals, green felt of card tables, glues
   - Green tattoo and cosmetic pigments
   - Green textile dyes (military green, green pool table felt)

ADHESIVES

Epoxy Resin
- Two-component adhesives
- Most common allergens: bisphenol A and epichlorohydrin
- Glue, laminates, eyeglass frames, vinyl gloves, handbags, plastic necklaces, dental bonding agents, microscopy immersion oil, floor coverings

OTHER ALLERGENS

Sodium Hypochlorite
- Chlorinated swimming pools
- Bleach
TABLE 6-5  Tattoo Components

<table>
<thead>
<tr>
<th>Tattoo Color</th>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue</td>
<td>Cobalt aluminate</td>
</tr>
<tr>
<td>Brown</td>
<td>Ferric oxide</td>
</tr>
<tr>
<td>Green</td>
<td>Chromic oxide, lead chromate, phthalocyanine dyes</td>
</tr>
<tr>
<td>Red</td>
<td>Cinnabar (mercuric sulfide), sienna (ferric hydrate), sandalwood, brazilwood, organic pigments (aromatic azo compounds)</td>
</tr>
<tr>
<td>Yellow</td>
<td>Cadmium sulfide</td>
</tr>
<tr>
<td>Black</td>
<td>Carbon (India ink), iron oxide, logwood</td>
</tr>
<tr>
<td>Purple</td>
<td>Manganese, aluminum</td>
</tr>
<tr>
<td>White</td>
<td>Titanium oxide, zinc oxide</td>
</tr>
</tbody>
</table>

PATCH TESTING

- T.R.U.E. Test (allergen patch test) (Table 6-6)
  - Ready-to-use contact allergen test
  - Contains 28 allergens and allergen mixes
  - Test also contains one negative control: uncoated polyester patch
  - Allergen mixes incorporated into hydrophilic gels attached to a waterproof backing

- Perspiration and transepidermal water loss rehydrate the dried gel layer, thereby releasing the allergens onto the skin
- T.R.U.E. Test is removed after 48 hours
- Reactions are interpreted at 72 to 96 hours after test application
  - Fragrance mix
  - Contains eight allergens
  - Geraniol, cinnamaldehyde, hydroxycitronellal

TABLE 6-6  True Test Panels

<table>
<thead>
<tr>
<th>Panel 1.1</th>
<th>Panel 2.1</th>
<th>Panel 3.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Caine mix</td>
<td>17. Cl + Me-isothiazolinone</td>
<td>29. Quinoline mix</td>
</tr>
<tr>
<td>6. Fragrance mix</td>
<td>18. Quaternium-15</td>
<td></td>
</tr>
<tr>
<td>7. Colophony</td>
<td>19. Mercaptobenzothiazole</td>
<td></td>
</tr>
<tr>
<td>8. Paraben mix</td>
<td>20. p-Phenylenediamine</td>
<td></td>
</tr>
<tr>
<td>10. Balsam of Peru</td>
<td>22. Mercapto mix</td>
<td></td>
</tr>
<tr>
<td>11. Ethylenediamine dihydrochloride</td>
<td>23. Thimerosal</td>
<td></td>
</tr>
<tr>
<td>12. Cobalt dichloride</td>
<td>24. Thiuram mix</td>
<td></td>
</tr>
</tbody>
</table>
cinnamyl alcohol, eugenol, isoeugenol, \( \alpha \)-amylcinnamaldehyde, and oak moss

- Mercapto mix
  - Composed of three chemical accelerators: benzothiazole sulfenamide derivatives
  - \( N \)-Cyclohexylbenzothiazyl-sulfenamide, dibenzothiazyl disulfide, and morpholinylmercaptobenzothiazole

- Thiuram mix
  - Composed of four substances in equal parts
  - Tetramethylthiuram monosulfide, tetramethylthiuram disulfide, disulfiram, dipentamethylenethiuram disulfide
  - Black rubber mix: \( N \)-Isopropyl-\( N' \)-phenylparaphenylenediamine, \( N \)-cyclohexyl-\( N' \)-phenyl paraphenylenediamine, \( N \), \( N' \)-diphenyl paraphenylenediamine

- Carba mix
  - Chemicals used to stabilize rubber products
  - Diphenylguanidine, zincedibutylthiuricarbamate, and zincediethylthiuricarbamate in equal parts

- Repeat open application test (ROAT)
  - For individuals who develop weak or 1+ positive reactions to a chemical in the T.R.U.E Test
  - Useful in determining whether the reaction is significant or in personal product testing (only leave-on products should be tested)
  - Consists of rubbing in the product twice daily for several days to the skin of the antecubital fossa
  - A reaction often consists of erythematous papules
  - Samples of the individual ingredients used by the cosmetic manufacturer may be requested and tested on the individual

- Finn chamber system
  - Allows for customized patch testing and flexibility
  - Employs a multiwell aluminum patch (Fig. 6-8)
  - Most common size is 8-mm chamber applied to Scanpor tape in two rows of five
  - Each well is filled with a small amount of the allergen being tested, and the patch is taped to normal skin on the patient’s upper back
  - After 48 hours, the patch is removed, and an initial reading is taken
  - Second reading is made a few days later; each 8-mm chamber holds 20 \( \mu L \)

**FIGURE 6-8** Finn chamber system for patch testing. (Courtesy of Dr. Giuseppe Militello.)

1. Which of the following formaldehyde related allergens is associated with textile dermatitis?
   - A. Diazolidinyl urea
   - B. DMDM hydantoin
   - C. Imidazolidinyl urea
   - D. Quaternium 15
   - E. Melamine formaldehyde

2. Ethylcyanoacrylate is used in which of the following cosmetic nail products?
   - A. Acrylic nails
   - B. Nail enamel
   - C. Pre-formed plastic tips
   - D. Silk wraps
   - E. C and D

3. Which of the following is the most common photoallergen?
   - A. Padimate A
   - B. Padimate O
   - C. Benzophenone 3 (oxybenzone)
   - D. PABA
   - E. Menthyl anthranilate

4. Which of the following is a screening agent for triamcinolone allergy?
   - A. Tixocortol pivalate
   - B. Budesonide
   - C. Clobetasol
   - D. Hydrocortisone butyrate
   - E. Desoximethasone

**Questions**

1. Which of the following formaldehyde related allergens is associated with textile dermatitis?
5. Diallyl disulfide is the allergen found in which plant?
   A. Garlic
   B. Lichen
   C. Ragweed
   D. Feverfew
   E. Daisy

6. Which of the following is used to screen for epoxy allergy?
   A. Ethyl acrylate
   B. Glycerol thioglycolate
   C. Dimethylaminopropylamine
   D. Diglycidyl ether of bisphenol A
   E. Polyurethane

7. Patients sensitized to urushiol can react to which of the following plants?
   A. Cashew
   B. Indian marking nut
   C. Japanese lacquer tree
   D. Mango
   E. All of the above

8. Which of the following metals is most commonly implicated in tattoo reactions?
   A. Chromic oxide
   B. Cobalt aluminate
   C. Cinnabar (mercuric sulfide)
   D. Ferric oxide
   E. Cadmium sulfide

9. Which of the following professions is at a higher risk for allergic contact dermatitis to glutaraldehyde?
   A. Florist
   B. Chef
   C. Car mechanic
   D. Dental assistant
   E. Hairdresser

10. Which of the following statements about thimerosal is true?
    A. The majority of reactions are relevant to a patient’s dermatitis.
    B. It is a preservative in certain vaccines.
    C. It is an arsenical compound.
    D. It is not on the T.R.U.E. Test.
    E. None of the above

**Answers**

1. E. Formaldehyde and its releasers are common preservatives in cosmetic products and topical medicaments. Diazolidinyl urea, imidazolidinyl urea, quaternium 15, and DMDM hydantoin are formaldehyde releasers used in such products. Melamine formaldehyde is one of several formaldehyde releasers used as a finishing resin in permanent press or “wrinkle-free” clothing. Patients may react to the resin or the formaldehyde itself. Other resins include urea formaldehyde and cyclized urea derivatives. Another group of allergens involved in textile dermatitis are the disperse dyes, of which the Disperse Blue dyes 106 and 124 are the most common allergens.

2. E. Ethylcyanoacrylate is used to adhere plastic nail tips and silk wraps to the nail plate. It is a rare allergen in nail cosmetics and does not cross react with other acrylic compounds which are used in nail products. Ethyl acrylate and methylmethacrylate are used to screen for acrylic nail allergy. The major allergen in nail enamel is toluene sulfonamide formaldehyde resin, also known as tosylamide formaldehyde resin.

3. C. Benzophenone 3 (oxybenzone) is a widely used sunscreen agent, and as a result has become the most common sunscreen chemical to cause allergy and photo-allergy. PABA and its derivatives used to be the most common allergens but after they were reported to be allergens, they were largely removed from products and subsequent sunscreens were marketed as “PABA free.” Padimate A and O are PABA derivatives. Menthyl anthranilate is a UVA absorber and a rare allergen.

4. B. Corticosteroids are organized into five groups according to chemical structure. Group A consists of hydrocortisone, hydrocortisone acetate, prednisone, and methylprednisolone. Tixocortol pivalate is the screening agent for group A allergy. Group B involves triamcinolone, fluocinolone acetonide, desonide, and budesonide. Screening agent for this group is budesonide. Group C steroids include desoximethasone and cloclortolone pivalate; this is the least allergenic class. Group D is subcategorized into D1 and D2 classes. Clobetasol is in group D1, while hydrocortisone butyrate and valerate are found in group D2. Group D2 may cross react with group A and budesonide.

5. A. Diallyl disulfide is the allergen found in garlic and is a common cause of fingertip dermatitis in chefs and food handlers. Usnic acid is the allergen found in lichens and commonly affects forest workers and woodcutters. Ragweed, feverfew, and daisies belong to the *Asteracea* family of plants. The main allergens in this family are the sequiterpene lactones.

6. D. Epoxy resin systems are used to manufacture plastics and adhesives. The basic building block or monomer of epoxy resin is diglycidyl ether of...
bisphenol A which is formed by combining bisphenol A and epichlorhydrin. Monomers are then polymerized with the help of curing agents or hardeners into polymerized plastics. Epoxy plastics that are fully polymerized are not allergenic. Reactions are usually occupational or to products that are contaminated with uncured monomer. Ethyl acrylate is a screening agent for acrylic plastics or polymers. Contact dermatitis is frequently encountered in nail cosmetics, Dimethylaminopropylamine is a byproduct in the manufacture of cocamidopropylbetaine, a surfactant in shampoos. Glyceryl thioglycolate is used in the acidic permanent wave solutions and can remain allergenic in the hair shaft for months. Polyurethane is a plastic manufactured by the polymerization of isocyanates.

7. E. The allergen in poison ivy, sumac, and oak is urushiol. These plants belong to the Anacardiaceae family. Patients may react to chemical derivatives of urushiol found in other plants in the same family. Cashew, Indian marking nut, Japanese lacquer, and mango all belong to the Anacardiaceae family.

8. C. Most allergic reactions in tattoos are to the red pigment. Cinnabar or mercuric sulfide is a common metal in red tattoos. Chromic oxide, cobalt aluminate, ferric oxide, and cadmium sulfide are found in green, blue, brown, and yellow tattoos, respectively.

9. D. Glutaraldehyde is used in cold sterilizing solutions. Allergic reactions are commonly seen in workers involved in cleaning medical equipment such as dental assistants.

10. B. Thimerosal is an organic compound commonly found in vaccines. It was also used as a preservative in ophthalmic solutions but has been removed from most consumer products. The majority of thimerosal patch test reactions are not relevant to a patient’s dermatitis, but rather an indication of past sensitization, most likely from childhood vaccinations. Thimerosal is one of the allergens found on the T.R.U.E. Test (Allerderm).

REFERENCES

Chan EF, Mowad C: Contact dermatitis to foods and spices. *Am J Contact Dermat* 1998;9(2):71–79.
**TERMINOLOGY**

### Indirect Immunofluorescence
- **Goal:** to detect circulating autoantibodies in the serum that are purposefully reacted with a test substrate
- **Use of serum containing an antibody of interest is directed against a substrate,** such as monkey esophagus or rat bladder, which is then followed “indirectly” by the addition of fluorescein-conjugated human anti-immunoglobulin to label the resultant complex

### Direct Immunofluorescence
- **Goal:** to detect antibody and immunoreactants already deposited in tissue of interest
- **Use of fluorescein-conjugated antibodies directed against complement fractions and immunoglobulins (IgG, IgM, and IgA) that are placed “directly” on sections of tissue

### Direct Immunofluorescence (DIF) on Salt-Split Skin
- **Incubate the patient’s skin biopsy sample in 1 mol/liter saline to induce a split through the lamina lucida prior to performing the DIF testing**
- **Allows for differentiation of immunobullous diseases by indicating the location of deposition of immunoreactants in the split skin (i.e., above or below the lamina lucida)**
  - Immunoreactants deposit in the “roof” (above the split) in bullous pemphigoid
  - Immunoreactants deposit in the “floor” (below the split) in
    - Bullous systemic lupus erythematosus (SLE)
    - Antiepiligrin cicatricial pemphigoid (autoantibodies to laminin-5 and laminin-6)
    - Anti-p105 pemphigoid (autoantibodies to a 105-kDa lower lamina lucida protein)
    - Epidermolysis bullosa acquisita (EBA)

### Nikolsky’s Sign
- **Lateral pressure applied to edge of bulla**
- **Positive test if bulla extends laterally with pressure**
- **Suggests extreme pidermal fragility**
- **Common causes of a positive Nikolsky sign include:**
  - Staphylococcal scalded skin syndrome (Ritter disease)
  - Toxic epidermal necrolysis
  - Pemphigus vulgaris

### AUTOIMMUNE BULLOUS DISEASES

#### Bullous Pemphigoid (Fig. 7-1)
- **Autoimmune, subepidermal, blistering skin disease**
- **The single most common immunobullous disease in dermatology**
- **Clinical**
  - Usually an older patient ( > 60 years), often with other co-morbidities
  - Does not normally begin in the mucosa (unlike pemphigus)
  - May begin as an urticarial eruption, often intensely pruritic
  - Tense blisters and bullae
  - Common locations include the abdomen, flexor forearms, and inner thighs
Chapter 7    AUTOIMMUNE BULLOUS DISEASES

Nikolksky’s sign is negative
Rarely involves mucous membranes: 10% to 35%
Drugs associated with bullous pemphigoid include: furosemide, ibuprofen and other nonsteroidal anti-inflammatory agents, captopril, penicillamine, and antibiotics

- Diagnosis
  - Histology: subepidermal blistering process, usually with prominent eosinophils in the blister cavity and superficial dermis
- Antigens
  - Bullous pemphigoid antigen 1 (BPAgI)
    ▲ 230 kDa
    ▲ Intracellular portion of hemidesmosome plaque, part of the plakin superfamily
  - Bullous pemphigoid antigen 2 (BPAgII)
    ▲ 180 kDa, type XVII collagen
    ▲ Transmembranous protein with a collagenous extracellular domain
- Direct immunofluorescence (DIF) (Fig. 7-2)
  - Optimal location for DIF testing is normal-appearing perilesional skin
  - False-negative results can be observed when it is performed on lesional skin
  - Linear band of C3 (90% to 100% of patients) and IgG (70% to 90% of patients) at basement membrane zone (BMZ)
  - DIF on salt-split skin reveals IgG deposition on the blister roof
- Indirect immunofluorescence (IIF)
  - Circulating IgG to BMZ in 70% to 80% of patients
  - Serum levels of autoantibodies against BPAbII (BP180) correlate with disease activity

Prognosis
Generally, a self-limited disease with good prognosis

- Fifty percent enter remission within 2 to 6 years
- Therapy: topical steroids or oral prednisone alone or in combination with tetracycline and nicotinamide, azathioprine, cyclophosphamide, dapsone, methotrexate, plasmapheresis, and intravenous immunoglobulin (IVIG)

Cicatricial Pemphigoid (Fig. 7-3)
- Clinical
  - Erosive lesions of the skin and mucous membranes
  - Skin involvement occurs in one-third of patients
    - Usually on scalp, face, and upper trunk
    - Heals with scars
  - Bullae are tense and located on an erythematous or urticarial base
  - Bullae often occur in the same places even after temporary resolution
  - Mucosal involvement
    - Oral mainly; may present with hoarseness or dysphagia
    - Can include the nasopharynx, larynx, esophagus, genitalia, and rectal mucosa
    - May lead to esophageal stenosis requiring dilatation procedures
  - Ocular lesions
    ▲ Characterized by chronic conjunctivitis progressing to keratinization of the corneal epithelium
    ▲ Progressive corneal injury secondary to trichiasis (ingrown eyelashes)
    ▲ Decreased vision, photosensitivity, and scarring (symblepharon) that eventually can cause blindness
- Brunsting-Perry variant (Fig. 7-4)
  - Variant of cicatricial pemphigoid without mucosal involvement
Sometimes CP can be a paraneoplastic condition.

**Therapy**
- Topical glucocorticoids
- Oral prednisone alone or in combination with tetracycline, azathioprine, cyclophosphamide, dapsone, methotrexate, plasmapheresis, and IVIG

**Bullous Lupus Erythematosus**

- **Clinical**
  - Blistering in the setting of the autoimmune disease systemic lupus erythematosus (SLE)
  - May coincide with the activity of the patient’s preexisting SLE or may be the initial presenting cutaneous eruption of SLE
  - Patients may exhibit any of the symptoms associated with SLE
  - Extensive vesiculobullous eruption develops suddenly
    - Arises either on erythematous areas or on clinically normal skin
    - Bullae are tense and range from herpetiform vesicles to large hemorrhagic bullae
    - Not associated with skin fragility or healing of lesions with scars and milia
    - Tends to favor the upper part of the trunk and the proximal upper extremities
- **Antigens:** noncollagenous domain of type VII collagen (similar to patients with epidermolysis bullosa acquisita)

**Histology**
- Subepidermal separation
- Neutrophil-predominant inflammatory infiltrate in the upper dermis

**Diagnosis**
- **Histology**
  - Blisters are subepidermal with a mixed inflammatory cell infiltrate
  - Often lesions demonstrate underlying dermal fibrosis (scar)
- **Antigens**
  - Bullous pemphigoid antigen 2 (BPAG2)
  - Bullous pemphigoid antigen 1 (BPAG1)
  - B4 integrin—pure ocular form
  - Epiligrin (laminin-5) or the EBA antigen (type VII collagen)
- **Direct immunofluorescence (DIF)**
  - Biopsy unaffected and perilesional skin
    - Reveals linear deposition of C3 and IgG continuously along the basement membrane
  - IgA and IgM also may be detected
- **Indirect immunofluorescence (IIF)**
  - Assay reveals circulating IgG in 20% of patients, typically at low titer
  - Antiepiligrin cicatricial pemphigoid circulating autoantibodies bind to the floor of salt-split skin
  - Patients with cicatricial pemphigoid associated with reactivity to BPAG2 binding to the epidermal roof

**Course**
- Chronic progressive
- Waxing and waning disease activity
Chapter 7    AUTOIMMUNE BULLOUS DISEASES

- Perivascular lymphocytic or mixed infiltrate
- Thickened and hyalinized BMZ
- Vacuolar degeneration of basal keratinocytes

**Direct immunofluorescence (DIF)**
- Perilesional skin
- Deposition of IgG/C3 in a linear, but also a course and granular pattern along BMZ, often with similar deposition of IgM, IgA, and C1q (a positive “lupus band”)
- Salt-split skin: deposition of immunoreactants on the floor of the blister cavity

**Indirect immunofluorescence (IIF):** subdivided immunohistologically into type 1 and type 2 depending on the presence or absence, respectively, of identifiable circulating and/or tissue-bound antibodies to type VII collagen

**Course:** bullous SLE often remits spontaneously, sometimes in less than 1 year

**Therapy**
- Dapsone
- Systemic steroids
- Hydroxychloroquine
- Azathioprine
- Methotrexate
- Cyclophosphamide

**Herpes Gestationis (Pemphigoid Gestationis) (Fig. 7-5)**

**Clinical**
- Rare autoimmune dermatosis of pregnancy (1 in 50,000–60,000 pregnancies in the United States)
- No relationship to the herpesvirus infection

**Diagnosis**
- **Histology**
  - Subepidermal blister with an eosinophil-pre-dominant infiltrate
  - Keratinocyte necrosis and dermal edema
  - Antigens
  - Extracellular domain of BP antigen II—180 kDa
    ▲ Type XVII collagen
    ▲ Transmembrane protein
- Complement fixation assay: serum demonstrated herpes gestationis factor (“HG factor”), a heat-stable form of IgG that binds normal human complement to the BMZ of healthy human skin in a complement fixation assay
- **Direct immunofluorescence (DIF)**
  - Normal skin and perilesional skin
  - Linear band of almost exclusively C3 deposited along the BMZ
- **Indirect immunofluorescence (IIF):** specific for IgG in 20% of patients

**Course**
- Maternal mortality rate is unaffected
- Regresses without scarring within days after delivery
- May recur in subsequent pregnancies and may be precipitated by menses and the use of oral contraceptives

**Therapy**
- Goal is to control pruritus and suppress extensive blistering
- Topical steroids and oral prednisone
Desmoglein 1: seen in patients with cutaneous and mucosal disease

Histology
- Biopsy the margin of a bulla
- Suprabasilar blister with acantholysis, leads to “tombstone” appearance of residual keratinocytes lining BMZ

Direct immunofluorescence (DIF) (Fig. 7-8)
- Intercellular deposition of IgG and C3 in a net-like pattern throughout the epidermis of perilesional skin

Indirect immunofluorescence (IIF)
- Monkey esophagus and guinea pig esophagus can be used
- Circulating IgG to keratinocyte cell surfaces in greater than 75% of patients with active disease
- Titers correlate with disease activity

Course: common cause of death is infection secondary to the immunosuppression required to treat the disease

Therapy
- Corticosteroids are the mainstay of treatment; prednisone (1 mg/kg per day), with or without other immunosuppressive agents

**Pemphigus Vulgaris (Fig. 7-6)**

- Clinical
  - Bullous disease involving the skin and mucous membranes
  - Fatal if not treated appropriately
  - Flaccid blisters rapidly progressing to erosions
  - Nikolsky’s sign present
  - Lesions usually begin in the oral mucosa, followed by the appearance of skin lesions months later
  - Primary skin lesion is a flaccid blister that ruptures easily
  - Drug-induced pemphigus foliaceus associated with penicillamine, nifedipine, or captopril or other medications with a cysteine-like chemical structure
  - Vegetating pemphigus vulgaris is called pemphigus vegetans (Fig. 7-7)
    - Erosions caused by pemphigus vulgaris may develop excessive granulation tissue and crusting
    - Lesions in skin folds readily form vegetating granulations
    - Can be more resistant to therapy

- Antigens
  - Desmoglein 3
    - 130-kDa glycoprotein (member of cadherin supergene family)
    - Desmosomal core protein
  - Less commonly
    - Plakoglobin: 85-kDa plaque protein found in desmosomes

**Pemphigus vegetans. (Courtesy of Dr. Robert Jordon.)**
Unidentified 170-kDa protein
Desmoglein I and desmoglein III antigens
Direct immunofluorescence (DIF) (Fig. 7-9): IgG and C3 deposits within the intercellular spaces and along the BMZ
Indirect immunofluorescence (IIF)
Positive IIF testing with rat bladder (transitional epithelium) distinguishes paraneoplastic pemphigoid from pemphigus vulgaris and pemphigus foliaceus
IgG autoantibodies are directed against abovementioned antigens

Course
Mortality rate is estimated at 75% to 80%
Both the presence of an underlying neoplasm and the adverse effects of the potent medications required to treat the disease add to both the morbidity and the mortality
Treatment: prednisone, azathioprine, cyclosporine, cyclophosphamide, rituximab (anti-CD20 antibody), IVIG

Paraneoplastic Pemphigus

Clinical
Tumor antigens are hypothesized to evoke an immune response that leads to the development of oral erosions or ulcerations
Most often related to a leukemia or non-Hodgkin lymphoma (NHL)
Other associated neoplasms: (malignant and benign): Waldenström’s macroglobulinemia, sarcomas, thymomas, and Castleman’s disease
Cutaneous lesions: highly variable
 – Diffuse erythema, vesiculobullous lesions, papules, scaly plaques, exfoliative erythroderma, erosions, or ulcerations
 – 100% have mucosal involvement (most often severe lingual ulceration)

Histology
Biopsy from noninvolved, perilesional skin
Suprabasilar acantholysis with an underlying lichenoid infiltrate, basal cell vacuolation, lymphocytic exocytosis, and dyskeratotic keratinocytes with satellitosis

Antigens
Desmoplakin I (250 kDa)
BPAG I (230 kDa)
Desmoplakin II (210 kDa)
Envolakin (210 kDa)
Periplakin (190 kDa)
HD1/plectin (500 kDa)

Paraneoplastic Pemphigus

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Tumor antigens are hypothesized to evoke an immune response that leads to the development of oral erosions or ulcerations
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Antigens
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BPAG I (230 kDa)
Desmoplakin II (210 kDa)
Envolakin (210 kDa)
Periplakin (190 kDa)
HD1/plectin (500 kDa)
Intraepidermal acantholysis and vesiculation occurring just below stratum corneum and within the granular layer.

Full thickness acantholysis may be present in the epidermis.

Dermal lymphocytic infiltrate occurs, often with the presence of eosinophils.

Direct immunofluorescence (DIF)
- Typically cannot distinguish with certainty from pemphigus vulgaris, although in pemphigus foliaceus the deposition of immunoreactants tends to be accentuated in the upper epidermis.
- Intercellular IgG and C3 in a net-like pattern.

Indirect immunofluorescence (IIF): guinea pig esophagus.

Therapy
- Topical glucocorticosteroids
- Immunosuppressants, including systemic corticosteroids, cyclophosphamide, and cyclosporine; plasmapheresis in patients with recalcitrant disease.

**Dermatitis Herpetiformis (Fig. 7-11)**
- Associated with HLA B8-DR3-DQ2.
- Clinical.
Chapter 7    AUTOIMMUNE BULLOUS DISEASES

Linear IgA Dermatoses/Chronic Bullous Disease of Childhood (Fig. 7-13)

- Clinical
  - Linear IgA dermatosis
    - Most commonly presents in patients older than 30 years of age
    - Annular or grouped papules, vesicles, and/or bullae symmetrically distributed on extensor surfaces: “cluster of jewels”
  - Most commonly involves perioral/perineal areas
  - Lesions may be clinically indistinguishable from dermatitis herpetiformis
  - Seventy percent have oral involvement
- Course
  - Disease persists indefinitely
  - Waxes and wanes without treatment
- Therapy
  - Dapsone or sulfapyridine (does not treat the gastrointestinal symptoms)
  - Gluten-free diet: protein present in barley, rye, and wheat but not in rice
  - Avoid iodine and NSAIDs
  - Several studies have shown an increased incidence of GI lymphoma in dermatitis herpetiformis (similar to that of celiac disease) that is mitigated by a gluten-free diet but not from medical management

- Intensely pruritic, chronic skin disease
- Onset tends to be between 20 and 40 years of age but may occur at any age, including childhood
- Intensely pruritic, chronic, grouped papules/vesicles giving a “herpetiform” appearance
- Symmetrically distributed on extensor surfaces, as well as buttocks, posterior hairline and nuchal areas
- Oral lesions rare
- Eruption commonly preceded by burning or itching
- Associated with a gluten (wheat, barley, rye ± oats)–sensitive enteropathy
- Can lead to steatorrhea, abnormal D-xylene absorption, and anemia
- NSAIDs and iodine can induce eruptions
- Patients with increased incidence of other autoimmune disorders: thyroid disease, type 1 diabetes mellitus, systemic lupus erythematosus, vitiligo, and Sjögren’s syndrome

- Antigens
  - IgA antibodies to gliadin (a portion of wheat protein), reticulum, and smooth muscle endomysium
  - IgA antiendomysial antibodies (tissue transglutaminase antibodies) that bind to intermyofibril substance in smooth muscle cells correlate with severity of intestinal disease and adherence to gluten-free diet
  - IgA endomysial antibodies are most specific for gluten sensitivity
  - Found in patients with dermatitis herpetiformis and those with isolated gluten sensitive enteropathy

- Histology
  - Subepidermal blister at level of lamina lucida
  - Neutrophilic microabscesses within dermal papillae, sometimes with fibrin deposition
- Direct immunofluorescence (DIF) (Fig. 7-12)
  - Granular IgA1 deposits in dermal papillae of lesional and non-lesional skin
  - Deposition of immunoreactants disappears with adherence to a gluten-free diet, but does not disappear with dapsone

- FIGURE 7-12 Dermatitis herpetiformis immunofluorescence. (Courtesy of Dr. Robert Jordan.)

- Intensely pruritic, chronic, grouped papules/vesicles giving a “herpetiform” appearance
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  - Deposition of immunoreactants disappears with adherence to a gluten-free diet, but does not disappear with dapsone

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- Therapy
  - Dapsone or sulfapyridine (does not treat the gastrointestinal symptoms)
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  - Avoid iodine and NSAIDs
  - Several studies have shown an increased incidence of GI lymphoma in dermatitis herpetiformis (similar to that of celiac disease) that is mitigated by a gluten-free diet but not from medical management

- Drug associations: vancomycin, lithium, diclofenac
Antigens
- 97-kDa extracellular portion of BP antigen II
- 120-kDa antigen also described
- 97- and 120-kDa antigens may represent cleaved fragments of BPAGII

Histology
- Subepidermal vesiculation
- Collections of neutrophils along the basement membrane

Direct immunofluorescence (Fig. 7-14): IgA in a linear pattern is noted along the basement membrane (occasionally IgG and C3)

Course
- Variable and unpredictable
- Disease may remit spontaneously in some cases
- May last for years with few episodes of remission in chronic bullous disease of childhood
- Resolution occurring within 2 years of onset in most cases
- Treatment: dapsone or sulfapyridine

**Epidermolysis Bullosa Acquisita (EBA)**

- Clinical
  - Chronic autoimmune subepidermal blistering disease
  - Primarily involves the skin, but it also can affect mucous membranes

**Inherited Epidermolysis Bullosa**

- See Tables 7-1 to 7-3
### TABLE 7-1  Revised Classification of Inherited Epidermolysis Bullosa, Based on Clinical Phenotype and Genotype, for the Most Commonly Observed and Well-Characterized Variants or Subtypes of This Disease

<table>
<thead>
<tr>
<th>Major EB Type</th>
<th>Major EB Subtype</th>
<th>Protein/Gene Systems Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBS (“epidermolytic EB”)</td>
<td>EBS-WC</td>
<td>K5, K14</td>
</tr>
<tr>
<td>EBS-K</td>
<td></td>
<td>K5, K14</td>
</tr>
<tr>
<td>EBS-DM</td>
<td></td>
<td>K5, K14</td>
</tr>
<tr>
<td>EBS-MD</td>
<td></td>
<td>Plectin</td>
</tr>
<tr>
<td>JEB</td>
<td>JEB-H</td>
<td>Laminin-5*</td>
</tr>
<tr>
<td>JEB-nH</td>
<td></td>
<td>Laminin-5; type XVII collagen</td>
</tr>
<tr>
<td>JEB-PA†</td>
<td></td>
<td>α6β4 Integrin‡</td>
</tr>
<tr>
<td>DEB (“dermolytic EB”)</td>
<td>DDEB Type VII</td>
<td>Collagen</td>
</tr>
<tr>
<td>RDEB-HS</td>
<td></td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>RDEB-nHS</td>
<td></td>
<td>Type VII collagen</td>
</tr>
</tbody>
</table>

*DDEB, dominant dystrophic EB; EBS-DM, EBS, Dowling-Meara; EBS-K, EBS, Köbner; EBS-MD, EBS with muscular dystrophy; EBS-WC, EBS, Weber-Cockayne; JEB-H, JEB, Herlitz; JEB-nH, JEB, non-Herlitz; JEB-PA, JEB with pyloric atresia; RDEB-HS, recessive dystrophic EB, Hallopeau-Siemens; RDEB-nHS, RDEB, non-Hallopeau-Siemens.

* Laminin-5 is a macromolecule composed of 3 distinct (α3, β3, γ2) laminin chains; mutations in any of the encoding genes result in a JEB phenotype.

† Some cases of EB associated with pyloric atresia may have intraepidermal cleavage or both intralamina lucida and intraepidermal clefts.

‡ α6β4 Integrin is a heterodimeric protein; mutations in either gene have been associated with the JEB-PA syndrome.

### TABLE 7-2  Genetic Modes of Transmission in Inherited Epidermolysis Bullosa*

<table>
<thead>
<tr>
<th>Major EB Type</th>
<th>Usual Mode(s) of Transmission</th>
<th>Rare Modes of Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBS†</td>
<td>Autosomal dominant</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>JEB</td>
<td>Autosomal recessive</td>
<td>—</td>
</tr>
<tr>
<td>DEB</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant/autosomal recessive heterozygosity</td>
</tr>
</tbody>
</table>

* Excluding de novo mutations, which have been reported to occur in most forms of inherited EB.

† An X-linked recessive disorder, referred to as Mendes da Costa disease, which was once included among the many variants of EBS, is no longer considered to be a subtype of any form of inherited EB.
### TABLE 7-3 Ultrastructural Findings Among Major Types and Selected Subtypes of Inherited Epidermolysis Bullosa

<table>
<thead>
<tr>
<th>EB Type or Subtype</th>
<th>Ultrastructural Site of Skin Cleavage</th>
<th>Other Ultrastructural Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBS</td>
<td>Intrastratum basale</td>
<td>Split may spread to the suprabasilar layer</td>
</tr>
<tr>
<td>EBS-WC</td>
<td>Intrastratum basale, just superficial to the HD</td>
<td>Dense, circumscribed clumps of keratin filaments (most commonly observed within lesional biopsy sites)</td>
</tr>
<tr>
<td>EBS-DM</td>
<td>Predominantly in the stratum basale, above the level of the HD attachment plaque</td>
<td>Lack of integration of keratin filaments with HD</td>
</tr>
<tr>
<td>EBS-MD</td>
<td>Intrastratum basale</td>
<td>Absent keratin filaments within basal keratinocytes</td>
</tr>
<tr>
<td>EBS-AR</td>
<td>Intrastratum basale</td>
<td>—</td>
</tr>
<tr>
<td>EBSS</td>
<td>Intrastratum granulosum</td>
<td>—</td>
</tr>
<tr>
<td>JEB</td>
<td>Intralamina lucida</td>
<td>Markedly reduced or absent HD; absent SBDP</td>
</tr>
<tr>
<td>JEB-H</td>
<td>Intralamina lucida</td>
<td>Variable numbers or rudimentary appearance of HDs</td>
</tr>
<tr>
<td>JEB-nH</td>
<td>Intralamina lucida</td>
<td>—</td>
</tr>
<tr>
<td>JEB-PA</td>
<td>Both intralamina lucida and lower stratum basale, above the level of the HD plaque</td>
<td>Small HD plaques often with attenuated SBDP, and reduced integration of keratin filaments with HD</td>
</tr>
<tr>
<td>DDEB</td>
<td>Sublamina densa</td>
<td>Normal or decreased numbers of AF</td>
</tr>
<tr>
<td>DDEB-TBDN</td>
<td>Sublamina densa</td>
<td>Electron-dense stellate bodies within stratum basale; reduced AF</td>
</tr>
<tr>
<td>RDEB</td>
<td>Sublamina densa</td>
<td>Absent AF</td>
</tr>
<tr>
<td>RDEB-HS</td>
<td>Sublamina densa</td>
<td>Reduced or rudimentary-appearing AF</td>
</tr>
<tr>
<td>RDEB-nHS</td>
<td>Sublamina densa</td>
<td>—</td>
</tr>
</tbody>
</table>

AF, anchoring fibril; HD, hemidesmosome; SBDP, subbasal dense plate; for explanation of other abbreviations, see footnote to Table 7-1.

1. All of the following are true of bullous pemphigoid EXCEPT:
   A. It is most common in patients older than 60 years
   B. It is a subepidermal vesiculatory process
   C. It involves the oral mucosa in a majority of cases
   D. Patients often suffer from other co-morbidities
   E. Urticarial forms may predate formation of frank blisters

2. In bullous pemphigoid, DIF examination of perilesional skin most often demonstrates:
   A. IgA deposition in a linear band along the dermoepidermal junction
   B. IgA deposition in a granular pattern within the papillary dermis
   C. IgG accumulation in a net-like pattern in the epidermis
   D. IgG accumulation in a linear band along the dermoepidermal junction
   E. C3 accumulation in a granular pattern along the dermoepidermal junction

3. The Brunsting-Perry variant of cicatricial alopecia involves the:
   A. Acral skin
   B. Conjunctiva
   C. Oral mucosa
   D. Scalp
   E. All of the above

4. DIF examination of salt-split skin demonstrates deposition of immunoreactants along the roof of the blister cavity in:
   A. Anti-epiligrin cicatricial pemphigoid
   B. Bullous pemphigoid
   C. Bullous lupus erythematosus
   D. Epidermolysis bullosa acquisita
   E. Epidermolysis bullosa simplex

5. Histologic and immunofluorescence findings in dermatitis herpetiformis may include:
   A. Accumulation of neutrophils in the papillary dermis
   B. Fibrin deposition in the papillary dermis
   C. Granular IgA deposition in the papillary dermis
   D. Subepidermal vesiculation
   E. All of the above

6. A gluten-free diet, used to manage dermatitis herpetiformis, can safely include cereal or grain products derived from:
   A. Barley
   B. Rice
   C. Rye
   D. Triticale
   E. Wheat

7. DIF examination of perilesional tissue involved with pemphigus vulgaris reveals deposition of:
   A. IgA in a linear pattern along the dermoepidermal junction
   B. IgA in a granular pattern along the dermoepidermal junction
   C. IgG in a linear pattern along the dermoepidermal junction
   D. IgG in a net-like pattern within the dermis
   E. IgG in a net-like pattern within the epidermis

8. Pemphigus foliaceus is characterized by antibodies to:
   A. Desmocollin 1
   B. Desmocollin 3
   C. Desmoglein 1
   D. Desmoglein 3
   E. Desmoplakin

9. By definition, paraneoplastic pemphigus always involves the ________.
   A. Acral surfaces
   B. Conjunctiva
   C. Oral mucosa
   D. Scalp
   E. Skin

10. Patients with bullous systemic lupus erythematosus and epidermolysis bullosa acquisita both may demonstrate antibodies to:
    A. BPAG I (230 kD)
    B. BPAG II (180 kD)
    C. Collagen VII
    D. Desmoglein 1
    E. Desmoglein 3

**Answers**

1. C. Patients with bullous pemphigoid are typically older (> 60 years old) with co-morbidities. Unlike pemphigus, most cases of bullous pemphigoid do not involve the mucosa. Urticarial bullous pemphigoid may predate development of frank blisters, sometimes by years. Bullous pemphigoid is a subepidermal vesiculatory process.

2. D. In bullous pemphigoid, DIF examination most often reveals linear deposition of C3 (90–100%) and IgG (70–90%) along the dermoepidermal junction. While C3 deposition is even more common
than IgG deposition in bullous pemphigoid, it is linear and not course and granular.

3. D. The Brunsting-Perry variant of cicatrical pemphigoid most often affects the scalp of elderly men. It is distinguished from other variants of cicatrical pemphigoid because it does NOT involve the mucosa.

4. B. Because cleavage occurs through the lamina lucida, DIF examination of salt-split skin from bullous pemphigoid demonstrates deposition of immunoreactants on the roof of the blister cavity. For all the other immunobullous diseases, salt-split DIF examination would result in deposition of immunoreactants in the floor of the cavity. Epidermolysis bullosa simplex is not an acquired immunobullous disorder, but a genetic bullous disorder.

5. E. Dermatitis herpetiformis demonstrates subepidermal vesiculation and an accumulation of neutrophils and fibrin in the papillary dermis. DIF demonstrates granular deposition of IgA in lesional and non-lesional skin, but it may disappear during strict adherence to a gluten-free diet.

6. B. Rice contains no gluten. The other grains contain gluten. The presence of gluten in oats is both variable and controversial, and it may depend upon processing techniques.

7. E. Pemphigus vulgaris and pemphigus foliaceus demonstrate deposition of IgG and C3 in a net-like pattern within the epidermis. Hence, these diseases are suprabasilar immunobullous conditions.

8. C. Pemphigus foliaceus is characterized by antibodies to desmoglein 1 (160 kD). The desmocollins are believed to play a role in subcorneal pustular dermatosis and possibly IgA pemphigus. Antibodies to desmoplakin are involved in paraneoplastic pemphigus.

9. C. Paraneoplastic pemphigus always involves the oral mucosa, usually with severe ulcerations of the tongue. In fact, severe painful stomatitis is one of the diagnostic criteria for the disease.

10. C. Patients with bullous systemic lupus erythematosus and epidermolysis bullosa acquisita may both demonstrate antibodies to collagen VII, a constituent of the anchoring fibrils of the skin.

REFERENCES

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CUTANEOUS DISORDERS OF CORNIFICATION

Ichthyoses

- Group of disorders characterized by generalized scaling of the skin
- Pathogenesis: increased cohesiveness of cells of the stratum corneum, abnormal keratinization, and abnormal proliferation

Ichthyosis Vulgaris (Fig. 8-1)

- Epidemiology: most common disorder of cornification; AD
- Pathogenesis
  - Loss of function mutation in filaggrin (FLG) gene
  - Increased adherence of the stratum corneum and scale formation is thought to result from a lack of water-retaining amino acids that derive from filaggrin metabolism
- Clinical features
  - Not present at birth; onset during infancy/childhood
  - Fine white, flaky scales develop on the extremities, especially the extensor surfaces with sparing of the groin and flexural areas due to increased humidity
  - Improves with advancing age
  - Associated with keratosis pilaris and atopic triad of asthma, hay fever and eczema
- Pathology
  - One-half lack granular layer on light microscopy and profilaggrin-containing keratohyalin granules by EM
- Treatment
  - Lubricants and emollients
  - Keratolytics—be careful with salicylic acid to avoid salicylism
  - Topical retinoids – can be irritating

Lamellar Ichthyosis (Fig. 8-2)

- Epidemiology: AR
- Pathogenesis
  - In the majority of patients, it is caused by transglutaminase-1 deficiency due to mutations in the TGM1 gene
  - Has also been mapped to the ATP binding cassette transporter gene (ABCA12) and the cytochrome P450 family 4, subfamily F, polypeptide 22 gene (CYP4F22)
- Clinical features
  - Apparent at birth and persists throughout life
  - Collodion baby
  - Characterized by large, dark-brown and plate-like scales that form a mosaic pattern with minimal to no erythroderma
  - Ectropion, eclabium and significant hypoplasia of nasal and auricular cartilage due to tautness of facial skin
  - Variable PPK, may have alopecia and nail dystrophy
- Treatment
  - Oral retinoids may be necessary from early childhood if severe
  - Keratolytics limited secondary to irritation and systemic absorption
- Topical vitamin D3 derivatives
- Palliation for heat intolerance
- Ophthalmology follow up

**Non-bullous Congenital Ichthyosiform Erythroderma**

- Epidemiology: AR
- Pathogenesis
  - Mapped to four different genes: transglutaminase 1, ALOXE3, ALOX12B, ichthyin
  - 12-LOX generates fatty acid hydroperoxide, eLOX functions as hydroperoxide isomerase to generate epoxy alcohols
- Clinical features
  - Presents at birth with a collodion membrane which persists throughout life
  - Characterized by intense erythroderma, white small powdery scale, ectropion and scarring alopecia
  - Palms and soles have diffuse, fissuring keratoderma
  - Obstruction of sweat ducts and pores results in hypohidrosis and heat intolerance
- Pathology
  - Increased lamellar bodies, accumulation of lipid droplets in the stratum corneum
- Treatment
  - See lamellar ichthyosis
  - Erythrodermic patients need supplemented fluid, calories, iron and protein to balance increased loss through the skin


X-Linked Ichthyosis

- Epidemiology: XLR; affects males almost exclusively
- Pathogenesis
  - Decreased or absent steroid sulfatase activity
  - Results in impaired hydrolysis of cholesterol sulfate and DHEA-S with subsequent accumulation of cholesterol 3-sulfate in the epidermis, which may inhibit TGM-1
- Clinical features
  - In women pregnant with an affected fetus, steroid sulfatase deficiency in the fetal placenta causes low or absent levels of estrogen, which causes failure of progression of labor
  - Presents within first weeks after birth with mild erythroderma and generalized peeling of large, translucent scale
  - The typical large, polygonal, dark-brown scale with tight adherence develops during infancy and is distributed on the extremities, trunk and neck
  - Palms, soles and face spared—except pre-auricular areas
  - Asymptomatic corneal opacities in 10–50%
  - 20 fold increase of cryptorchidism and testicular cancer and hypogonadism
- Treatment
  - Emollients
  - Topical keratolytics
  - Topical retinoids

Ichthyosis Bullosa of Siemens

- Epidemiology: AR
- Pathogenesis: heterozygous mutations in gene for keratin 2—expressed in uppermost spinous and granular cell layers of the epidermis
- Clinical features
  - At birth—may appear normal or show mild blistering
  - Trauma induced blistering in infancy
  - Hyperkeratosis develops in early childhood
  - Predilection for skin overlying joints, flexures and dorsa of hands/feet—spares palms and soles
  - Characteristic feature is superficially denuded areas with collarette-like borders
- Pathology: clumping of tonofilaments on EM
- Treatment: see bullous CIE

Bullous Congenital Ichthyosiform Erythroderma

- Epidemiology: AD; ~50% occur sporadically (new mutations)
- Pathogenesis
  - Heterozygous mutations in keratins 1 and 10, which are expressed in the suprabasal and granular layers of the epidermis
  - KRT1 is associated with severe PPK
  - KRT10 spares the palms/soles—not expressed there
  - Epidermal acantholysis and hyperkeratosis result from hyperproliferation, decreased desquamation and other factors
- Clinical features
  - Presents at birth with erythroderma, erosions, peeling and widespread areas of denuded skin
  - Over time, blistering and erythroderma resolve and hyperkeratosis prevails
  - Increased transepidermal water loss and bacterial colonization of the stratum corneum due to disturbed barrier function
  - Sepsis and fluid and electrolyte imbalances account for perinatal morbidity and mortality
- Pathology: epidermolytic hyperkeratosis—massive, dense orthokeratotic hyperkeratosis, acanthosis with hypergranulosis and cytolysis of the suprabasal and granular layers
- Treatment
  - NICU during neonatal period
  - Keratolytics—limited due to irritation and salicylism
  - Topical emollients, tretinoin and vitamin D
  - Antibiotics as needed for bacterial infection; antiseptics or antibacterial soaps
  - Systemic retinoids

Ichthyosis Hystrix Curth-Macklin

- Epidemiology: AR
- Pathogenesis: mutations in the keratin 1 gene
- Clinical features
  - No skin fragility
  - Ranges from severe, mutilating PPK to generalized hystrix-like hyperkeratosis
  - Pseudoainhum, starfish-like hyperkeratoses, knuckle pads, flexural digital contractures and secondary bacterial infections have been described
- Treatment: systemic retinoids and topical keratolytic agents
- Ichthyosis hystrix—descriptive name for a clinically and genetically heterogenous group of skin disorders with massive hyperkeratosis that has a verrucous surface or protruding, porcupine-like spines

Harlequin Fetus

- Epidemiology: AR
- Pathogenesis
  - Massive cell retention in the stratum corneum, abnormal or absent lamellar bodies and lack of intercellular lipid lamellae
  - Loss of function mutations in the ABC transporter gene ABCA12—codes for lamellar bodies involved in energy dependent lipid transport
REFSUM DISEASE
- Epidemiology: AR
- Pathogenesis
  - Excessive accumulation of phytanic acid caused by a deficiency of peroxisomal enzyme phytanoyl-CoA hydroxylase
  - Two genes are implicated: PHYH and PEX7
  - Inactivating mutations in PHYH lead to an enzymatic block with subsequent accumulation of phytanic acid in plasma and tissues
- Clinical features
  - Cutaneous symptoms are variable and tend to develop during childhood or adolescence
  - Starts with insidious neurologic symptoms
  - Waxes and wanes with resulting gradual neurologic deterioration
  - Cardinal features are atypical retinal pigmentosa leading to concentric visual field constriction, peripheral polyneuropathy, cerebellar dysfunction and elevated protein in CSF
  - Cardiomyopathy resulting in arrythmias, AV conduction impairment and cardiomegaly are responsible for the increased incidence of sudden death
- Pathology: diagnosis established by detecting increased phytanic acid levels in serum
- Treatment
  - Reducing dietary phytanic acid intake (in dairy products and animal fats)
  - Retinal changes are irreversible
  - Therapeutic plasma exchange my be useful for acute toxicity
  - ICU care
  - Ophthalmology for severe ectropion
  - Systemic retinoids

SJÖGREN-LARSON SYNDROME
- Epidemiology: AR
- Pathogenesis: Deficiency of microsomal enzyme fatty aldehyde dehydrogenase (FALDH), which catalyzes the NAD dependent oxidation of long-chain aliphatic aldehydes
- Clinical features
  - Presents at birth with varying degrees of erythema and ichthyosis
  - Rare collodion membrane
  - After infancy, erythema fades, while hyperkeratosis and scaling become more prominent
  - Predilection sites are the lower abdomen, side and nape of neck and large flexures
  - 70% develop PPK
  - Associated with persistent pruritus
  - Presence of perifoveal glistening white dots in the ocular fundus
  - Involvement of the CNS manifests in the first year of life with delayed motor development, abnormal gait, pyramidal signs and spasticity
  - Progressive neurologic decline results in di- or tetraplegia and severe MR
- Treatment
  - Topical keratolytics and topical vitamin D
  - Skin hydration
  - Systemic retinoids
  - 5-lipoxygenase inhibitors—for pruritus
  - Symptomatic treatment for CNS effects

NEUTRAL LIPID STORAGE DISEASE WITH ICHTHYOSIS
- Epidemiology: AR
- Pathogenesis
  - Inborn error of lipid metabolism with multiorgan accumulation of triglycerides
  - Germline mutations in CGI-58 gene
- Clinical features
  - Congenital generalized ichthyosis, vacuolated leukocytes, myopathy, cataracts and sensorineural deafness
  - Widespread tissue deposition of neutral lipids results in a broad array of systemic manifestations in childhood
  - Prognosis depends on the course of liver disease and extent of hepatic fibrosis
- Pathology: Diagnostic feature is the presence of numerous lipid-containing vacuoles in circulating granulocytes (Jordan’s anomaly)
- Treatment
  - Topical emollients and keratolytics
Conradi-Hünermann Syndrome

- Epidemiology: XLD
- Pathogenesis
  - Caused by a primary defect in cholesterol biosynthesis
  - Distinct mutations in EBP gene encoding emopamil-binding protein
- Clinical features
  - Generalized erythema with thick adherent scale and linear or whorled hyperkeratosis at birth
  - Erythroderma resolves substantially or completely within first weeks/months of life
  - In older children, hyperkeratosis is replaced by linear or patchy follicular atrophoderma
  - Skeletal abnormalities are usually asymmetric
  - Widespread calcifications manifest as stippled epiphyses (chondrodysplasia punctata)—typically involves the trachea and vertebra; can be detected on radiographs in childhood, but not apparent when bone maturation progresses
  - Unilateral cataracts
  - Normal life expectancy
- Treatment
  - Emmollients, urea or lactic acid containing products
  - Orthopedic and ophthalmology consults

CHILD

- Epidemiology: XLD
- Pathogenesis: Inactivating mutation in NSDHL—encodes 3β-hydroxyysteroid-dehydrogenase
- Clinical features
  - Presents at birth or neonatal period with striking unilateral erythema and skin thickening with a waxy surface or yellowish adherent scale
  - Often involves right side of body and sharply demarcated at midline
  - Spares the face
  - Ipsilateral skeletal abnormalities range from hypoplasia of digits or ribs to complete amelia
  - Stippled epiphyses can be seen on radiographs in early infancy but resolve during childhood
  - Organ hypoplasia affects brain, kidney, heart and lungs
- Treatment
  - Multidisciplinary depending on organ involvement
  - Topical tretinoin, systemic retinoids or surgical excision

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Netherton Syndrome (Ichthyosis Linearis Circumflexa)

- Epidemiology: AR
- Pathogenesis: caused by mutation in the SPINK5 gene—encodes multi-domain serine protease inhibitor LEKT1, predominantly expressed in lamellar granule system of epithelia and lymphoid tissue
- Clinical features
  - Presents at or soon after birth with generalized erythroderma and scaling
  - Collodion membrane usually not present
  - Usually, ichthyosis evolves into serpiginous or circinate scaling and erythematous plaques which are bordered by a double-edged scale
  - Hair shaft abnormalities develop during infancy and improve with age—incude trichorrhexis invaginata and trichorrhexis nodosa
  - Increased levels of IgE, eosinophilia and increased allergic reactions
  - Increased susceptibility to skin, respiratory tract or systemic infections
- Treatment
  - Symptomatic
  - May require NICU
  - Topical emollients, keratolytics, tretinoin and corticosteroids
  - Avoid topical tacrolimus due to percutaneous absorption
  - Treatment of bacterial/fungal infections as needed

ERYHROKERATODERMA VARIABILIS
(MENDES DE COSTA DISEASE)

- Epidemiology: AD
- Pathogenesis: Mutations in the connexin genes GJB3 & GJB4—encode gap junction proteins connexin 31 and connexin 30.3
- Clinical features
  - Hallmark is the coexistence of transient erythematous patches and more stable hyperkeratosis
  - Erythematous component more prevalent during childhood
  - Individual lesions persist for minutes to hours
  - Over time, hyperkeratosis develops
  - Stabilizes after puberty
  - May be triggered by other factors, including stress, temperature changes, friction and sun exposure
- Treatment
  - Keratolytic agents for mild disease
  - Systemic retinoids for extensive disease

KERATOSIS-ICTHYOSIS-DEAFNESS SYNDROME (KID)

- Epidemiology: AD
- Pathogenesis: Mutations in GJB2 encoding connexin 26
HOWEL-EVANS SYNDROME
- Epidemiology: AD; TOC gene
  - Type A—late onset PPK and increased risk of esophageal carcinoma
  - Type B—early onset PPK and benign course
- Clinical features
  - PPK often limited to pressure areas
  - Associated with keratosis pilaris, dry rough skin and oral leukokeratosis
  - Esophageal carcinoma arises in the 5th decade

VOHWINKEL SYNDROME (MUTILATING PALMOPLANTAR KERATODERMA)
- Epidemiology: AD
- Pathogenesis
  - Mutation in gene encoding loricrin, a major cornified envelope protein
  - Mutation in connexin 26
- Clinical features
  - Honeycombed, diffuse hyperkeratosis of the palms of soles that appears in infancy and becomes transgradient
  - Early childhood development of constricting bands of the digits, which may lead to autoamputation (pseudoainhum)
  - Starfish shaped keratoses over the knuckles of the fingers and toes
  - Moderate hearing loss

MAL DE MALEDA
- Epidemiology: AR; inhabitants off the Dalmatian coast
- Pathogenesis: SLURP-1 mutation
- Clinical features
  - Onset of diffuse palmar and plantar thickening with an erythematous border, shortly after birth
  - Progressive and transgradient with knee and elbow involvement
  - Severe hyperhidrosis and malodor
  - Complicated by fissuring and secondary fungal or bacterial infections

PAPILLON-LEFEVRE SYNDROME
- Epidemiology: AR
- Pathogenesis: mutations in cathepsin C
- Clinical features
  - Diffuse transgradient PPK
  - Destructive periodontitis beginning in childhood
  - Frequent cutaneous and systemic pyogenic infections

RICHNER-HANHART SYNDROME
- Epidemiology: AR
- Pathogenesis: mutations in TAT gene – encodes hepatic tyrosine aminotransferase
• Clinical features
  • Photophobia, dendritic keratitis with corneal ulcerations in the 1st year of life
  • Elevated serum and urine tyrosine levels
  • Painful, focal hyperkeratotic plaques on the palms and soles
  • Progressive mental retardation
• Treatment: diet restricted in tyrosine and phenylalanine will clear the keratitis and skin lesions and may delay or prevent cognitive impairment

**NAXOS DISEASE**
• Epidemiology: AR
• Pathogenesis: deletion of the plakoglobin gene
• Clinical features: arrhythmogenic right ventricular cardiomyopathy, mild non-transgradient, non-epidermolytic PPK and wooly hair

**CARVAJAL SYNDROME**
• Epidemiology: AR; in 3 families from Ecuador
• Pathogenesis: mutation in gene that encodes desmoplakin
• Clinical features: striate epidermolytic PPK, left ventricular dilated cardiomyopathy and wooly hair
• Treatment: needs cardiac evaluation—as do patients with Naxos disease

**DARIER DISEASE**
• Epidemiology: AD; men and women equally affected
• Pathogenesis
  • Mutations in the endoplasmic reticulum Ca\(^{2+}\) ATPase ATP2A2-protein product SERCA2
  • Defects in Ca\(^{2+}\) sequestration into the endoplasmic reticulum produce acantholysis by impairing the normal processing of junctional proteins (desmoplakin)
  • Keratinocyte ER Ca\(^{2+}\) depletion is also associated with apoptosis
• Clinical features
  • Peak onset during puberty
  • Primary lesions are keratotic, red to brown papules in a seborrheic distribution, involving the trunk, scalp, face and lateral neck
  • Malodor is frequent
  • Nail changes include longitudinal red and/or white lines, longitudinal ridging, subungual hyperkeratosis and V-shaped notches
  • Worsens in summer and with lithium
  • Chronic course without spontaneous remission
  • Prone to secondary infection including bacteria, yeast, dermatophytes or Kaposi’s varicelliform eruption (HSV)
• Pathology
  • Acantholysis and dyskeratosis
  • Corps ronds—acantholytic enlarged keratinocytes in malphigian layer with darkly staining and partially fragmented nuclei surrounded by a clear cytoplasm and encircled by a bright ring of collapsed keratin bundles
  • Grains—small, oval cells in the stratum corneum characterized by a strongly eosinophilic cytoplasm composed of collapsed keratin bundles containing shrunken parakeratotic nuclear remnants
• Treatment
  • Lightweight clothing and sunscreen
  • Topical retinoids and emollients

**BART-PUMPHREY SYNDROME**
• Epidemiology: AR
• Pathogenesis: mutation in GJB2 gene that encodes connexin 26
• Clinical features
  • Profound hearing impairment from birth
  • Early childhood development of diffuse PPK (pitted or stippled) and knuckle pads
  • Variable leukonychia that improves with age

**HURIEZ SYNDROME**
• Epidemiology: AD
• Clinical features
  • Red, atrophic skin on the dorsal aspects on the hands and feet since birth
  • Mild and diffuse PPK
  • Sclerodactyly and nail changes with time
  • Increased risk of SCC in areas of atrophic skin
• Pathology: characteristic finding is almost complete absence of Langerhans cells in the affected skin

**HIDROTIC ECTODERMAL DYSPLASIA (CLOUSTON SYNDROME)**
• Epidemiology: AK
• Pathogenesis: mutations of GJB6 gene that encodes connexin 30
• Clinical features
  • Diffuse PPK in conjunction with hypotrichosis and nail dystrophy
  • Thickened skin may develop over the knuckles, knees and elbows
  • Loss of hair shaft cuticle

**OLMSTED SYNDROME**
• Epidemiology: AD and XLR
• Clinical features
  • Well-defined erythematous hyperkeratotic plaques in the perioral, inguinal, genital, and intergluteal areas during the 1st year of life
  • PPK that begins in infancy that becomes diffuse and severe
  • Autoamputation may result from constricting PPK and SCC or melanoma may occur
• Antimicrobial washes and intermittent use of antibiotics/antifungals
• Systemic retinoids
• Excision followed by STSG, dermabrasion or laser removal

**POROKERATOSES (FIG. 8-3)**

- Epidemiology: AD
- Pathogenesis: clonal hyperproliferation of atypical keratinocytes: causes cornoid lamella, which expands peripherally and forms the raised boundary between abnormal and normal keratinocytes
- Clinical features: five clinical variants
  - Classic porokeratosis Mibelli
    - Childhood, asymptomatic
    - Irregularly shaped annular plaque with a raised, ridge-like border
    - Sex predominance: M: F 2:1 to 3:1
    - Few lesions
    - Mucous membrane involved
    - Localized, anywhere
    - Koebner phenomenon reported
  - Disseminated superficial porokeratosis (DSP) and disseminated superficial actinic porokeratosis (DSAP)
    - Indistinct, light brown patches with a thread-like border
    - Predominantly on the extensor surfaces of the legs and the arms
    - Fair-skinned women in their third or fourth decade of life, with a history of excessive ultraviolet exposure (DSAP)
    - Sex predominance: M: F 1:3

**Pityriasis Rubra Pilaris (PRP)**

- Epidemiology: AD
- Pathogenesis: vitamin A deficiency and abnormal vitamin A metabolism
- Clinical features
  - Rare, onset at any age, chronic course
  - Both sexes equally affected
  - Orange-red or salmon-colored scaly plaques with sharp borders, islands of uninvolved skin
  - Juvenile, adult, limited forms
  - Tendency for erythroderma
  - Follicular hyperkeratosis
  - Palmoplantar keratoderma
  - Nails: distal yellow-brown discoloration, subungual hyperkeratosis, longitudinal ridging, nail plate thickening, and splinter hemorrhages
  - Mucous membrane: diffuse whitish appearance of the buccal mucosa, lacy whitish plaques, and erosions
POROKERATOSE

- Griffith’s classification
  - Type I: classic adult, most common and good prognosis
  - Type II: atypical adult
  - Type III: classic juvenile, most common and good prognosis
  - Type IV: circumscribed juvenile
  - Type V: atypical juvenile
  - Type VI: HIV-associated
- Pathology
  - Hyperkeratosis with alternating orthokeratosis and parakeratosis forming a checkerboard pattern in the stratum corneum
  - Focal or confluent hypergranulosis; follicular plugging with perifollicular parakeratosis forming a shoulder effect;
  - Thick suprapapillary plates; broad rete ridges; narrow dermal papillae; and sparse superficial dermal lymphocytic perivascular infiltration, acantholysis
- Treatment: topical corticosteroids, calciptiol, emollients, acitretin, methotrexate, azathioprine

Lichen Simplex Chronica (Fig. 8-4)
- Epidemiology
  - Older adults
- Pathogenesis
  - Secondary to habitual scratching/rubbing of skin

FIGURE 8-4 Lichen simplex. (Courtesy of Dr. Asra Ali.)

- Linked to obsessive-compulsive disorder (OCD)
- Predisposing factors: xerosis, atopy
- Clinical features
  - Hyperpigmented, lichenified, well-circumscribed leathery plaques
  - Common distribution
    - Women: occipital/nuchal areas
    - Men: perineum/scrotum
    - Wrists, extensor forearms, lower legs
- Pathology
  - Hyperkeratosis, acanthosis, hypergranulosis, fibrosis and increased number of dilated capillaries
  - Sometimes excoriations are found
- Treatment
  - Break the itch-scratch cycle
  - Anti-pruritics/moisturizers
  - Topical corticosteroids under occlusion
  - Intrallesional corticosteroids
  - Reduce situational stressors/counseling/support groups
  - SSRIs = in patients with OCD

Tyloma (Callus)
- Pathogenesis
  - Caused by chronic external pressure
- Pathology
  - Prominent hyperkeratosis, usually without parakeratosis

Clavus
- Pathogenesis
  - Caused by chronic pressure at the site of bony prominences
- Clinical findings
  - Hyperkeratotic lesion
- Pathology
  - Hyperkeratosis with parakeratosis
  - Epidermis is centrally atrophic and peripherally acanthotic
  - Perivascular infiltration of upper dermis

Pityriasis Lichenoides (Fig. 8-5)
- Epidemiology
  - More common in children and males
- Pathogenesis
  - Postulated to be a response to foreign antigens (infection, drugs)
  - Two forms
    - Acute: pityriasis lichenoides et variolaformis acuta (PLEVA; Mucha-Habermann disease)
    - Chronic: pityriasis lichenoides chronica (PLC; guttate parapsoriasis)
  - Contain lesional T-cell infiltrates that may exhibit clonality; may explain occasional association with...
other lymphoproliferative disorders such as CTCL, Hodgkin’s disease, and other lymphomas
- PLEVA: predominance of CD8+ T cells
- PLC: predominance of CD4+ T cells

- Clinical features
  - PLEVA
    - Individual lesions develop crusts/ulcers/pustules/vesicles → heal to varioliform scars
    - Lesions are asymptomatic and usually resolve within weeks
    - Rarely associated with systemic symptoms: fever, malaise, generalized lymphadenopathy, arthritis, or bacteremia
  - PLC
    - Red/brown scaly papules → heal to hypopigmented macules
    - Lesions are more indolent and regress over weeks to months

- Duration of disease
  - Diffuse < central < peripheral

- Pathology
  - Superficial perivascular interface dermatitis
  - Focal parakeratosis
  - Epidermal damage: edema to necrosis
  - Erythrocyte extravasation with occasional lymphocytic vasculitis
  - Features are more blunted in chronic lesions
  - Lymphoid atypia is not a standard feature of PL; if present, consider lymphomatoid papulosis

- Treatment
  - Discontinue suspected responsible agent
  - First line: topical corticosteroids, topical coal tar preparations, tetracycline, erythromycin (for children), phototherapy
  - Antibiotics are for anti-inflammatory rather than antibiotic effects
  - Low dose weekly methotrexate for fulminant cases
  - Cases with systemic symptoms – give systemic corticosteroids

Pityriasis Rosea (Pityriasis Rosea Gilbert) (Fig. 8-6)

- Epidemiology
  - Healthy adolescents and young adults
  - No racial predilection
  - Female > male
  - May peak in spring/fall

- Pathogenesis: may have viral etiology as suggested by occasional prodromal symptoms, clustering of cases, and complete absence of recurrent episodes; historically HHV-6 and HHV-7 were considered to be associated but not proven

- Clinical features
  - Herald patch: solitary lesion on trunk that precedes the remainder of the eruption by hours/days; pink/salmon patch/plaque with central fine scale and marginal trailing collarette of scale with free edge pointing inwards
  - Few have mild prodromal symptoms

**Lichen Planus (Fig. 8-7)**

- **Epidemiology**
  - No racial/gender predisposition

- **Pathogenesis**
  - T-cell mediated autoimmune damage to basal keratinocytes that express altered self-antigen on their surface secondary to exposure to exogenous agents

- **Exogenous agents**
  - Hepatitis C virus (associated with HLA-DR6)
  - Transfusion-transmitted virus (TTV)
  - HHV-6
  - HBV vaccine
  - Oral contact allergens (metallic dental restorations/reconstructions [amalgum/mercury, copper, gold])
  - Drugs: captopril, enalapril, labetalol, methyl-dopa, propranolol, chloroquine, hydroxychloroquine, quinacrine, chlorothiazide, HCTZ, gold salts, penicillamine, quinidine
  - Paraneoplastic process

- **Clinical features**
  - Peak onset in 5th–6th decade
  - Pruritic violaceous papules – small, polygonal, flat-topped, occasionally umbilicated; shiny/transparent surface
  - Distribution: flexor surface of wrists/forearms, dorsal surface of hands, anterior lower legs, neck, and presacral areas
  - Mucosal involvement in ~75% of patients with cutaneous LP

- **Variants**
  - Actinic LP/LP tropicus/lichenoid melanoderma: occurs in spring/summer on sun-exposed skin with red/brown plaques
  - Acute LP/exanthematous LP/eruptive LP: widely distributed with rapid dissemination
  - Annular LP: papules spread peripherally and central area resolves; annular edge is raised and purple to white in color. Usually on axilla or penis
- **Atrophic LP**: papules coalesce to form larger plaques that become centrally depressed/atrophic with residual hyperpigmentation; secondary to thinning epidermis and not due to degeneration of elastic fibers
- **Bullous LP**: bullous or vesiculobullous lesions develop within pre-existing LP
- **LP pemphigoides**: bullous or vesiculobullous lesions develop on previously uninvolved skin; have circulating IgG autoantibodies
- **Hypertrophic LP/LP verrucosus**: extremely pruritic, thick hyperkeratotic plaques on shins/dorsal foot; may have fine adherent scale; usually symmetric and chronic; may lead to squamous cell carcinoma
- **Inverse LP**: violaceous papules/plaques in intertriginous zones
- **LP pigментosus**: occurs in patients with skin types III–IV as brown/gray macules in sun-exposed areas of face/neck; reticulated pigmentation; can have linear distribution following Blaschko’s lines
- **Lichen planopilaris/follicular LP/LP acuminatus**: multiple hyperkeratotic plugs with narrow violaceous rim primarily on scalp resulting in scarring and alopecia. Women > men
- **Linear LP**: spontaneously occur within the lines of Blaschko
- **LP-lupus erythematosus overlap syndrome**: prefers acral sites
- **Nail LP**: lateral thinning, longitudinal ridging and fissuring; can lead to dorsal pterygium formation
- **Oral LP**: reticular pattern is the most common = whitish linear lines in a lace-like pattern or rings with short radiating spines; buccal mucosa > gingival; check for esophageal and genital involvement
- **Vulvovaginal LP**: erosions; can evolve into malignancy

**Pathology**
- Hyperkeratosis without parakeratosis
- Focal increases in granular cell layer
- Irregular acanthosis with a “saw-tooth” appearance
- Liquefactive degeneration of the basal cell layer
- Band-like lymphocytic infiltrate at dermal-epidermal junction
- Small separations between dermis and epidermis (Max-Joseph spaces)
- Oral LP: parakeratosis rather than hyperkeratosis

**Treatment**
- Spontaneous remission of cutaneous LP in 2/3 of patients after 1 year; whereas oral LP lasts ~ 5 years (erosive form rarely resolves)
- Topical calcineurin inhibitors
- Intraleisonal corticosteroids – especially for hypertrophic LP
- Miscellaneous: griseofulvin, metronidazole, cyclosporine, mycophenolate mofetil
- Phototherapy
- Systemic steroids – first line for severe acute cutaneous LP

**Lichenoid Keratosis (Lichen Planus-Like Keratosis)**
- **Epidemiology**
  - 35–65 years old; women > men
  - mostly Caucasians
- **Pathogenesis**
  - Thought to represent inflammation of a benign lentigo (benign lichenoid keratosis, BLK), actinic keratosis (lichenoid actinic keratosis), or SK (irritated SK)
  - Suggested that lichenoid infiltrate of lymphocytes is secondary to a stimulus from Langerhans cells after their processing of an unidentified epidermal antigen (similar to mechanism for lichen planus)
- **Clinical features**
  - Solitary pink to red/brown, often scaly, papules ranging 0.3–1.5cm in diameter; most closely resembles a BCC (most frequent reason for biopsy)
  - Usually asymptomatic but can have slight pruritus/stinging
  - Distribution: forearm and upper chest > shins (women) > chronically sun-exposed areas
- **Pathology**
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  - Phototherapy
  - Systemic steroids – first line for severe acute cutaneous LP

**Lichen Nitidus**
- **Epidemiology**: rare disease – poor data
- **Pathogenesis**: limited study; no causative agents discovered
- **Clinical features**
  - Tiny discrete skin-colored uniform pinhead-sized papules with occasional central depression; usually flat with shiny surface
  - Distribution: flexor surface of upper extremities, genitalia, chest, abdomen, dorsal hands
  - Oral lesions: minute, flat, gray/white papules on soft mucosa or white plaques on tongue/hard palate
  - Nails (10%): pitting, rippling, longitudinal ridging, terminal splitting, increased

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  - Distribution: flexor surface of upper extremities, genitalia, chest, abdomen, dorsal hands
  - Oral lesions: minute, flat, gray/white papules on soft mucosa or white plaques on tongue/hard palate
  - Nails (10%): pitting, rippling, longitudinal ridging, terminal splitting, increased
| Porokeratoses
| --- |
| **Continuous/interrupted band of discrete/clustered**
| **pink/skin-colored/tan papules**
| that are flat-topped/smooth/scaly, 2–4mm in size
| **Typically a single unilateral streak on an extremity**
| **Appears suddenly → develops over days/weeks → spontaneous resolution after a year or more with post-inflammatory hypopigmentation**

**Pathology**
- Well-circumscribed infiltrate of lymphocytes, epitheloid cells, and occasional Langhans giant cells that are “clutched” by surrounding hyperplastic rete ridges in a “ball and claw” configuration
- Epidermis is atrophic +/− parakeratotic “cap” centrally
- Absence/thinning of granular layer
- Liquefactive degeneration of basal layer

**Treatment**
- Most patients have spontaneous clearing within one to several years
- Primarily symptomatic (topical steroids, oral antihistamines)
- Topical calcineurin inhibitors
- Narrowband UVB or PUVA

**Lichen Striatus (Linear Lichenoid Dermatoses/Blaschko Linear Acquired Inflammatory Skin Eruptions [BLAISE]) (Fig. 8-8)**

**Epidemiology**
- Female > male; primarily children (4mo–15yrs)

**Pathogenesis**
- theory: during fetal development, aberrant clones of epidermal cells produced by somatic mutation migrate out along lines of Blaschko → exposure to infectious agent triggers intolerance by inducing novel membrane antigen

**Clinical features**
- Typically asymptomatic

**FIGURE 8-8** Lichen striatus. (Courtesy of Dr. Jason Miller.)

**Pathology**
- Border of active lesions: vacuolization of basal layer, occasional colloid bodies, lichenoid infiltrate of varying degrees
  - Immunofluorescence: IgM, IgG, fibrinogen, C3 staining colloid bodies (like in LP)
- Inactive ashy-colored lesions: pigment incontinence, variable epidermal change, including atrophy and effacement of epidermal ridges

**Treatment**
- Usually not effective
- Sun protection
- Topical corticosteroids/retinoids
- Vitamin C, chemical peels, oral antibiotics, vitamin A, dapsone, antimalarials, griseofulvin, oral corticosteroids

**Erythema Dyschromium Perstans (Ashy Dermatoses/Dermatitis)**

**Epidemiology**
- Darkly pigmented Latin Americans > Asians > Whites
- Favors skin types III + IV
- No gender predisposition
- Onset: 1st–3rd decade

**Pathogenesis**
- Sporadic case reports of temporal associations with ingestion of ammonium nitrate, whipworm infestation, and HIV seroconversions

**Clinical features**
- Gray/brown/blue macules/patches
- Uncommon erythematous peripheral margin measuring 1–2mm in width
- Lesion is usual oval in shape with long axes following skin cleavage lines (similar pattern to pityriasis rosea)
- Distribution: neck, trunk, proximal arms; usually symmetric; sparing of palms, soles, scalp, nails, and mucous membranes
- Spontaneous clearing can occur in children but usually persists for years in adults

**Pathology**
- Depends on age of lesion
- Lichenoid tissue reaction with parakeratosis, dyskeratosis, and focal/diffuse lysis of basal layer
- Langerhans cells are decreased (early) or increased (late)

**Treatment**
- not needed except for significant pruritus (topical corticosteroids)
Transient Acantholytic Dermatosis (Grover’s Disease)

- Epidemiology
  - Caucasian men > 40 years old
  - Peak in winter months
- Pathogenesis
  - Exact etiology unknown; may be secondary to acute/chronic radiation (UV or ionizing), excessive sweating (on the back of a febrile bedridden patient), heat, and xerosis
  - Predisposition with asteatotic, atopic, and allergic contact dermatitis
- Clinical features
  - Discrete round papules/papulovesicles: skin-colored or erythematous, crusted, extremely pruritic
  - Distribution: upper/mid trunk > lower trunk/proximal extremities
  - Can be acute, chronic, or relapsing
  - Exacerbations with heat, friction, sweating, and sunlight exposure
- Pathology
  - Focal acantholysis and dyskeratosis in association with intraepidermal clefting and vesicle formation
  - Four histological variants (more than one pattern can be seen in the same biopsy specimen)
    - Darier disease-like
      - Suprabasal cleft formation
      - Most pronounced dyskeratotic changes (corps ronds and grains)
    - Hailey-Hailey disease-like
      - Clefting in stratum spinosum
    - Pemphigus vulgaris or foliaceous-like
      - PV-like: subbasal cleft formation
      - PF-like: clefting in superficial epidermis
    - Spongiotic with acantholysis
  - Direct immunofluorescence is negative
- Treatment
  - Avoid exacerbators – sunlight, exercise, occlusive fabrics, heat
  - First line: topical corticosteroids
  - Topical calcipotriol and topical calcineurin inhibitors
  - More aggressive: phototherapy, oral corticosteroids, PUVA, UVA1, trichloroacetic acid peel

Erythema Gyratum Repens (EGR)

- Epidemiology: associated with malignancy in as many as 80% of patients; often precedes the detection of malignancy
- Pathogenesis
  - Associated malignancies: lung (most common), breast, urinary bladder, uterus and/or cervix, gastrointestinal tract (stomach), and prostate
  - Associated with some nonneoplastic conditions: pulmonary tuberculosis, lupus erythematosus, CREST (calcinosis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia) syndrome
- Clinical features
  - Clinical findings: wood-grain appearance; concentric mildly scaling bands of patches or plaques of erythema; rapid migration (up to 1 cm/day); intense pruritus
  - Course of rash closely mirrors the course of the underlying illness
  - Spongiosis, focal parakeratosis, and a superficial perivascular lymphohistiocytic infiltrate, with eosinophils and melanophages; exocytosis of neutrophils and eosinophils
- Treatment: steroids for pruritus; symptoms disappear with resolution of underlying disease

FIGURATE ERYTHEMAS

Erythema Annulare Centrifugum (Erythema Figuratum)

- Epidemiology: unknown

URTICARIA

- Epidemiology
  - Any age
  - More common in women: chronic urticaria, dermatographism, cold urticaria
  - More common in men: pressure urticaria
Pathogenesis
- High affinity IgE receptors are crosslinked, which initiates a chain of calcium/energy-dependent steps leading to fusion of storage granules and externalization of contents (degranulation)
- Degranulation can also be stimulated by anti-IgE and anti-IgE receptor antibodies, opiates, C5a anaphylatoxin, stem cell factor, neuropeptides (substance P)
- Mast cell granules contain histamine, cytokines (TNF-alpha, interleukins [3, 4, 5, 6, 8, 13]), GM-CSF, proinflammatory eicosanoids (prostaglandin [PGD2], leukotrienes [LTC4, D4, E4])
- Clinical features
  - Multiple pruritic wheals of different sizes erupt anywhere on the body and then fade within 2–24 hours without bruising; often appears in evening or upon waking; most intense at night
  - In severe cases: can be associated with fatigue, lassitude, sweats, chills, indigestion, arthralgias
    - Acute urticaria
      - Duration <6 weeks
      - Triggers: 50% idiopathic, 40% viral URI, 9% drugs, 1% food
      - Common in children with atopic dermatitis
    - Chronic urticaria
      - Duration >6 weeks and continuous
        (occurs at least 2x/wk when off of treatment)
      - Associations with HLA-DR4 and HLA-DQ8, H. pylori gastritis, and intestinal strongyloidiasis
      - Triggers: 60% ordinary (autoimmune, pseudoallergic, infection-related, idiopathic), 35% physical, 5% vasculitic
    - Episodic urticaria
      - Duration >6 weeks but not continuous
    - Physical urticaria: induced by exogenous physical stimulus; lesions occur within minutes of provocation and generally resolve <2 hours and are localized to the stimulated area
      - Triggered by mechanical stress
        △ Dermatographism (factitious urticaria)
        △ Delayed pressure urticaria (DPU)
        △ Vibratory angioedema (see AE section)
      - Triggered by temperature changes
        △ Heat/stress = cholinergic urticaria
        △ Adrenergic urticaria
        △ Localized heat contact urticaria
        △ Primary/secondary cold contact urticaria
        △ Reflex cold urticaria
        △ Familial cold urticaria
  - Triggered by other exposures
   △ Primary/secondary solar urticaria
   △ Aquagenic urticaria
   - Contact urticaria
     △ Immunologic (allergic reaction with specific IgE): sensitized to environmental allergens (grass, animals, foods)
     △ Non-immunologic (IgE-independent): secondary to direct effects of urticants on blood vessels (cinnamic aldehyde in cosmetics, nettle stings)
- Pathology: perivascular infiltrate of lymphocytes and eosinophils with some neutrophils with extension of eosinophils into the dermis, arrayed between collagen bundles
- Treatment
  - Antipruritic lotions and avoidance of triggers
  - First line: antihistamines (first H1 antihistamine, then add H2 antagonist if necessary)
  - Second line: systemic corticosteroids (for emergencies; avoid in chronic urticaria), epinephrine (for severe throat angioedema/anaphylaxis only), doxepin combos
  - Third line: immunotherapy (for severe refractory autoimmune urticaria only): IVIG, cyclosporine, plasmapheresis

Angioedema (AE)
- Epidemiology: hereditary form is AD
- Pathogenesis
  - Hereditary AE: mutation in structural gene for C1 inhibitor leading to
    - Reduced quantity (type 1) secondary to trans inhibition of the normal allele or increased catabolism of C1 INH
    - Reduced function (type 2)
  - Acquired AE: secondary to formation of inhibitory autoantibodies against C1 INH or persistent low-level activation of C1q by anti-idiotypic antibodies
- Clinical features
  - Can merge with wheals, especially at eyelids
  - Can be a feature of anaphylaxis if the throat is involved
  - AE without wheals is a separate clinical entity as this occurs in C1 INH deficiency, ACEi or NSAID reactions, and are managed differently
  - Hereditary AE: low C4
  - Acquired AE: low C4 and low serum C1q
  - Vibratory AE: hereditary (AD) or acquired; vibratory stimulus (jogging, motorcycles) lead to localized swelling and erythema in minutes
  - Food/exercise-induced anaphylaxis: occurs within minutes of exercise after prior ingestion of specific foods or within 4 hours of a heavy meal
Psoriasis, plaque
Tinea corporis

Id Reaction (Autoeczematization)
Epidemiology: exact prevalence unknown
Pathogenesis
- Exact cause of the id reaction is unknown
- Abnormal immune recognition of autologous skin antigens
- Increased stimulation of normal T cells by altered skin constituents
- Lowering of the irritation threshold
- Dissemination of infectious antigen with a secondary response
- Hematogenous dissemination of cytokines from a primary site
Clinical features
- Symmetric, pruritic, erythematous, maculopapular, or papulovesicular eruption at a site distant from the primary infection or dermatitis
- Begins 1 to 2 weeks after primary infection or dermatitis
Pathology
- Superficial perivascular lymphohistiocytic infiltrate with a spongiotic epidermis and vesiculation
- Infectious agents not found in the specimens
Treatment
- Systemic or topical corticosteroids
- Wet compresses
- Systemic or topical antihistamines

Urticarial Vasculitis
Epidemiology: Middle-aged women
Clinical features
- Actually considered an urticarial dermatosis and not urticaria
- Lesions last > 24 hours (unlike urticaria) although clinically appears like urticaria
- Lesions are pruritic and/or painful (burning sensation)
- Often occurs at pressure points and may resolve with residual purpura
- 40% develop angioedema; 50% develop arthralgia (transient/migratory)
- Course is unpredictable and usually more severe in hypocomplementemic patients
- Acute hemorrhagic edema of childhood: urticarial vasculitis with prominent cutaneous hemorrhage in young children
Pathology
- Evidence of leukocytoclastic vasculitis, fibrinoid deposits in/around blood vessels, extravasation of red cells, endothelial cell swelling, perivascular cellular infiltrate rich in neutrophils
- Need to biopsy a lesion that is < 24 hours old for accuracy
Treatment
- No universally effective therapy (no randomized trials)
- Antihistamines are usually insufficient except in mild cases
- 50% improve with NSAIDs
- Isolated positive reports with colchicine, dapsone, hydroxychloroquine

Acrokeratosis Verruciformis of Hopf
Epidemiology: AD
Clinical features: flat wart-like papules on the dorsal aspects of the extremities; debatable if truly a separate disease vs part of Darier’s disease

Hailey-Hailey Disease
Epidemiology: AD
Pathogenesis
- Mutations in the gene ATP2C1 that encodes the Golgi-associated Ca\(^{2+}\) ATPase
- Golgi Ca\(^{2+}\) depletion may impair complete processing of junctional proteins, resulting in a loss of cellular adhesion in the stratum spinosum (acantholysis)
Clinical features
- Initial symptoms and lesions usually develop during the second or third decade
- Sites of predilection include intertriginous areas, lateral neck
- Initial lesion is a flaccid vesicle on erythematous or normal skin, which easily ruptures

Other Figurate Erythemas (Covered in Separate Chapters)
- Bullous pemphigoid
- Erythema annulare centrifugum
- Erythema multiforme
- Glucagonoma syndrome
- Granuloma annulare
- Lupus erythematosus, subacute cutaneous
- Lyme disease
- Pityriasis rubra pilaris
lymphocytes, neutrophils, plasma cells and eosinophils in the dermis

- Treatment
  - Often resistant to therapy
  - IL corticosteroids
  - Oral dapsone or clofazimine
  - PUVA

**Sweet’s Syndrome (Acute Febrile Neutrophilic Dermatosis) (Fig. 8-10)**

- Epidemiology
  - Worldwide distribution
  - Female predominance 4:1
  - Average age of onset 30–60 years
  - Up to 20% have internal malignancies (no female predominance)
  - Drug induced cases occurs more often in women
- Pathogenesis: unknown
- Clinical features
  - Initial cutaneous lesions are tender, non-pruritic, erythematous plaques or papules, which may coalesce
  - Vesiculobullous variant most frequently associated with myelogenous leukemia and can break down with ulceration

**Granuloma Faciale (Fig. 8-9)**

- Epidemiology: idiopathic; predominantly in middle-aged white men
- Pathogenesis: unknown
- Clinical features
  - Solitary, asymptomatic smooth red-brown to violaceous plaque on the face
  - Predominantly on the face
  - Chronic and only occasionally spontaneously resolves
  - Not associated with systemic disease
- Pathology: normal epidermis, Grenz zone and a dense, nodular and diffuse infiltrate of
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• Favors the head, neck and upper extremities, but tends to be more widespread when associated with malignancy
• An upper respiratory tract infection or flu-like illness frequently precedes the development of the syndrome
• Fever is common
• Extracutaneous involvement common, including ocular involvement, arthralgias, myalgias, arthritis, neutrophilic pulmonary alveolitis, multifocal sterile osteomyelitis
• Associated diseases include the following
  – Streptococcal infection
  – GI yersiniosis
  – Hematologic malignancy (especially AML)
  – Solid tumors—carcinoma of the GU tract, breast and colon
  – Inflammatory bowel disease
  – Drugs (GM-CSF, furosemide, hydralazine, minocycline, Bactrim and all-trans-retinoic acid)
  – Autoimmune disease: SLE, Behcet’s autoimmune thyroid disease, dermatomyositis, sarcoid
• Diagnostic criteria: (requires 2 major and 2 minor)
  • Major criteria
    – Abrupt onset of typical cutaneous lesions
    – Histopathology consistent with Sweet’s syndrome
  • Minor criteria
    – Preceded by one of the associated infections or vaccinations; accompanied by one of the associated malignancies or inflammatory disorders; associated with drug exposure or pregnancy
    – Presence of fever and constitutional signs and symptoms
    – Leukocytosis
    – Excellent response to corticosteroids
• Pathology
  • Papillary dermal edema
  • Dense diffuse dermal nodular and perivascular neutrophilic infiltrate without vasculitis
• Treatment
  • Cutaneous lesions may involute spontaneously
  • Recurrences occur in 30% (with or without treatment)
  • Treatment of underlying condition
  • Oral prednisone (0.5–1 mg/kg/day) for 4–6 weeks

Pyoderma Gangrenosum (Fig. 8-11)

• Epidemiology
  • Most commonly women between 20–50 years old
  • 50% have underlying systemic disease
  (Inflammatory bowel disease, arthritis, and myeloproliferative disorders)
• Pathogenesis
  • idiopathic in 25–50%
  • immunologic abnormality (autoimmune)
  • 15% have monoclonal gammopathy (usually IgA)
  • PAPA syndrome (pyogenic sterile arthritis, PG, and acne): mutations in CD2 binding protein 1, which is thought to lead to an abnormal inflammatory response
• Clinical features
  • Painful cutaneous lesions that occur on lower extremities (pretibial) but can occur anywhere
  • Start as a tender papulopustule/bulla/nodule with surrounding erythematous/violaceous base
  • All lesions undergo necrosis leading to a central shallow/deep ulcer with a purulent base and irregular, undermined/overhanging gunmetal-colored border that extends centrifugally
  • Re-epithelialization occurs from the margins and heals with atrophic cribriform pigmented scars
  • Lesion number varies from one to over a dozen and can coalesce
  • Classically described as rapidly expanding but can be more indolent
• Variants
  – Vesiculobullous form (atypical or bullous PG)
    ▲ Associated with AML, myelodysplasia, and myeloproliferative disorders (CML)
    ▲ Favors face and upper extremities (dorsal hands)
  – Pustular PG
    ▲ Associated with IBD
    ▲ Multiple small sterile pustules that regress without scarring
- Superficial granulomatous PG
  ▲ Associated with trauma, i.e., surgery
  ▲ Localized superficial vegetative/ulcerative lesion; favors the trunk
- Pyostomatitis vegetans: associated with IBD; chronic vegetative sterile pyoderma of labial/buccal mucosa
- Children: favors head, genital, and perianal areas
- Pathology
  - Non-specific, especially if partially treated or minimally inflamed
  - Early lesions: neutrophilic vascular reaction that may be folliculocentric
  - Active lesions: neutrophilic infiltrates with leukocytoclasis
  - Fully developed ulcers: necrosis with surrounding mononuclear cell infiltrates and fibrosing inflammation at the edge of the ulcer
- Treatment
  - First line: local +/- systemic corticosteroids +/- adjunctive systemic therapies
  - 2nd line: cyclosporine, tacrolimus, thalidomide
  - For concomitant Crohn’s disease: infliximab
  - Total colectomy for ulcerative colitis is not a guaranteed cure for associated PG

GRANULOMATOUS PROCESSES

Granuloma Annulare (Pseudorheumatoid Nodule) (Fig. 8-12)

- Epidemiology
  - Two-thirds are < 30 years of age
  - Female: male: 2:1
- Pathogenesis
  - Etiology unknown but postulated to be a delayed-type hypersensitivity reaction to an unknown antigen (possibly a TH1-mediated inflammatory reaction)
  - Thought to be primarily a disorder of elastic tissue injury
  - Rare familial cases reported: associated with HLA-Bw35
- Clinical features
  - Self-limited benign disease
  - Annular plaques that favor the extremities: hands/arms > legs/feet > trunk
  - Plaques can be skin-colored, violaceous, or pink and are composed of individual small papules that can be umbilicated
- Variants
  - Generalized GA: symmetric distribution on trunk and extremities; later age of onset; poorer response to therapy; increased prevalence of HLA-Bw35 allele; 45% have lipid abnormalities
  - Perforating GA: small papules with central umbilications/crusts/ulcerations on dorsal hands/fingers; exhibits transepidermal elimination of degenerating collagen histologically
  - Deep dermal/subcutaneous GA: large, painless, skin-colored nodules = “pseudorheumatoid nodules”; more common in children 5–6 yo
  - Patch GA: patches of erythema on extremities/trunk or symmetrical lesions on dorsal feet; can lack annular configuration
  - Paraneoplastic GA: associated with solid tumors, Hodgkin disease, non-Hodgkin lymphoma, and granulomatous mycosis fungoides
    - Classic GA and perforating GA can occur in herpes zoster scars
- Pathology
  - Focal degeneration of collagen and elastic fibers, mucin deposition, and a perivascular/interstitial lymphocytic infiltrate in the upper/mid dermis
- Histiocyte patterns
  - Infiltrative/interstitial: scattered histiocytes between collagen fibers with mucin deposition between collagen bundles (highlighted with Alcian blue and colloidal iron stains)
  - Palisading granulomas: with central connective tissue degeneration surrounded by histiocytes and lymphocytes; mucin is abundant in the center of the granuloma (more common in deep GA)
  - Epitheliod histiocytic nodules (like sarcoidosis)
- Vascular changes: variable; can have fibrin, C3, and IgM deposition in vessel walls with occlusion; can be predictive of associated systemic disease
- Treatment
  - Localized/asymptomatic disease: reassurance/observation
  - First line: high-potency topical corticosteroids +/- occlusion, intralesional corticosteroid injections
  - Cryosurgery, PUVA/UVA1, CO2 laser, dapsone
  - Spontaneous resolution in 50% but recurrence in 40% (occurs at original sites but clears more rapidly)

**Actinic Granuloma (Annular Elastolytic Giant Cell Granulomas)**
- Clinical presentation
  - Annular/serpiginous areas with raised erythematous borders
  - Located on heat/sun-damaged skin
  - Presents with 1-10 plaques
- Pathology: may lack the classic palisaded arrangement observed in GA; elastosis is abundant in the mid-dermis outside the granuloma; elastic tissue is absent from the center

**Chondrodermatitis Nodularis Helices**
- Epidemiology: occurs in adults > 40 yo
- Pathogenesis
  - Predisposing factors: actinic damage, cold exposure, trauma, local ischemia, radiotherapy
  - Helical lesions: may begin with perichondritis/folliculitis
  - Antihelical lesions: may begin with pressure-induced ischemia, involving the cartilage secondarily
- Clinical features
  - Skin-colored to erythematous dome-shaped nodules with central crusts or keratin-filled craters
  - Most occur on upper helical rim or the mid-lower antihelical rim; sites often correspond to outermost portions of pinna
  - Often exquisitely tender to palpation
  - Women: commonly on antihelix
  - Men: commonly on helix
- Pathology
  - Well-circumscribed area of acanthosis, parakeratosis, and hypergranulosis
  - Central crater with epidermal disruption +/- keratotic plug/dermal debris
  - Lymphohistiocytic infiltrate extends into thickened perichondrium
- Treatment
  - Relieve/eliminate pressure (special “donut hole” pillows)
  - Topical corticosteroids/antibiotics

**Sarcoidosis**
- Epidemiology
  - Bimodal age distribution: peaks at 25–35 years and 45–65 years
  - In the United States: higher incidence in African-Americans, who have more acute and severe disease (commonly 40 yo African-American female)
  - New-onset most common in winter/spring
- Pathogenesis
  - Upregulation of CD4+ T-helper cells of Th1 subtype after antigen presentation → epitheliod granulomas
  - Etiology unknown: may be autoimmune or infectious
  - Genetic susceptibility: HLA-1, HLA-B8, HLA-DR3 alleles; ACE gene polymorphisms
- Clinical features
  - Papules/plaques – red/brown, yellow/brown, erythematous, or violaceous (lupus pernio)
  - Favor the face, lips, neck, and upper trunk/extremities
  - Usually fairly symmetric without scale
  - Commonly develop within pre-existing scars or sites of prior trauma
  - Upon diascopy, pressure induces blanching and lesions appear to have “apple jelly” color
  - Can have prominent telangiectasias = angiolupoid sarcoidosis

**FIGURE 8-13** Sarcoidosis. (Courtesy of Dr. Asra Ali.)
bodies (silica, wood, suture material, glass) are birefringent (identify with polarized light).

- Treatment: surgical removal of the foreign body.

**CUTANEOUS DISORDERS OF INFILTRATION**

**Scleromyxedema (Generalized and Sclerodermoid Lichen Myxedematosus)**

Chronic idiopathic disorder characterized by numerous firm papules and areas of induration that are due to dermal mucin deposition in association with an increase of dermal collagen.

- Epidemiology: affects middle-aged adults of both sexes equally.
- Pathogenesis: unknown; significance of monoclonal gammopathy is uncertain.
- Clinical features:
  - Numerous 2–3 mm firm, waxy closely spaced papules develop in a widespread symmetrical distribution pattern.
  - Most common sites are hands, forearms, neck.
  - Almost always associated with monoclonal gammopathy—IgG with $\gamma$ light chains.
  - Less than 10% progress to multiple myeloma.
  - Can have internal manifestations: muscular, neurologic, rheumatologic, pulmonary, renal, and cardiovascular.
- Pathology:
  - Diffuse deposits of mucin in the upper and mid reticular dermis.
  - Increase in collagen.
  - Marked proliferation of irregularly arranged fibroblasts.
- Treatment:
  - Corticosteroids (topical, intralesional, or systemic).
  - Hydroxychloroquine, chloroquine.
  - Methotrexate, thalidomide, isotretinoin, minocycline, allopurinol.

**Localized Variants of Lichen Myxedematosus**

- Clinical features:
  - Small, firm, waxy papules limited to a few sites (upper and lower limbs and trunk).
  - Skin is the only site of involvement.
  - Not associated with sclerosis, paraproteinemia, systemic involvement or thyroid disease.
- Four subtypes:
  1. Discrete papular form.
  2. Acral persistent papular mucinosis.
  3. Cutaneous mucinosis of infancy.
  4. Pure nodular form.
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Associated hematologic disorders: plasma cell dyscrasias, myelodysplasia, myeloproliferative disorders, hairy cell leukemia

Immune complex deposition as a result of chronic antigenic exposure or high circulating antibody levels are thought to be the underlying pathologic mechanism

Clinical features
• Red-violet to red-brown papules, plaques and nodules that favor extensor surfaces
• Arthralgias can develop in underlying joints
• Chronic course, but majority resolve spontaneously over 5–10 years

Pathology
• Neutrophilic infiltrate in the upper and mid dermis with eosinophils
• Late stage lesions with extracellular cholesterol deposits and fibrosis

Treatment
• Dapsone with relapse upon discontinuation
• NSAIDs, niacinamide, tetracyclines, chloroquine, colchicine, plasmapheresis
• Intralesional corticosteroids

Scleredema
Symmetrical diffuse induration of the upper part of the body caused by a thickened dermis and depositions of mucin

Epidemiology
• Any age but more common in middle-aged and older adults
• Male to female ratio is equal
• No racial predilection

Pathogenesis
• Associated infections: β-hemolytic streptococcus, HIV, hepatitis B virus
• Associated autoimmune or inflammatory conditions: Wegener’s granulomatosis, inflammatory bowel disease, relapsing polychondritis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)

• Associated with HIV, exposure to toxic oil or L-tryptophan, hepatitis C virus

Colloid Milium
• Clinical features
  • Grouped whitish papules on sun-exposed skin—dorsal hands, face, neck, ears
  • Three forms: nodular, adult onset and juvenile (AD)
• Pathology
  • Nodular fissured masses of amorphous eosinophilic material in the superficial dermis
  • Congo red and crystal violet often stain positive
• Treatment: dermabrasion, cryotherapy, diathermy

Favre-Racouchot Syndrome (Fig. 8-14)
• Clinical features
  • Multiple large open comedones develop on the lateral in inferior aspects of the periorbital area
  • Associated with marked solar elastosis
• Pathology: dilated pilosebaceous openings and cyst-like spaces filled with horny material

Erythema Elevatum Diutinum
• Epidemiology
  • Any age but more common in middle-aged and older adults
  • Male to female ratio is equal
  • No racial predilection
• Pathogenesis
  • Associated infections: β-hemolytic streptococcus, HIV, hepatitis B virus
  • Associated autoimmune or inflammatory conditions: Wegener’s granulomatosis, inflammatory bowel disease, relapsing polychondritis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)

• Associated with HIV, exposure to toxic oil or L-tryptophan, hepatitis C virus

FIGURE 8-14  Favre racouchot. (Courtesy of Dr. Asra Ali.)
CALCIUM DEPOSITS

Subepidermal Calcifying Nodule (Solitary Congenital Nodular Calcification, Winer’s Nodular Calciosis)

- Epidemiology: idiopathic (dystrophic calcification), most common in children
- Pathogenesis: trauma in utero, calcification of pre-existing milia, eccrine duct hamartoma, or nevi
- Clinical features
  - Solitary firm nodule
  - Most often found on head and neck, most common on ears
  - Lateral aspects of the digits
- Pathology: focal amorphous masses of calcium with inflammatory infiltrate
- Treatment: surgical removal if lesions are symptomatic

Calciphylaxis (Fig. 8-15)

- Epidemiology: predominant in females and diabetics; patients with obesity and poor nutritional status at higher risk
- Pathogenesis
  - Necrosis of skin secondary to calcification and occlusion of small cutaneous arterioles
  - Associated with: chronic renal failure, hypercalcemia, hyperphosphatemia, an elevated calcium-phosphate product, and secondary hyperparathyroidism; common in patients with endstage renal disease (ESRD)
- Clinical features
  - Early lesions are violaceous reticulated patches
  - Bullae may develop with tissue necrosis and ulcer formation
  - Lesions are extremely painful
  - Lower extremities most common location (90%); proximal greater than distal, where body fat is most abundant
  - Mortality rate of calciphylaxis is reported to be as high as 60% to 80%; the leading cause of death is sepsis from infected, necrotic skin lesions
  - Calcium-phosphate product frequently exceeds 60 to 70 mg\(^2/dL^2\)
  - Laboratory tests for blood urea nitrogen and creatinine levels; calcium, phosphate, alkaline phosphatase, and albumin levels; parathyroid hormone level, and coagulation factors: prothrombin time (PT), activated partial thromboplastin time (aPTT), protein C, protein S, anticardiolipin, lupus anticoagulant, factor V Leiden, and homocysteine

Cutaneous Myxoma

- Clinical features
  - Papular lesion
  - May be seen in Carney complex (33% of patients)
  - Perifollicular in orientation
  - Includes subungual myxomas
  - Propensity for local recurrence if incompletely excised
- Pathology
  - Myxoid and variably cellular
  - Localized accumulation of mucin within the reticular dermis

• Pathology: Calcium deposits within the walls of blood vessels, mixed inflammatory infiltrate; subcutaneous calcium deposits with lobular panniculitis and fat necrosis vascular microthrombi, epidermal necrosis

• Treatment
  • Supportive with appropriate wound care and surgical debridement
  • Serum calcium and phosphate concentrations must be brought to low-normal levels; aggressive wound care, parathyroidectomy, hyperbaric oxygen, low calcium dialysis and systemic corticosteroids with cimetidine

**Osteoma Cutis (Cutaneous Ossification)**

• Epidemiology
  • Equal incidence in men and women
  • Four genetic disorders that feature cutaneous or subcutaneous ossification:
    – Fibrodysplasia ossificans progressive (FOP)
    – Progressive osseous heteroplasia (POH)
    – Plate-like osteoma cutis (POC)
    – Albright’s hereditary osteodystrophy (AOH)

• Pathogenesis
  • Intramembranous ossification begins in the dermis
  • Familial occurrence of Albright’s hereditary osteodystrophy (pseudohypoparathyroidism and pseudopseudohypoparathyroidism) may be present

• Clinical features
  • Face, extremities, scalp, digits, and subungual regions
  • POH is more progressive and has associated morbidity due to extensive ossification, lesions are symptomatic papules and nodules
  • POC has one or few areas of involvement, non progressive
  • AHO associated with pseudohypoparathyroidism and brachydactyly

• Pathology: mature bone is found in the dermis or extends into the subcutaneous tissue

• Treatment
  • Underlying abnormalities of calcium/or phosphorus should be addressed
  • Excision of the neoformed bone
  • Recurrence is common in genetic disorders that result in ossification of skin

**Calcinosis Cutis (Cutaneous Calcification)**

• Pathogenesis
  • Calcium deposits form in the skin
  • Insoluble compounds of calcium (hydroxyapatite crystals or amorphous calcium phosphate) are deposited within the skin

• Clinical features: four major types
  • Dystrophic: due to trauma, inflammatory processes, tumors, infections
  • Metastatic: abnormal calcium or phosphate metabolism
  • Iatrogenic: secondary to a treatment or procedure
  • Idiopathic: no causative factor identifiable
    – Ectopic calcification can occur in the setting of hypercalcemia and/or hyperphosphatemia (if calcium-phosphate product exceeds 70 mg²/dL²)
    – Multiple, firm, whitish dermal papules, plaques, nodules, or subcutaneous nodules
    – Laboratory studies: serum calcium, inorganic phosphate, alkaline phosphatase, and albumin

• Pathology: granules and deposits of calcium are seen in the dermis, with or without a surrounding foreign-body giant cell reaction

• Treatment: correct the underlying problem

**Gout**

• Epidemiology
  • More common in men
  • Patients with hypertension, diabetes, hyperlipidemia, chronic kidney disease, or the metabolic syndrome are at increased risk for developing gout

• Pathogenesis
  • Over 99% of cases associated with decreased renal excretion of uric acid
  • Rarely, overproduction of uric acid (Lesch–Nyhan syndrome with self-mutilation)
  • Secondary elevation in leukemia, polycythemia, hemolytic anemia, tumor chemotherapy; diuretics, chronic renal disease, and ketoacidosis (diabetes mellitus, fasting)

• Clinical features
  • Acute arthritis with exquisite pain, swelling; most often involves great toe (podagra) (60%), less often other digits (10%), feet (10%), or other joints. Renal stones a risk
  • Cutaneous findings include uric acid deposits (tophi) most often on ears or periaicular; differential includes rheumatoid nodule

• Pathology
  • Epidermis normal or ulcerated; large deposits of amorphous, basophilic material with parallel, needle-shaped clefts within the dermis and subcutis; lymphohistiocytic infiltrate, often with granulomatous foreign-body reaction
  • Fixation in 100% ethanol, crystals are birefingent; crystals dissolve if tissue fixed with formaldehyde; the fixation fluid can be tested for presence of urates
PERFORATING DISORDERS

- Treatment: acute flares treated with NSAID or colchicine; prophylaxis with diet, probenecid or allopurinol

Hemosiderin

- Pathogenesis
  - Intradermal deposits of iron (hemosiderin), chemical degredation
  - Associated with hemorrhage (purpura, stasis dermatitis)
- Clinical features
  - Clinical: brown, reddish-brown macules, patches
  - Skin pigmentation in hemochromatosis is caused by epidermal melanin, but hemosiderin is present as well
- Pathology: siderosis around foreign bodies (Perl’s iron stain)
- Treatment: focuses on limiting the effects of the underlying disease leading to continued deposition. In hemochromatosis, this entails frequent phlebotomy

Elastosis Perforans Serpiginosa (EPS)

- Epidemiology
  - Begins during childhood or early adulthood
  - 40% of cases occur in association with genetic disorders, including
    - Down’s syndrome
    - Ehler-Danlos syndrome
    - Osteogenesis Imperfecta
    - Marfan’s syndrome
    - Pseudoxanthoma elasticum
    - Rothmund-Thompson syndrome
    - Cutis laxa
    - Acrogyria
  - Can be induced by penicillamine
- Clinical features
  - Keratotic 2–5 mm papules, arranged in a serpiginous pattern
  - Most commonly on the lateral neck, face arms and flexural areas
  - Minimal pruritus
- Pathology
  - Plug of hyperkeratosis +/− parakeratosis
  - Elastic fibers are seen within the plug or epidermis
  - If penicillamine induced, characteristic lumpy-bumpy elastic fibers with lateral buds seen in lesional and non-lesional skin
- Treatment
  - Inherited forms are often mild and don’t require treatment
  - Local cryotherapy
  - Tangential excision
  - Electrosurgical destruction
  - Cellophane tape stripping

Kyrle’s Disease

- Epidemiology
  - Adult onset
  - Occurs in up to 10% of dialysis patients
  - Usually in association with diabetes mellitus and/or pruritus of renal failure
  - Rarely occurs with the pruritus of liver disease or internal malignancy
  - May represent end stage of perforating folliculitis
- Pathogenesis
  - Increased fibronectin levels are found in diabetics and patients with uremia
  - Fibronectin binds to type IV collagen and keratinocytes and may incite epithelial proliferation and perforation
- Clinical features: occurs most commonly on the legs
- Pathology
  - Plug of crusting or hyperkeratosis with variable parakeratosis
  - Transepidermal elimination of elastic fibers and collagen
- Treatment
  - Phototherapy
  - Intralesional steroids
  - Oral/topical retinoids

Perforating Folliculitis

- Epidemiology: more common in women
- Clinical features
  - Onset in young adulthood
  - Primarily affects the trunk and extremities
  - May be ordinary folliculitis with follicular rupture
- Pathology: necrotic material extruded
- Treatment
  - Intraleisional corticosteroids
  - Oral/topical retinoids

Reactive Perforating Collagenosis

- Epidemiology: rare
- Clinical features
  - Begins during childhood
  - After superficial trauma, patients develop keratotic papules over the following 3–4 weeks
  - Koebnerization can occur
  - Arms and hands most commonly involved
  - Tend to spontaneously resolve over 6–8 weeks
  - Rare familial variant: verrucous perforating collagenoma in which severe trauma triggers
Chapter 8  DISORDERS OF CORNIFICATION, INFILTRATION, AND INFLAMMATION

Clinical features
- Primary anetoderma occurs when there is no underlying disorder—there are Two types
  - Jadassohn-Pellizzari type—with preceding inflammatory lesions
  - Schweninger-Buzzi type—without preceding inflammatory lesions
- Secondary anetoderma occurs in the same site as a previous skin lesion or in association with underlying diseases (including HIV or antiphospholipid antibody syndrome)
- Characteristic lesions are flaccid circumscribed areas of slack skin that are a reflection of markedly reduced or absent dermal elastic fibers—can appear as depressions, wrinkling or sac-like protrusions
- “Buttonhole sign” present
- Chest, back, neck and upper extremities are sites of predilection
- Described in premature infants and possibly related to the use of cutaneous monitoring leads or adhesives

OTHER DISORDERS

**Flegel's Disease (Hyperkeratosis Lenticularis Perstans)**
- Epidemiology: AD or sporadic
- Pathogenesis: lamellar granule’s (Odland bodies) are absent or altered on electron microscopy, which results in hyperkeratosis
- Clinical features
  - Numerous symmetric keratotic papules no the dorsal aspects of the feet and distal arms and legs, including the palms and soles
  - Attached scale, more prominent at periphery—removal may result in bleeding
  - Associated with endocrine disorders such as diabetes mellitus and hyperthyroidism
- Treatment
  - Topical 5-fluorouracil cream
  - PUVA with topical calcipotriol

**Malignant Atrophic Papulosis (Degos Disease)**
- Epidemiology: equal incidence in men and women; typically occurs between the 2nd and 4th decades
- Clinical features
  - Vaso-occlusive disorder that affects the skin, gastrointestinal tract and CNS
  - Skin lesions begin as crops of small 2–5 mm erythematous papules on the trunk or extremities that over 2–4 weeks evolve to have a central depression and porcelain white scar with a rim of telangiectasias
  - Skin findings usually precede systemic findings
- Pathology: wedge shaped area of altered dermis with a sparse perivascular lymphocytic infiltrate and atrophic epidermis
- Treatment: no proven treatment—consider pentoxifylline or aspirin

**Anetoderma (Fig. 8-16)**
- Epidemiology: more frequently in women aged 15–25 years
• Pathology: focal, complete loss of elastic tissue in the papillary and/or mid-dermal dermis
• Treatment: surgical excision in patients with limited lesions

**Idiopathic Atrophoderma of Pasini and Pierini**

- Epidemiology
  - Women to men 6:1
  - Starts insidiously during the 2nd or 3rd decade of life
- Pathogenesis: possible role for Borrelia burgdorferi (+ serology in 40–60%)
- Clinical features
  - Lesions appear on the trunk, especially the back and lumbosacral regions
  - Often symmetric and bilateral, but can appear along Blaschko’s lines
  - The borders or edges are sharply defined with “cliff-drop” borders
  - Perilesional skin is normal
  - The course is progressive
- Treatment
  - No treatment has been proven effective
  - Penicillin has been used with inconclusive results
  - Q switched alexandrite laser for hyperpigmentation

**Ainhum: Autoamputation of a Digit**

- Epidemiology: triggered by trauma
- Pathogenesis: fibrotic band develops from a flexural groove and progressively encircles the toe until spontaneous autoamputation occurs
- Clinical features: most commonly the fifth toe
- Pathology: fissuring and epidermal hyperkeratosis and parakeratosis, followed by a fibrotic reaction under the deepening fissure; as scar tissue contracts, it constricts and narrows neurovascular bundles
- Treatment: no current treatment appears to halt the progression of ainhum

**Pseudoainhum (Amniotic Band Syndrome)**

- Epidemiology: may be acquired or congenital
- Pathogenesis
  - Due to a collagen band around the affected area;
  - Occurs as a secondary event resulting from certain hereditary and nonhereditary diseases leading to annular constriction of digits
  - Can occur after premature rupture of the amniotic membrane
- Clinical features
  - Ring-like constriction bands, presenting as circumferential grooves of variable depth on the digits, extremities, neck or trunk
  - Early in gestation can result in the body wall complex, characterized by body wall defects

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![FIGURE 8-17 Pseudoxanthoma elasticum.](image-url)
Calcified blood vessels of the gastric and intestinal mucosa may increase the propensity for rupture and hemorrhage leading to GI bleeding

Pathology: calcified elastic fibers in the mid and reticular dermis

Treatment
- Reconstructive surgery for skin sagging
- Ophthalmology referral
- Regular exercise, weight control, avoidance of smoking and excessive alcohol, treatment of dyslipidemia and hypertension

**Hypertrophic Osteoarthropathy (HOA)**
Divided into primary (pachydermoperiostosis) and secondary (hypertrophic pulmonary osteoarthropathies) forms

- Epidemiology
  - Pachydermoperiostosis (PDP): autosomal dominant; accounts for 5% of all cases
  - Hypertrophic osteoarthropathy (pulmonary hypertrophic osteoarthropathy): associated with underlying cardiopulmonary diseases and malignancies
  - Digital clubbing and subperiosteal new bone formation
  - Associated with polyarthritis, cutis verticis gyrata, seborrhea, and hyperhidrosis

- Treatment: NSAIDs or corticosteroids may alleviate the polyarthritis associated with PDP

**Dermatofibrosis Lenticularis Disseminata (Buschke-Ollendorf Syndrome)**

- Epidemiology: AD
- Pathogenesis: mutation causes loss of function in LEMD3 gene
- Clinical features
  - Multiple skin-colored or slightly yellowish papules
  - Osteopoikilosis (stippled appearance to bones) represents islands of increased bone density
  - Nasolacrimal duct obstruction, amblyopia, strabismus, benign lymphoid hyperplasia, hypopigmentation, and short stature
- Pathology: poorly demarcated area of increased dermal collagen bundles in a haphazard array

**Pseudocyst of the Auricle**

- Epidemiology: middle-aged men
- Clinical features
  - Usually arises in the scaphoid fossa
  - Usually unilateral
  - Presents as a painless swelling and tends to arise over a course of a few weeks

- Pathology
  - Cavity within the auricular cartilage that contains clear fluid
  - Cartilage lining may show degenerative changes

- Treatment
  - Aspiration, with or without intralesional corticosteroids
  - Incision and drainage with destruction of the cavity

**ULCERATION**

**Pressure Sores (Decubitus Ulcers)**

- Epidemiology: common in elderly patients who are confined to hospital beds
- Pathogenesis
  - Prolonged immobility and recumbency
  - Vascular disease
  - Neurological disease causing diminished sensation
  - Malnutrition, severe systemic disease and general debility

- Clinical features
  - Occur in immobilized patients
  - Due to chronic pressure in tissues overlying bony prominences
  - Lumbosacral region, greater trochanters, and heels are the most common areas
  - Tissue ischemia and neural damage lead to necrosis
  - Varying degrees
    - I: erythema
    - II: induration, blisters
    - III: shallow ulcers
    - IV: deep necrosis of fat and muscle
    - V: bone destruction
  - Underlying a small skin defect, there can be vast necrosis of deep tissues and proliferation of granulation tissue

- Pathology: epidermal necrosis, subepidermal bulla, vascular proliferations, often secondary inflammation

- Treatment
  - Prevention: turning recumbent patients regularly
  - Treatment of malnutrition
  - Debridement.
  - Regular cleansing with normal saline or 0.5% aqueous silver nitrate
  - Antibacterial, absorbent dressings and semipermeable dressings such as Opsite, if there is no infection
  - Appropriate systemic antibiotic if an infection is spreading
  - Plastic surgical reconstruction may be indicated in the young when the ulcer is clean
**Questions**

1. Which of the following ichthyoses is associated with atopy?
   - A. Ichthyosis vulgaris
   - B. Lamellar ichthyosis
   - C. X-linked ichthyosis
   - D. Ichthyosis linearis circumflexa
   - E. Ichthyosis bullosa of Siemens

2. All of the following ichthyoses have an associated ocular finding **EXCEPT**:
   - A. Conradi-Hunerman syndrome
   - B. X-linked ichthyosis
   - C. Netherton syndrome
   - D. Sjogren-Larson syndrome
   - E. Refsum syndrome

3. Which 2 of the following ichthyoses are associated with scarring alopecia?
   - A. CHILD syndrome
   - B. Keratitis-ichthyosis-deafness syndrome
   - C. X-linked ichthyosis
   - D. Conradi-Hunerman syndrome
   - E. Lamellar ichthyosis

4. Which of the palmoplantar keratodermas has a predisposition for malignancy?
   - A. Mal de Meleda
   - B. Vohwinkel syndrome
   - C. Howel-Evans syndrome
   - D. Papillon-Lefevre syndrome
   - E. Unna-Thost syndrome

5. Auditory testing is recommended for patients with which of the following palmoplantar keratodermas?
   - A. Richner-Hanhart syndrome
   - B. Vohwinkel syndrome
   - C. Howel-Evans syndrome
   - D. Papillon-Lefevre syndrome
   - E. Unna-Thost syndrome

6. According to Griffith’s classification of pityriasis rubra pilaris, which type is associated with HIV?
   - A. Type I
   - B. Type II
   - C. Type III
   - D. Type IV
   - E. Type V
   - F. Type VI

7. The two most likely drugs to cause an actinic lichenoid drug eruption confined to sun-exposed areas are:
   - A. Beta-blockers
   - B. Gold
   - C. Quinidine
   - D. Quinine
   - E. HCTZ
   - F. Mepacrine

8. Which of the following is associated with the Koebner phenomenon?
   - A. Lichen nitidus
   - B. Lichen striatus
   - C. Lichen planus
   - D. Lichen simplex
   - E. Benign lichenoid keratosis

9. All of the following are associated with pruritus **EXCEPT**:
   - A. Grover’s disease
   - B. Lichen planus
   - C. Pityriasis rosea
   - D. Pityriasis lichenoides
   - E. Lichen simplex

10. Erythema gyratum repens is associated with all of the following **EXCEPT**:
    - A. Lung cancer
    - B. Lupus erythematosus
    - C. Rapid migration of erythema (up to 1 cm/day)
    - D. Trailing scale present on the inner aspect of the advancing edge
    - E. Wood-grain appearance

11. Type I and type II acute angioedema is associated with all of the following **EXCEPT**:
    - A. Low C1q
    - B. Low C2
    - C. Low C4
    - D. Low C1-INH
    - E. Low C4 between episodes

12. Which of the following are recommended for treatment of refractory chronic urticaria?
    - A. Colchicine
    - B. Montelukast
    - C. Dapsone
    - D. Epinephrine
    - E. Glucocorticoids
    - F. Antihistamines

13. Urticarial vasculitis can be associated with each of the following **EXCEPT**:
A. Connective tissue diseases
B. Lymphoreticular malignancies
C. Serum sickness
D. ACE inhibitors
E. Schnitzler’s syndrome
F. Infectious mononucleosis

14. Which of the following is a major criterion of Sweet’s syndrome?
A. Lesions preceded by nonspecific respiratory or gastrointestinal tract infection
B. General malaise and fever
C. ESR > 20 mm/h
D. Abrupt onset of painful or tender erythematous plaques or nodules
E. Excellent response to treatment with systemic corticosteroids or potassium iodide
F. Histopathologic evidence of predominantly neutrophilic infiltration in the dermis with leukocytoclastic vasculitis

15. All of the following perforating disorders are associated with chronic renal failure EXCEPT:
A. Reactive perforating collagenosis
B. Perforating folliculitis
C. Elastosis perforans serpiginosa
D. Kyrle disease
E. Calciphylaxis

16. Which test assists with the diagnosis of elastosis perforans serpiginosa (EPS)?
A. Verhoeff-van Gieson stain
B. Perl’s iron stain
C. Alizarin red stain
D. Congo red stain
E. Kveim test

**Answers**

1. A and D. Both ichthyosis vulgaris and ichthyosis linearis circumflexa are associated with atopic dermatitis. None of the other diseases listed have any known association with atopy.

2. C. Netherton syndrome patients do not have ocular manifestations of disease. X-linked ichthyosis is associated with comma-shaped corneal opacities. Sjogren-Larsson syndrome patients show “glistening dots” of the retina by 1 year of age. Refsum syndrome is associated with “salt and pepper” retinitis pigmentosa, night blindness, and cataracts. Conradi-Hunerman syndrome is associated with focal cataracts.

3. B and E. Keratitis-ichthyosis-deafness syndrome and lamellar ichthyosis are the 2 ichthyoses associated with scarring alopecia. CHILD syndrome patients have ipsilateral non-scarring alopecia. Conradi-Hunerman syndrome patients have patchy non-scarring alopecia. X-linked ichthyosis has no association with alopecia.

4. C. Howel-Evans syndrome is associated with an increased risk of esophageal cancer. None of the other PPK syndromes are associated with malignancy.

5. B. Vohwinkel syndrome is associated with high-frequency hearing loss and requires auditory testing. Patients with Papillon-Lefevre syndrome need referral to a dentist as they can have periodontitis with loss of teeth. Patients with Howel-Evans syndrome need further work-up for detection of esophageal cancer. Richner-Hanhart syndrome patients need a referral to a nutritionist for a low-phenylalanine/tyrosine diet as well as an ophthalmologist as they can develop corneal ulcers and blindness.

6. F. HIV is associated with type VI. Types I and II are associated with adult disease. Types III, IV, and V are associated with juvenile disease.

7. D and E. Quinine and thiazide diuretics are most likely to cause an actinic lichenoid drug eruption. The other drugs listed are medications associated with lichenoid drug eruptions in general.

8. A. Lichen nitidus is the only one associated with the Koebner phenomenon. Lichen planus is associated with hepatitis C virus infection and Wickham striae. Lichen simplex is associated with prurigo nodularis of Hyde.

9. D. Both the acute (PLEVA) and chronic (PLC) forms of pityriasis lichenoides are non-pruritic. All other disorders listed have pruritus, which can be especially severe in lichen simplex.

10. D. Trailing scale on the inner aspect of the advancing edge is associated with erythema annulare centrifugum. All other answer choices are true for erythema gyratum repens.

11. E. C4 may be normal between angioedema episodes. All other answer choices are true.

12. A and C. Colchicine and dapsone are recommended for refractory urticaria. All other answer choices can be used for treatment of chronic urticaria, but are not the drugs of choice for refractory cases.

13. B. Lymphoreticular malignancies are associated with acute urticaria, not urticarial vasculitis. All other choices are associated with urticarial vasculitis. Schnitzler’s syndrome is urticarial vasculitis associated with fever, hepatosplenomegaly, bone pain with osteosclerosis, sensorimotor neuropathy, lymphadenopathy, and monoclonal IgM.

14. D. Answer choice F resembles the other major criterion except that histologically there is no associated leukocytoclastic vasculitis in Sweet’s syndrome.
Answers A, B, C, and E are all minor criteria. To make the diagnosis of Sweet’s syndrome, the patient must fulfill 2 major and 2 minor criteria.

15. C. Elastosis perforans serpiginosa (EPS) has no known association with chronic renal failure. EPS can be associated with inherited fibrous tissue abnormalities, D-penicillamine, or idiopathic etiologies. A, B, and D can be associated with chronic renal failure. Answer choice E is not a perforating disorder but is common in patients with end-stage renal disease.

16. A. Acid orcein-Giemsa, adlehyde fuchsin, and Verhoeff-van Gieson stains are used to diagnosis EPS. Perl’s iron stain is used to detect hemosiderin deposition. The alizarin red stain can be used to diagnose pseudoxanthoma elasticum (PXE). PXE can also be diagnosed with Verhoeff-van Gieson stain (choice A). Congo red stain shows green birefringence in colloid milium. The Kveim test is the most specific test for sarcoidosis where intradermal injection from the spleen or a lymph node of a patient with sarcoidosis is biopsied in 4–6 weeks to examine histologically for noncaseating granuloma formation.

REFERENCES


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MELANOCYTES

- Epidermal melanocytes are dendritic cells
- Provide melanin for 36 neighboring basal and spinous layer keratinocytes
- Number and distribution are the same in all skin types
- Production and distribution/retention of melanin causes different skin colors
- Types of melanin:
  - Phaeomelanin: red-yellow
  - Eumelanin: brown-black
- Melanosomes
  - Membrane-bound spherical organelles, site of melanin synthesis and storage
  - Found in melanocytes; they move from melanocytes to keratinocytes = epidermal melanin unit
- Types of melanosomes:
  - Eumelanosomes: large, elliptical in shape and contain organized fibrillar glycoprotein matrix needed for eumelanin synthesis
  - Pheomelanosomes: smaller, spherical in shape, loose fibrillar glycoprotein matrix
- Four stages of maturation:
  - **Stage I melanosomes (premelanosomes)**
    - Found in the cytoplasm of melanocytes
    - Amorphous matrix; contain unprocessed glycoprotein
  - **Stage II melanosomes**
    - Found in the cytoplasm of melanocytes
    - Round or oval, with longitudinally oriented filaments
    - Contain tyrosinase
    - No active melanin synthesis in eumelanosomes; melanin synthesis (not melanogenesis) in pheomelanosomes
  - **Stage III melanosomes**
    - Found in the cytoplasm or dendrites of melanocytes
    - Round or oval, electron dense, melanin on the internal filament network
    - Tyrosinase activity becomes positive
    - Melanization begins at this stage
  - **Stage IV melanosomes**
    - Found in the cytoplasm or dendrites of melanocytes
    - Round or oval, electron opaque
    - Fully melanized
    - Possess melanin, no enzymatic activity
- Tyrosinase
  - Cofactor: copper (Cu^{2+})
  - Catalyzes two reactions
    - Hydroxylation of tyrosine to dopa (dihydroxyphenylalanine)
    - Oxidation of dopa to dopaquinone

PIGMENTED LESIONS

**Melasma (Fig. 9-1)**

- Increased number of melanocytes, increased melanized melanosomes
- Genetic and hormonal influences in combination with UV radiation
- May be precipitated by the following: oral contraceptive pills, pregnancy thyroid dysfunction, cosmetics, phototoxic or photoallergic drugs
- Clinical findings
  - Brownish hyperpigmented macules and patches, can be confluent or punctate
  - Most commonly seen centrofacial/malar/mandibular distribution
  - Depth may be epidermal, dermal, or mixed
Diagnosis
- Wood’s light (wavelength, 340 to 400 nm): locates pigment; epidermal pigment enhanced, dermal pigment is not

Treatment
- Sunscreen, hydroquinone, tretinoin, chemical peels/microdermabrasion, azelaic acid, compounded agents (steroids, retinoids, hydroquinones), kojic acid, lasers (intense pulsed light, 1064-nm Q-switched Nd:YAG)

Becker’s Nevus (Fig. 9-2)
- Acquired lesion in adolescents, most commonly on the scapular area of the back
- Normal number of basal melanocytes, increased epidermal melanotic hypermelanosis with increased melanin in the basal cell layer
- Increased number of testosterone receptors found in the lesion
- Clinical findings
  - Large, focal, brown, hair-bearing verrucous plaque
  - Back, shoulder, submammary areas are common
  - Associated with underlying musculoskeletal abnormalities (smooth muscle hamartomas, ipsilateral limb hypoplasia) and cutaneous hypoplasias
- Histology
  - Normal number of melanocytes with increased melanin pigment of basal layer, mature hair follicles with increased arrector pili muscles, thick bundles of smooth muscles
- Treatment
  - Surgical excision, laser hair removal

Congenital Nevomelanocytic Nevus (CNN) (Fig. 9-3)
- Presence of a pigmented lesion is noted at birth or soon thereafter
- Categorized by size:
  - Small (<1.5 cm in diameter)
  - Medium (1.6 to 19.9 cm)
  - Large or giant (>20 cm in adolescents and adults or comprising 5% of the body surface area or greater in infants, children, and preadolescents):
- Lifetime risk of developing a melanoma for patients with a large CNN is 6.3%
- Related physical findings
  - Leptomeningeal melanocytosis/neurocutaneous melanosis: giant pigmented nevi located on the head, neck, or posterior midline and/or with multiple satellite lesions may present with
pigmented lesions

present as widespread eruptive lesions or as grouped lesions (agminated)
- Red color due to ectatic blood vessels
- Pigmented spindle cell nevus of Reed: variant of Spitz nevus, usually in adolescent girls; dark brown or black papule on the thigh

Histology
- Spitz nevus: predominantly compound, junctional and intradermal lesions may be seen; large and/or spindle-shaped melanocytes, usually in nests with artifactual clefts; periodic acid Schiff-positive and diastase resistant eosinophilic globules (Kamino bodies or colloid bodies), and dermal inflammatory cell infiltrate
- Pigmented spindle cell nevus of Reed: melanocytes are spindle shaped, vertically oriented, can extend down eccrine ducts and/or involve hair follicles

Treatment
- Excision (narrow to 5-mm margins, based on clinical factors and degree of atypia)

Blue Nevus (Fig. 9-4)

- Origin unknown
- Blue color due to Tyndall effect: preferential absorption of long wavelengths of light by melanin and the scattering of shorter wavelengths

Diagnostic of CNN
- Histology: epidermal nevomelanocytes, dermal nevomelanocytes in sheets, nests, cords and/or single cells around and within adnexal components
- Dermoscopy: globular/cobblestone or reticular pattern
- Treatment
  - surgical excision if clinically indicated, chemotherapy for metastatic disease

Spitz Nevus (Spindle Cell Nevus)
- Benign, usually acquired proliferations of melanocytes
- 50% of cases occur in children younger than 10 years of age
- Usually located on the face and lower extremities
- rapid initial growth phase
- Clinical findings
  - Typically solitary dome-shaped red/brown papule with a smooth surface/face; may occasionally

FIGURE 9-4  Blue nevus.
• Clinical findings
  • Three main types of blue nevi:
    – **Common blue nevus**: blue-black papule, usually less than 10 mm in diameter, over 50% are found on the dorsa of the hands and feet
    – **Cellular blue nevus**: gray-blue solitary, larger than common blue nevus (usually 1–2 cm in diameter), usually smooth-surfaced papules; buttocks, the sacral region; malignant transformation of cellular blue nevus has been reported
    – **Combined**: blue nevus with a nevomelanocytic nevus; blue nevus may be either a common or cellular type with an associated overlying intradermal, compound, junctional, or Spitz nevus component
  • Malignant blue nevus may develop in relation to a cellular blue nevus; presents as a growing dermal nodule with or without ulceration
• Other physical findings
  • **Carney syndrome (complex)**: autosomal dominant, cardiac, cutaneous, and mammary myxomatous masses; lentigines, blue nevi, endocrine disorders, and testicular tumors
  • **LAMB syndrome**: lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi
  • **NAME syndrome**: nevi, atrial myxomas, myxoid tumors (neurofibromas), and ephelides
  • **Familial multiple blue nevus syndrome**: autosomal dominant, multiple lesions are present on the head and the neck, the trunk, the extremities, and the sclera, not associated with other cutaneous or systemic findings
• Histology
  • **Common**: dermal elongated, dendritic, finely pigmented melanocytes, Grenz zone usually separates the lesion from the epidermis
  • **Cellular**: two distinct cell types, dendritic melanocytes as in the common type, together with islands of plump, oval melanocytes with abundant cytoplasm, a round or oblong nucleus and central nucleolus, may extend into the subcutis with a diffuse or nested pattern.
  • **Combined**: macrophages with melanin, single dendritic melanocytes at the dermoepidermal junction with intraepidermal prolongations
  • **Epithelioid blue nevus**: majority of large- to medium-sized pigmented cells that are globular and polygonal (epithelioid), and a minority of cells that are spindled and dendritic
• Treatment
  • Simple excision

**Café-au-Lait Macules (Fig. 9-5)**

- Discrete, pale brown macules, smooth or irregular margins

**FIGURE 9-5 Café-au-lait macules. (Courtesy of Dr. Jason Miller.)**

- **Appear at or soon after birth and may enlarge in size**
- **Isolated lesions occur in up to 20% of the population,**
- **Increased melanin in melanocytes and basal keratinocytes**
- **Associated diseases**
  • Neurofibromatosis type 1 (seen in 95% of patients), also seen in McCune-Albright syndrome, tuberous sclerosis, Fanconi anemia (mental retardation, aplastic anemia, and risk for malignancy), Silver-Russel syndrome; Bloom’s, Watson’s, and Westerhof’s syndromes; multiple endocrine neoplasia type IIb; Banyan-Riley-Ruvalcaba and Maffucci’s syndromes;
  • McCune-Albright syndrome (Albright’s syndrome): sporadic, GNAS1 gene mutation (stimulates G protein, which increases cAMP), large café-au-lait macule with “coast of Maine” border, polyostotic fibrous dysplasia (pseudocysts of long bones), recurrent fractures, limb-length discrepancies, precocious puberty, hyperthyroidism, normal life span
- **Treatment**: not necessary, although can consider Q-switched laser (Nd:YAG, ruby) or intense pulsed light to lighten lesion, with variable response.

**Nevus Spilus (Fig. 9-6)**

- **Presents during late infancy or early childhood**
- **Clinical findings**
  • Circumscribed, lightly pigmented patch with darkly pigmented, speckled nevomelanocytic macules or papules
- **Histology**
  • Increased number of melanocytes in the tan background; flat dark areas resemble a lentigo
PIGMENTED LESIONS

Most patients are older than age 50 at the time of presentation

Clinical findings
- Patchy alopecia, circumscribed hypermelanosis with lentigo-like macules on extremities, nail dystrophy
- Sessile or semipedunculated polyps in the colon but also in the stomach and small intestine with malignant potential

Histology
- Increase in melanin within the basal layer without the melanocyte proliferation

Solar Lentigo
- Slowly increase in number and in size with increased ultraviolet light exposure
- Acquired lesions on sun exposed skin, most commonly seen in Fitzpatrick skin types I–III
- Lesions are light brown; ink spot lentigo: black in color
- Histology
  - elongated epidermal rete ridges with club-shaped extensions; increased numbers of epidermal melanocytes (no nesting)

Ephelides (Freckles)
- Occur on sun-exposed areas; common on central face and noted in early childhood
- Lesions appear in the summer months, may fade when sun exposure is decreased; may persist throughout life
- Light brown macules; color of the lesions tends to deepen after sun exposure
- Histology
  - increased melanin deposition in the basal layer

Nevocellular Nevus
- Benign neoplasms that are acquired after birth and composed of nests of melanocytes
- Stimulated by exposure to ultraviolet light, prevalence varies according to ethnicity-higher number of nevi in lighter skinned individuals
- Types of nevi
  - Halo nevi: occurs when nevus is attacked by immune cells; overall prevalence rate of 0.9%; usually occurs before age of 20 years; pink or brown central nevomelanocytic nevus surrounded by a symmetric round or oval halo of depigmented skin; may present with single or multiple lesions; when associated with melanoma, the central lesions usually appears atypical
  - Junctional nevi (Fig. 9-7): brown to brown/black macules, melanocytes are located at epidermal-dermal junction

Lentigo Simplex
- Acquired brown to dark variegated to uniformly colored macules
- Not induced by sun exposure and may occur anywhere on the skin
- Associated with the following syndromes
  - Peutz-Jeghers syndrome (see Chapter 32): autosomal dominant, oral pigmentation, benign gastrointestinal polyps
  - LEOPARD syndrome: lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness
  - LAMB syndrome: lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi
  - Laugier-Hunziker syndrome: oral pigmentation, nail hyperpigmentation, absence of intestinal polyps or systemic abnormalities
- Histology
  - Mild acanthosis and basilar hyperpigmentation with melanocyte proliferation

Cronkhite-Canada Syndrome
- Sporadically occurs
- Mutations of a tumor suppressor gene PTEN (phosphatase and tensin homologue deleted on chromosome 10)

FIGURE 9-6 Nevus Spilus. (Courtesy of Dr. Jason Miller.)

with increased melanocytic hyperplasia or melanocytic dysplasia, collection of nevus cells are seen in the dark papular areas (junctional nevus)
Proportion of cutaneous melanomas that originate from dysplastic nevi relative to those that arise from apparently normal skin and from other melanocytic nevi is not known.

Familial Atypical Multiple Mole and Melanoma (FAMMM) Syndrome:
- Also known as the dysplastic nevus syndrome; germline mutations in the INK4alpha antioncogene encoding p16 in 40% of patients; increased risk for developing melanoma and other malignant neoplasms (i.e., pancreatic cancer)
- Presence of the following features: (1) occurrence of malignant melanoma in one or more first- or second-degree relatives, (2) presence of numerous (often >50) melanocytic nevi, some of which are clinically atypical, (3) many of the associated nevi show certain histologic features and have an elevated lifetime risk for the development of melanoma
- Histology
  - Single melanocytes, elongation of rete ridges, with cytologic atypia of melanocytes and enlarged, hyperchromatic nuclei
  - Bridging: melanocytes aggregate into variably sized nests, which fuse with adjacent rete ridges
  - Dermal fibroplasia: lamellar and concentric, lymphocytic infiltrate
  - Shouldering: junctional component extends beyond the last dermal nest

Nevus of Ota (Nevus Fuscocaeruleus Ophthalmomaxillaris) (Fig. 9-8)
- Melanocytes that have not migrated completely from the neural crest to the epidermis during the embryonic stage
- Asian population most commonly affected, usually congenital
- Malignant melanoma has been reported to develop in a nevus of Ota
- Clinical findings
  - Blue to gray speckled macules or patches
  - Unilateral (90%). Can be bilateral (may appear similar to Hori nevus: acquired bilateral blue/gray macules, no mucosal involvement)
  - Forehead, temple, malar area, or periorbital skin; mucosal involvement is possible and may involve the sclera, conjunctiva and tympanic membrane (oculodermal melanocytosis); increased risk of glaucoma (10%)
- Histology
  - Dendritic melanocytes are present and surrounded by fibrous sheaths; dermal melanophages, five types based on the locations of the dermal melanocytes, which are (1) superficial, (2) superficial dominant, (3) diffuse, (4) deep dominant, and (5) deep
PIGMENTED LESIONS

other areas include thorax, abdomen, arms, legs, and shoulders.

Histology
- Dermal spindle–shaped melanocytes with fully melanized melanosomes; usually oriented parallel to the epidermis.
- Prognosis
- Regression during childhood is the typical course, but they can persist.

Dowling-Degos Disease (DDD/Reticulate Pigmented Anomaly of the Flexures)

Autosomal dominant, mutation of the keratin 5 gene on chromosome 12q.

Clinical findings
- Reticular, macular hyperpigmentation
- Initially affects axillae and groin, other flexural areas
- Comedo-like lesions and pitted acneiform scars near angle of mouth, neck, and back
- Galli–Galli disease (GGD): acantholytic variant of Dowling-Degos disease, clinically indistinguishable from DDD.

Histology
- Acanthosis, irregular elongation of thin branching rete ridges with a concentration of melanin at the tips, no increase in melanocytes, but increase in melanosomes.

Treatment
- Q-switched: alexandrite, Nd:YAG, ruby lasers.
- Prognosis
- Slowly progressive but not life-threatening.

Nevus of Ito (Nevus Fusco-Caeruleus Acromiodeltoideus) (Fig. 9-9)

Congenital, blue to gray speckled macules or patches, lesions are present over the shoulder girdle region.

May appear simultaneously with nevus of Ota.

Histology, treatment, and prognosis is similar to nevus of Ota.

Mongolian Spot [Congenital Dermal Melanosis (CDM)]

Common in the following ethnic groups: Asian, African, and Hispanic.

Entrapment of melanocytes in the dermis during their migration from the neural crest into the epidermis.

Clinical findings: blue-gray macules, most commonly seen on lumbosacral skin, buttocks;
Other Reticulated Hyperpigmentation Disorders

CONFLUENT AND RETICULATED PAPILLOMATOSIS OF GOUGEROT AND CARTEAUD (CRP)
- Grayish blue plaques with peripheral reticulated pattern maybe a chronic condition
- Favors neck and upper trunk
- Treatment: antitymotic agents, tretinoin, antimicrobial agents (i.e., minocycline, erythromycin)

ERYTHEMA AB IGNE
- Net like pigment pattern due to heat injury (heating pads or laptops)
  - Treatment: ND: YA6, alexandrite lasers

DYSKERATOSIS CONGENITA
- Usually XLR but sometimes autosomal dominant or recessive
- DKC1 (dyskerin) – telomerase defect
- Reticulate hyperpigmentation, nail dystrophy, premalignant leukoplaikia, epiphora (continuous lacrimation)

NAEGELI-FRANCESCHETTI-JADASSOHN SYNDROME
- Autosomal dominant – keratin 14
- Reticulate hyperpigmentation starts at age 2 and fades over time
- Hypohidrosis, heat intolerance, dental abnormalities, PPK with loss of dermatoglyphics

DERMATOPATHIA PIGMENTOSA RETICULARIS
- Autosomal dominant – keratin 14
- Persistent truncal reticulated pigment; nonscarring alopecia; onychodystrophy; absent dermatoglyphics with punctate keratoderma in some

RETICULATE ACROPIGMENTATION OF KITAMURA
- Autosomal dominant
- Atrophic pigment over dorsal hands and feet; palmar pits

HYPOPIGMENTED LESIONS (TABLE 9-1)

**Nevus Depigmentosus**
- Occurs sporadically, congenital condition
- Decreased number of melanosomes in keratinocytes, reduced dopa activity, underdeveloped dendrites, defect in melanosome transfer (melanin remains in melanocytes instead of transferring to keratinocytes)
- Clinical findings
  - Unilateral well circumscribed irregular, oval, or round hypopigmented macular lesion

**Nevus Anemicus (Fig. 9-10)**
- Appears at birth in early childhood
- Defect at motor end plate of smooth muscle effector cells of blood vessels

**TABLE 9-1 Hypopigmented Diseases and Defects**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albinism</td>
<td>Decreased melanin synthesis</td>
</tr>
<tr>
<td>Nevus depigmentosus</td>
<td>Melanosome transfer</td>
</tr>
<tr>
<td>Menkes kinky hair</td>
<td>Decreased tyrosinase activity</td>
</tr>
<tr>
<td>Cross syndrome</td>
<td>Decreased number of melanocytes</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Decreased number of melanocytes, decreased melanin synthesis, decreased melanosome size</td>
</tr>
<tr>
<td>Vogt-Koyanagi-Harada</td>
<td>Decreased melanocytes</td>
</tr>
</tbody>
</table>

**FIGURE 9-10** Nevus anemicus. *(Courtesy of Dr. Asra Ali.)*

- Focal area of blood vessel that have increased sensitivity to catecholamines; vessels are persistently vasoconstricted resulting in an area of cutaneous blanching
- Clinical findings
  - Well defined, hypopigmented, irregularly shaped, confluent macules forming a patch, most common on trunk; stroking the adjacent skin causes it to become erythematous, while the lesion remains pale in color
HYPOPIGMENTED LESIONS

Idiopathic Guttate Hypomelanosis (Fig. 9-12)
- Common, acquired, discrete hypomelanosis
- Usually on extremities of sun exposed skin
- Incidence increases with age
- Clinical findings
  - Discrete, well-circumscribed, porcelain white round macules
- Histology
  - Flatting of the dermal-epidermal junction, moderate to marked reduction of melanin granules and melanocytes in the basal layer, epidermal atrophy, hyperkeratosis
- Treatment
  - Cryotherapy, superficial abrasion, topical retinoids

Futcher's Lines (Voigt's Lines) (Fig. 9-13)
- Pigmentary demarcation lines
- Abrupt transitions from deeply pigmented skin to lighter-pigmented skin
- Often present at birth tend to darken with time
- More common in black population and becomes visible during the first 6 months of life, or may be apparent at birth becoming more noticeable with age or during pregnancy.
- Classification:
  - Based on location of lines of demarcation
    - a. Lateral aspects of upper anterior portion of the arms across pectoral area
    - b. Posteromedial portion of the lower limbs
    - c. Vertical hypopigmented line in the pre- and parasternal areas
    - d. Posteromedial area of the spine
    - e. Bilateral aspect of the chest, marking from the mid-third of the clavicle to the periareolar skin

Pityriasis Alba (Fig. 9-11)
- Melanocytes decreased in number with fewer and small melanosomes
- Commonly affects children
- Characterized as a mild form of atopic dermatitis
- Clinical findings:
  - Pale pink/light brown macules with indistinct margins, powdery scale: more apparent on darker skinned patients
- Treatment:
  - Topical steroids, emollients

Ash-Leaf Macules (See Chapter 32)
- Initial expression of tuberous sclerosis (seen in 90% of patients with TSC)
- Normal or decreased number of melanocytes with underdeveloped dendrites, and small, poorly melanized melanosomes
- Clinical findings:
  - Oval hypopigmented macules, posterior trunk, upper and lower extremities
- Histology
  - Mononuclear infiltrate concentrated in the area of hair follicles and sweat glands, absence of melanin

Figure 9-11 Pityriasis alba. (Courtesy of Dr. Asra Ali.)

Figure 9-12 Idiopathic guttate hypomelanosis. (Courtesy of Dr. Asra Ali.)
pigmentary disorders

- Pain, retinal detachment, cataracts, glaucoma, dysacusis, deafness, tinnitus (50%)
  - Poliosis stage (90%): symmetric vitiligo, white eyelashes and brows, alopecia
- Laboratory studies:
  - Cerebrospinal fluid: pleocytosis
- Treatment
  - High dose corticosteroids, cyclosporine, cyclophosphamide, chlorambucil, and azathioprine

Oculocutaneous Albinism (OCA)
- Autosomal recessive disorders caused by either a complete lack or a reduction of melanin biosynthesis in melanocytes resulting in hypopigmentation of the hair, skin and eyes
- The various types of OCA are caused by mutations in different genes (Table 9-2)

Oculocutaneous Albinism IA (OCA1)
- Autosomal recessive
- Mutated tyrosinase (TYR) gene, chromosome 11q
- Complete loss of tyrosinase function; no pigmented lesions
- Melanosomes are normal
- Clinical findings
  - Complete absence of melanin in skin, hair, eyes; “Albino” phenotype; white hair and skin, pink irides that turn blue-gray over time, decreased visual acuity, photophobia

Oculocutaneous Albinism IB
- Mutated tyrosinase (TYR) gene, with some tyrosinase function

TABLE 9-2 Types of Oculocutaneous Albinism (OCA)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene product</th>
<th>Disease name</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYR</td>
<td>Tyrosinase (TYR)</td>
<td>OCA1, OCA1A, OCA1B (Yellow alb.)</td>
</tr>
<tr>
<td>OCA2</td>
<td>OCA2</td>
<td>OCA2 (Brown OCA in Africans)</td>
</tr>
<tr>
<td>TYRP1</td>
<td>Tyrosinase-related protein 1 (TYRP1)</td>
<td>OCA3 (Rufous OCA)</td>
</tr>
<tr>
<td>MATP</td>
<td>Membrane-associated transporter protein (MATP)</td>
<td>OCA3 (Rufous OCA)</td>
</tr>
</tbody>
</table>
Hypomelanosis Syndromes

Clinical findings
• Develop varying pigment with age, hair with pheomelanin (spherical yellow melanosomes) resulting in light yellow to brown hair color, irides can turn light tan or brown, pigmented lesions can develop (nevi, freckles, lentigines)
• Temperature sensitive variant: melanin synthesis in cooler areas of the body (i.e. extremities), but not warmer areas (> 35°C)

Oculocutaneous Albinism II (OCA2)
• Autosomal recessive, tyrosinase positive
• “Brown” OCA
• Mutation in the OCA2 gene (previously P gene) (OCA2 protein is needed for melanosomes biogenesis and as a membrane transport protein); chromosome 15
• Most common OCA worldwide
• Clinical findings
  • Hair pigment present at birth (different from OCA I), yellow to blond at birth owing to pheomelanin, irides blue-gray, skin is creamy white at birth, does not tan, and does not develop further pigment, pigmented nevi may develop
  • Brown OCA type (variant of OCA2): seen in African/African American populations; skin and hair are lighter brown, irides gray to tan at birth; over time, hair and irides may darken, but skin remains the same
• Syndromes associated with OCA2 gene mutations:
  • Prader-Willi syndrome
    △ Deletion of long arm of paternal chromosome 15 (imprinting) (70% of patients)
    △ Developmental syndrome
      △ Neonatal hypotonia, hyperphagia and obesity, hypogonadism, small hands and feet, mental retardation, skin hypopigmented, no ocular albinism
  • Angelman
    △ Autosomal recessive, defect in OCA2 gene on maternal chromosome 15 (imprinting) Might represent a spectrum of OCA IB/OCA II
      △ Clinical findings:
        △ Light skin and hair, iris translucency, ocular albinism

Oculocutaneous Albinism III (OCA3)
• Autosomal recessive
• Mutation in tyrosinase-related protein 1 (TRP1) on chromosome 9
• Acts as a dihydroxyindole-2 carboxylic acid (CDHICA); oxidase needed in the eumelanin pathway
• Common in South Africa, can present as rufous/red OCA or brown OCA

Clinical findings
• Red to brownish skin, red hair, hazel to brown eyes

Oculocutaneous Albinism IV (OCA4)
• Defect in membrane associated transport protein (MATP) on chromosome 5
• Clinical
  • Similar to OCA II

Hermansky-Pudlak Syndrome (HPS)
• Autosomal recessive; etiology has been related to defects in 7 genes: HPS1, HPS2 (AP3B1), HPS3, HPS4, HPS5, HPS6, and HPS7.
• HPS-1 patients have the most severe phenotype of HPS
• Lysosomal membrane defect with abnormal formation of intracellular vesicles; results in accumulation of ceroid lipofuscin in macrophages in lung and gastrointestinal tract
• Lack of platelet dense bodies resulting in increased bleeding times
• Tyrosinase positive
• Clinical findings
  • Skin: pigment dilution; skin color varies from white to light brown, pigmented nevi, ecchymosis
  • Hair: cream to red/brown
  • Eyes: lack of retinal pigment, decreased pigment of irides, photophobia, nystagmus, decreased visual acuity, strabismus
  • Hematologic: epistaxis, gingival bleeding, prolonged bleeding
  • Lymphohistiocytic: ceroid (chromolipid) deposition in macrophages
  • Lung: pulmonary fibrosis
  • Gastrointestinal: granulomatous colitis (15% of patients)
  • Cardiac: cardiomyopathy
• Diagnosis
  • Prothrombin time/partial thromboplastin time (PT/PTT)
  • Platelet count
  • Pulmonary function test, chest x-ray, and colonoscopy if symptomatic
• Treatment
  • Avoid aspirin and other blood thinners, DDAVP, platelet and red blood cell transfusions as clinically necessary; granulomatous colitis: steroids, TNF-α inhibitors

Chediak-Higashi Syndrome
• Autosomal recessive
• Lysosomal tansport protein (LYST/CHS1) gene defect
• Incomplete oculocutaneous albinism
• Decreased chemotaxis of neutrophils, decreased antibody-dependent cellular cytotoxicity, presence of giant peroxidase-positive lysosomal granules in peripheral blood granulocytes; results in severe infections

• Clinical findings
  - Childhood CHS: accelerated phase: early onset with fever, anemia, neutropenia
  - Adolescent CHS: severe infections in early childhood, no accelerated phase
  - Adult CHS: mild form, develop progressive and fatal neurologic dysfunction in middle age
  - Eyes: ocular hypopigmentation causes photophobia, nystagmus, and strabismus
  - Hair: silvery sheen
  - Skin: pale, deep ulcerations, petechiae, bruising, gingival bleeding
  - Neurologic: seizures
  - Lymphoma: "accelerated phase" precipitated by viruses (e.g., Epstein-Barr virus); widespread infiltration of visera
  - Other: hepatosplenomegaly, lymphadenopathy, pancytopenia, pseudomembrane, sloughing of the buccal mucosa

• Laboratory findings
  - Giant granules in circulating neutrophils, melanocytes, neurons, and renal tubular cells
  - Granules form secondary to delayed disorder of lysosomal enzymes from cells

• Treatment
  - Bone marrow (or stem cell) transplant, acyclovir, interleukin, gammaglobulin, vincristine, prednisone
  - Course
    - Death at about 6 years old secondary to infection, lymphoma-like accelerated phase

Alezzandrini Syndrome
• Etiology unknown, possibly due to an autoimmune process destroying melanocytes

• Clinical findings
  - Facial vitiligo, poliosis, deafness, unilateral tapetoretinal (retinal pigmented epithelia) degeneration

Vitiligo (Fig. 9-14)
• Various theories on etiology of melanocyte destruction:
  - Autoimmune hypothesis: due to defects in humoral and cellular immunity
  - Neural theory: neurochemical mediator destroys melanocytes
  - Oxidant stress: accumulation of free radicals toxic to melanocytes, resulting in melanocyte destruction
  - Associated with autoimmune conditions: thyroid disease (Hashimoto’s thyroiditis, Graves disease), diabetes mellitus, pernicious anemia, alopecia

• Clinical findings
  - Depigmented, sharply circumscribed macules or patches
  - Poliosis = leukotrichia = whiteness of hair
  - Canities = premature graying of hair (37% of patients)

• Clinical classification
  - Localized: focal (one area of the body affected), segmental (dermatomal or quasidermatomal pattern), mucosal (mucous membranes are solely affected)
  - Generalized: acrofacial (distal fingers and periocular affected), vulgaris (widely distributed scattered patches), mixed: acrofacial and vulgaris or segmental and acrofacial and/or vulgaris
  - Universal: complete or nearly complete depigmentation

• Diagnosis
  - Wood’s lamp: bright white or blue white
  - Histology: absence of melanocyte and melanin in the affected area

• Treatment
  - Narrow-band ultraviolet B, oral or topical psoralen plus UV-A (PUVA), topical calcineurin inhibitors, topical steroids; surgery: donor grafts: punch grafts, minigrafts, suction blister

Piebaldism
• Autosomal dominant
• C-KIT mutation on chromosome 4, encodes steel factor (C-kit ligand); protooncogene, tyrosine kinase
transmembrane cellular receptor for mast/stem cell growth factor.

- Present at birth, does not progress
- Clinical findings
  - Cutaneous: depigmented patches midforehead, extremities; pigmented islands present
  - Hair: white forelock (80% to 90% of patients)
  - Gastrointestinal: Hirschsprung disease
  - Neurologic: mental retardation, cerebellar ataxia, deafness

**Waardenburg Syndrome**

- Autosomal dominant
- Defect in neural crest migration, absent melanocytes
- Four subtypes (I to IV)
  - Type I: autosomal dominant, \( PAX3 \) (paired box) gene; transcription factor
  - Type II: Autosomal dominant, \( MITF \) (microphthalmia-associated transcription factor) gene, chromosome 3; \( SLUG \) gene
  - Type III (Klein-Waardenburg syndrome): Autosomal dominant, \( PAX3 \) (paired box) gene, transcription factor
  - Type IV (Shah-Waardenburg syndrome): Autosomal recessive, \( EDN3 \) (endothelin receptor), \( EDNRB \), G-protein coupled receptor; Autosomal dominant, \( SOX10 \) (sex determining region) gene
- Diagnostic criteria (Table 9-3):
  - WSI: two major or one major and two minor criteria

<table>
<thead>
<tr>
<th>TABLE 9–3 Diagnostic Criteria for Waardenburg Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Congenital sensorineural hearing loss</td>
</tr>
<tr>
<td>Pigmentary disturbances of iris; complete heterochromia</td>
</tr>
<tr>
<td>iridis, partial or segmental heterochromia iridis,</td>
</tr>
<tr>
<td>hypoplastic blue iridis</td>
</tr>
<tr>
<td>White forelock</td>
</tr>
<tr>
<td>Dystopia canthorum</td>
</tr>
<tr>
<td>Affected first degree relative</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Congential leukoderma: several areas of hypopigmentation</td>
</tr>
<tr>
<td>Synohryys</td>
</tr>
<tr>
<td>Broad and high nasal root</td>
</tr>
<tr>
<td>Hypoplasia of ala nasi</td>
</tr>
<tr>
<td>Premature graying of hair</td>
</tr>
</tbody>
</table>

- WSII: two major criteria and dystopia canthorum instead of premature graying as one of the major criteria
- WSIII: two major or one major and two minor criteria along with musculoskeletal abnormalities
- Clinical findings
  - Skin: depigmentation
  - Hair: white forelock at birth (80%), synophrys (70%)
  - Oral: tooth caries
  - Eyes: heterochromia, dystopia canthorum (99%), lateral displacement of medial canthi with normal interpupillary distance; inner/outer canthi > 0.6
  - Nose: broad nasal root
  - Ears: congenital sensorineural deafness (20%)
  - Gastrointestinal: Hirschsprung disease (<5%)
- Symptoms additional to main symptoms:
  - Type I: dystopia canthorum, heterochromia
  - Type II: heterochromia
  - Type III: musculoskeletal, limb abnormalities (hypoplasia, contracture of elbows, fingers)
  - Type IV: Hirschsprung’s disease

**Questions**

1. A 40-year-old woman presents with a history of fever, seizures, photophobia, and poliosis of her eyebrows. The most likely explanation is:
   - A. New onset of generalized vitilgo
   - B. Molecular mimicry following a viral infection
   - C. Genetic abnormality in lysosomal trafficking
   - D. \( PAX3 \) mutation
   - E. Cocaine use

2. The most common worldwide oculocutaneous albinism, presenting with yellow/blonde hair and pigmented nevi, occurs due to a mutation on which chromosome?
   - A. 17
   - B. 22
   - C. 15
   - D. 10
   - E. X

3. Axillary reticular hyperpigmentation with increased melanosomes and acantholysis on histology is most consistent with:
   - A. Cronkhite-Canada syndrome
   - B. Brooks-Spiegler syndrome
   - C. Tuberous sclerosis
   - D. Galli-Galli disease
   - E. Erythema ab igne
4. A 14-year-old patient presents with numerous ephelides, blue nevi, and a history of endocrine abnormalities. Which of the following examinations should be ordered?
   A. Skeletal survey  
   B. MRI of the brain  
   C. Duplex ultrasound of leg veins  
   D. Cardiac sonogram  
   E. Urinary metanephrines

5. Which of the following syndromes consists of abnormal pigmentary deposition without the presence of GI abnormalities?
   A. Cronkhite-Canada syndrome  
   B. Peutz-Jeghers syndrome  
   C. Laugier-Hunziker syndrome  
   D. All of the above  
   E. None of the above

6. A 3-month-old infant presents with a 25 × 21 cm deeply pigmented patch over the central upper back, present since birth. Which is the most sensitive imaging study to identify potential leptomeningeal melanosis?
   A. Contrast CT  
   B. Noncontrast CT  
   C. PET CT  
   D. Contrast MRI  
   E. Noncontrast MRI

7. Which of the following gene mutations has been associated with both an increase in inner canthal distance and gastrointestinal nerve plexus dysfunction?
   A. SOX10  
   B. Pax3  
   C. MITF  
   D. endothelin 2  
   E. c-kit

8. An 8-month-old child presents with a silver sheen to her hair, seizures, hepatosplenomegaly, lymphadenopathy, pancytopenia, recurrent Staph aureus skin infections, and enlarged granules noted within neutrophils on peripheral smear. Which of the following gene defects is most likely to be identified?
   A. c-kit  
   B. LYST  
   C. Pax3  
   D. HPS1  
   E. RAB27a

9. A 35-year-old woman, currently 30 weeks pregnant with her second child, presents with 2 months of worsening centrofacial hyperpigmentation that enhances upon Woods lamp fluorescence. This pigmentation was initially noted during her last pregnancy, but no treatment has yet been initiated. Which of the following would be the most appropriate initial treatment regimen?
   A. Sunscreen and topical tretinoin  
   B. Sunscreen, topical tretinoin, and topical hydroquinone  
   C. Sunscreen alone  
   D. Sunscreen, topical hydroquinone, and topical steroids  
   E. Sunscreen and topical hydroquinone

10. Which of the following ions is necessary for the proper function of the enzyme tyrosinase?
    A. Ca$^{2+}$  
    B. Mg$^{2+}$  
    C. Fe$^{2+}$  
    D. Fe$^{3+}$  
    E. Cu$^{2+}$

**Answers**

1. B. Vogt-Koyangi-Harada is a T-cell mediated autoimmune disorder that may be related to molecular mimicry following infection. Stages include a pro-drome, ophthalmic and auditory stage, and poliosis stage.

2. C. Oculocutaneous albinism type 2 is the most common form worldwide and represents a tyrosinase positive albinism. Mutations in the OCA 2 gene (P gene) on chromosome 15 disrupt melanosome transport.

3. D. Galli-Galli disease is an acantholytic variant of Dowling-Degos disease, characterized clinically by reticulate hyperpigmentation and comedo-like lesions with pitted scars.

4. D. Carney complex consists of an autosomal dominant syndrome featuring lentigines, blue nevi, endocrine disorders, testicular tumors, and myxomatous masses of the heart, skin, and breasts. A cardiac sonogram would be useful in identifying atrial myxomas.

5. C. Laugier-Hunziker syndrome presents with oral and genital lentigines without the present of GI polyps. Peutz-Jeghers syndrome consists of oral and genital lentigines with GI hamartomatous polyposis. Cronkhite-Canada syndrome presents with nail atrophy, alopecia, pigment deposition, digital melanotic macules, and GI polyps (premalignant).

6. D. A contrast-enhanced MRI is the most sensitive imaging study to identify melanosis or melanoma.
metastasis in the central nervous system. Clinical signs and symptoms may include irritability, photophobia, seizures, and hydrocephalus.

7. A. Waardenburg syndrome type IV consists of dystopia canthorum and Hirschsprung disease, likely due to neural crest developmental abnormalities. Associated mutations include SOX10 and endothelin-3 genes. Types I–III do not develop Hirschsprung disease. C-kit mutations are found in Piebaldism where, although Hirschsprung disease has been rarely reported, no dystopia canthorum would be noted.

8. B. Chediak-Higashi syndrome consists of an autosomal recessive mutation in the LYST gene resulting in abnormal microtubule-associated lysosomal trafficking. Features include hair with a silver sheen, pigmented nevi, infections (staph aureus of the skin and pneumonia), ecchymoses, lymphoma (accelerated phase), neurologic degeneration, and pancytopenia. Neutrophils will characteristically show giant granules on smear.

9. C. This patient presents with melasma that will likely require treatment in the future. However, as the patient is currently pregnant, the safest modality of treatment at this time consists of sunscreens alone. Topical hydroquinone and topical tretinoin are both FDA category C during pregnancy and likely require treatment in the future. However, as the patient is currently pregnant, the safest modality of treatment at this time consists of sunscreens alone. Topical hydroquinone and topical tretinoin are both FDA category C during pregnancy and lactation are complete.

10. E. Copper is a necessary cofactor for the function of tyrosinase, an enzyme that catalyzes the hydroxylation of tyrosine to dopa and the oxidation of dopa to dopaquinone.

REFERENCES


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NEOPLASMS OF THE SUBCUTANEOUS FAT

Lipoma
- Most common benign mesenchymal tumor
- Nonpainful, round, mobile soft masses, with normal overlying skin
- Histology
  - Mature adipocytes arranged in lobules, forming a well circumscribed nodule surrounded by a thin, fibrous capsule
  - Thin strands of tissue intersect the sheets of adipocytes
- Histologic variants
  - Angiolipoma
    - Lipoma with co-existing vascular proliferation
    - May be painful and usually arise shortly after puberty
  - Pleomorphic lipomas
    - Bizarre, multinucleated giant cells are admixed with normal adipocytes
    - Occur predominantly in men 50 to 70 years of age
  - Spindle cell lipomas
    - Slender spindle cells admixed in a localized portion of regular-appearing adipocytes
  - Adenolipoma
    - Characterized by the presence of eccrine sweat glands in the fatty tumor
    - Often located on the proximal parts of the limbs
  - Intramuscular lipomas: lipomas that extend into skeletal muscle
  - Fibrolipoma: thick bundles of collagen in the lipoma
  - Sclerotic lipoma: thickened collagen bundles with few persisting adipocytes
  - Myxolipomas: stromal deposits of mucopolysaccharides
  - Myelolipomas: ectopic hematopoietic bone marrow elements
- Infarcted lipomas: necrotic fat surrounded by multinucleate histocytic giant cells, lymphocytes, and extravasated erythrocytes
- Other types of lipomas
  - Chondroid lipoma
    - Females > males; subcutaneous fat, muscle of hips, extremities
    - Histology: eosinophils, vacuolated cells that resemble chondroblasts, arranged in sheets, cords, mucinous stroma (cartilage), scalloped nuclei
  - Myolipoma/lipoleiomyoma
    - Resemble large lipomas, abdomen, retroperitoneum, > 15 cm, slimy, yellow-white cut surface
    - Histology: biphasic: mature adipocytes with smooth muscle cells, no atypia
  - Angiomyolipoma/angiolipoleiomyoma
    - Usually in kidney; associated with tuberous sclerosis; can occur in skin (acral, elbows, ears); these are not associated with tuberous sclerosis; slow growing; asymptomatic
    - Histology: blood vessels, smooth muscle bundles, adipose tissue, vessels with thick walls
  - Hibernoma
    - Red-brown, mobile, brown fat, solitary, between scapulae, lower cervical/mediastinal (most common), axillary
    - Histology: vacuolated cells, large round central nuclei with prominent nucleoli, abundant eosinophilic, granular cytoplasm secondary to mitochondria (mulberry cell)
  - Lipoblastoma/lipoblastomatosis
    - Appears only in infants, first three years of life, > 12 cm, solitary subcutaneous mass, trunk, limbs
    - Two variants:
      ▲ Benign (circumscribed lipoblastoma): subcutaneous, well demarcated


**Chapter 10  DISORDERS OF FAT**

- **Diffuse (lipoblastomatosis):** deep-seated infiltrates of soft tissue and skeletal muscle
  - Histology: mature adipocytes separated into small lobules by fibrovascular septa; filled with cytoplasmic fat vacuoles displacing the nucleus to periphery (signet ring)
- **Liposarcoma**
  - Most common soft tissue malignancy in adults; arises de novo; elderly; nonmobile; rapidly enlarging; causes pain by compression
  - Histology: well-differentiated pleomorphic adipocytes; enlarged nuclei in thickened septa; sclerosing: abundant dense and fibrillary collagen; myxoid: most common variant, mucinous stroma

**Syndromes**

- **Dercum’s disease/adiposis dolorosa:** tender nodules, idiopathic, obese, postmenopausal women, arms, trunk, paraarticular
- **Madelung’s disease/benign symmetric lipomatosis (Fig. 10-1):** upper trunk, proximal extremities, middle-aged men, alcoholics or those with liver disease; “horse collar” appearance: confluence on neck; laboratory abnormalities: hyperuricemia, decreased glucose tolerance

**LIPODYSTROPHY**

- Absence of subcutaneous adipose tissue with no evidence of inflammation, however, if previous inflammation was present, then the term lipoatrophy may be used
- Heterogeneous group of disorders defined by loss of subcutaneous adipose tissue and classified into two types: genetic and acquired.
  - Associated with insulin resistance and its complications, such as impaired glucose tolerance, diabetes, hyperinsulinemia, dyslipidemia, hepatic steatosis, acanthosis nigricans, polycystic ovarian disease, and hypertension
  - Congenital (recessive or autosomal dominant) disorders or acquired localized lipodystrophies (include drug-induced, pressure induced, panniculitis-associated, and idiopathic lipodystrophy)
  - Histology: small adipocytes and intervening hyaline or myxoid connective tissue and proliferation of small blood vessels; second type has some inflammation with lymphocytes, foamy histiocytes, and plasma cells within the small fat lobules

**Genetic Lipodystrophies**

**Autosomal Recessive**

1. **Congenital generalized lipodystrophy (CGL; Berardinelli-Seip syndrome)**
   - CGL type 1: AGPAT2 (1-acylglycerol-3-phosphate O-acyltransferase 2) mutations
   - CGL type 2: BSCL2 (Berardinelli-Seip congenital lipodystrophy 2) mutations
2. **Lipodystrophy associated with mandibuloacral dysplasia**
   - Partial lipodystrophy (type A pattern): LMNA (lamin A/C) mutations
   - Generalized lipodystrophy (type B pattern): ZMPSTE24 (zinc metalloproteinase) mutations
3. **Lipodystrophy associated with SHORT syndrome**
   - (short stature, hyperextensibility, ocular depression, Reiger anomaly, teething delay)
4. **Lipodystrophy associated with neonatal progeroid syndrome**

**FIGURE 10-1** Symmetric lipomatosis. (*Reprinted with permission from Wolff, K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.*)
**Autosomal Dominant Syndromes**

1. Familial partial lipodystrophy (FPL)
   - Dunnigan variety (FPLD): *LMNA* (lamin A/C) mutations
   - FPL associated with *PPARG* (peroxisome proliferator-activated receptor γ) mutations
   - FPL associated with *AKT2* (*v-AKT murine thymoma oncogene homolog 2*) mutations

**Other Varieties**

1. Lipodystrophy associated with Hutchinson-Gilford progeria syndrome (failure to thrive, scleroderma-like skin, limited growth, alopecia)
2. Pubertal-onset generalized lipodystrophy due to *LMNA* mutations
3. Generalized lipodystrophy (GL)
   - Berardinelli-Seip syndrome (Autosomal recessive)
   - Mutations in the following genes: type 1-AGPAT2 (1-acylglycerol-3-phosphate O-acyltransferase 2), band 9q34 and type 2-BSCL2 (Seipin), band 11q13
   - Diagnosis: Three major criteria or two major criteria and two or more minor criteria:
     - Major criteria: lipoatrophy affecting the trunk, limbs, and face; generalized lipoatrophy present at birth, insulin resistance with acanthosis nigricans, acromegaloid features, hypertriglyceridemia, hepatomegaly
     - Minor criteria: hypertrichosis, psychomotor retardation, hypertrophic cardiomyopathy, bone cysts, phlebomegaly
4. Acquired generalized lipodystrophy: *(AGL)*
   - Lawrence-Seip syndrome
   - Selective loss of body fat from large regions of the body occurring after birth
   - Three varieties: type 1, panniculitis variety (25%); type 2, autoimmune disease variety (25%); and type 3, the idiopathic variety (50%)
   - Characteristics: patients may have a voracious appetite, fatigue, acanthosis nigricans, hepatomegaly, fasting and/or postprandial hyperinsulinemia, diabetes mellitus, hypertriglyceridemia, and low serum levels of high-density lipoprotein cholesterol.
5. Partial lipodystrophy (PL)
   - Barraquer-Simons syndrome (Fig. 10-2)
   - Sporadic or autosomal dominant: *LMNB2* gene encodes Lamin B2
   - Loss of subcutaneous fat in demarcated symmetric areas of the body
   - Begins on the face and spreads downward, stopping at any level, often simultaneous fat hypertrophy of lower extremities
   - More common in females
   - Occasionally correlated with onset of an acute febrile illness

**FIGURE 10-2** Partial lipodystrophy. *(Reprinted with permission from Wolff, K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)*

- Associated with C3 nephritic factor (binds factor H) inhibitor of C3; results in uncontrolled activation of C3
- Glomerulonephritis: direct toxicity from C3 nephritic factor
- Histology: marked decrease or absence of subcutaneous fat cells
- Treatment: renal transplant for increased uremia

6. Familial partial lipodystrophy (FPL)
   - Dunnigan-Kobbering syndrome (Autosomal dominant)
   - Mutations in *LMNA* gene that encodes laminins A and C, alters plasma leptin concentration
   - FPL associated with mutation in *PPARG* (peroxisome proliferator-activated receptor γ)
   - FPL associated with *AKT2* (*v-AKT murine thymoma oncogene homolog 2*)
   - Subcutaneous loss of fat from limbs, spares face
   - Metabolic disorders: insulin-dependent diabetes mellitus (IDDM), acanthosis nigricans
   - Treatment for lypodystrophy: oral hypoglycemic drugs and/or insulin therapy, diet and exercise
     - (low-fat diet)
7. HIV-associated lipodystrophy
   - Associated with highly active antiretroviral therapy (HAART); commonly associated medications include stavudine and to a lesser degree zidovudine
   - Loss of subcutaneous fat of upper and lower extremities and from the face
   - Fat increases at the posterior neck and upper back and on the breasts
- Laboratory findings: insulin resistance and hyperglycemia
- Treatment: changes within or between a class of HAART drugs, recombinant human growth hormone (rhGH), metformin, dehydroepiandrosterone, nonsteroidal anti-inflammatory drugs, liposuction of the upper back, filler substances (silicone, poly-L-lactic acid, calcium hydroxylapatite)

8. Other lipodystrophies/lipoatrophy
- Prior inflammatory processes involving the subcutis: lupus profundus, morphea, or panniculitis
- Iatrogenic causes: subcutaneous injections of corticosteroids, insulin, or methotrexate
- Subtypes of idiopathic lipoatrophies:
  - Annular lipoatrophy of the ankles: may be due to an inflammatory panniculitis that resolves with lipoatrophy; histology: mixed lobular panniculitis with lipophages
  - Lipoatrophia semicircularis: semicircular depressions of the anterolateral aspects of the thighs may be due to repeated mechanical trauma
  - Lipodystrophia centrifugalis abdominalis infantalis: acquired localized lipodystrophy, mainly reported in Asians, loss of subcutaneous fat of the abdomen, slightly red and scaly skin in the surrounding area, lymphadenopathy, onset before age 5 years, and no significant associated diseases; histologically, loss of subcutaneous fat in the depressed area with panniculitis in the surrounding area.

PANNICULITIS

- Group of heterogeneous inflammatory diseases that involve the subcutaneous fat
- Diagnosis using histology is essential since different panniculitides may show the same clinical appearance, which consists of erythematous nodules on the lower extremities
- Panniculitides are subdivided depending on the location of the inflammatory infiltrate: primarily lobular or septal (Table 10-1)

Panniculitis (Septal)

ERTHEMA NODOSUM (EN) (FIG. 10-3)
- Most common type of septal panniculitis
- Most commonly affects young female patients
- Red or oval, slightly raised, nonulcerative painful red nodules, symmetric on the anterior surfaces of lower legs with fever, malaise, arthralgias (70%)
- Lesions last from 3 to 6 weeks and resolve with brownish/yellow discoloration (erythema contusiformis)
- Chronic (EN migrans): several red subcutaneous nodules unilateral on the lower extremities
- Etiologic factors: see Table 10-2
- May also be idiopathic
- Streptococcal infections are the most frequent etiologic factor for erythema nodosum in children, whereas drugs, sarcoidosis, and inflammatory diseases of the bowel are the most commonly associated disorders in adults
- Diagnosis: biopsy, increased erythrocyte sedimentation rate, chest x-ray, complete blood count (CBC), antistreptolysin (ASO) titer, virologies, PPD for tuberculosis, fungal, bacterial and viral cultures
- Histology: septal panniculitis without vasculitis; Miescher’s radial granulomas: small, well-defined nodular aggregations of small histiocytes around a central stellate or banana-shaped cleft
- Treatment: spontaneous resolution (3–6 weeks), nonsteroidal anti-inflammatory drugs (NSAIDs), oral steroids, potassium iodide

NECROBIOSIS LIPOIDICA

- Deep extension to the subcutis of the dermal process of palisading granulomas
- Asymptomatic, yellow-brown, indurated plaques with an atrophic and slightly depressed center and a well-defined raised erythematous edge
- Most commonly affects the bilateral shins symmetrically
- Associated with diabetes mellitus
- Histology: within the septa of adipocytes are histiocyte filled palisading granulomas surrounded by areas of degenerated collagen; IgM and complement depositions in the walls of the blood vessel of necrobiotic areas; dermis has alternating bands of inflammatory cells and fibrosis
- Treatment: intralesional steroids, aspirin and dipyridamole, pentoxifylline

NECROBIOTIC XANTHOGRANULOMA

- Chronic and progressive, sharply demarcated indurated yellow to violaceous plaques commonly ulcerate, predilection toward the periorbital region
- Associated with paraproteinemia, mostly of IgG κ type, also found in patients with multiple myeloma
- Histology: large areas of necrobiosis (occasionally with cholesterol crystals in the center) alternating with granulomatous inflammation; occasional formation of lymphoid follicles
- Treatment: correct paraproteinemia, melphalan, prednisolone, plasmapheresis
### TABLE 10-1  Panniculitis: Septal and Lobular

<table>
<thead>
<tr>
<th>With vasculitis</th>
<th>Without vasculitis</th>
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<tbody>
<tr>
<td><strong>Septal</strong></td>
<td><strong>Lobular</strong></td>
</tr>
<tr>
<td>(See Chap. 23) Leukocytoclastic vasculitis</td>
<td>Erythema nodosum leprosum (see also Chap. 15)</td>
</tr>
<tr>
<td>• Superficial thrombophlebitis</td>
<td>• Lucio’s phenomenon (see also Chap. 15)</td>
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<tr>
<td>• Cutaneous polyarteritis nodosa</td>
<td>• Nodular vasculitis (erythema induratum of Bazin)</td>
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<td>• Crohn’s disease</td>
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<td></td>
<td>• Neutrophilic lobular (pustular) panniculitis associated with rheumatoid arthritis (not covered in this chapter)</td>
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<td><strong>With</strong></td>
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<td>• Erythema nodosum</td>
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<td>• Necrobiosis lipoidica</td>
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<td>• Necrobiotic xanthogranuloma</td>
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<td>• Rheumatoid nodule</td>
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<td>• Scleroderma/deep morphea</td>
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<td>• Subcutaneous granuloma annulare</td>
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<td>• α₁-Antitrypsin deficiency</td>
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<td>• Calciniphaxis</td>
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<td>• Cold panniculitis</td>
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<td>• Cytophagic histiocytic panniculitis</td>
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<td>• Subcutaneous “panniculitic” lymphoma</td>
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<td>• Factitial panniculitis</td>
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<td>• Iatrogenic</td>
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<td>• Infection</td>
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<td>• Lupus panniculitis (lupus erythematosus profundus)</td>
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<td>• Oxalosis</td>
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<td>• Pancreatic panniculitis</td>
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<td>• Poststeroid panniculitis</td>
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<td>• Sclerema neonatorum</td>
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<td>• Subcutaneous fat necrosis of newborn</td>
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<td>• Sclerosing panniculitis (lipodermatosclerosis)</td>
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<td>• Subcutaneous sarcoidosis</td>
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<td>• Traumatic</td>
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<td></td>
<td>• Panniculitis in dermatomyositis</td>
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<td></td>
<td>• Lipoatrophy (see previous section)</td>
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<td></td>
<td>• Gout panniculitis (patients with hyperuricemia may show urate crystal deposition in the fat lobule of the subcutis)</td>
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<td>• Crystal-storing histiocytosis (subcutis with aggregations of histiocytes containing crystalline deposits of immunoglobulins)</td>
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<td></td>
<td>• Postirradiation pseudosclerodermatous panniculitis (not covered)</td>
</tr>
</tbody>
</table>

### Rheumatoid Nodule
- Found in 20% of rheumatoid arthritis patients
- Usually asymptomatic firm nodules with normal overlying skin; predilection for the elbows and fingers
- Histology: large areas of necrobiosis (homogeneous and eosinophilic) surrounded by palisaded granulomas involving the dermis and subcutaneous fat
- Treatment: surgical excision if ulcerated or symptomatic

### Scleroderma (Deep Morphea, Morphea Profunda)
- Extension from the deep dermis into the septa of subcutaneous fat; process can be entirely a panniculitis
- Bound down indurated plaques or nodules, heal with atrophy and residual hyperpigmentation
- Histology: extensive fibrosis of the septa of subcutaneous adipose tissue, collagen replaces fat normally present around the eccrine coils, atrophy of the adnexal structures, inflammation, with lymphocytes and plasma cells in active lesions
- Treatment: intralesional steroids, penicillamine

### Subcutaneous Granuloma Annulare
- Subcutaneous nodules with a normal appearing skin surface; lesions are most often found on the head, hands, buttocks, and the anterior aspect of the lower legs
- Bound down indurated plaques or nodules, heal with atrophy and residual hyperpigmentation
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FIGURE 10-3 Erythema nodosum. (Reprinted with permission from Wolff, K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)

- Occurs most commonly in children and young adults
- Classic granuloma annulare can coexist 25% of the time with subcutaneous granuloma annulare
- Histology: necrobiosis with peripheral palisading granulomas involving the septa of adipose tissue

Panniculitis, Mostly Lobular With Vasculitis

ERYTHEMA NODOSUM LEPROSUM
- Type 2 reaction: Immune complex–mediated vasculitis in patients with lepromatous leprosy
- Painful erythematous and violaceous nodules, mostly involving the extremities
- Disease usually affects dermis only, but it can extend to the subcutis
- Histology: fibrinoid necrosis of vessel walls and luminal thrombi, direct immunoflourescence shows IgG and complement deposits in the vessel walls
- IgG and complement in the walls of the involved vessels
- Treatment: thalidomide, clofazimine, prednisone

LUCIO’S PHENOMENON
- Type 2 reaction: variant of lepromatous leprosy with hemorrhagic ulcers due to necrotizing vasculitis
- Histology: necrotizing vasculitis of the small vessels with foamy histiocytes that contain numerous acid-fast bacilli
- Treatment: thalidomide

ERYTHEMA INDURATUM OF BAZIN (NODULAR VASCULITIS)
- Most common form of lobular panniculitis with vasculitis
- Erythematous, tender, subcutaneous nodules and plaques on posterior aspects of lower extremities
- May ulcerate and heal with atrophic scars, recurrence is common
- Usually seen in middle-aged women with venous insufficiency
- Erythema induratum of Bazin: if related to infection with Mycobacterium tuberculosis diagnosis can be made by Manoux test or by PCR for DNA of M. tuberculosis
- Histology: lobular panniculitis with vasculitis; ischemic necrosis of fat lobule with decreased septal involvement; tuberculoid-type granulomas, necrosis of adipocytes, foamy histiocytes, granulomatous infiltrate with epithelioid histiocytes, multinucleated giant cells and lymphocytes.
- Treatment: if M. tuberculosis is present, then nine months of antituberculosis triple-agent therapy is recommended, potassium iodide, treatment of venous insufficiency, NSAIDS to aid with pain of ulceration

CROHN’S DISEASE
- Abscesses, sinuses, and fistulas of the genital and perianal areas
- Commonly presents with erythema nodosum
- Histology: noncaseating granulomas composed of epithelioid histiocytes

Lobular Panniculitis Without Vasculitis

α1-ANTITRYPSIN DEFICIENCY (α1-PROTEASE INHIBITOR DEFICIENCY/SERINE PROTEASE)
- Affects homozygous patients; proenzyme of α1-antitrypsin is not released from the liver
- Alpha 1 antitrypsin is a protease inhibitor of trypsin (produced in liver), as well as the following: chemotrypsin, plasmin, thrombin, neutrophilic elastase, pancreatic elastase, serine proteinases, collagenase, factor VIII, and kallikrein
- Clinical findings: cirrhosis, pancreatitis, emphysema, glomerulonephritis, vasculitis, acquired angioedema
- Panniculitis: lesions may occur after trauma; painful, recurrent nodules that drain a yellow fluid derived from fat breakdown; most commonly located on the lower extremities
- Diagnosis: serum α1-antitrypsin decreased
- Histology: fat necrosis with “skip areas”(areas of normal fat adjacent to necrotic adipocytes) or septal and lobular inflammation, splaying of neutrophils between collagen bundles of the reticular dermis in
<table>
<thead>
<tr>
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<th>Drugs</th>
<th>Malignancy</th>
<th>Misc.</th>
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<td>Granulomatous mastitis</td>
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<td>Coccidioidomycosis</td>
<td>Hepatitis B vaccine</td>
<td>Vogt-Koyanagi disease</td>
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<td>Nitrofurantoin</td>
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<td>Chlamydia psittaci infections</td>
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<td>Mycoplasma pneumoniae infections</td>
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early lesions; later lesions show fibrosis and a lymphohistiocytic infiltrate
- Treatment: avoid trauma, dapsone, supplemental infusion of exogenous alpha-1-protease inhibitor concentrate, liver transplantation

**CALCIPHYLAXIS (SEE FIG. 8-15)**
- Associated with chronic renal failure
- Calcification of cutaneous vessel walls causing necrosis and ulceration (see Chapter 8)

**COLD PANNICULITIS**
- Cheeks of children sucking ice cubes, ice packs, or popsicles
- Equestrian panniculitis: subtype of cold panniculitis; occurs in healthy women during cold months when riding horses and wearing tight trousers
  - Painful red nodules on superior lateral thighs develop 48 to 72 hours after exposure
- Indurated erythematous plaques with ill-defined margins
- Histology: lobular panniculitis, with lymphocytes and histiocytes in the fat lobules; edematous papillary dermis, perivascular lymphocytic infiltrate

**Cytophagic Histiocytic Panniculitis**
- May be part of a spectrum of disease with subcutaneous panniculitis-like T-cell lymphoma (see below)
- Presents with multiple subcutaneous nodules and plaques over limbs and trunk
- Non-fatal type has little/no systemic symptoms
- Histology: lobular panniculitis with lymphohistiocytic infiltrate with bean-bag cells (macrophages that phagocytize erythrocytes, leukocytes, or lymphocytes)
- Treatment: prednisone or cyclosporine

**Subcutaneous “Panniculitic” Lymphoma**
- High-grade aggressive lymphoma (most commonly cytotoxic T-cell) with appearance of panniculitis
- Persistent fever, hepatosplenomegaly, serosal effusions, pancytopenia and lethal hemorrhagic diathesis
- Histology: subcutaneous fat with pleomorphic lymphocytes large and hyperchromatic nuclei, karyorrhexis, and frequent atypical mitotic figures
- Immunohistochemical stains positive CD3, CD8, and cytotoxic granular proteins (TIA-1 and perforin); negative CD4
- Serologic and/or genotypic evidence of EBV infection

**Factitial Panniculitis**
- Self-inflicted: injections of foreign substances into the subcutaneous fat
- Histology: mostly lobular panniculitis; initially, inflammation mainly contains neutrophils and later, a more granulomatous infiltrate develops; polarization may show the refractile foreign material; (sclerosing lipogranuloma: due to mineral oil injections, “swiss cheese” appearance with pseudocystic spaces in the subcutis surrounded by fibrotic tissue with foamy histiocytes and multinucleated giant cells)

**Iatrogenic Panniculitis**
- Drugs injected in the subcutaneous fat, such as povidone, meperidine, pentazocine, and vitamin K1, or substances used to correct facial wrinkles, such as silicone, polymethyl-methacrolate (PMMA)-microspheres
- Histology: similar changes as seen with factitial panniculitis: mostly lobular panniculitis; early inflammation is primarily neutrophilic in and more granulomatous in late-stage lesions; polarization of the slide may identify the refractile foreign material; silicone injections show polygonal translucent angulated foreign bodies (impurities in the silicone) surrounded by multinucleated giant cells, foamy histiocytes are also present.

**Infective Panniculitis**
- Bacteria or fungi may cause lobular panniculitis mainly in immunosuppressed patients
- Due to:
  - Direct physical inoculation or from an indwelling catheter (primary)
  - Direct extension to the chest wall in pulmonary infections or hematogenous spread most commonly from the respiratory tract (secondary)
- Histology:
  - *Primary cutaneous infections*: superficial dermis with inflammatory infiltrate; and thrombosed vessels void of the pathogenic organisms
  - *Secondary cutaneous infections*: epicenter of inflammation is found in deeper reticular dermis or subcutis; vessels are thrombosed, dilated, and contain organisms
- Diagnosis: culture of tissue and special stains of biopsy specimen
- Treatment: antimicrobial agents depending on the organism

**Lupus Panniculitis (Lupus Erythematosus Profundus)**
- One to three percent of patients with cutaneous lupus erythematosus
Panniculitis

- May precede, appear simultaneously, or develop after systemic disease
- Trauma to subcutaneous fat can be a precipitating factor
- Deeply situated subcutaneous nodules or plaques on the upper arms, shoulders, face, and buttocks, overlying skin may show signs of chronic cutaneous lupus
- Atrophy after resolution
- Histology: 50% of patients with epidermal and dermal changes of discoid lupus erythematosus (epidermal atrophy, dermal-epidermal junction vacuolar changes, enlarged basement membrane, interstitial mucin, and superficial and deep perivascular lymphocytic infiltrate); the remaining cases have changes present only in the subcutis with a lobular panniculitis and a predominantly lymphocytic infiltrate, lymphoid follicles with germinal centers and peripheral plasma cells may also be found
- Immunofluorescence: linear deposition of IgM and C3 along the dermal-epidermal junction (lupus band)
- Treatment: systemic steroids or hydroxychloroquine

Pancreatic Panniculitis

- Associated with acute and chronic pancreatitis, 2% to 3% of all patients with other pancreatic diseases (such as pseudocysts, fistulas), and pancreatic cancer (mostly acinar cell type)
- Tender, fluctuant, erythematous subcutaneous nodules ulcerate spontaneously and exude an oily brown material (liquefaction necrosis of adipocytes)
- Pretibial area most common site, ankle arthralgias (may result from necrosis in periarticular fat tissue)
- Fat necrosis can occur internally (bone marrow fat, abdominal fat)
- Calcium necrosis can occur internally (bone marrow fat, abdominal fat)
- Calcium precipitation can produce hypocalcemia
- Histology: ghostlike fat cells (thick cell wall, no nuclear staining, lobular, calcification), necrotic fat cells, polymorphous fat infiltrate
- Saponification: dystrophic calcification in ghost adipocytes (hydrolytic action of pancreatic enzymes on fat followed by calcium deposition)
- Treatment: resolution of the underlying pancreatic disease

Poststeroid Panniculitis

- Mainly in children who receive a short course of high dose systemic steroids with doses that were decreased quickly or steroid therapy was suddenly discontinued
- Deep nodules appear 1 to 10 days after cessation of steroid treatment; commonly seen on the cheeks
- Histology: lobular panniculitis with needle-shaped clefs (represent former sites of fatty acid crystals dissolved by tissue processing) within lipocytes, foamy histiocytes
- Prognosis: resolve with no complications; atrophic scars may result if ulceration occurs
- Treatment: reinstitution of steroid therapy with a gradual taper

Sclerema Neonatorum

- Develops during first few days of life
- Affects low weight debilitated premature newborns
- Greater ratio of saturated to unsaturated fatty acids than in adult fat
- Rapidly spreading induration of the skin; begins on buttocks to thighs, back; usually symmetric
- Histology: lobular panniculitis without fat necrosis, little inflammation, enlarged lipocytes with needle-like clefs (crystals of triglycerides), in a radial array
• Prognosis: poor, usually death within a few days

**Subcutaneous Fat Necrosis of the Newborn (SFNN)**
- Occurs in first 2–3 weeks of life in healthy full-term neonates
- Localized erythematous, violaceous, firm nodules and plaques; spares anterior trunk
- Greater ratio of saturated to unsaturated fatty acids compared to adults
- Hypercalcemia (unknown significance)
- Histology: granulomatous inflammation, lymphocytes, epithelioid cells, foreign-body giant cells, radially arranged needle-shaped clefts (crystals of triglycerides), fat in macrophages and giant cells, calcium deposition
- Prognosis: lesions regress spontaneously, may leave lipoatrophy
- Treatment: self limited, etidronate (for associated hypercalcinia)

**Sclerosing Panniculitis (Lipodermatosclerosis, Hypodermitis Sclerodermiformis)**
- Indurated plaques with erythema, edema, telangiectasias, and hyperpigmentation involving the lower legs with a stocking distribution; resembles an “inverted wine bottle”
- Associated with chronic venous insufficiency, arterial ischemia, and previous episodes of thrombophlebitis
- Histology: stasis dermatitis changes (increased numbers of capillaries and venules in the papillary dermis, fibrosis, and deposition of hemosiderin), atrophy of the subcutaneous fat, late stages with lipomembranous changes (necrosis causes the formation of cystic spaces in the fat lobule that are lined with a homogeneous eosinophilic membrane with convoluted projections (stain brightly with periodic acid–Schiff and Sudan black and are resistant to diastase)
- Treatment: decrease venous stasis, stanozolol

**Subcutaneous Sarcosis**
- Subcutaneous nodules on the lower extremities without superficial cutaneous involvement
- Histology: noncaseating granulomas of the fat lobules and few lymphocytes at the periphery (“naked” granulomas); occasional calcification
- Treatment: systemic steroids

**Traumatic Panniculitis**
- Accidental blunt trauma, especially frequent in women with large breasts (excessive weight affects mammary subcutaneous fat)
- Mammary traumatic panniculitis: indurated nodules deeply situated on the breast tissue, surface of the skin with occasional appearance of peau d’orange, may resolve with lipoatrophy
- Histology: cystic spaces within fat lobules, due to necrotic fat cells, surrounded by foamy histiocytes; fibrosis and hemorrhage may be present

**Disorders Erroneously Considered as Specific Variants of Panniculitis**

**WEBER DISEASE**
- Lobular panniculitis without vasculitis and systemic manifestations including fever and involvement of visceral fat tissue
- The term *Weber-Christian disease* was used as a diagnosis for cases of lobular panniculitis; however, now a more specific diagnosis may exist

**ROTHMANN-MAKAI DISEASE**
- Cases of relapsing nodular panniculitis without other systemic manifestations
- Obsolete term that is no longer used

**LIPOMEMBRANOUS OR MEMBRANOCYSTIC PANNICULITIS**
- Histopathologic pattern rather than a distinct disease
- Cystic spaces that form due to necrotic adipocytes in the fat that are lined with a homogeneous eosinophilic membrane with convoluted projections into the cystic cavity (positive for periodic acid–Schiff and Sudan black and diastase resistant).

**EOSINOPHILIC PANNICULITIS**
- Septal or lobular panniculitis in which eosinophils predominate in the inflammatory infiltrate; histopathologic pattern rather than a distinct disease
- Nonspecific reactive process found in many different disorders

**QUIZ**

1. A 40-year-old man presents with a tender mobile subcutaneous nodule. On biopsy, pathology shows a well circumscribed mass consisting of adipocytes with prominent vascular pattern with occasional thrombi. What is it?
   A. Spindle cell lipoma
   B. Angiolipoma
   C. Liposarcoma
   D. Pleomorphic lipoma

2. A 55-year-old man presented with an enlarging subcutaneous mass on his thigh. Wide excision revealed a delicate plexiform capillary network that is associated with both normal appearing lipocytes and lipoblasts with a myxoid stroma. What other location is this tumor found?
A. Mediastinum  
B. Head and neck  
C. Acral  
D. Retroperitoneum

3. A 38-year-old woman presents with loss of subcutaneous fat in her face and torso. She states that it has been progressive. What lab should you check?
A. Complete blood count  
B. Protein electrophoresis  
C. Urine analysis  
D. Chest x-ray

4. A 22-year-old female college student presents with tender erythematous nodules on her lower legs. She started a new medication 3 weeks ago. What is the next step in management?
A. Biopsy for H&E and fungal culture.  
B. NSAID, rest, elevation  
C. Colonoscopy  
D. Throat culture

5. A 68-year-old woman presents with a well demarcated yellow-brown plaque on her left cheek. Pathology reveals areas of necrobiosis with granulomatous inflammation and occasional cholesterol crystals. What is the most likely association?
A. IgG paraproteinemia  
B. IgA paraproteinemia  
C. Non-Hodgkin’s lymphoma  
D. Bilateral hilar infiltrates on chest x-ray

6. A 53-year-old man from El Salvador with known lepromatous leprosy presents with tender violaceous nodules on his legs, fever, and arthralgias. What type of reaction is this?
A. Type 1  
B. Type 2  
C. Jarisch-Herxheimer  
D. Lucio reaction

7. A 60-year-old woman on hemodialysis develops dusky reticulated patches on her thighs that ulcerate and form eschars. Biopsy of the affected area would show?
A. Thrombi in small- and medium-sized vessels  
B. Sheets of calcified dermis  
C. Necrotizing vasculitis  
D. Calcification of vessel walls

8. You are asked to evaluate a full-term infant that was brought to the emergency room at 3 weeks of life. You see erythematous, violaceous, firm nodules and plaques on the back and buttocks. What is your diagnosis?
A. Sclerema neonatorum  
B. Subcutaneous fat necrosis of the newborn  
C. Erythema nodosum  
D. Alpha-1-antitrypsin deficiency

9. A 9-year-old boy is brought to your office in July for the onset of an ill-defined erythematous plaque on his left cheek. He is otherwise healthy but his mother says that he eats popsicles every day in the summer. What is your next step?
A. Biopsy  
B. Topical corticosteroid  
C. Reassurance  
D. Warm compresses

10. A 32-year-old man presents to your office with tender erythematous nodules on his lower legs. He has a scar on his lower abdomen and has chronic diarrhea. What other findings may be present?
A. Pyostomatitis vegetans  
B. Posterior uveitis  
C. Bilateral hilar infiltrates on chest x-ray  
D. Recent treatment for UTI with trimethoprim/sulfamethoxazole

Answers

1. B. This is a pathologic description of an angiolipoma
2. D. This is a pathologic description of a liposacoma. It is the most common soft malignancy in adults. It is most commonly found on the thighs, retroperitoneum and inguinal region.
3. C. This is acquired partial lipodystrophy which is associated with C3 nephritic factor. This binds factor H, an inhibitor of C3 and results in uncontrolled activation of C3 causing glomerulonephritis. They also have association with diabetes mellitus so you should check glucose or insulin levels.
4. B. This is erythema nodosum, likely occurring after the start of oral contraceptives. Given the history of the new medicine a biopsy is not necessary. EN is related to IBD but colonoscopy is not the best choice. In children, EN is related to strep pharyngitis. Supportive care is the best management in this case.
5. A. This necrobiotic xanthogranuloma. It is most commonly pericocular and associated with IgG.
6. B. This is erythema nodosum leprosum which is a type 2 reaction usually in lepromatous leprosy. It is due to circulating immune complexes and treated with thalidomide. Type 1 reaction is a reversal reaction. Jarisch-Herxheimer reaction is seen in Lyme disease, syphilis after treatment with antibiotics. Lucio’s reaction is due to mycobacterium invading vessels and is treated with rifampin.
7. D. This is calciphylaxis. The other answers are incorrect.
8. B. This is subcutaneous fat necrosis of the newborn because it is a full-term infant. Sclerema neonatorum occurs in premature infants. EN occurs in children but is usually related to strep pharyngitis and is found on the legs. Alpha-1-antitrypsin deficiency does not occur in this age group.
9. C. This is cold panniculitis likely induced by the child’s fondness for popsicles. It should resolve with cessation of the offending agent and no treatment is needed.
10. B. This is erythema nodosum in the setting of inflammatory bowel disease, either Crohn’s or UC. Pyostomatitis vegetans in an ulcer in of the oral mucosa with the characteristic “snail tracks.” EN is also associated with sarcoid, Behçet’s, and sulfa drugs, but these are not consistent with the given scenario.

REFERENCES

SURFACE EPITHELIAL TUMORS

Seborrheic Keratosis (Fig. 11-1)
- Appearance: warty, sharply delineated, often scaly hyperpigmented plaques with greasy crust that appear “stuck on” the surface of the skin
- Location: trunk, shoulder, face, and scalp (areas with sebaceous glands), but can occur anywhere (except palms and soles)
- Demographics: > 30 years
- Histology: benign proliferation of epidermal keratinocytes that can be endophytic, exophytic, or flat. They contain horn pseudocysts (called “pseudo” because they connect to surface, and have no true epithelial lining) and are characterized by hyperkeratosis, papillomatosis, and acanthosis
- Syndrome
  - Leser-Trelat syndrome: sudden onset of numerous seborrheic keratoses associated with internal malignancies, most common adenocarcinoma of stomach, but also leukemia, lymphoma and other carcinomas
- Variants
  - Inverted follicular keratosis: verrucous, intradermal or “inverted” form of irritated seborrheic keratosis, arising in close approximation to a hair follicle, with prominent squamous eddies
  - Dermatosis papulosa nigra: multiple small, pedunculated, and heavily pigmented tag-like papules on the face of African-American and Afro-Caribbean patients (Fig. 11-2)
  - Stucco keratosis (keratosis alba): white-to-light brown (depigmented), flat keratotic lesions on dorsa of the feet, the ankles, and the dorsa of the hands and forearms

- Melanoacanthoma: deeply pigmented seborrheic keratoses in which an epidermal proliferation of large dendritic melanocytes is identified

Epidermal Nevus
- Appearance: yellowish-brown warty papules or plaques (Fig. 11-3)
- Location: usually on trunk and extremities
- Demographics: present at birth or develop during childhood
- Characterization: congenital hamartoma (nevus) of proliferating epidermis
- Three subtypes
  - Nevus verrucosus: solitary or multiple localized lesions
  - Nevus unius lateralis: extensive unilateral linear distribution
  - Ichthyosis hystrix: extreme involvement with bilateral or generalized distribution
- Histology: hyperkeratosis, papillomatosis, acanthosis, and elongation of the rete ridges
- Syndrome
  - Leser-Trelat syndrome: sudden onset of numerous seborrheic keratoses associated with internal malignancies, most common adenocarcinoma of stomach, but also leukemia, lymphoma and other carcinomas
- Variants
  - Inverted follicular keratosis: verrucous, intradermal or “inverted” form of irritated seborrheic keratosis, arising in close approximation to a hair follicle, with prominent squamous eddies
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- Melanoacanthoma: deeply pigmented seborrheic keratoses in which an epidermal proliferation of large dendritic melanocytes is identified
Nevus comedonicus: groups of open comedones on face, trunk, neck, and upper extremities that histologically show keratin-filled, epithelium-lined invaginations of the epidermis.

Nevus comedonicus syndrome: nevus comedonicus with abnormalities in the central nervous system (CNS), skeletal system, skin, and eye.

Acrokeratosis Verruciformis of Hof
- Appearance: dry, rough, skin-colored verrucoid, keratotic papules.
- Characterization: if multiple, can be associated with Darier disease.
- Histology: hyperkeratosis, acanthosis, orthokeratosis, hypergranulosis, and mild papillomatosis with a "church spire" appearance.

Intraepidermal Epithelioma of Borst-Jadassohn
- Characterization: currently regarded as a histopathological appearance rather than a precise clinicopathological entity.
- Histology: nests of clonal keratinocytes in the background of a seborrheic keratosis, actinic keratosis, hidrocanthoma simplex, intraepidermal eccrine poroma, and Bowen disease.

Porokeratosis (Fig. 11-4)
- Appearance: annular hyperkeratotic papule or plaque with atrophic center and peripheral grooved keratotic ridge.
- Characterization: misnomer, no relationship to pore of eccrine duct.
SURFACE EPITHELIAL TUMORS

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found in medications, Fowler solution, and well water
• Can turn into squamous cell carcinoma (most commonly) or basal cell carcinoma; also associated with internal malignancies (gastrointestinal tract adenocarcinoma)
• Mees lines on the fingernails (Fig. 11-5)
• Histology: thick, compact hyperkeratosis, parakeratosis, and acanthosis with atypical keratinocytes; may resemble Bowen’s disease

Large Cell Acanthoma
• Appearance: solitary, slightly hyperkeratotic lesion with sharply demarcated borders, usually < 1 cm; occurs on sun-exposed areas
• Characterization: thought to represent at type of actinic keratosis, but now is considered by many to be a stage of solar lentigo evolution
• Histology: hyperkeratosis; keratinocytes are two times larger than normal without atypia; lentiginous hyperpigmentation

Clear Cell Acanthoma (Pale Cell Acanthoma)
• Appearance: solitary nodules and papules with well defined borders and covered with a crust, < 2 cm
• Location: usually on anterior surface of lower extremities
• Histology: proliferation of pale keratinocytes (periodic acid–Schiff (PAS) staining positive, due to cytoplasmic glycogen accumulation) with sharp demarcation from normal epidermis; neutrophils within the epidermis, often with microabscesses in stratum corneum and dilated capillaries in dermal papillae

Warty Dyskeratoma (Isolated Dyskeratosis Follicularis)
• Appearance: solitary, benign, hyperkeratotic, umbilicated lesion with keratotic plug
• Location: usually limited to the head, neck, or face (sun-exposed skin)
• Histology: epidermal cup-shaped invagination with focal acantholysis, dyskeratosis (corps ronds and grains), and overlying parakeratosis

Arsenical Keratosis
• Appearance: gray, hard, hyperkeratotic papules
• Location: usually on palms, forearms, soles, trunk, and face
• Characterization
  • Arsenic impairs nucleotide excision repair and enhances proliferation of human keratinocytes; found in medications, Fowler solution, and well water
Chapter 11  CUTANEOUS TUMORS

Location:
• most often on face, neck, and trunk, but can occur anywhere

Demographics: young and middle-aged adults

Characterization: most common type of cyst of the skin

Histology: cyst wall lined by squamous epithelium with large basophilic keratohyaline granules and intracytoplasmic eosinophilic bodies (epidermolytic hyperkeratosis)

Variations
• Milium (plural: milia): Much smaller epidermoid cyst (1–2 mm) (Fig. 11-8)

Epidermolytic Acanthoma

• Appearance: solitary tumor arising on the trunk of older patients
• Histology: compact hyperkeratosis, papillomatosis, acanthosis, perinucleolar vacuolization of keratinocytes in stratum spinosum, hypergranulosis with large basophilic keratohyaline granules and intracytoplasmic eosinophilic bodies (epidermolytic hyperkeratosis)

Prurigo Nodularis

• Appearance: multiple or solitary nodules, usually symmetric with excoriations present, extremely pruritic (Fig. 11-6)
• Characterization: part of the spectrum of lichen simplex
• Histology: psoriasiform hyperplasia, hyperkeratosis, hypergranulosis and focal parakeratosis, occasional spongiosis and exocytosis of mononuclear cells

Granuloma Fissuratum

• Appearance: firm, flesh-colored nodule with a central groove (site of focal pressure or friction)
• Location: lateral aspect of nose and retroauricular region
• Histology: acanthosis with broad rete ridges and central depressed area corresponding to the groove

CYSTS

Epidermoid Cyst (Epidermal Inclusion Cyst, Follicular Infundibular Cyst)

• Appearance: smooth dome-shaped swellings; punctum can be present (Fig. 11-7)
• Location: most often on face, neck, and trunk, but can occur anywhere
• Demographics: young and middle-aged adults
• Characterization: most common type of cyst of the skin
• Histology: cyst wall lined by squamous epithelium similar to surface epidermis with granular layer and containing lamellated keratin; cyst rupture can result in a prominent foreign body inflammatory reaction with foreign body giant cells, lymphocytes, plasma cells, and neutrophils
• Variations
  • Milium (plural: milia): Much smaller epidermoid cyst (1–2 mm) (Fig. 11-8)
**Dermoid Cyst**
- Appearance: subcutaneous freely mobile cyst; occasionally may fix to periosteum
- Location: most commonly found on the lateral upper eyelid, nose, and scalp; may have intracranial extension
- Demographics: develops in infancy or early childhood
- Characterization: hamartomatous lesion; due to sequestration of epithelium along embryonal lines of closure
- Histology: cyst wall lined by squamous epithelium with associated hair follicles and sebaceous glands and containing keratin and hair shafts

**Pilar Cyst (Trichilemmal Cyst)**
- Appearance: smooth, firm, mobile nodules
- Location: usually on scalp
- Characterization: derived from the outer root sheath of the hair follicle
- Histology: fibrous capsule lined by squamous epithelium lacking a granular layer with compact, dense keratin; calcification and cholesterol clefts common

**Steatocystoma**
- Appearance: moderately firm, translucent to yellow cystic nodules
- Location: commonly found in the axilla and on the arms, trunk, head, and neck.
- Characterization: true sebaceous cyst with epithelial lining that extrudes a yellowish oily material when punctured
- Steatocystoma simplex: solitary; adults
- Steatocystoma multiplex: autosomal dominant disorder (mutations in gene encoding keratin 17); adolescents
- Histology: dermal, folded cyst wall composed of keratinocytes with peripheral palisading basal cells; wall embedded with flattened lobules of sebaceous glands; cyst filled with eosinophilic cuticle along corrugated keratin layer; K17 and K10 staining positive

**Hidrocystoma (Cystadenoma) (Fig. 11-9)**
- Appearance: solitary, translucent, bluish cyst, 1–3 mm
- Location: most common on eyelid or cheek
- Histology: unilocular or multilocular intradermal cyst, lined by a double layer of cuboidal cells

**Branchial Cleft Cyst**
- Appearance: solitary, painless mass
- Location: lateral part of the neck; occurs along the lower third of the anteromedial border of the sternocleidomastoid muscle; 2–3% of cases are bilateral
- Demographics: child or young adult
- Characterization: congenital epithelial cyst; remnant of the second branchial cleft in embryonic development

**Thyroglossal Duct Cyst**
- Appearance: solitary, fluctuant, painless mass; < 3 cm
- Location: midline neck, near hyoid bone; moves with swallowing
- Characterization: congenital, vestigial remnant of the tubular thyroid gland precursor
- Histology: lined by cuboidal, columnar, or stratified squamous ciliated epithelium associated with mucous glands, thyroid follicles, and lymphocytic infiltrate; smooth muscle is not present

**Steatocystoma simplex:** solitary; adults
**Steatocystoma multiplex:** autosomal dominant disorder (mutations in gene encoding keratin 17); adolescents
- Histology: dermal, folded cyst wall composed of keratinocytes with peripheral palisading basal cells; wall embedded with flattened lobules of sebaceous glands; cyst filled with eosinophilic cuticle along corrugated keratin layer; K17 and K10 staining positive

**FIGURE 11-9 Hidrocystoma. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)**
- Histology: lined by stratified squamous or respiratory (pseudostratified ciliated columnar) epithelium; lymphoid tissue often is present outside the epithelial lining

**Thyroglossal Duct Cyst**
- Appearance: solitary, fluctuant, painless mass; < 3 cm
- Location: midline neck, near hyoid bone; moves with swallowing
- Characterization: congenital, vestigial remnant of the tubular thyroid gland precursor
- Histology: lined by cuboidal, columnar, or stratified squamous ciliated epithelium associated with mucous glands, thyroid follicles, and lymphocytic infiltrate; smooth muscle is not present

**Bronchogenic Cyst**
- Appearance: small, solitary, painless mass
- Location: above sternal notch
- Demographics: present at birth
- Characterization: formed from portions of foregut during development of tracheobronchial tree
- Histology: intradermal, folded cyst lining; pseudostratified, cuboidal, or columnar ciliated epithelium with or without goblet cells, smooth muscle, or mucous glands

**Vellus Hair Cyst**
- Appearance: small solitary cysts, 1–2 mm
- Location: particularly over the parasternal area
- Histology: intradermal cyst lined by squamous epithelium (with granular layer) containing laminated
keratin and vellus hair shafts; K17 staining positive and K10 staining negative (in contrast to steatocystoma above)
- Variations:
  - Eruptive vellus hair cysts: multiple cysts on chest of children

**DUCTAL (APOCRINE/ECCRINE) TUMORS**

**Apocrine/Eccrine Nevus**
- Location: scalp, axilla, upper extremities, presternal, or inguinal area
- Characterization: rare hamartoma of apocrine or eccrine unit
  - Apocrine type usually located in axilla and lacks hyperhidrosis, while eccrine type usually has hyperhidrosis
- Histology: increased size or number of mature apocrine or eccrine glands

**Eccrine Hamartoma**
- Variations
  - Eccrine angiomatic hamartoma: increased number of eccrine glands with small blood vessels, nerve fibers, mucin, or fat
  - Porokeratotic eccrine ostial nevus: coranoid lamellae associated with eccrine ducts
  - Acrosyringial nevus: PAS-positive acrosyringeal keratinocytes, which extends into the dermis as anastomosing cords
  - Linear eccrine nevus with comedones: similar to nevus comedonicus together with basaloid nests in the dermis

**Tubular Apocrine Adenoma**
- Appearance: rare, slow growing intradermal nodule; female predominance (2:1)
- Location: most often on scalp and perianal skin
- Histology: well-circumscribed dermal tumor (without epidermal connection) composed of well-formed tubules lined by a double layer of epithelium with abundant eosinophilic cytoplasm; luminal layer shows columnar cells with decapitation secretions, while the peripheral layer is composed of flattened or cuboidal myoepithelial cells

**Nipple Adenoma (Erosive Adenomatosis, Florid Papillomatosis, Superficial Papillary Adenomatosis)**
- Appearance: unilateral crusted papule or plaque
- Location: on the nipple; may mimic Paget disease
- Characterization: ductal hyperplasia of the lactiferous ducts

- Histology: mixture of intraductal papilloma and tubular glands with apocrine decapitation, lined by epithelial and myoepithelial cells, usually communicating with the surface epithelium; plasma or lymphocyte-rich inflammatory cell infiltrate sometimes in surrounding connective tissue

**Hidradenoma Papilliferum**
- Appearance: solitary, mobile nodule which may exhibit superficial erosion
- Location: vulva or perianal regions
- Demographics: young or middle-aged women
- Histology: well-circumscribed, cystic tumor (usually without communication with surface) with maze-like glandular spaces and epithelial covered papillary processes cover by two types of epithelium: tall columnar cells with decapitation secretions and peripheral flattened or cuboidal myoepithelial cell layer

**Syringocystadenoma Papilliferum (Fig. 11-10)**
- Appearance: erythematous, warty solitary plaque or linear arrangement of papules
- Location: most common on scalp
- Characterization: often found in association with nevus sebaceus (5–20%)
- Histology: epithelial-lined papillae invaginating from the overlying epidermis, lined with a double layer of cells (columnar layer with apocrine decapitation on the luminal side and a cuboidal layer at the periphery); fibrovascular cords with plasma cell-rich infiltrates

**Cylindroma**
- Appearance: pink, firm, rubbery nodules; solitary or multiple (turban tumors); arising sporadically or as part of the Brooke-Spiegler syndrome

**FIGURE 11-10 Syringocystadenoma papilliferum.**
(Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)
DUCTAL (APOCRINE/ECCRINE) TUMORS

- Appearance: solitary, skin-colored, slow growing •
- Location: head and neck •
- Demographics: middle age, males more than females •
- Histology: located in the dermis and subcutaneous tissue (no epidermal connection); multilobulated, clusters and solid cords of tumor cells together with ductal structures set in a chondroid, myxoid, and fibrous stroma; ductal structures are lined by two layers of cuboidal cells (resembling apocrine cells); areas of ossification (pseudocartilagenous appearance)

Eccrine Poroma

- Appearance: solitary, skin-colored, painless, firm to rubbery, dome-shaped nodule, <2 cm in diameter •
- Location: usually on scalp and sole of foot or palms •
- Demographics: middle age •
- Histology: solid masses of cuboidal or basaloid epithelial cells with ovoid nuclei; tumor in continuity with overlying epidermis; small sweat ducts with inner eosinophilic cuticle are usually present

Variations
- Eccrine poromatosis: greater than 100 papules on palms/soles •
- Intraepidermal poroma (hidroacanthoma simplex): nests of clonal basaloid cells with tubular differentiation; confined to the surface epidermis •
- Juxtaepidermal poroma: nests and thick cords of cells in continuity with the epidermis but also involving the superficial dermis

Eccrine Acrospiroma (Nodular Hidradenoma)

- Appearance: solitary, slow growing, painless intra-dermal nodule •
- Location: usually on scalp and sole of foot or palms •
- Demographics: middle age •
- Histology: solid masses of cuboidal or basaloid epithelial cells with ovoid nuclei; tumor in continuity with overlying epidermis; small sweat ducts with inner eosinophilic cuticle are usually present

Variations
- Eccrine poromatosis: greater than 100 papules on palms/soles •
- Intraepidermal poroma (hidroacanthoma simplex): nests of clonal basaloid cells with tubular differentiation; confined to the surface epidermis •
- Juxtaepidermal poroma: nests and thick cords of cells in continuity with the epidermis but also involving the superficial dermis

Eccrine Acrosiroma (Nodular Hidradenoma) (Fig. 11-12)

- Appearance: solitary, slow growing, painless intra-dermal nodule; usually <2 cm in diameter •
- Location: usually on scalp, face, or trunk •
- Characterization: some authors consider hidroacanthoma simplex, poroma, dermal duct tumor, and hidradenoma under the unifying term of “eccrine acrosiroma” •
- Histology: well circumscribed (not connected to epidermis) nests of tumor cells often in lower dermis

Syringoma

- Appearance: usually multiple, skin-colored to tan, soft, pinpoint papules (Fig. 11-11) •
- Location: lower eyelids and upper cheeks •
- Demographics: commonly seen in females at puberty; associated with Down syndrome, Marfan syndrome, and Ehlers-Danlos syndrome •
- Characterization: eccrine duct adenoma •
- Histology: small ducts with elongated tails of epithelial cells (tadpole appearance) embedded in a sclerotic stroma; walls of the ducts usually lined by two rows of cuboidal epithelial cells; lumen filled with PAS staining positive eosinophilic, amorphous debris •
- Histologic differential diagnosis: sclerosing (morphea-like) basal cell carcinoma, desmoplastic trichoepithelioma, and microcystic adnexal carcinoma •
- Variations
  - Eruptive syringomas: large crops on anterior chest, in children 4 to 10 years old, 18% of Down syndrome patients •
  - Clear cell syringomas: associated with diabetes mellitus

Histologic differential diagnosis: sclerosing (morphea-like) basal cell carcinoma, desmoplastic trichoepithelioma, and microcystic adnexal carcinoma

Syndrome:
- Brooke-Spiegler syndrome (BSS): autosomal dominant disease (CYLD gene on chromosome 9p21) characterized by the development of multiple trichoepitheliomas and cylindromas

Histology: dermal tumor without connection to the overlying epidermis; multiple lobules of basaloid tumor cells, surrounded by a hyaline basement membrane and fit together like pieces of a jigsaw puzzle; eosinophilic hyaline sheaths and hyaline droplets are PAS staining positive (composed of type IV collagen and laminin)

**Figure 11-11** Syringoma. (Courtesy of Dr. Melissa Bogle.)
or subcutaneous tissue with two types of cells: fusiform, eosinophilic cells and polygonal, clear cells; sweat duct lumina present within tumor

- Variations
  - Clear cell hidradenoma: pale or clear cells containing glycogen (PAS staining positive)
  - Cystic nodular hidradenoma: common on scalp; prevalence of cysts (solid structures are present as well, as opposed to apocrine hidrocystoma)

**Malignant Sweat Gland Tumors**

- Appearance: solitary, slow growing papule or indistinct plaque
- Location: usually on upper lip, nasolabial area, or periiorbital regions
- Characterization: infiltrating malignant tumor involving the dermis with ductal or glandular differentiation
- Histology: deeply infiltrating dermal strands of ductal cells with small lumina; pleomorphic, hyperchromatic, highly mitotic with areas of necrosis; perineural invasion common
- Variations
  - Primary mucinous carcinoma (cutaneous adenocystic carcinoma): slow growing, skin-colored, erythematous, or blue nodules or plaques; head and neck (especially eyelids); middle-age to elderly males (2:1); locally aggressive but rare metastasis
    - Histology: duct forming tumor cells suspended in abundant pools of mucin, compartmentalized by delicate fibrous septa
  - Adenoid cystic carcinoma: painful plaques; >3 cm in diameter; middle-age to elderly women; affecting scalp, trunk and extremities
    - Histology: irregularly shaped, dermal aggregation of basaloid cells arranged in solid and/or sieve-like patterns (cribriform); the tumor nests are surrounded by hyaline basal-like material and cystic spaces contain mucin; propensity for perineural invasion; carcinoembryonal antigen (CEA) and EMA positive
  - Microcystic adnexal carcinoma: indurated plaques or nodules on the upper lip, chin, nasolabial fold, cheek; aggressive local invasion and indolent course
    - Histology: desmoplastic stroma; keratinous cysts and abortive hair follicles in the superficial portion of the lesion and nests of basaloid cells (resembling sclerosing basal cell carcinoma) and small ducts lined by one or two layers of cuboidal cells (can have tail-like cellular extensions reminiscent of syringoma) in the deeper aspect of lesion; perineural invasion frequently seen; epithelial membrane antigen (EMA) and CEA staining positive
  - Apocrine carcinoma (Fig. 11-13): rare, solitary or multiple nodules and plaques measuring 2 to 8 cm in diameter in the axillae or anogenital area
    - Histology: infiltrating dermal or subcutaneous nonencapsulated papillary tumor; ductal, solid, or mixed pattern; apocrine secretions and cords of neoplastic cells with variable pleomorphism; abnormal mitotic activity and necrosis; CAM 5.2, CEA, and S–100 protein immunoreactivity
  - Malignant chondroid syringoma (malignant mixed tumor): extremely rare, solitary, painful, flesh-colored or erythematous nodule,
FOLLICULAR TUMORS

Trichoblastoma
- Appearance: well-circumscribed, solitary papule, < 1 cm
- Location: predominantly on the head and neck
- Histology: well-circumscribed dermal aggregates of epithelial, basaloid, and mesenchymal components in a fibromyxoid stroma that extend into the subcutaneous tissue; increased mitotic activity; minimal pleomorphism

Trichoepithelioma
- Appearance: dome-shaped papules
- Location: face, usually nasolabial folds
- Characterization: multiple lesions present as an autosomal dominant trait
- Syndromes
  - Brooke-Spiegler syndrome: multiple trichoepithelioma papules, particularly on the head and neck; also cylindromas in addition to spiradenomas and milia; increased risk of basal-cell adenomas and adenocarcinomas of the parotid glands and minor salivary glands; see cylindroma above
  - Rombo syndrome: vermiculate atrophoderma; milia; hypotrichosis; vellous hair cysts; basal cell carcinoma and peripheral vasodilatation with cyanosis
  - Bazex syndrome: follicular atrophoderma; hypotrichosis; basal cell carcinoma and localized or generalized hypohidrosis
- Histology: palisading basaloid cells in a dense stroma; horn cysts with keratinized center; calcification; papillary mesenchymal bodies; artifactual clefting is uncommon (in contrast from basal cell carcinoma); lack of deep and infiltrating growth pattern, perineural infiltration, and ductal differentiation (in contrast from microcystic adnexal carcinoma)
- Variations
  - Desmoplastic trichoepithelioma: prominent sclerotic stroma, narrow strands of tumor cells, and keratinous cysts with calcification (resembling sclerosing basal cell carcinoma); pleomorphism, palisading, and peripheral clefting are not seen; particularly important to exclude microcystic adnexal carcinoma
  - Solitary giant trichoepithelioma: deep involvement of the reticular dermis and subcutaneous tissue
  - Trichoadenoma: rare solitary tumor located on the face, up to 5 cm in size; groups of horn cysts connected by epithelial strands; cells more squamous than basaloid

Paget’s Disease (Mammary and Extramammary)
- Appearance: resembles non-resolving eczema, contact dermatitis, or Bowen’s disease with intense pruritis
- Location: extramammary Paget’s occurs in areas rich in apocrine sweat glands (groin, perianal, scrotum, or vulva)
- Characterization: association with internal malignancy
- Mammary Paget’s: close to 100% intraductal breast cancer
- Extramammary Paget’s: up to 15% underlying carcinoma (e.g., adnexal apocrine carcinoma, colonic carcinoma, etc.)
- Histology: Paget cells (large, vacuolated cells with a bluish cytoplasm) in the lower epidermis which spread along the rete ridges and adnexal (pagetoid spread); stain sialomucin with PAS and diastase, colloidal iron, and mucicarmine; Paget’s cells are immunoreactive with EMA, CEA, cytokeratin 7
- Immunostaining sometimes helpful for excluding associated internal malignancy

Porocarcinoma: verrucoid plaque or polypoid growth; older individuals; usually on the lower extremities; metastasis about 20%
- Histology: large islands and small, irregularly shaped nests with infiltrative borders; focal necrosis with clear cell areas, ductal structures, intracytoplasmic lumina formation, and squamous differentiation; PAS staining positive and usually diastase labile, cytokeratin, CEA, and EMA staining positive

Trichofolliculoma
- Appearance: small, solitary, elevated papule, or flattened nodule with central depression and protruding tuft of small, short, white, or pigmented thread-like hairs (trichoids)

FOLLICULAR TUMORS
systemic malignancies (e.g., thyroid, breast, and endometrial carcinomas); dysfunctional lipid phosphatase enzyme secondary to loss of PTEN (10q23)

- Histology: endophytic epithelial lobule with peripheral basal cell palisading; thickened eosinophilic hyaline basement membrane zone; cells located toward the center are clear (increased glycogen, PAS staining positive)

- Variations
  - Desmoplastic tricholemmoma: lobulated tumor that has at the base narrow, irregular cords that infiltrate into the dermis; infiltrating pattern commonly mistaken for malignant tumor (e.g., trichilemmal carcinoma, squamous cell carcinoma, or morpheaform basal cell carcinoma)
  - Tumor of the follicular infundibulum: solitary keratotic papule on the face; dermal growth of clear epithelial cells parallel to the epidermis; peripheral palisading of the basal cells

**Fibrofolliculoma**

- Appearance: multiple small dome-shaped papules
- Location: face, neck, and upper trunk
- Syndrome
  - Birt-Hogg-Dube syndrome: Autosomal dominant (BHD gene on 17p11.2); association of fibrofolliculomas, acrochordons, trichodiscomas and pulmonary disease (spontaneous pneumothorax); renal tumors
- Histology: cystically dilated, well-formed hair follicle with a central keratin plug and anastomosing strands of basaloid cells arising from the infundibulum; surrounded by a fibrous stroma; residual sebaceous glands are often incorporated into the lesion

**Trichodiscoma**

- Appearance: small dome-shaped papules
- Location: face, neck, and upper trunk
- Characterization: proliferation of the hair mantle
  - Fibrofolliculoma and trichodiscoma may represent various stages in the natural history of a single hamartomatous tumor
  - Histology: horizontally oriented proliferation of epithelial cords surrounded by prominent stroma that contains fusiform and stellate fibroblasts and thin-walled blood vessels within the substance of the tumor

**Trichilemmoma (Tricholemma)**

- Appearance: single papule or multiple, small, flesh-colored papules or warty lesions
- Syndrome
  - Cowden syndrome: autosomal dominant; multiple facial trichilemmomas, acral keratoses, dermal fibromas, oral mucosal papillomas, and systemic malignancies (e.g., thyroid, breast, and endometrial carcinomas); dysfunctional lipid phosphatase enzyme secondary to loss of PTEN (10q23)
- Histology: endophytic epithelial lobule with peripheral basal cell palisading; thickened eosinophilic hyaline basement membrane zone; cells located toward the center are clear (increased glycogen, PAS staining positive)

- Variations
  - Desmoplastic tricholemmoma: lobulated tumor that has at the base narrow, irregular cords that infiltrate into the dermis; infiltrating pattern commonly mistaken for malignant tumor (e.g., trichilemmal carcinoma, squamous cell carcinoma, or morpheaform basal cell carcinoma)
  - Tumor of the follicular infundibulum: solitary keratotic papule on the face; dermal growth of clear epithelial cells parallel to the epidermis; peripheral palisading of the basal cells

**Pilomatricoma (Calcifying Epithelioma of Malherbe)**

- Appearance: solitary, firm, deep-seated dermal or subcutaneous nodule
- Perforation with extrusion of contents; “tent sign” elevates skin (clinically mistaken for a cyst)
- Location: predilection for the head, shoulders, and upper extremities
- Demographics: occurs at any age; most common in children and young adults
- Characterization: activating point mutation in CTNNB1 with accumulation of nuclear beta-catenin
- Histology: irregularly shaped islands embedded in cellular stroma; composed of two cell types: small uniform basaloid cells with high mitotic activity (early lesion) and necrotic cells with eosinophilic cytoplasm and lost nucleus (shadow cells, older lesion); transitional areas where basal cells turn into shadow cells; calcification, ossification, keratin debris predominant in older lesions with foreign body giant cell reaction; pilomatrical features can rarely be seen in the epidermoid inclusion cysts and is believed to be pathognomonic of Gardner syndrome

**Proliferating Trichilemmal Cyst (Pilar Tumor)**

- Appearance: rare, large dermal nodule
- Location: most common on scalp
- Characterization: arises as proliferating wall of pilar cyst with abrupt trichilemmal keratinization
- Histology: well-circumscribed nodule with trichilemmal keratinization (without granular layer); horn pearls and squamous eddies


**Sebaceous Tumors**

### Sebaceous Hyperplasia
- **Appearance:** white-yellow, well-demarcated, small papules with central umbilication (Fig. 11-14)
- **Location:** face, especially forehead and nose
- **Histology:** increased number of enlarged sebaceous lobules grouped around a centrally located, wide sebaceous duct

### Sebaceous Adenoma
- **Appearance:** solitary, yellow papule or nodule; < 1 cm
- **Location:** usually on the face or scalp
- **Syndrome**
  - Muir-Torre syndrome: autosomal dominant, defect in DNA mismatch repair (MMR) gene with loss of hMSH2 or (less commonly) hMLH1 protein expression; one or more sebaceous neoplasms (sebaceous adenoma, sebaceoma, or rarely sebaceous carcinoma) and one or more visceral malignancies (most commonly gastrointestinal, endometrial or genitourinary carcinomas)
- **Histology:** well-circumscribed multilobulated neoplasm composed of mature sebaceous cells (sebocytes) representing up to 50% of the tumor and peripheral, smaller basaloid (germinative) cells

### Sebaceoma
- **Appearance:** solitary, yellow ill-defined plaque, 1–3 cm in diameter
- **Location:** face and scalp
- **Demographics:** 6th–9th decade; female predominance (4:1)
- **Syndrome:**
  - Muir-Torre syndrome: see Sebaceous Adenoma above
- **Histology:** composed of sebocytes and smaller basaloid (germinative) cells that represent more than 50% of the total lesional cells

### Nevus Sebaceus of Jadassohn (Fig. 11-15)
- **Appearance:** three clinical stages
  - **At birth:** solitary, hairless, pinkish, yellow, orange, or tan plaque with a smooth or somewhat velvety macular surface
  - **Puberty:** lesion becomes verrucous and nodular; sebaceous glands enlarge and cause papillomatosis
  - **Later in life:** lesions may develop various types of appendageal tumors including: syringocystadenoma papilliferum (8–10%), trichoblastoma (5%), and rarely trichilemmoma (2–3%), sebaceoma (2–3%), syringoma, apocrine cystadenoma, hidradenoma or keratoacanthoma

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**FIGURE 11-14** Sebaceous hyperplasia. *(Courtesy of Dr. Asra Ali.)*

**FIGURE 11-15** Nevus sebaceus. *(Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)*
• Apparently benign basaloid epithelial proliferations resembling basal cell carcinoma can be identified in 5–7% of cases of nevus sebaceus
• Malignant tumors (apocrine carcinoma, basal cell carcinoma, squamous cell carcinoma) have been described to arise in association with nevus sebaceus on occasion

- Location: face or scalp
- Syndrome
  - Neurocutaneous syndrome: mental retardation; epilepsy; neurologic deficits; skeletal deformities (rare)
  - Epidermal nevus syndrome (Schimmelpenning-Feuerstein-Mims syndrome, organoid nevus phakomatosis): combination of extensive sebaceous nevi with central nervous system, cardiac, ophthalmic, and skeletal muscle disorders
- Histology: papillomatous and acanthotic hyperplasia; numbers of mature or nearly mature sebaceous glands are increased in the dermis; ectopic apocrine glands in the deep dermis beneath sebaceous glands; reduced number of hair follicles, incompletely differentiated

Sebaceous Carcinoma

- Appearance: firm, slow growing, yellowish nodule
- Location: 75% arise in the periocular region: upper lid two to three times more common than lower lid, often mistaken for a chalazion; can mimic keratoconjunctivitis, blepharoconjunctivitis
- Demographics: 6th–7th decade
- Characterization: aggressive clinical course with high recurrence rate (up to 40%); metastasis occurs in 14–25% of cases, first to the draining lymph nodes with progression to distal or visceral metastases
- Syndrome
  - Muir-Torre syndrome: non-periocular sebaceous carcinomas are much more commonly associated with the syndrome; see Sebaceous Adenoma
- Histology: infiltration of dermis by lobules composed of a mixture of small basaloid (germinative) cells and poorly differentiated sebaceous cells; marked pleomorphism and frequent abnormal mitoses, necrosis common; pagetoid spread is seen in 40–80% of cases; oil red-O staining can be performed in frozen sections to highlight the sebocytes

FIBROUS AND “FIBROHISTIOCYTIC” TUMORS

Fibroma

- Appearance: pale brown, soft, small tumors in friction areas: neck, axilla, internal aspects of thighs
- Histology: tumors are formed by connective tissue; fibrocytes are regular and mature; mitoses are not present

Angiofibroma (Fibrous Papule)

- Appearance: small, reddish-brown papules
- Location: usually over the nose and medial cheeks
- Syndrome
  - Tuberous sclerosis: autosomal dominant, genetic linkage to chromosome 9q34 (TSC1) or 16p31 (TSC2) in families with tuberous sclerosis; two-thirds of cases are sporadic and majority appear to be related to new mutations of TSC2: multiple, bilateral angiofibromas near the nasal labial folds at puberty (adenoma sebaceum); periungal fibromas; white macular lesions (shagreen patches), enamel teeth pits; central nervous system involvement (epilepsy and low intelligence); ophthalmological, cardiac, and pulmonary manifestations, among others
  - Multiple endocrine neoplasia type I: familial tumor syndrome with facial angiofibromas, collagenomas, lipomas, gastrinomas, insulinomas, prolactinomas, and carcinoid tumors.

- Histology: concentrically oriented (around follicles) or perpendicular (to the epidermis) laid collagen fibers with stellate fibroblasts; teleangiectasia
- Variations
  - Pearly penile papules: angiofibromas in penile coronal sulcus

Dermatofibroma (DF), (Benign Fibrous Histiocytoma) (Fig. 11-16)

- Appearance: usually firm, solitary, pink, brown, yellowish nodule, sometimes polypoid; dimples with pressure
- Location: often on the extremities
- History: fibrohistiocytic proliferation entrapping eosinophilic bundles of collagen at the periphery of the lesion; foamy histiocytes, multinucleated giant cells, and vessels in variable proportion are also seen; the overlying epidermis is acantholytic with tabbed rete ridges and increased pigmentation of basal keratinocytes (induction phenomenon)
- Variations
  - Cellular dermatofibroma: larger with higher recurrence rate, more cellular with greater number of fibroblasts, can infiltrate fat and resemble dermatofibrosarcoma protuberans
  - Aneurysmal (hemosiderotic) dermatofibroma: large dilated blood spaces without endothelial lining; extravasated red blood cells with associated hemosiderin deposition; commonly mistaken for a vascular tumor
FIBROUS AND "FIBROHISTIOCYTIC" TUMORS

- Palisading dermatofibroma: prominent nuclear palisading; Verocay-like bodies; can resemble Schwannoma
- Epithelioid cell histiocytoma: exophytic nodule or polypoid tumor with epidermal collarette, clinically resembling pyogenic granuloma or intradermal Spitz nevus; composed of epithelioid cells with abundant cytoplasm, numerous giant cells, and foamy macrophages
- Sclerotic fibroma: hypocellular with well circumscribed hyalinized plywood pattern of dense collagen
- Dermatomyofibroma: shoulder of younger women, bundles of spindle cells parallel to epidermis, can resemble leiomyoma or dermatofibrosarcoma protuberans; actin staining positive and CD34 staining negative; may be a distinct entity rather than BFH variant

Scar
- Characterization: due to dermal and/or subcutaneous traumatic or iatrogenic tissue damage
- Histology: bands of fibroblasts and dense collagen, often oriented parallel to the epidermis; granulation tissue present early with progression to collagen deposition and fibrosis
- Variations
  - Hypertrophic scar: thick, elevated scar that does not extend beyond the boundaries of the initiating injury; most frequently on the head and neck, shoulders, chest, and knees; no racial predilection (Fig. 11-17)
  - Keloid (Fig. 11-18): same as hypertrophic scar but extends beyond the boundaries of the initiating injury; more common on head and...
neck (especially ear) and chest; more frequent in African descent; thick hyalinized bundles of eosinophilic collagen, less cellular than hypertrophic scar

**Fibromatosis**
- **Demographics:** present at birth or developing later in life.
- **Characterization:** group of benign soft tissue tumors characterized by proliferation of mature fibroblasts and collagen with infiltrative growth pattern, and potential local recurrence
- **Histology:** whorls of spindle cells; no mitosis
- **Variations**
  - Infantile myofibromatosis: multiple, solitary, rubbery slow growing nodules at birth; whorls of spindle cells with no mitoses; if multiple, associated with visceral involvement (35% cases); surgical excision with spontaneous remission and scarring
  - Congenital generalized fibromatosis: multiple, one to hundreds of nodules; bone can be involved
  - Infantile digital fibromatosis (inclusion body fibromatosis, Reye tumor): small (<1 cm), rapidly growing dermal or subcutaneous nodule(s), on dorsolateral digits; surgical excision with spontaneous remission, but local recurrence common (up to 50%)
    - **Histology:** eosinophilic intracytoplasmic inclusion bodies (smooth muscle actin staining positive, Masson-trichrome positive).
  - Juvenile hyaline fibromatosis: autosomal recessive; slow growing, skin-colored papules and nodules; often on the face, scalp, and back; preceded by flexural contractures and gingival hyperplasia
- **Genetics:** mutations of 4q21 which encodes capillary morphogenesis protein 2 (CMG2)
- **Histology:** irregular, poorly circumscribed masses of deeply eosinophilic, hyalinized, collagen-like material (PAS staining positive, EM: microfilaments) and spindle fibroblasts
  - Palmar and plantar fibromatosis (Dupuytren’s contracture and Ledderhose disease): firm nodules in the distal palmar aponeurosis with progression to crippling flexion at the metacarpophalangeal joints (4th and 5th digits); questionable association with alcoholism
  - Penile fibromatosis (Peyronie’s disease): solitary or multiple fibrous plaques adjacent to the corpora cavernosa, causing curvature of the dorsal surface of the shaft; middle aged to adult males
  - Knuckle pads: hyperkeratosis of the dorsal aspect of the joints of the fingers, without significant symptoms or contracture
  - Desmoid fibromatosis: deeper fibromatosis usually only secondarily involving dermis; associated with activating mutations in CTNNB1, the gene encoding β-catenin; a variant is associated with Gardner syndrome (Gardner fibroma)

**Angiomatoid Fibrous Histiocytoma**
- **Appearance:** slow growing, painless subcutaneous nodule
- **Location:** extremities or trunk
- **Demographics:** children or young adults of either sex
- **Characterization:** sometimes present with systemic symptoms including fever, weight loss, anemia, and paraproteinemia; *FUS-ATF1*, *EWSR1-CREB1*, and *EWSR1-ATF1* (most frequent genetic alteration in clear cell sarcoma) have been detected in the few cases published, pointing to the interchangeable role of *FUS* with *EWSR1* and *ATF1* with *CREB1*
- **Histology:** relatively uniform, pale, round or short spindle-shaped eosinophilic cells with ovoid vesicular nuclei, interspersed with blood-filled sinusoidal spaces and foci of hemorrhage; desmin, muscle actin (HHF-35), CD99, and CD68 immunoreactive (up to 50% of cases), smooth muscle actin is negative

**Giant Cell Tumor of the Tendon Sheath** *(Fig. 11-19)*
- **Appearance:** slow growing, painless nodules fixed to a tendon sheath or fascia
- **Location:** dorsal aspect of the hand
- **Demographics:** 3rd-5th decade, slightly female predominance
FIBROUS AND “FIBROHISTIOCYTIC” TUMORS

Inflammatory MFH: usually in deep soft tissue; bland or atypical xanthomatous cells, neutrophils, and giant cells

Giant cell MFH: osteoclast-like giant cells

Dermatofibrosarcoma Protuberans (DFSP) (Fig. 11-20)

Appearance: slow growing plaque that often progresses to a multinodular mass

Location: trunk or extremities

Demographics: 3rd–4th decade

Characterization: rare metastasis with local recurrences; ring chromosomes derived from chromosome 22 (adults) and t(17;22) are the most frequent finding, leading to fusion of $COL1A1$ and $PDGFB$ with strong overexpression of PDGFβ (platelet-derived growth factor)

Histology: proliferation of fibroblasts, histiocyte-like cells, and bizarre giant cells with severe pleomorphism; may show atypical mitosis

Variations

Bednar tumor (pigmented DFSP): prominent deposits of melanin and dendritic melanocytes;

Fibrosarcomatous DFSP: more cellularity, atypia, and mitosis; focal fascicular or “herring-bone”
Leiomyosarcoma
- Appearance: pink dermal or subcutaneous nodule
- Location: common on extremities
- Demographics: peak in 5th-6th decade
- Characterization: malignant tumor of smooth muscle; negligible metastatic rate if confined to dermis, high metastatic rate if found deeper
- Histology: high cellularity with pleomorphic and hyperchromatic spindle cells; high mitotic activity; occasional necrosis; desmin and smooth muscle actin immunoreactive

Smooth Muscle Tumors

Congenital Smooth Muscle Hamartoma
- Appearance: solitary patch with or without a follicular pattern; diffuse skin involvement produces a “Michelin-tire baby” appearance; vellus hairs prominent
  - Vermiculation: wormlike movements upon stroking the lesion.
  - Pseudo-Darier’s sign: stroking induces transient induration with piloerection
- Location: trunk
- Histology: marked increase of smooth muscle fibers in the dermis; grouped fibers are in bundles arranged haphazardly and are not attached to hair follicles; basal hyperpigmentation

Leiomyoma
- Appearance: small, firm, pink solitary or multiple nodules; often painful
- Location: limbs or trunk
- Demographics: young adults
- Histology: fascicles of smooth muscle with blunt borders; fusiform cells with longitudinal striations and thin, cigar-shaped nuclei with blunt ends; desmin and smooth muscle actin staining positive, Verhoeff-van Gieson staining positive (yellow), trichrome staining positive (pink-red)
- Variations
  - Piloleiomyoma: arise from arrector pili muscle, infiltrative pattern
  - Dartotic leiomyoma: arise from the scrotal dartos muscle
  - Angioleiomyoma: benign deep dermal or subcutaneous nodule, well-circumscribed, arising from vascular smooth muscle; most common on lower leg
    - Histology: numerous thick walled blood vessels with a thick wall surrounded by bundles of smooth muscle
  - Angiomyolipoma: adipose tissue present with smooth muscle and vessels in variable degree

Adipose Tissue Tumors

Lipoma (Fig. 11-21)
- Appearance: solitary or multiple elastic nodules of the subcutis
- Location: usually on the arms, shoulders, back, lower extremities
- Characterization: benign tumor of the mature fat
- Histology: well-circumscribed proliferation of mature fat; fine capsule sometimes
- Variations
  - Angiolipoma: usually seen in young adults as subcutaneous lesions, sometimes painful; many small blood vessels, often thrombi
  - Fibrolipoma: intermixed fibrous tissue
  - Myolipoma: smooth muscle actin and desmin staining positive
  - Infiltrating lipoma: skeletal muscle between adipocytes

FIGURE 11-21 Lipoma. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)
NEURAL TUMORS

Demographics: infancy and childhood (<3 yrs age)
Histology: lipoblasts, mature adipocytes, and pre-lipoblasts in a lobular pattern and separated by a loose fibrous septa; can resemble well-differentiated liposarcoma but found in young children

Nevus Lipomatosis Superficialis
• Appearance: multiple soft, yellow to skin colored papules and nodules
• Location: hip or buttock
• Demographics: newborn or infant
• Histology: lobules of mature adipose tissue in the superficial dermis

NEURAL TUMORS

Neuroma
• Appearance: skin-colored papules or nodules, often painful
• Syndrome
  • Multiple mucosal neuroma syndrome (multiple endocrine neoplasm, MEN type IIb or III): autosomal dominant; multiple mucosal neuromas (e.g., lip, tongue, and eyelid); pheochromocytoma and medullary carcinoma of the thyroid
• Histology: normal appearing or hyperplastic nerve bundles surrounded by fibrotic stroma; S-100 protein and myelin basic protein staining positive
• Variations
  • Traumatic neuroma (amputation neuroma): sites of trauma (e.g., scars)
  • Palisaded encapsulated neuroma (PEN): solitary; found on face (e.g., nose, nasolabial folds, and cheeks) of adults; usually well-circumscribed, but not truly encapsulated; palisading not as common as name implies
  • Morton neuroma: not a true neuroma, but represents a degenerative response to chronic low-grade tissue damage; usually found between the toes

Neurofibroma
• Appearance: solitary, soft papules or polypoid nodules
• Syndrome
  • Neurofibromatosis type I (NF-1, von Recklinghausen disease, peripheral neurofibromatosis): autosomal dominant, mutation of a gene on chromosome 17q (defect in neurofibromin protein, a negative regulator of the Ras oncogene); café-au-lait macules; freckling of axilla or groin (Crowe sign); optic gliomas, iris hamartomas, and distinctive osseous lesions (e.g., sphenoid dysplasia and thinning of long bone cortex)

Liposarcoma
• Appearance: malignant tumor of soft tissues with rapid growth, usually larger than lipomas
• Location: deep soft tissue (retroperitoneum, thigh and buttock)
• Demographics: >5th decade
• Histology: lipoblasts with cytoplasmic lipid-laden vacuoles; causes indentation of the hyperchromatic nucleus; variable nuclear polymorphism
• Variations
  • Well-differentiated liposarcoma: can be lipoma-like with occasional lipoblasts and scattered atypical cells with hyperchromatic nuclei; sometimes history of large recurrent lipoma
  • Dedifferentiated liposarcoma: areas of well differentiated liposarcoma with adjacent nonlipogenic (dedifferentiated) component, usually with abrupt interface; dedifferentiated zones have appearance of high grade sarcoma or malignant fibrous histiocytoma
  • Myxoid liposarcoma: spindle cells in a mucinous stroma and prominent vascular pattern (branched “chicken wire” capillaries); associated with t(12;16) fusing DDIT3 and FUS
  • Round cell liposarcoma: more cellular with dense, small round hyperchromatic nuclei (variant of myxoid liposarcoma that is more aggressive, but with same translocation)
  • Pleomorphic liposarcoma: highly pleomorphic spindle cells and bizarre multinucleated multi-vacuolated giant cells; increased mitosis

Lipoblastoma
• Appearance: slow growing subcutaneous mass
• Location: extremities, head and neck, trunk
• Demographics: infancy and childhood (<3 yrs age)
• Histology: lipoblasts, mature adipocytes, and pre-lipoblasts in a lobular pattern and separated by a loose fibrous septa; can resemble well-differentiated liposarcoma but found in young children

Liposarcoma
• Appearance: malignant tumor of soft tissues with rapid growth, usually larger than lipomas
• Location: deep soft tissue (retroperitoneum, thigh and buttock)
• Demographics: >5th decade
• Histology: lipoblasts with cytoplasmic lipid-laden vacuoles; causes indentation of the hyperchromatic nucleus; variable nuclear polymorphism
• Variations
  • Well-differentiated liposarcoma: can be lipoma-like with occasional lipoblasts and scattered atypical cells with hyperchromatic nuclei; sometimes history of large recurrent lipoma
  • Dedifferentiated liposarcoma: areas of well differentiated liposarcoma with adjacent nonlipogenic (dedifferentiated) component, usually with abrupt interface; dedifferentiated zones have appearance of high grade sarcoma or malignant fibrous histiocytoma
  • Myxoid liposarcoma: spindle cells in a mucinous stroma and prominent vascular pattern (branched “chicken wire” capillaries); associated with t(12;16) fusing DDIT3 and FUS
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  • Pleomorphic liposarcoma: highly pleomorphic spindle cells and bizarre multinucleated multi-vacuolated giant cells; increased mitosis

Lipoblastoma
• Appearance: slow growing subcutaneous mass
• Location: extremities, head and neck, trunk
• Neurofibromatosis type II (NF-2, multiple inherited schwannomas, meningiomas, and ependymomas—MISME—syndrome): autosomal dominant, mutation of a gene on chromosome 22 band q11–13.1 (defect in Merlin, tumor suppressor protein); bilateral cranial nerve (CN) VIII masses; multiple schwannomas (e.g., vestibulocochlear schwannomas), meningiomas, gliomas, and ependymomas; juvenile posterior subcapsular lenticular opacity (juvenile cortical cataract)
• Demographics: 3rd–6th decade
• Histology: round cells with brightly eosinophilic, granular cytoplasm (pustule-ovoid bodies of Millan; phagolysosomes; PAS staining positive); pseudoepitheliomatous hyperplasia; S-100 protein positive

OTHER TUMORS

Acquired Digital Fibrokeratoma (Fig. 11-22)
• Appearance: slow growing, firm nodule or outgrowth from a digit or acral skin
• Histology: pedunculated papule with hyperkeratosis and acanthosis; mature fibroblasts, small blood vessels, and elastic tissue in the dermis; dense dermal collagen fibers oriented parallel to the long axis of the lesion

Osteoma Cutis (Cutaneous Ossification)
• Appearance: dermal or subcutaneous white papule or nodule
• Syndrome
  • Albright’s hereditary osteodystrophy: short stature, obesity, round face, mental weakness, and cutaneous ossifications of the dermis and fat; characterized by a lack of renal responsiveness to parathyroid hormone
• Histology: spicules of bone in the dermis or subcutaneous tissue with cement lines, osteocytes, osteoblasts, and multinucleated osteoclasts

Supernumerary Digit
• Appearance: skin-colored outgrowth
• Location: hands, feet; usually near the fifth finger

Schwannoma (Neurilemmoma)
• Appearance: benign, solitary or multiple, small papules or nodules, sometimes painful
• Histology: encapsulated subcutaneous nodule; proliferation of Schwann cells with elongated nuclei and blunted ends; two often intermixed histologic patterns (Antoni A and B)
  • Antoni A: cells form loose fascicles with nuclei aligned in parallel arrays (Verocay bodies); S-100 protein positive
  • Antoni B: less cellular areas; myxoid and edematous

Dermal Nerve Sheath Myxoma (Neurothekeoma)
• Appearance: solitary, raised soft papules and nodules, < 3 cm in diameter
• Location: usually on the face or upper extremities
• Histology: well-defined, lobulated dermal mass with lobules of spindle and epithelioid cells in myxoid matrix, separated by thin fibrous septa; sparse mitotic activity; S-100 protein positive

Granular Cell Tumor
• Appearance: small papules and nodules
• Location: can occur anywhere, but frequent on oral mucosa (especially tongue), trunk or extremities (especially arms)
OTHER TUMORS

- Demographics: congenital
- Histology: dome-shaped, fibrous stroma with many nerves and sometimes cartilage or bone

**Acrochordon (Skin Tags, Fibroepithelial Polyp)**
- Appearance: solitary or multiple, skin-colored papules (Fig. 11-23)
- Location: neck, axilla, inguinal areas, and eyelids
- Histology: pedunculated polyps covered by epidermis; papillomatosis and acanthosis; fibrovascular stroma with fat tissue and dilated blood vessels
- Variations
  - Lipofibroma: acrochordon with large percentage of fat cells

**Accessory Tragus (Fig. 11-24)**
- Appearance: asymptomatic congenital structure
- Location: preauricular area or neck

- Histology: pedunculated papule or nodule with connective tissue, fat, and sometimes cartilage; many vellus hair follicles

**Accessory Nipple (Supernumerary Nipple)**
- Appearance: small congenital pigmented or skin-colored macule or concave/umbilicated papule (Fig. 11-25)
- Location: embryonic milk line
- Histology: identical to that of the regular nipple; epidermis present over central pilosebaceous structure, and dermis containing smooth muscle bundles and mammary glands/ducts

**Merkel Cell Carcinoma (Neuroendocrine Carcinoma of the Skin, Trabecular Carcinoma)**
- Appearance: rapidly growing nodules
- Location: sun-damaged skin (e.g., head and neck)
- Demographics: elderly
- Characterization: aggressive tumor with high metastatic potential
- Histology: strands or trabeculae, as well as nests, of undifferentiated tumor cells with scant cytoplasm, round to oval nuclei with fine chromatin,
1. A patient with multiple trichilemmomas is at increased risk of which of the following malignancies?
   A. Oral squamous cell carcinoma
   B. Microcystic adnexal carcinoma
   C. Basal cell carcinoma
   D. Breast carcinoma
   E. Malignant chondroid syringoma

2. An 8-year-old girl presents with multiple syringomas on her anterior chest. What syndrome is this entity most commonly found?
   A. Birt-Hogg-Dube syndrome
   B. Brooke-Spiegler syndrome
   C. Down syndrome
   D. Muir-Torre syndrome
   E. Epidermal nevus syndrome

3. Which of the following entities is virtually pathognomonic of neurofibromatosis 1?
   A. Plexiform neurofibroma
   B. Café-au-lait macule
   C. Optic glioma
   D. Sphenoid dysplasia
   E. Iris hamartoma

4. Which one of the following tumors is S-100 protein immunostaining negative?
   A. Granular cell tumor
   B. Cellular neurothekeoma
   C. Adenoid cystic carcinoma
   D. Schwannoma
   E. Melanoma

5. A patient with multiple sebaceous adenomas should be screened with which of the following examinations?
   A. CT scan of the chest
   B. Retinal examination
   C. Mammogram
   D. Renal ultrasound
   E. Colonoscopy

6. Which of the following is associated with Darier’s disease?
   A. Clear cell syringoma
   B. Acrokeratosis verruciformis of Hopf
   C. Syringocystadenoma papilliferum
   D. Fibrofolliculoma
   E. Sebaceous adenoma
7. Which of the following malignant tumors is least likely to metastasize?
   A. Porocarcinoma
   B. Malignant chondroid syringoma
   C. Dermatofibrosarcoma protuberans
   D. Sebaceous carcinoma
   E. Merkel cell carcinoma

8. A 14-year-old boy presents with bilateral angiofibromas near the nasal labial folds. A characteristic dental finding in this patient would be the following:
   A. Congenital missing teeth
   B. Odontodysplasia
   C. Hutchinson’s teeth
   D. Enamel teeth pits
   E. Odontogenic cysts

9. Which is the most common tumor arising in association with nevus sebaceus of Jadassohn?
   A. Basal cell carcinoma
   B. Apocrine carcinoma
   C. Sebaceous carcinoma
   D. Syringocystadenoma papilliferum
   E. Sebaceoma

10. Which syndrome is characterized by the development of multiple trichoepitheliomas and cylindromas?
    A. Rombo syndrome
    B. Birt-Hogg-Dube syndrome
    C. Bazex syndrome
    D. Cowden syndrome
    E. Brooke-Spiegler syndrome

11. Which epithelial neoplasm is usually not associated with Borst-Jadassohn phenomenon?
    A. Actinic keratosis
    B. Squamous cell carcinoma
    C. Seborrheic keratosis
    D. Basal cell carcinoma
    E. Hidroacanthoma simplex

Answers

1. D. Cowden’s syndrome is an autosomal dominant disorder variable expression that results from a mutation in the PTEN gene on chromosome arm 10q resulting in a dysfunctional tyrosine kinase phosphatase enzyme. The clinical picture includes hamartomatous neoplasms of skin and mucosa (mucosal papillomatosis, oral-plantar keratosis), GI tract, bones, central nervous system, eyes and genitourinary tract. It can be associated with several types of malignancy: breast, endometrial and thyroid carcinomas.

2. C. The young girl is presenting with a rare case of eruptive syringoma, known to be associated with Down syndrome.

3. A. Plexiform neurofibroma is a peripheral nerve tumor that clinically feels like a “bag of worms” on palpation. It is virtually pathognomonic of neurofibromatosis 1 (NF-1). Sphenoid dysplasia is a prominent facial feature of NF1, but not entirely pathognomonic. The other entities are associated with NF1, but can be seen in other conditions as well.

4. B. Although dermal nerve sheath myxoma (neurothekeoma) stains positive for S-100 protein, cellular neurothekeoma does not.

5. E. Muir-Torre syndrome is an autosomal dominant cancer predisposition condition defined by one or more sebaceous neoplasms (sebaceous adenoma, sebaceous epithelioma, or rarely sebaceous carcinoma) and one or more visceral malignancies, including colon cancer. Patients and first-degree relatives should be screened by colonoscopy as colonic adenocarcinomas may precede the development of cutaneous tumors.

6. B. Acrokeratosis verruciformis of Hopf is an autosomal dominant disorder that can be associated with Darier’s disease. Clear cell syringoma is associated with diabetes, while syringocystadenoma papilliferum and fibrofolliculoma are seen in nevus sebaceous and Birt-Hogg-Dube syndrome, respectively. Sebaceous adenoma can be associated with Muir-Torre syndrome.

7. C. Dermatofibrosarcoma protuberans (DFSP) generally do not metastasize unless they become fibrosarcomatous. Malignant chondroid syringoma metastasizes in up to 60% of cases, while sebaceous carcinoma metastasizes in 14–25% of cases. Porocarcinoma and Merkel cell carcinoma also have significant metastatic potential.

8. D. The adolescent boy is presenting with tuberous sclerosis, an autosomal dominant condition characterized by multiple, bilateral angiofibromas near the nasal labial folds at puberty in addition to periungual fibromas, enamel teeth pits, central nervous system defects (epilepsy and low intelligence), and ophthalmological, cardiac, and pulmonary disorders. Hutchinson’s teeth are seen in congenital syphilis and odontogenic cysts are found in Gorlin syndrome.

9. D. Various types of appendageal tumors may develop in association with nevus sebaceous of Jadassohn. They include: syringocystadenoma papilliferum (8–10%), trichoblastoma (5%), and rarely trichilemmoma (2–3%), sebaceaoma (2–3%), syringoma, apocrine cystadenoma, hidradenoma or keratoacanthoma. Basaloid epithelial proliferations resembling basal cell carcinoma can be identified.
in 5–7% of cases of nevus sebaceus. Malignant tumors (apocrine carcinoma, basal cell carcinoma, squamous cell carcinoma) have been described to arise seldom in association with nevus sebaceus.

10. Autosomal dominant disease (CYLD gene on chromosome 9p21) characterized by the development of multiple trichoepitheliomas and cylindromas

11. Borst-Jadassohn phenomenon is currently regarded as a histopathological appearance rather than a precise clinicopathological entity (was formerly known as intraepidermal epithelioma of Borst-Jadassohn). It is characterized by intraepithelial nests of clonal keratinocytic proliferation in the background of a seborrheic keratosis, actinic keratosis, hidroacanthoma simplex, intraepidermal eccrine poroma, and Bowen’s disease (squamous cell carcinoma in situ).

REFERENCES


**NON-MELANOMA SKIN CANCER**

**Tumor Suppressor Genes**
- Negative cancer regulators
- Cause apoptosis of DNA-damaged cells and blocks cell division
- Encode cell-cycle regulators, adhesion molecules, DNA repair enzymes, or signal transduction pathway molecules
- Are recessive
- Even if heterozygosity exists, tumor suppression continues
- p53 (Fig. 12-1)
  - Found on chromosome 17p
  - Mutation of a single copy of the two copies is enough for the deleterious effect
  - Most common cancer mutation (mutated in one-half of all human cancers)
  - Ninety percent of squamous cell carcinomas (SCCs) and in most basal cell carcinomas (BCCs) and actinic keratoses
  - Extrinsic and intrinsic apoptotic pathways
    - Lead to the activation of the aspartate-specific cysteine proteases (caspases) that mediate apoptosis
    - **Extrinsic pathway**
      - Involves engagement of particular “death” receptors that belong to the tumor necrosis factor receptor (TNF-R) family (e.g., Fas, DR5, and PERP)
      - Also causes the formation of the death-inducing signaling-complex (DISC)
    - **Intrinsic pathway**
      - Triggered in response to DNA damage

- Associated with mitochondrial depolarization and release of cytochrome c from the mitochondrial intermembrane space into the cytoplasm
- Cytochrome c, apoptotic protease-activating factor 1 (APAF-1), and procaspase-9 form a complex termed the **apoptosome** (caspase-9 is activated and promotes activation of caspase-3, caspase-6, and caspase-7)
  - Mutation is not the only way to inactivate tumor suppressor genes; function also can be blocked by methylation of their promoter

**Oncogenes**
- Genes with growth-promoting activity
- Mutated gene causes cellular products to become constitutively active
- Are dominant
- If a normal gene (protooncogene) is present at a locus along with one mutated gene (oncogene), the abnormal product takes control
- May derive from viruses (e.g., Src, ras, cmyc)

**Carcinogenesis**
- Two-hit theory of Knudsen
  - First: inheriting a defect in the familial form (5% to 10% of cancers result from germ-line mutations) or exposure to a carcinogen
  - Second: ongoing exposure to the carcinogen that acts as a tumor promoter or co-carcinogen
- Repeated assault on the DNA leads to mutations that cause the cell cycle to lose control
- Mutations from ultraviolet B (UV-B) light cause cytosine (C) to change to thymine (T)
AP-1 (Activating Protein-1)
- Negative regulator for procollagen transcription; blocked by retinoids
- Collective term referring to dimeric transcription factors composed of Jun, Fos, or ATF subunits (protooncogenes)
- UV-B induces AP-1 binding to DNA at the AP-1-binding site
- AP-1 upregulates mRNA expression for gelatinase and collagenase
- AP-1 blocks collagen gene expression in dermal fibroblasts
- AP-1 proteins regulate the expression and function of cell-cycle regulators such as p53

- Absence of c-Jun results in elevated expression of the tumor suppressor gene p53
- Overexpression of c-Jun supresses p53

Basal Cell Carcinoma
- Neoplasm derived from non-keratinizing cells that originate in the basal cell layer
- Most common malignancy in humans
- Mutations in the p53 tumor suppressor gene, which resides on chromosome 17p
- Clinical and histologic subtypes
  - Nodular (Fig. 12-2)
  - Pigmented (Fig. 12-3)
  - Cystic
  - Superficial (Fig. 12-4)
  - Micronodular
  - Morpheaform/sclerosing and infiltrating
- Risk Factors/Etiological factors
  - Ultraviolet radiation
  - Other radiation: x-rays and Grenz rays
  - Arsenic exposure
  - Xeroderma pigmentosum
- Nevvoid BCC syndrome (also known as basal cell nevus syndrome or Gorlin syndrome)
  - Autosomal dominant; abnormalities in the patched (PTCH) gene, chromosome 9
  - 1 in 60,000–120,000
  - Complete penetrance with variable expressivity

**FIGURE 12-1** A model for p53-mediated apoptosis.

**FIGURE 12-2** Basal cell carcinoma. (Courtesy of Dr. Adelaide Hebert.)
NON-MELANOMA SKIN CANCER

Rombo syndrome
- Autosomal dominant
- Milia
- Hypertrichosis
- Trichoepitheliomas
- Peripheral vasodilation

Course
- Incidence of new NMSC after initial skin cancer diagnosis
  - 35% at 3 years
  - 50% at 5 years

Staging
- TNM classification
- Stage 0: Tis, N0, M0
- Stage I: T1, N0, M0
- Stage II: T2, N0, M0; T3, N0, M0
- Stage III: T4, N0, M0; any T, N1, M0
- Stage IV: any T, any N, M1

Low-risk tumors
- Borders are well defined; primary tumor; nonimmunosuppressed; nodular or superficial subtype
- Trunk and extremities: <2 cm
- Cheek/forehead/scalp/neck: <1 cm

High-risk tumors
- Aggressive histology: recurrent, micronodular, metatypical, sclerosing/morpheaform, infiltrative, perineural
- Recurrent, immunosuppressed, BCCNS, ill defined borders, setting of irradiated skin
- Trunk and Extremites: >2 centimeters
- Cheek/forehead/scalp/neck: ≥1 cm
- Mask areas of face [central face (nose, periorbital, cutaneous and mucosal lips, chin), periauricular, temple]

Treatment
- Electrodesiccation and curettage
- Cryotherapy
- Imiquimod cream
- Photodynamic therapy (PDT)
- Radiation therapy: nonsurgical candidates, debilitated patients
- Excision
- Mohs micrographic surgery
- Intralesional interferon

Squamous Cell Carcinoma In Situ
[Bowen's Disease (BD)]
- Malignant tumor of keratinocytes (Fig 12-5)
- Neoplastic process limited to the epidermis
- Vulvar BD associated with increased risk of uterine, cervical, and vaginal cancer, possibly due to HPV infection
- Erythroplasia of Queat (EQ) occurs on mucosal surfaces of penis in uncircumcised males

- Starts at an early age (starting at age 20 or earlier)
- Characteristic facies: broad nasal root, frontal bossing, hypertelorism
- Multiple BCCs
- Opacity and cataract or glaucoma
- Odontogenic keratocysts
- Palmoplantar pitting
- Intracranial calcification; calcification of the falx
- Bifid ribs
- Various tumors: medulloblastomas, meningioma, fetal rhabdomyoma, ameloblastoma, ovarian fibromas
- Acrokeratosis paraneoplastica of Bazex

- Bazex-Dupre-Christol syndrome
- X-linked dominant
- Follicular atrophoderma (“ice pick” marks, especially on dorsal hands)
- Multiple BCCs: face, the neck, and the upper part of the trunk
- Local anhidrosis/hypohidrosis
- Hypotrichosis
- Respiratory tract or digestive tract carcinomas

Figure 12-3 Pigmented basal cell carcinoma. (Courtesy of Dr. Asra Ali.)

Figure 12-4 Superficial basal cell carcinoma. (Courtesy of Dr. Asra Ali.)
Co-infection with HPV subtypes 8, 16, 39, 51
- Progresses to invasive SCC in approximately 10%
- Preventive measures: circumcision and hygiene
- Solitary, rapidly growing, dome-shaped papulonodule with a central, horn-filled, craterlike depression

**Leukoplakia**
- Most common precancerous lesion of oral mucosa
- White plaque on oral mucosa that cannot be rubbed off
- Potential to become oral SCC
- Risk factors: tobacco, alcohol, HPV

**Erythroplakia**
- Red macule or patch of oral mucosa
- Least common but greatest potential to become oral SCC
- Treatment: complete excision or Mohs surgery

**Squamous Cell Carcinoma**
- Second most common form of skin cancer
- Malignant tumor of keratinocytes
- Predisposing conditions
  - Immunosuppression (especially solid-organ transplant recipients, chronic lymphocytic lymphoma, human immunodeficiency virus infection)
  - Psoralen and ultraviolet A light (> 300 treatments)
  - Chemical carcinogens (tar, soot, arsenic)
  - Smoking
  - Genetic syndromes (i.e., xeroderma pigmentosum)
  - Chronic inflammatory conditions (i.e., discoid lupus erythematosus, erosive oral lichen planus, morphea, lichen sclerosus)
  - Chronic infections (i.e., osteomyelitis)
  - Chronic scarring conditions (i.e., burn scars, chronic ulcers, thermal injury, irradiated skin [ionizing radiation])
  - Periungual SCC—often associated with HPV 16
  - Keratoacanthoma (Fig. 12-6)
    - Well-differentiated SCC
    - Solitary, rapidly growing, dome-shaped papulonodule with a central, horn-filled, craterlike depression
  - Verrucous carcinoma
    - Rare, indolent form of SCC that presents as an exophytic verrucous tumor
    - Oral cavity (oral florid papillomatosis)
    - Foot (epithelioma cuniculatum)
    - Genitals (giant condyoma of Buschke and Lowenstein)
  - High-risk SCCs and metastatic rate
    - Metastasis to primary or first echelon draining lymph nodes
    - Size > 2 cm
    - External ear: 11%
    - Lip: 10% to 14%
    - Histologic risk factors: depth >4 mm or Clark level IV, poorly differentiated or spindle-cell type, lack of inflammatory infiltration
  - Marjolin ulcer
    - SCC arising in a chronic site of inflammation: old burn scar or a draining sinus tract
  - Organ transplant patient metastatic rate is 18 to 36 times that of the general population
Perineural invasion: 35%; local recurrence rate as high as 47%

Treatment
- Small, low-risk lesions in non-surgical candidates
  - Cryosurgery
  - Electrodesiccation and curettage
  - Photodynamic therapy (PDT)
  - Topical therapy (imiquimod, fluorouracil)
- Standard treatment
  - Excision
  - Radiation
  - Mohs’ micrographic surgery
- Patients with regional disease
  - Focused neck dissection
  - Superficial parotidectomy
  - Adjuvant radiation therapy
  - Primary radiation if inoperable tumor
  - Five-year survival for patients with metastases 26.8%

MELANOMA

Accounts for 4% of all skin cancer; accounts for 79% of deaths related to skin cancer

More than 50% of cases are believed to arise de novo

10% to 20% of all patients with melanoma have a family history of melanoma

Risk factors for cutaneous melanoma
- Dysplastic nevi in familial melanoma
- Greater than 50 nevi 2 mm or greater in diameter
- One family member with melanoma
- Previous history of melanoma
- History of acute, severe, blistering sunburns
- Freckling

Clinical types
- **Superficial spreading** (Fig. 12-7): most common type (70%)
- **Lentigo maligna** (Fig. 12-8): 10% of all melanomas
- **Acral lentiginous melanoma (ALM)**
  - 2% to 8% of melanoma in Caucasians
  - 29% to 72% of melanoma in dark-skinned individuals
- **Amelanotic melanoma**: <2% of melanomas
- **Mucosal**: approximately 3%
- **Nodular**: 10% to 15%

Genes implicated in the development of melanoma
- Cyclin-dependent kinase inhibitor 2A (CDKN2A) resides on chromosome 9p
  - Cell-cycle regulatory gene
  - Protein target: inhibitor of cyclin-dependent kinase 4 (CDK4)
  - Encodes two distinct gene products that are regulators of cell division cycle

\[ p16(INK4a): \text{INK4 proteins inhibit complexes formed by the cell cycle kinases CDK4 and CDK6 and the D-type cyclins} \]
\[ p19 \text{ (ARF): acts on the p53 pathway} \]

Associated with 25% to 60% of familial melanoma
Chapter 12  MELANOMA AND NON-MELANOMA SKIN CANCER

- Prognosis
  - Ulceration, Breslow depth, and tumor thickness, important histologic determinants
  - Breslow depth: measured vertically in millimeters from the top of the granular layer (or base of superficial ulceration) to the deepest point of tumor involvement
- Immunohistochemical staining
  - Homatropine methylbromide 45 (HMB-45)
    - Spindle cell and desmoplastic variants fail to react with HMB-45
    - Shown to react with other neural crest-derived tumors and occasionally with adenocarcinomas and other neoplasms
    - Specificity for detecting melanoma is 96.9%
  - S-100: specificity of 70%
  - Microphthalmia transcription factor (Mitf): nuclear transcription factor critical for melanocyte development and survival
- Tyrosinase: enzyme involved in the early stages of melanin production
  - Melan-A (or MART-1)
    - Product of the MART-1 gene
    - Cytoplasmic protein that is expressed in mature melanocytes
  - Ki67: Proliferating cell nuclear antigen
- Revised AJCC TNM classification and staging
  - T classification
    - T1: ≤1.0 mm
      ▲ a: without ulceration
      ▲ b: with ulceration or level IV or V
    - T2: 1.01–2.0 mm
      ▲ a: without ulceration
      ▲ b: with ulceration
    - T3: 2.01–4.0 mm
      ▲ a: without ulceration
      ▲ b: with ulceration
    - T4: > 4.0 mm
      ▲ a: without ulceration
      ▲ b: with ulceration
  - N classification
    - N1: one lymph node
      ▲ a: micrometastasis
      ▲ b: macrometastasis
    - N2: 2–3 lymph nodes
      ▲ a: micrometastasis
      ▲ b: macrometastasis
      ▲ c: in-transit metastasis(-es)/satellite(s) without metastatic lymph nodes
    - N3: 4 or greater metastatic lymph nodes, matted lymph nodes, or combinations of in-transit metastasis(-es)/satellite(s) and metastatic lymph nodes
  - M classification
    - M1: distant skin, subcutaneous, or lymph node metastasis
      ▲ M2: lung metastasis
      ▲ M3: all other visceral or any distant metastasis with elevated LD14
- Treatment: wide local excision
  - Tumors ≤1 mm depth: 1 cm margin
  - Tumors 1 to 4-mm in depth: 2–3 cm margins
  - Overall survival rates: Delayed lymph node dissection was not statistically significant compared with immediate node dissection
- Sentinel lymph node biopsy/lymphatic mapping
  - Absence of clinically palpable nodes
  - Thicker melanomas (≥1 mm in depth)
    - Determines presence of micrometastasis; if positive sentinel lymph node, then therapeutic lymph node dissection proceeds
  - Lymphoscintigraphy: preoperative radiographic mapping and vital blue dye injection around the primary melanoma or biopsy scar; isosulfan blue dye plus sulfur-colloid-labeled technetium isotope increases accuracy of finding sentinel node
    - Performed at the time of wide local excision or re-excision
    - Identifies and removes the initial draining regional node(s)
    - Yields prognostic information but no evidence SLN; removal improves survival (current studies ongoing)
  - Risk of primary tumor recurrence
    - Desmoplastic subtype
    - Positive microscopic margins
    - Recurrent disease
    - Thick primary lesions with ulceration or satellitosis
  - High risk of nodal relapse
    - Extracapsular extension
    - Involvement of four or more lymph nodes
    - Lymph nodes measuring at least 3 cm
    - Cervical lymph node location
    - Recurrent disease
  - Interferon alfa (IFN-α)
    - Approved by the Food and Drug Administration (FDA) for treatment of melanoma
    - Adjuvant treatment after excision in patients who are free of disease but are at high risk for recurrence: stages IIB and III
    - For primary tumors > 4 mm depth and regional nodal disease
    - Binds to cell surface receptors, interacting with specific gene sites in both normal and neoplastic cells
    - Modulates the expression of host natural killer cells, T cells, monocytes, dendritic cells, and class I and II major histocompatibility (MHC) antigens in both neoplastic and nonneoplastic host tissues
    - Shown to have a growth-inhibitory effect when added to tumor cells in vitro
11% increase (26% to 37%) in survival rates at 5 years in the IFN-α treatment group compared with the observation arm
• Interleukin 2 (IL-2): indirectly causes tumor cell lysis by proliferating and activating cytotoxic T-lymphocytes

Dendritic cell vaccines
• Recombinant viral and bacterial vaccines
• Direct transduction
Cytokine and growth factor modulation
• IL-2, interferons (IFN-α, IFN-β, IFN-γ), GMCSF, and TNF
• Allow sustained local release of cytokines to enhance a potent local inflammatory response

DNA and RNA vaccines
• Induce activation of APCs, which then present antigens to T cells

Merkel Cell Carcinoma (MCC)
• Neuroendocrine carcinoma of the skin
• Mortality rate is approximately 25%
• Most frequent sites: head, neck region, and extremities
• Located in or near the basal layer of the epidermis

Clinical
• Painless, indurated, solitary dermal nodule, slightly erythematous to deeply violaceous color
• Regional lymph nodes at presentation: 10% to 45%
• Regional lymph node metastases during course of disease: 50% and 75%
• Distant metastases: 50%
• Common sites: lymph nodes, liver, bone, brain, lung, and skin
• Local recurrence develops in 25% to 44% after primary tumor excision

Histology: three distinct subtypes
• Trabecular: interconnecting strands of tumor cells in the dermis, with grouping of cells that appear as glands or neural rosettes
• Intermediate: neoplastic cells in solid nests, most common pattern
• Diffuse pattern: tumor cells interspersed among dermal collagen bundles

Staging: classification based on clinical presentation
• Stage IA: primary tumor ≤2 cm, with no evidence of spread to lymph nodes or distant sites
• Stage IB: primary tumor >2 cm, with no evidence of spread to lymph nodes or distant sites
• Stage II: regional node involvement but no evidence of distant metastases
• Stage III: presence of systemic metastases beyond the regional lymph nodes

Treatment
• Stage I
  • Wide local excision: 2-cm margins
  • Elective lymph node dissection (ELND)
  ▲ Larger tumors, tumors with greater than 10 mitoses per high-power field, lymphatic or vascular invasion, and the small cell histologic subtypes
Aggressive variations
- Sézary syndrome (SS): leukemic variant of MF
- Adult T-cell leukemia/lymphoma
- Extramedullary NK/T-cell lymphoma, nasal type
- Primary cutaneous peripheral T-cell lymphoma, unspecified
- Primary cutaneous aggressive epidermotropic CD8 T-cell lymphoma
- Cutaneous γ/δ T-cell lymphoma

Mycosis fungoides (MF)/Sézary syndrome (SS) (Figs. 12-9, 12-10, 12-11)
- Appearance: patches/plaques/tumors with various shape, color, and scales +/- erythroderma (diffuse skin erythema of > 80% body surface area [BSA])
  - Classic: poikilodermatous MF (epidermal atrophy often with telangiectasia, pigment alteration)
  - Atypical: hypopigmented/vitiliginous MF, granulomatous MF, granulomatous slack skin, Woringer-Kolopp disease (pagetoid reticulosis), folliculocentric MF, pigmented purpuric eruption-like MF, interstitial MF, and papular MF
- Location: “bathing trunk” distribution in non-sun exposed areas
- Characterization: MF can lead to SS; SS can lead to MF; or both can arise de novo

Histology (Figs. 12-12, 12-13): proliferation of CD4+CD45RO+ helper T cells that often lack normal antigens (CD7−, CD26−) and make a superficial lymphoid infiltrate without spongiosis

Sentinel lymph node (SLN) biopsy
- MCC sites with indeterminate lymphatic drainage
- Effective in preventing short-term regional nodal recurrence

Adjuvant radiation therapy
- Primary site and to the regional lymph node basin
- Larger tumors, tumors with lymphatic invasion, tumors approaching the surgical margins of resection, and locally unresectable tumors
- 50 Gy to the surgical bed and the draining regional lymphatics: delivered in 2-Gy fractions

Stage II
- Wide local excision of the primary tumor
- Regional lymph node dissection
- Adjuvant radiation therapy: primary site and to the regional lymph node basin
- Larger tumors, tumors with lymphatic invasion, tumors approaching the surgical margins of resection, and locally unresectable tumors
- 50 Gy to the surgical bed and the draining regional lymphatics: delivered in 2-Gy fractions
- Adjuvant chemotherapy: regimens similar to patients with small cell lung cancer
- Cyclophosphamide, doxorubicin, and vincristine and etoposide plus cisplatin are the most commonly used regimens
- Impact on survival uncertain

Stage III
- Chemotherapy: unresectable recurrent tumors
- Regional lymph node dissection and adjuvant radiation therapy if the regional draining nodes have not been treated previously
- Adjuvant radiation therapy: site of recurrence as well as regional lymph node beds

Cutaneous T-Cell Lymphoma (CTCL)
- Definition: diverse group of non-Hodgkin’s lymphomas presenting as skin lesions containing malignant, skin-homing T-lymphocytes
- Indolent variations
  - Mycosis fungoides (MF): most common
  - Primary cutaneous CD30 lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma (ALCL)
  - Lymphomatoid papulosis (LyP)
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Primary cutaneous CD4 small/medium-sized pleomorphic T-cell lymphoma

FIGURE 12-9 Mycosis fungoides patches and plaques. (Courtesy of Dr. Madeline Duvic.)
MELANOMA

+/- lymphoid atypia; +/- clonal T-cell receptor (TCR) gene rearrangement; +/- Pautrier’s microabscesses (collections of neoplastic lymphocytes). {Note: In SS, atypical cells surround venules because the epidermotropism is lost unless the patient had prior MF.}

- Algorithm to diagnose early MF (add up points):
  - Clinical criteria: persistent and/or progressive patches and plaques plus:
    - Non-sun-exposed location
    - Size/shape variation
    - Poikiloderma
    - Any 2 = 2 points; any 1 = 1 point (cannot give 3 points)
Histopathologic criteria: superficial lymphoid infiltrate plus:
- Epidermotropism without spongiosis
- Lymphoid atypia (enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours)
- Both = 2 points; either = 1 point
- Molecular/biologic: clonal TCR gene rearrangement; 1 point if present
- Immunopathologic:
  - CCD2,3,5 < 50% T cells
  - CD7 < 10% T cells
  - Epidermal discordance from expression of CD2,3,5 or 7 on dermal T cells
  - One or more criteria = 1 point
  - Total: need at least 4 points to diagnose MF

TNM Definitions: Updated in 2007
- Skin (T):
  - T1: limited patches/papules/plaques < 10% BSA
  - T2: patches/papules/plaques ≥ 10% and < 80% BSA
  - T3: one or more tumors
  - T4: erythroderma (confluent erythema ≥ 80% BSA)
- Node (N):
  - Abnormal lymph node: > 1.5 cm in longest transverse diameter or with abnormal palpable qualities (firm, irregular, fixed, clustered); sample by core aspiration or excisional biopsy; classify according to lymph node (LN) pathology guidelines (Dutch system or NCI-VA classification)
  - N0: no clinically abnormal peripheral lymph nodes
  - N1: clinically abnormal; +/- TCR clone
  - N2: clinically abnormal; +/- TCR clone
  - N3: clinically abnormal; +/- TCR clone
- Staging: determines later treatment options
  - IA: T1 N0 M0 B0-1: limited patch/plaque (< 10% BSA)
  - IB: T2 N0 M0 B0-1: generalized patch/plaque (≥ 10% but < 80% BSA)
  - IIA: T1-2 N1-2 M0 B0-1
  - IIB: T3 N0-2 M0 B0-1: tumors
  - IIA: T4 N0-2 M0 B0: erythroderma without blood involvement
  - IIB: T4 N0-2 M0 B1: erythroderma with low blood tumor burden
  - IVA1: T1-4 N0-2 M0 B2: SS (high blood tumor burden)
  - IVA2: T1-4 N3 M0 B0-2: very abnormal nodes
  - IVB: T1-4 N0-3 M1 B0-2: visceral involvement
- Diagnostic testing
  - Skin biopsy: select the most indurated area that has not been treated for at least two weeks, CD30+ (for ALCL, LyP, or large cell transformation (LCT)), CD2,3,4,5,7,8 and TCR rearrangements (polymerase chain reaction or western blot)
- Blood: CBC, LFTs, LDH, magnesium, chemistries, flow cytometry (✓CD4 + CD26– cells, CD3-CD4 + cells, and CD3-CD8 + cells), ✓ HIV/HTLV, ✓ immunoglobulins (for advanced patients)
- Imaging
  - Clinically normal lymphadenopathy: CXR or ultrasound to rule out lymphadenopathy
  - Potential lymphadenopathy: CT scans of chest, abdomen, and pelvis (lymphoma screen) + / – FDG-PET scan
- Lymph node biopsy: prefer largest lymph node draining involved skin or node with highest standardized uptake value (SUV) on PET scan; if all nodes equal: cervical > axillary > inguinal.
- Bone marrow biopsy: if B2 blood involvement or unexplainable hematologic abnormalities
- Prognosis:
  - Positive: ↑CD8+ cells on biopsy or on flow cytometry, earlier stages rarely have progression to later stages
  - Negative: large cell transformation (LCT) within 2 years of diagnosis, ↓CD8+ cells, increased age, WBC > 20,000, ↑LDH
- Treatment: (for latest info: www.nccn.org)
  [* = experimental]
  - Skin-directed therapy
    - Use alone for early stage (IA – IIA) disease with only cutaneous involvement
    - Use in combination with systemic therapy or for adjuvant/palliative purposes in any stage
    - Topical corticosteroids: class I-III
    - Topical retinoids: bexarotene/tazarotene/aldara (anecdotal)
    - Phototherapy
      - Ultraviolet B (UVB) (290–320nm)/narrow-band UVB (311nm): for patch disease + / – thin plaques
      - Psoralen + Ultraviolet A (PUVA): for thicker plaques; often in combination with interferon-alpha (IFNα) or oral bexarotene
    - Topical nitrogen mustard ointment 10%/20%*/40%*
    - Electron beam radiation
      - Spot radiation: for single lesion MF or tumors
      - Total skin electron beam (TSEB): for generalized extensive skin involvement with severe symptoms; can be palliative; most intense skin-directed therapy
  - Generalized systemic therapies: (no comparative trials exist to guide therapy choices)
    - Reserved for late stage disease (IIB+) or early stage disease refractory to skin-directed therapy
    - Interferon – alpha (IFNα)
    - Oral retinoids/rexinoids: Isotretin/Bexarotene
    - Common combination: PUVA + retinoids (RePUVA)
  - Extracorporeal photopheresis (ECP): phototherapy with leukopheresis (photoactivated 8-methoxypsoralen crosslinks DNA in peripheral blood cells after ex vivo UVA irradiation; then blood reinfused into patients); most commonly used in SS and erythrodermic MF.
  - Histone deacetylase (HDAC) inhibitors: Class I-IV; Vorinostat (FDA approved)/Belinostat*/Panobinostat*/Romidepsin*
  - Pralotrexate:* competitive antagonist for dihydrofolate reductase; like methotrexate but has greater internalization into cells
  - Mono-chemotherapy: gemcitabine/liposomal doxorubicin
  - Combo-chemotherapy: CHOP/CMED/ESHAP (stage IV)
- Targeted systemic therapies
  - Denileukin diftitox (Ontak®): recombinant IL-2 diptheria toxin fusion protein targeted to the high and intermediate affinity IL-2 receptor on T-cells → inhibits protein synthesis; biopsy for >20% CD25+
  - Alemtuzumab (Campath-H1®):* anti-CD52 monoclonal antibody; targets T, B, and NK cells. Used for erythrodermic MF or SS; not useful for tumors or lymphadenopathy; very immunosuppressive.
  - Zanolimumab (HuMax-CD4®): anti-CD4 monoclonal antibody → blocks receptor-mediated T-cell signaling
  - SGN-30:* anti-CD30 monoclonal antibody (useful in LCT or ALCL/LyP)
  - Forodesine (BCX-1777®):* inhibits purine nucleoside phosphorylase (PNP)
- Symptomatic (anti-pruritic) therapies
  - Diligent skin care (antibiotic soap, acidification with 0.25% vinegar rinses) to rid skin of Staphylococcus aureus
  - Anti-histamines, gabapentin, mirtazapine, doxepin
- Allogenic hematopoietic stem cell transplant (HSCT)
  - Graft-vs-T-cell lymphoma effect; potentially curative.
  - For healthy patients (can tolerate immunosuppression) with advanced disease (IIB +) refractory to all primary and salvage therapy options who have matched donors.
  - May pretreat with TSEB to debulk skin disease prior to HSCT

Blood: CBC, LFTs, LDH, magnesium, chemistries, flow cytometry (✓CD4 + CD26– cells, CD3-CD4 + cells, and CD3-CD8 + cells), ✓ HIV/HTLV, ✓ immunoglobulins (for advanced patients)
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- Allogenic hematopoietic stem cell transplant (HSCT)
  - Graft-vs-T-cell lymphoma effect; potentially curative.
  - For healthy patients (can tolerate immunosuppression) with advanced disease (IIB+) refractory to all primary and salvage therapy options who have matched donors.
  - May pretreat with TSEB to debulk skin disease prior to HSCT
A. Skin biopsy of the most indurated area
B. Lymph node biopsy of a 1-cm mobile smooth lymph node
C. Flow cytometry to assess level of blood involvement
D. Bone marrow biopsy in B2 patients
E. Check HIV and HTLV in blood

8. A 49-year-old black male with a history of mycosis fungoides stage IB on narrow-band UVB and topical corticosteroids now presents for his 3-month follow-up with a new 1-cm tumor on his right arm and a new palpable 2-cm lymph node in his right axilla. What is the next step?
   A. Bone marrow biopsy
   B. Change from skin-directed therapies to systemic therapies
   C. Biopsy of new axillary lymph node and tumor
   D. Reassign to stage IIB (tumor)
   E. No change in treatment. Continue to monitor.

9. A patient has erythroderma but no blood, visceral, or lymph node involvement. What is the stage?
   A. IIIa
   B. IIIb
   C. IVA1
   D. IVA2
   E. IVB

10. The most common first line treatment regimen used for SS patients involves:
    A. Alemtuzumab (Campath-H1®)
    B. Extracorporeal photopheresis (ECP) plus interferon or bexarotene
    C. External beam radiation
    D. Topical nitrogen mustard
    E. PUVA

Answers
1. A. Oncogenes behave in a dominant fashion such that if a normal gene (protooncogene) is present at a locus along with one mutated gene (oncogene), the abnormal product takes control.
2. C. Poorly differentiated squamous cell carcinomas and those with perineural invasion, spindle-cell features, or depth of infiltration greater than 4 mm have high risk of recurrence and metastases. Squamous cell carcinomas arising in actinically damaged skin are considerably low risk with an average metastatic rate of just over 5%.
3. B. Radiation therapy of verrucous carcinoma can lead to anaplastic transformation.
4. B. Rombo syndrome is autosomal dominant. Patients develop multiple basal cell carcinomas, milia, hypertrichosis, trichoepitheliomas, and peripheral vasodilation.

5. C. This is a T2b, N0, M0 melanoma and hence it would be stage IIA.

6. B. The biopsy must show evidence of epidermotropism. Spongiosis should not be present. If spongiosis is present, then a different diagnosis should be considered. Pautrier’s microabscesses and TCR rearrangements are variably present and not essential for the diagnosis of MF.

7. B. This lymph node does not qualify as an abnormal lymph node; therefore, it does not meet the criteria for biopsy. An abnormal lymph node is defined as >1.5 cm in its longest transverse diameter or with abnormal palpable qualities (firm, irregular, fixed, clustered). Skin biopsy is necessary for initial diagnosis. Bone marrow biopsy is merited in patients with high blood tumor burden (B2) and in those with an unexplained hematologic abnormality. HIV and HTLV are checked as they are the etiologies of other non-MF/SS CTCLs.

8. C. He now has a clinically significant lymph node which may be positive for MF. Many would also order a repeat CT or PET/CT scan to detect other lymphadenopathy as well as a flow cytometry to see if this increased aggressiveness in the skin is also manifested in the blood. It would be premature to reassign to stage IIB (D) as his lymph node pathology grade could make him stage IVA2. Bone marrow biopsy (A) is not merited unless the re-staging flow cytometry shows B2 blood involvement. Once the full re-staging work-up is complete, the stage is reassigned. Changing therapies (B) is necessary but dependent on confirmation of these new findings. Therefore changing therapies is secondary to the re-staging workup and not the next step. Continuing to monitor (E) can only result in more aggressive disease as his current regimen is not sufficient.

9. A. IIIA describes erythroderma without any blood involvement. If the patient also had low blood tumor burden, they would be IIIb. If they had high tumor burden they would be IVA1. Since the patient does not have any lymph nodes or organs involved, he/she does not qualify for stage IVA2 or IVB, respectively.

10. B. ECP in combination with interferon and bexarotene is most commonly used for SS patients. Alemtuzumab (A) is also emerging as a secondary agent for SS but is immunosuppressive. The other treatments (C, D, E) are less effective as they are skin-directed therapies, and SS is a leukemic variant.

REFERENCES


Olsen E, Vonderheid E, Pimpinelli N et al. Revisions to the staging and classification of mycosis fungoides and


OVERVIEW

- Vascular tumors: dynamic lesions that clinically demonstrate proliferation and are characterized histologically by endothelial cell hyperplasia: epidermis appears atrophic, few vellus hair follicles, no subcutaneous fat
- Vascular tumors of infancy and childhood
  - Infantile hemangioma
  - “Congenital hemangiomas” (noninvoluting, or NICH; rapidly involuting, or RICH)
  - Kaposiform hemangioendothelioma
  - Tufted angioma
  - Pyogenic granuloma
  - Endovascular papillary angioendothelioma (Dabska tumor)
- Vascular tumors of adulthood
  - Kaposi sarcoma
  - Angiolymphoid hyperplasia with eosinophilia
  - Intravascular papillary endothelial hyperplasia (Masson’s tumor)
  - Low-grade angiosarcomas
    - Epithelioid hemangioendothelioma
    - Spindle cell hemangioendothelioma
    - Retiform hemangioendothelioma
  - Angiosarcoma
- Vascular malformations
  - Almost always present at birth (although they may not manifest until later in childhood)
  - Arise from dysmorphogenesis
  - Exhibit normal cellular turnover
  - Are static or undergo slow expansion over time
- Can be further subdivided on the basis of
  - Flow rate
    - Slow flow: capillary, venous, or lymphatic
    - Fast flow: arteriovenous fistulas and arteriovenous malformations
  - Resemblance to vessel type: capillary, lymphatic, venous, or arteriovenous; can occur alone or in combination
  - Capillary
    - Salmon patch
    - Port wine stain
    - Phakomatosis pigmentovascularis
    - Telangiectasia
    - Cutis marmorata telangiectatica congenita
    - Unilateral nevoid telangiectasia
    - Angiokeratomas
  - Lymphatic: microcystic, macrocystic, or combined
  - Venous
    - Blue rubber bleb nevus syndrome
    - Glomuvenous malformations: glomus tumors, glomangiomas, and glomangiomatosis
  - Arterial
    - Arteriovenous fistula
    - Arteriovenous malformation
  - Combined
    - Klippel-Trenaunay syndrome (capillary-lymphaticovenous malformation)
VASCULAR TUMORS OF INFANCY AND CHILDHOOD

Infantile Hemangioma (IH)

- **Characteristics**
  - Most common tumor of infancy
  - Characterized by endothelial cell proliferation
  - GLUT-1 (glucose transporter) is an immuno-histochemical stain specific for IH in all phases of growth and involution
  - Positive staining occurs *only* with IH and *not* with any other vascular tumor or malformation
  - Proliferative phase: 6 to 12 months; rarely longer
  - Involution phase: gradual over several or more years
  - Risk factors: Caucasian, female, low birth weight, multiple gestation
  - Location: more than 60% occur on head or neck, most commonly midcheek, lateral upper lip, and upper eyelid

- **Types**
  - Superficial, deep, or combined
    - Superficial
      - Most common
      - Raised, bright-red papule, nodule or plaque
    - Deep: soft, flesh-colored nodule that often has a bluish hue and/or central telangiectasias
    - Combined (Fig. 13-1)
  - Localized, segmental, or multiple

- **Classification by morphology**
  - Localized: papules or nodules that appear to arise from a single focal point and demonstrate clear spatial containment
  - Segmental (Fig. 13-2)
    - Plaque-like and show a linear and/or geographic pattern over a cutaneous territory
    - Much more likely to be complicated, require more intensive and prolonged therapy, and have a poorer overall outcome
  - Multifocal
    - Generally defined as five or more small, localized lesions
    - Multiple hemangiomas are associated with multiple births

- **Complications**
  - Ulceration
    - Most common in proliferative phase
    - Often leads to pain, scarring, bleeding, secondary infection
  - Scarring
    - Favors IH in trauma-prone sites: lip, perineum, intertriginous, posterior scalp, back
  - Vital organ compromise
    - Visual obstruction
abnormal genitalia, renal abnormalities, lipomeningomyelocele
– MRI best study for spinal dysraphism
• Developmental anomalies
– PHACE syndrome
  ▲ Posterior fossa (Dandy-Walker) brain malformations, hemangioma (segmental, usually cervicofacial), cerebrovascular arterial anomalies, cardiac defects/coarctation of the aorta, eye anomalies
  ▲ Sometimes referred to as PHACE(S) when ventral developmental defects such as sternal clefting and supraumbilical raphe are present
  ▲ Structural cerebral and cerebrovascular anomalies: most common and potentially serious manifestations
  ▲ Cerebrovascular anomalies can lead to progressive vasculopathies causing stroke in early childhood
▲ Workup
  △ MRI/MRA of brain and neck
  △ Cardiac echo or MRI/MRA of chest
  △ Eye examination
• Diagnosis
  • Generally clinical
  • Surgical biopsy (± GLUT-1 staining) warranted if any suspicion for malignancy
  • Imaging studies cannot generally be relied on to distinguish a benign from malignant vascular tumor
• Treatment
  • Most common indications: ulceration, vital organ compromise, to improve the ultimate cosmetic outcome
• Options
  – Meticulous wound care for ulceration
  – Corticosteroids: topical, intralesional, or systemic
    ▲ Second-line agents
      △ Vincristine
      △ Interferon (20% risk of spastic diplegia in infants)
      △ Excisional or laser surgery in select patients

**“Congenital” Hemangiomas**

• Types: noninvoluting (NICH), rapidly involuting (RICH)
  – Uncommon
  – Fully developed at birth and GLUT-1-negative
• RICH
  – Gray-violaceous tumor
  – Most common on an extremity
  – Undergoes rapid involution during the first year of life with characteristic atrophy

**FIGURE 13-3** Segmental hemangioma. (Courtesy of Dr. Denise Metry.)


- **NICH**
  - Most commonly presents on the trunk
  - Oval to round plaque with coarse, central telangiectasias and a surrounding rim of pallor
  - Often feels warm to palpation and may have a slight bruit
  - Path is hybrid between a vascular tumor and malformation

**Kaposiform Hemangioendothelioma**

- **Characteristics**
  - Rare
  - Histologically benign but clinically aggressive tumor
  - Most commonly affects children younger than 2 years of age and is often present at birth
  - Male-female incidence equal
  - Generally solitary
  - Favors the skin (particularly trunk, extremities) or retroperitoneum
  - Grows rapidly
  - Early on develops distinct violaceous color as a clue to underlying Kasabach-Merritt phenomenon (KMP)
  - KMP = life-threatening thrombocytopenia as a result of platelet trapping within the tumor
    - Consumption coagulopathy with very low platelet counts and low fibrinogen levels
    - Does not occur with IH
  - Pathology: densely infiltrated nodules composed of spindle cells with minimal atypia and infrequent mitoses and slit like vessels containing hemosiderin; GLUT-1-negative
  - Treatment
    - Corticosteroids often used as first-line therapy but rarely effective alone
    - Complete surgical excision if feasible
    - Interferon-α, vincristine
    - Platelets and heparin should be avoided

**Tufted Angioma (Angioblastoma of Nakagawa) (Fig. 13-4)**

- **Characteristics**
  - Uncommon, histologically benign tumor
  - Presents during infancy or early childhood; presence at birth uncommon
  - Most common on trunk, extremities
  - Slow, lateral extension occurs over months to years
  - Spontaneous regression may occur, though rarely
  - Variable presentation
    - Large, erythematous plaque with cobblestone surface
    - Sometimes with overlying vellus hair growth, tenderness, sweating

**Pyogenic Granuloma (Fig. 13-5)**

- **Characteristics**
  - Can be seen at any age, but majority occur during childhood
  - Prior history of trauma in minority
  - Most common on head and neck; mucosal lesions more common in females, especially during pregnancy
  - Usually presents as rapidly growing, bright-red papule or nodule
  - Bleeds repeatedly and profusely; generally does not regress
VASCULAR TUMORS OF ADULTHOOD

• Umbilical granulomas seen in neonates have similar clinical appearance, but if persistent, may represent umbilical remnant (imaging recommended)
• Histology: well-circumscribed lobular proliferation of capillaries; possible erosion of epidermis
• Treatment
  • Depends on location/size
  • Most small lesions can be shave excised or curetted with light electrodessication to the base
  • Alternatives: excision, pulsed-dye or carbon dioxide laser, cryotherapy
• Course: recurrence more common with larger lesions

VASCULAR TUMORS OF ADULTHOOD

Kaposi Sarcoma (KS)
• Associated with human herpesvirus type 8
• Subtypes
  • Classic KS
    – Males, older than 50 years of age, predominant in Mediterranean and Jewish populations
    – Increased risk of lymphoreticular neoplasms
    – Violaceous macules with slow progression to plaques
    – Distal lower extremities, unilateral involvement with centripetal spread to a disseminated and multifocal pattern
    – Oral cavity and GI tract (90%); possible involvement of lung, spleen, and heart
    – Benign course owing to slow progression
  • African endemic KS
    – Black Africans, males > females, third to fourth decades
    – In children, the disease runs a fulminant course with rapid dissemination
    – Clinicopathologic subvariants
      ▲ Nodular: benign, similar to classic KS
      ▲ Florid or vegetating type: nodules extend into deep dermis, subcutis, muscle, and bone
      ▲ Infiltrative: like florid/vegetating type but more aggressive
      ▲ Lymphadenopathic: affects children and young adults, usually confined to lymph nodes but may affect skin and mucous membranes
  • KS in iatrogenically immunocompromised patients
    – Presents in organ-transplant, autoimmune, and cancer patients
    – Discontinuation of therapy may cause regression of KS lesions
  • Epidemic HIV-associated KS
    – Oral mucosa (palate most common) is initial site of presentation in 10% to 15%
    – Early lesions appear as small pink/reddish macules or dermatofibroma-like papules
    – Extracutaneous sites: lymph nodes, gastrointestinal tract (80% of AIDS patients, usually duodenum and stomach), and lungs (bronchospasm, cough, respiratory insufficiency)
• Histology
  • Patch stage: proliferation of spindle-shaped cells in upper dermis; neoplastic cells outline irregular, bizarre slits and clefts
  • Plaque stage: multiple dilated and angulated vascular spaces outlined by attenuated endothelium, solid cords, and fascicles of spindle cell arranged between jagged vascular channels
  • Tumor stage: spindle cells in interlacing fascicles in dermis; lack of pronounced pleomorphism and nuclear atypia, slit like vascular spaces with extravasated red blood cells (RBCs)
• Treatment
  • Ionizing radiation
  • (Poly) chemotherapy: vinblastin or vincristin; combination with actinomycin D, adriamycin, bleomycin, and dacarbazine; liposomal encapsulated doxorubicin and daunorubicin
  • Interferon-α in combination with antiretrovirals (zidovudine)
  • Topical tretinoin gel
  • Topical imiquimod
  • Intralesional injections of β-human chorionic gonadotropin (β-hCG)

Angiolymphoid Hyperplasia with Eosinophilia
• Characteristics
  • Occurs mainly in the West
  • Thought to be inflammatory or reactive process
• Location: head, trunk, extremities
• Presentation
  • Peripheral eosinophilia
  • Papules or nodules
  • Young adults, females > males
• Diagnosis/pathology
  • Irregular vessels lined by plump endothelial cells with “hobnail” appearance
  • Infiltrate of lymphocytes, histiocytes, and eosinophils

Kimura’s Disease
• Characteristics
  • Occurs mainly in Asia
  • Classified as cutaneous lymphoid hyperplasia
• Location: head
• Presentation
  • Solitary or multiple nodules
Chapter 13  VASCULAR TUMORS AND MALFORMATIONS

**Histology**
- Multiple vascular channels that interconnect
- Lined by atypical endothelial cells; vacuolated cytoplasm, and hyperchromatic eccentric nuclei
- Weibel-Palade bodies may be present

**Treatment:** wide local excision is the treatment of choice; regional lymph node dissection if clinically necessary

**Prognosis:** favorable prognosis; however, they can be locally invasive and have the potential to metastasize

---

**Hemangioendothelioma (Epithelioid and Spindle)**

**Characteristics**
- Poorly circumscribed, usually biphasic proliferation of venous or capillary vessels
- Minimal dysplasia, few mitotic figures, and minimal differentiation toward a vascular lumen or channel
- A third of epithelioid hemangioendotheliomas develop metastases in regional lymph nodes
- Red/blue nodules that may be multiple and are usually superficial
- Distal extremities (particularly the hands)
- Second and third decades of life

**Types**
- Epithelioid hemangioendothelioma: vessels are intermixed with solid sheets of epithelioid cells
- Spindle cell hemangioendothelioma: spindle-shaped mesenchymal cells; this can occur at any age; thought to represent a reactive vascular tumor arising in conjunction with malformed vasculature (primarily lymphatic); can be associated with Maffucci’s syndrome

**Histology:** slit-like vascular channels, mild extravasation of erythrocytes, and hemosiderin deposition; epithelioid cells have abundant eosinophilic cytoplasm; spindle cell variant has bland bipolar mesenchymal fibroblast-like cells that may contain vacuoles that stain with Ulex europaeus and cytoplasmic factor VIII–associated antigen

**Treatment:** wide surgical excision

**Dabska Tumor (Papillary Intralymphatic Angioendothelioma)**

**Characteristics**
- Low-grade angiosarcoma that affects the skin of children
- Slow-growing, painless, intradermal nodule that grows to 2 to 3 cm

**Laboratory studies**
- Immunoreactivity for factor VIII–related antigen, Ulex europaeus agglutinin I, vimentin, blood group isoantigens, and C2.1 antibody

**Histology**
- Multiple vascular channels that interconnect
- Lined by atypical endothelial cells; vacuolated cytoplasm, and hyperchromatic eccentric nuclei
- Weibel-Palade bodies may be present

**Treatment:** wide local excision is the treatment of choice; regional lymph node dissection if clinically necessary

**Prognosis:** favorable prognosis; however, they can be locally invasive and have the potential to metastasize
VASCULAR MALFORMATIONS

Capillary

**Salmon patch (nevus simplex) (Fig. 13-7)**
- Characteristics
  - Best classified as capillary malformation
  - Prognosis generally differs from port-wine stain
  - Thought to represent persistent fetal circulatory patterns in the skin

PORT-WINE STAIN (nevus flammeus) (FIG. 13-8)
- Characteristics
  - Capillary malformation
  - Slow flow
- Location: variable
- Presentation
  - Present at birth as erythematous patch
  - Persists throughout life
  - With age (predominantly with facial lesions), can develop a dark red or deep purple color with nodules and/or pyogenic granuloma like lesions
- Complications/associations
  - Bony and soft tissue hypertrophy, especially in the V2 and V3 facial distributions
  - Sturge-Weber syndrome (encephalotrigeminal angiomatosis)
    - Triad
    - Facial port-wine stain
      ▲ Usually trigeminal V1 dermatome: forehead and upper eyelid
      ▲ Approximately 10% of infants with port-wine stain in trigeminal V1 location will have Sturge-Weber syndrome

ANGIOSARCOMA (Fig. 13-6)
- Characteristics: subtypes
  - Idiopathic angiosarcoma
    - Elderly patients
    - Purpuric macule, plaque, nodule, or ulceration
    - Location: scalp, upper forehead
  - Lymphedema-associated angiosarcoma
    - Edematous arm of women after mastectomy on side with lymphadenectomy (Stewart-Treves syndrome)
    - Bluish plaques, nodules, and vesicles
  - Post irradiation angiosarcoma: years after radiotherapy
- Diagnosis
- Histology
  - Irregular anastomosing vascular channels
  - Lined by hyperchromatic, pleomorphic endothelial cells; mitosis prominent
- Immunohistochemistry: CD31, CD34, and factor VIII–related antigen are less specific

“hobnail” endothelial cells, prominent stromal lymphocytic infiltrate

FIGURE 13-6 Angiosarcoma. (Courtesy of Dr. Adelaide Hebert.)

FIGURE 13-7 Nevus simplex. (Courtesy of Dr. Denise Metry.)
Hereditary disorder thought to be explained by the “twin spot” phenomenon

**CUTIS MARMORATA TELANGIECTATICA CONGENITA**

- Congenital, with reticulate purple network
- Most cases occur sporadically
- May be associated with atrophy and/or ulceration
- Limb +/- trunk
- Limb girth discrepancy: common; other associated anomalies probably less common

Diagnosis: generally clinical

Treatment: no treatment is needed unless associated anomalies

Erythema improves over time

**UNILATERAL NEVOID TELANGIECTASIA (UNT)**

- Congenital or acquired patches of superficial telangiectases in a unilateral linear distribution
- May result from a somatic mutation during embryologic development
- Third and fourth cervical dermatomes most common sites, thoracic dermatomes or scattered distant sites also may be involved
- Pathogenesis of UNT remains unknown, possibly related to hormonal causes

Diagnosis/pathology: dilated, mature capillaries in the superficial dermis

Treatment: pulsed-dye lasers

- Ipsilateral ocular vascular anomalies: can lead to retinal detachment, glaucoma, and blindness
- Leptomeningeval vascular anomalies: can lead to early-onset seizures
- Midline facial stains have been associated with Beckwith-Wiedemann syndrome
- Diagnosis/pathology: dilated, mature capillaries in the superficial dermis
- Treatment
  - Flashlamp-pumped, pulsed-dye laser (585 and 595 nm)
    - Low risk of scarring
    - Multiple treatments required
    - Most patients achieve lightening but not complete clearance
    - V2 and distal extremity lesions less responsive
  - Cosmetic camouflage

**PHAKOMATOSIS PIGMENTOVASCULARIS**

- Coexistence of capillary malformation with a melanocytic or epidermal lesion (dermal melanocytosis, nevus spilus or speckled lentiginous nevus, nevus anemicus)
  - Hereditary disorder thought to be explained by the “twin spot” phenomenon

**CUTIS MARMORATA TELANGIECTATICA CONGENITA (FIG. 13-9)**

- Characteristics
  - Congenital, with reticulate purple network
  - Most cases occur sporadically
  - May be associated with atrophy and/or ulceration
  - Limb +/- trunk
  - Limb girth discrepancy: common; other associated anomalies probably less common

Diagnosis: generally clinical

Treatment: no treatment is needed unless associated anomalies

Erythema improves over time

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  - Third and fourth cervical dermatomes most common sites, thoracic dermatomes or scattered distant sites also may be involved
  - Pathogenesis of UNT remains unknown, possibly related to hormonal causes

Diagnosis/pathology: dilated capillaries in the superficial dermis

Treatment: pulsed-dye lasers
VASCULAR MALFORMATIONS

ANGIOKERATOMA

- Characteristics
  - Slow flow
  - Capillary ectasia in the papillary dermis
  - May produce papillomatosis, acanthosis, and hyperkeratosis of the epidermis

- Types
  - Angiokeratomas of Fordyce
    - Uncommon
    - 2- to 4-mm red-to-blue domed papules with keratotic surface
    - Peak incidence after the third decade; more common in males
    - Most often on the scrotum and vulva
    - Lesions number from one to many (>100)
  - Angiokeratoma circumscriptum
    - Uncommon
    - Small red macules coalesce to form large acanthokeratotic plaques
    - Usually occurs in childhood; equally common in males and females
    - Often found on the extremities
    - Associated with vascular malformations and atrophy or hypertrophy of regional soft tissue and bone
  - Angiokeratoma corporis diffusum (Fabry’s disease)
    - Rare
    - X-linked inherited disorder
    - Caused by a deficiency of the lysosomal enzyme α-galactosidase
    - Unremitting deposition of neural glycosphingolipids in the lysosomes of: vascular endothelium, fibroblasts, and pericytes of the dermis, heart, kidneys, and autonomic nervous system
    - Clinical findings:
      ▲ Skin: verrucous papules, deep red to blue-black in color, between the umbilicus and the knees, with a predilection for the scrotum, penis, lower back, thighs, hips, buttocks
      ▲ Ocular: corneal opacities, posterior capsular cataracts
      ▲ Neurologic: burning, tingling paresthesias, hemiplegia, hemianesthesia, balance disorders, and personality changes
      ▲ Extremities: chronic edema of the feet, arthritis of the distal interphalangeal joints
      ▲ Cardiac: infiltration results in angina, myocardial infarction, mitral valve prolapse, congestive heart failure, hypertension, mitral insufficiency, and ventricular hypertrophy
      ▲ Urinalysis: urinary maltese crosses of lipid globules

- Angiokeratoma of Mibelli
  - Uncommon
  - Multiple 3- to 5-mm dark red papules with verrucous surface
  - Most often affects females younger than 20 years
  - Most often found on dorsa of fingers and toes; less commonly observed on elbows, knees, shoulders, and earlobes
  - Associated with recurrent chilblains and acrocyanosis
  - Autosomal dominant inheritance with variable penetrance

- Solitary angiokeratoma (Fig. 13-10)
  - Most common type
  - 2- to 10-mm dark papules or plaques that keratinize and turn blue-black
  - Peak incidence during third to fourth decades of life; more common in males
  - Presents most often on the lower extremities

- Treatment
  - Either ablation or excision can be performed
  - Erbium or carbon dioxide laser to remove the hyperkeratotic-acanthotic epidermis, followed by the use of lasers that target hemoglobin
  - Cryotherapy

LYMPHATIC MALFORMATION (Fig. 13-11)

- Characteristics
  - Slow flow
  - Microcystic (lymphangioma circumscriptum, lymphangioma)
  - Macrocystic (cystic hygroma)
  - Combined

- Location
  - Macrocystic
    - Neck, axilla, groin, or chest wall

FIGURE 13-10 Solitary angiokeratoma. (Courtesy of Dr. John Browning.)
Additional sclerotherapeutic agent useful for macrocystic lesions
- Laser photocoagulation: can be temporizing measure for microcystic cutaneous lesions
- Elastic compression stockings for extremity lesions

VENOUS MALFORMATION: GENERAL
- Characteristics: slow flow
- Location: skin, subcutaneous tissues, mucosa
- Presentation
  - Present, though not always evident, at birth
  - Usually solitary, localized
  - Soft, deep-blue masses that are easily compressible and slowly refill on release
  - Swell with dependency or activity
  - Undergo slow expansion over time
  - Phleboliths (progressive calcifications) are a hallmark of venous malformation and a common source of localized pain
  - Pain and stiffness on morning awakening and dull aching are other common complaints
- Associated conditions
  - Blue-rubber bleb nevus syndrome: autosomal dominant
    - Clinical
      ▲ Skin (most commonly trunk, palms and soles) and bowel venous malformations
      ▲ Latter commonly leads to chronic gastrointestinal bleeding
    - Diagnosis
      ▲ Histology: anomalous, dilated veins with irregularly thickened walls
      ▲ MRI best means of determining lesion extent
    - Treatment
      ▲ Elastic support stockings of affected extremity
      ▲ Low-dose aspirin may be useful for painful thrombosis
      ▲ Sclerotherapy and/or surgery reserved for lesions causing significant functional compromise or cosmetic deformity
- Glomuvenous malformations: also known as glomus tumors, glomangiomas, or glomangiomatosis (Fig. 13-12)
  - Characteristics
    ▲ Solitary tumors most common in adults, sporadically inherited
    ▲ Multiple more common in childhood and generally autosomal dominant (linked to chromosome 1p21-22)
    ▲ Solitary, extremely tender lesions most common on upper extremities, especially in nail beds

VENOUS MALFORMATION: GENERAL

End stage lesion: ulceration, bleeding, intractable pain, disfigurement
Location: intracranial > extremities > trunk > viscera

Treatment
- Always complex and difficult
- Generally should not be considered until significant symptoms develop
- Embolization
- Surgery

Maffucci Syndrome
- Inheritance: sporadic
- Clinical
  - Triad of chondrodysplasia of one or more limbs, multiple enchondromas, and vascular lesions
  - Vascular lesions include venous malformations and spindle cell hemangioendotheliomas
  - Enchondromas, exostoses, recurrent fractures
  - Neurologic deficits result from cerebral enchondromas.
  - Risk of chondrosarcoma (15% to 20%), angiosarcoma, fibrosarcoma, osteosarcoma, lymphangiosarcoma, intracranial tumors

Cobb Syndrome (Cutaneomeningospinal Angiomatosis)
- Inheritance: sporadic
- Clinical
  - Arteriovenous malformation (AVM) of the spinal cord with overlying cutaneous “blush” of the posterior thorax
  - Neurologic problems secondary to cord compression by the AVM or spinal subarachnoid hemorrhage
  - May result in pain, subarachnoid hemorrhage, motor or sensory deficit
- Treatment: see AVM

Complex Vascular Malformation Syndromes

Arteriovenous Malformation
- Characteristics: fast flow, the most dangerous type of vascular anomaly
- Presentation
  - Present at birth but may manifest later.
  - Early lesions may appear as a faint vascular stain that is often mistaken for a capillary malformation
  - Will eventually manifest itself, often following trauma or with the onset of puberty, as a warm, pulsatile mass with draining veins and deepening of color

\[ \text{FIGURE 13-12} \] Superficial glomuvenous malformation on the thigh; note presence of mural glomus cells on H&E stained histologic sample. (Reprinted with permission from Wolff et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)

\[ \text{\textbullet} \text{ Multiple lesions may be scattered or grouped, often in a segmental distribution} \]
\[ \text{\textbullet} \text{ Congenital lesions tend to be large and plaque like and are bluish purple with a “cobblestone” and/or hyperkeratotic appearance} \]
\[ \text{\textbullet} \text{ Resemble venous malformation but lack tendency toward mucosal or deep muscle involvement, are firmer and less compressible, and frequently tender to palpation} \]
- Histology: shows overlapping features of capillary-venous malformation and glomus cell tumor
- Treatment: surgical excision only reliable treatment

Klippel-Trenaunay-Weber Syndrome
- Inheritance
  - Sporadic, males > females
  - Most common vascular malformation syndrome
- Clinical
  - Triad of port-wine stain, venous and/or lymphatic malformation, and bony and/or soft tissue hypertrophy
  - Typically limited to a single extremity
  - Lymphatic component common, evidenced by lymphedema or cutaneous lymphatic vessels
  - Overgrowth of affected limb apparent at birth or occurs within the first few months to years of life
- Treatment
  - Compression hose
3. PHACE patients with cerebrovascular anomalies are most at risk for which of the following complications during infancy:
   A. Motor developmental delay
   B. Language developmental delay
   C. Acute arterial ischemic stroke
   D. Migraine-like headaches

4. The Kasabach-Merritt phenomenon may be seen with:
   A. Infantile hemangioma (IH)
   B. Rapidly involuting congenital hemangioma (RICH)
   C. Non-involuting congenital hemangioma (NICH)
   D. Kaposiform hemangioendothelioma
   E. All the above

5. A 2-month-old female presents with a large segmental hemangioma of the face; all of the following studies are indicated EXCEPT:
   A. MRI/MRA of the head and neck
   B. Echocardiogram
   C. Renal ultrasound
   D. MRI of the heart
   E. All of the above are indicated

6. The following are subtypes of Kaposi sarcoma (KS), EXCEPT:
   A. African endemic KS
   B. Classic KS
   C. Epidemic HIV-associated KS
   D. Asian endemic KS
   E. All of the above are subtypes

7. All of the following statements regarding classic Kaposi sarcoma are true, EXCEPT:
   A. It is more common in men than women
   B. Involvement of the upper extremities is more common than the lower extremities
   C. Ionizing radiation may be used as a form of treatment
   D. Topical imiquimod may slow progression of the disease
   E. The lungs, spleen, and heart may be involved

8. Upon histologic examination of a vascular neoplasm, tufts of capillaries in a cannonball pattern are seen throughout the dermis. What is the most likely diagnosis?
   A. Kaposi sarcoma
   B. Pyogenic granuloma
   C. Tufted angiomA
   D. Infantile hemangioma
   E. Kimura’s disease

QUIZ

Questions

1. Which immunohistochemical stain is specific to infantile hemangioma?
   A. aGLUT-1
   B. Ulex europaeus agglutinin 1
   C. Vimentin
   D. Factor VIII-related antigen
   E. Endothelin-1 antibody

2. Other than the facial hemangioma, the most common features of PHACE are:
   A. Structural and cerebrovascular anomalies of the brain
   B. Ocular anomalies
   C. Cardiovascular anomalies
   D. Ventral developmental defects

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   A. Kaposi sarcoma
   B. Pyogenic granuloma
   C. Tufted angiomA
   D. Infantile hemangioma
   E. Kimura’s disease
9. Which of the following statements best describes Dabska tumor?
   A. A rare, low-grade angiosarcoma that often affects the skin of children
   B. Reactive hyperplasia after intravascular thrombosis
   C. An exophytic tumor in young adults, predominantly located on the lower extremities
   D. A vascular tumor present at birth that undergoes rapid involution
   E. A violaceous tumor associated with thrombocytopenia

10. Rapid involuting hemangioma (RICH) can be distinguished from non-involuting congenital hemangioma (NIC) by all of the following EXCEPT:
   A. Clinical course
   B. Location on the body
   C. Color
   D. GLUT-1 staining
   E. Presence of a bruit

**Answers**

1. Inhantile hemangioma is positive for GLUT-1, a stain which is also positive in placental tissue.

2. A. PHACE stands for Posterior fossa (Dandy-Walker) brain malformations, Hemangiom (segmental, usually cervico-facial), cerebrovascular Arterial anomalies, Cardiac defects/coarctation of the aorta, Eye anomalies. Structural cerebral and cerebrovascular anomalies are the most common and potentially serious manifestations.

3. C. Structural cerebral and cerebrovascular anomalies are the most common and potentially serious manifestations in PHACE patients. Cerebrovascular anomalies can lead to progressive vasculopathies causing stroke in early childhood.

4. D. Patients with kaposiform hemangioendothelioma are at risk of developing Kasabach-Merritt phenomenon (KMP), a life-threatening thrombocytopenia as a result of platelet trapping within the tumor. KMP is a consumption coagulopathy with very low platelet counts and low fibrinogen levels. KMP does not occur with IH.

5. C. A patient with a large segmental hemangioma of the face is at risk of having PHACE syndrome. PHACE stands for Posterior fossa (Dandy-Walker) brain malformations, Hemangioma (segmental, usually cervico-facial), cerebrovascular Arterial anomalies, Cardiac defects/coarctation of the aorta, Eye anomalies. Renal anomalies are not part of PHACE syndrome.


7. B. Classic KS typically affects males older than 50 years of age, predominant in Mediterranean and Jewish populations. These patients have increased risk of lymphoreticular neoplasms. Clinically, classic KS appears as violaceous macules with slow progression to plaques. It involves the distal lower extremities, with unilateral involvement and centripetal spread to a disseminated and multifocal pattern. The oral cavity and GI tract (90%) are commonly affected; possible involvement of lung, spleen, and heart. Classic KS has a benign course owing to slow progression.

8. C. Histologic examination of tufted angioma shows tufts of capillaries throughout dermis in a “cannon-ball” pattern.

9. A. Dabska tumor is a low-grade angiosarcoma that affects the skin of children. It is a slow-growing, painless, intradermal nodule. Dabska tumor has immunoreactivity for factor VIII–related antigen, Ulex europaeus agglutinin I, vimentin, blood group isoantigens, and C2.1 antibody. Histologically, multiple vascular channels that interconnect are lined by atypical endothelial cells; vacuolated cytoplasm, and hyperchromatic eccentric nuclei. Weibel-Palade bodies may be present. Wide local excision is the treatment of choice; regional lymph node dissection if clinically necessary. Prognosis is favorable; however, the tumor can be locally invasive and has the potential to metastasize.

10. D. Only infantile hemangioma is GLUT-1 positive.

**REFERENCES**


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EPIDERMOLYSIS BULLOSA

- Disorder with the formation of bullae and erosions following mechanical trauma to the skin and mucosa.
- Gene defects cause abnormalities in structural proteins of the epidermis and the epidermal-dermal junction.
- Subtypes are classified based on the ultrastructural level of blisters (Table 14-1), mode of inheritance, and the clinical features.
- There are four major EB types (Table 14-2) and multiple related subtypes (Table 14-3).

**Diagnosis:**

- Transmission electron microscopy (EM): evaluation of level of skin cleavage: intraepidermal, intra-lamina lucida, or sub-lamina densa
- Immunofluorescence mapping (IFM): monoclonal antibodies, can identify the structural protein most likely mutated resulting in the different forms of EB. (Table 14-4)
- Mutational analysis: determines the mode of inheritance and the precise site(s) and type(s) of molecular mutation present. (Table 14-5)

**Epidermolysis Bullosa Simplex (EBS)**

- Autosomal dominant (most common) or recessive
  - Targeted proteins include: keratins 5 and 14 (encode basal cell keratin), desmoplakin, plakophilin-1. (Table 14-6)
  - When the defect involves keratins 5 and 14 a split through lowest part of basal keratinocyte and the formation of bullae occurs.
  - All types of EB patients exhibit fragile skin, blisters, scarring, nail dystrophy, milia and scarring alopecia.

- Dominant subtypes
  - Localized EBS:
    - Weber-Cockayne type: localized lesions on the palms and soles, hyperhidrosis, most common type of EBS
  - Generalized EBS:
    - Koebner type: AD, presents during infancy and early childhood, generalized lesions (extremities are more severely involved), palmoplantar hyperkeratosis
    - Dowling-Meara type (EBS herpetiformis): AD, onset at birth, herpetiform grouped vesicles on annular erythematous base, nail dystrophy, oral mucosal involvement
  - Other subtypes:
    - EB simplex with mottled pigmentation: onset at birth, generalized distribution, mottled or reticulate brown pigmentation
    - Superficial type: disruption of the stratum granulosum
    - Acantholytic type: hyperkeratosis and bullae of the palms and soles

- Recessive subtypes:
  - Muscular dystrophy type: abnormality of plec 1 (plectin 1/ intermediate filament binding protein), hemidesmosomal protein 1 (HD1/ protein needed for hemidesmosome formation), causes split through lowest part of basal keratinocyte, muscular dystrophy occurs in the limb-girdle
  - Type unrelated to muscular dystrophy: homozygous K14 nonsense mutation
  - Skin fragility syndrome: abnormal PKP1 (encodes the desmosome protein plakophilin 1), classified as a variant of acantholytic EB, but also considered a form of ectodermal dysplasia; formation of intraepidermal acantholysis;
<table>
<thead>
<tr>
<th>EB Type or Subtype</th>
<th>Ultrastructural Site of Skin Findings</th>
<th>Other Ultrastructural Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB simplex (EBS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBS, localized</td>
<td>Basal layer</td>
<td>Split may spread to suprabasilar layer</td>
</tr>
<tr>
<td>EBS, DM</td>
<td>Basal layer in subnuclear cytoplasm</td>
<td>Dense, circumscribed clumps of keratin filaments (most commonly observed)</td>
</tr>
<tr>
<td>EBS-MD</td>
<td>Predominantly in basal layer, above level of HD attachment plaque</td>
<td>Reduced integration of keratin filaments with HD</td>
</tr>
<tr>
<td>EBS-AR</td>
<td>Basal keratinocytes</td>
<td>Absent or reduced keratin filaments within basal keratinocytes</td>
</tr>
<tr>
<td>EBSS</td>
<td>Split usually at interface between granular and cornified cell layers</td>
<td>—</td>
</tr>
<tr>
<td>EBS, lethal acantholytic</td>
<td>Suprabasal cleavage and acantholysis</td>
<td>Perinuclear retraction of keratin filaments</td>
</tr>
<tr>
<td>EBS, plakophilin-1 deficiency</td>
<td>Mid-epidermal cell-cell separation</td>
<td>Diminutive suprabasal desmosomes; perinuclear retraction of keratin filaments</td>
</tr>
<tr>
<td>EBS-PA</td>
<td>Lower basal layer, above level of HD plaque</td>
<td>Reduced integration of keratin filaments with HD</td>
</tr>
<tr>
<td>Junctional EB (JEB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JEB-H</td>
<td>Lamina lucida</td>
<td>Markedly reduced or absent HD; absent SBDP</td>
</tr>
<tr>
<td>JEB-nH</td>
<td>Lamina lucida</td>
<td>HDs may be normal or reduced in size and number</td>
</tr>
<tr>
<td>JEB-PA</td>
<td>Lamina lucida</td>
<td>Small HD plaques often with attenuated SBDP</td>
</tr>
<tr>
<td>Dominant dystrophic EB (DDEB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDEB, generalized</td>
<td>Sub–lamina densa</td>
<td>Normal or decreased numbers of AFs</td>
</tr>
<tr>
<td>DDEB-BDN</td>
<td>Sub–lamina densa</td>
<td>Electron-dense stellate bodies within basal layer; reduced AFs</td>
</tr>
<tr>
<td>Recessive dystrophic EB (RDEB)</td>
<td></td>
<td></td>
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<tr>
<td>RDEB, severe generalized</td>
<td>Sub–lamina densa</td>
<td>Absent or rudimentary AFs</td>
</tr>
<tr>
<td>RDEB, generalized other</td>
<td>Sub–lamina densa</td>
<td>Reduced or rudimentary-appearing AFs</td>
</tr>
<tr>
<td>RDEB-BDN</td>
<td>Sub–lamina densa</td>
<td>Electron-dense stellate bodies within basal layer; reduced AFs</td>
</tr>
</tbody>
</table>

AF, Anchoring fibril; AR, autosomal recessive; BDN, bullous dermolysis of the newborn; DM, Dowling-Meara; EBSS, EBS superficialis; H, Herlitz; HD, hemidesmosome; MD, muscular dystrophy; nH, non-Herlitz; PA, pyloric atresia; SBDP, sub-basal dense plate.

### TABLE 14-2  The Four Major EB Types

<table>
<thead>
<tr>
<th>Level of Skin Cleavage</th>
<th>Major EB Type</th>
<th>Known Targeted Protein(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraepidermal (“epidermolytic”)</td>
<td>EBS</td>
<td>Keratins 5 and 14; plectin; α6β4 integrin; plakophilin-1; desmoplakin</td>
</tr>
<tr>
<td>Intra–lamina lucida (“lamina lucidolytic”)</td>
<td>JEB</td>
<td>Laminin-332 (laminin 5); type XVII collagen; α6β4 integrin</td>
</tr>
<tr>
<td>Sub–lamina densa (“dermolytic”)</td>
<td>DEB</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>Mixed</td>
<td>Kindler syndrome</td>
<td>Kindlin-1</td>
</tr>
</tbody>
</table>

DEB, Dystrophic EB; EBS, EB simplex; JEB, junctional EB.


### TABLE 14-3  The Major EB Subtypes

<table>
<thead>
<tr>
<th>Major EB Type</th>
<th>Major EB Subtypes</th>
<th>Targeted Protein(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBS</td>
<td>Suprabasal EBS</td>
<td>Plakophilin-1; desmoplakin; ? others</td>
</tr>
<tr>
<td></td>
<td>Basal EBS</td>
<td>Keratins 5 and 14; plectin; α6β4 integrin</td>
</tr>
<tr>
<td>JEB</td>
<td>JEB-H</td>
<td>Laminin-332 (laminin-5)</td>
</tr>
<tr>
<td></td>
<td>JEB, other</td>
<td>Laminin-332; type XVII collagen; α6β4 integrin</td>
</tr>
<tr>
<td>DEB</td>
<td>Dominant DEB</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td></td>
<td>Recessive DEB</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>Kindler syndrome</td>
<td>—</td>
<td>Kindlin-1</td>
</tr>
</tbody>
</table>

DEB, Dystrophic EB; EBS, EB simplex; JEB, junctional EB.


alopecia, palmoplantar keratoderma, painful fissures, nail dystrophy, cheilitis, hypohidrosis

- **EBS with pyloric atresia**: (possibly AR), widespread congenital absence of skin, pyloric atresia, malformed pinnae and nasal alae; joint contractures; cryptorchidism

### Junctional Epidermolysis Bullosa (JEB)

- Autosomal recessive
  - Split within lamina lucida
  - Targeted proteins include: Laminin 5, type XVII collagen, α6β4 Integrin (Table 14-7)
- Two main subtypes:
  - **JEB-Herlitz**: defect of laminin-5 gene (codes for an anchoring filament glycoprotein), more severe than other subtype with associated premature death, generalized blistering, multisystem disease: eyes (corneal, conjunctival), mucosa (tracheobronchial, oral, pharyngeal, esophageal, rectal, and genitourinary); delayed puberty, exuberant granulation, pitted teeth
  - **JEB-non-Herlitz**: defect found in laminin-5 and bullous pemphigoid antigen-2 (type XVII collagen, 180 kDa), milder form of JEB; corneal erosions, teeth with pitted enamel

- **Generalized atrophic benign EB (GABEB)**: ambient temperature causes increased blistering, blisters heal with atrophy

- **Junctional epidermolysis bullosa with pyloric atresia**: AR, defect in α6β4 integrin gene; affects hemidesmosome, split within lamina lucida, pyloric atresia present at birth, rudimentary ears, GU malformations, may be associated with large areas of aplasia cutis, focal segmental glomerulosclerosis
### TABLE 14-4 Antigenic Alterations in EB Skin

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Abnormal Staining in:</th>
<th>Usual Pattern of Staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratin 14</td>
<td>EBS-AR</td>
<td>Absent or markedly reduced</td>
</tr>
<tr>
<td>Laminin-332 (laminin-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>JEB-H</td>
<td>Absent or markedly reduced</td>
</tr>
<tr>
<td></td>
<td>JEB-nH generalized</td>
<td>Reduced</td>
</tr>
<tr>
<td>Collagen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>JEB-nH, generalized</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>JEB-nH, localized</td>
<td>Reduced</td>
</tr>
<tr>
<td>Type VII collagen</td>
<td>RDEB, severe generalized</td>
<td>Absent or markedly reduced</td>
</tr>
<tr>
<td></td>
<td>RDEB-nH, localized</td>
<td>Reduced</td>
</tr>
<tr>
<td>Type VII collagen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RDEB, severe generalized</td>
<td>Absent or markedly reduced</td>
</tr>
<tr>
<td></td>
<td>RDEB, generalized other</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td>RDEB, inversa</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>DEB-BDN (only during period of active blistering)</td>
<td>Granular staining within basal and suprabasal keratinocytes; absent or markedly reduced staining along DEJ</td>
</tr>
<tr>
<td>Plectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EBS-MD</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td></td>
<td>EBS-PA</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td></td>
<td>EBS-Ogna</td>
<td>Reduced</td>
</tr>
<tr>
<td>α6β4 Integrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>JEB-PA</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td></td>
<td>EBS-PA</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td></td>
<td>JEB-nH</td>
<td>Reduced</td>
</tr>
<tr>
<td>Kindlin-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kindler syndrome</td>
<td>Absent, reduced, or normal</td>
</tr>
</tbody>
</table>


**JEB inversa**
- Blisters located in intertriginous areas, presents at birth, atrophic scarring, dystrophic or absent nails, intraoral erosions; esophagus and anus may be severely involved.

**Laryngo-onycho-cutaneous syndrome (LOC syndrome, Shabbir’s syndrome):** AR; associated with mutations in the a3 chain of laminin-332.; blisters commonly found on face and neck, onset first few months of life, hoarseness, exuberant granulation of conjunctiva and/or larynx.

**JEB, late onset (EB progressive)**
- AR, onset young adulthood or later, hyperhidrosis, absent dermatoglyphs; affects hands, feet, elbows, and knees; nails are absent or dystrophic, intraoral erosions.

**Epidermolysis Bullosa Dystrophica (Fig. 14-1)**
- Autosomal dominant and recessive types
- Due to defects of type VII collagen found in the anchoring fibril protein and in most cases are related to COL7A1 gene mutations (Table 14-8)

**Dominant Dystrophic Epidermolysis Bullosa**
- Fewer anchoring fibrils (Type VII collagen)
- Subepithelial split below lamina densa
- **Generalized type (Pasini; Cockayne-Touraine):** AD, Cockayne-Touraine: onset at birth with generalized
### TABLE 14-5 Mutational Analyses and Inherited EB: Summary of Findings by EB Type and Subtype

<table>
<thead>
<tr>
<th>EB Type</th>
<th>EB Subtype</th>
<th>Target Gene (Protein)</th>
<th>Types of Mutations Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBS</td>
<td>Suprabasal</td>
<td>PKP1 (plakophilin-1)</td>
<td>Spl, Del, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSP (desmoplakin)</td>
<td>NS, Del</td>
</tr>
<tr>
<td></td>
<td>Basal</td>
<td>KRT5 (keratin-5)</td>
<td>MS, NS, Del, Spl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KRT14 (keratin-14)</td>
<td>MS, NS, Del, Ins, Spl, in-frame del/ins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PLEC1 (plectin)</td>
<td>MS, NS, Del, Ins, in-frame del/ins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ITGA6, ITGB4 (alpha6β4 integrin)</td>
<td>MS, NS, Del, Ins, Spl</td>
</tr>
<tr>
<td>JEB</td>
<td>Herlitz</td>
<td>LAMA3, LAMB3, LAMC2 (laminin-332)</td>
<td>NS, Del, Ins, Spl</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>LAMA3, LAMB3, LAMC2 (laminin-332)</td>
<td>MS, NS, Del, Ins, Spl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COL17A1 (type XVII collagen)</td>
<td>MS, NS, Del, Ins, Spl</td>
</tr>
<tr>
<td>DEB</td>
<td>Dominant</td>
<td>COL7A1 (type VII collagen)</td>
<td>MS Spl</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>COL7A1 (type VII collagen)</td>
<td>MS Ins Del NS Spl</td>
</tr>
<tr>
<td>Kindler syndrome</td>
<td>KIND1 (kindlin-1)</td>
<td>NS Spl Ins Del</td>
<td></td>
</tr>
</tbody>
</table>

*Del, Deletion; in-frame del/ins, in-frame deletion and insertion; Ins, insertion; MS, missense mutation; NS, nonsense mutation; Spl, splice site mutation. In many cases with recessive inheritance, two different mutations are present in one individual compound heterozygosity.


### TABLE 14-6 EBS Subtypes

<table>
<thead>
<tr>
<th>Major EBS Types</th>
<th>EBS Subtypes*</th>
<th>Targeted Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprabasal</td>
<td><em>Lethal acantholytic EB</em></td>
<td>Desmoplakin</td>
</tr>
<tr>
<td></td>
<td>Plakophilin deficiency</td>
<td>Plakophilin-1</td>
</tr>
<tr>
<td></td>
<td><em>EBS superficialis (EBSS)</em></td>
<td>?</td>
</tr>
<tr>
<td>Basal</td>
<td>EBS, localized (EBS-loc)†</td>
<td>K5, K14</td>
</tr>
<tr>
<td></td>
<td>EBS, Dowling-Meara (EBS-DM)</td>
<td>K5, K14</td>
</tr>
<tr>
<td></td>
<td>EBS, other generalized (EBS, gen-nonDM; EBS, gen-nDM)†</td>
<td>K5, K14</td>
</tr>
<tr>
<td></td>
<td><em>EBS-with mottled pigmentation (EBS-MP)</em></td>
<td>K5</td>
</tr>
<tr>
<td></td>
<td>EBS with muscular dystrophy (EBS-MD)</td>
<td>Plectin</td>
</tr>
<tr>
<td></td>
<td><em>EBS with pyloric atresia (EBS-PA)</em></td>
<td>Plectin; EBS, 6β4 integrin</td>
</tr>
<tr>
<td></td>
<td><em>EBS, autosomal recessive (EBS-AR)</em></td>
<td>K14</td>
</tr>
</tbody>
</table>

*Rare variants shown in italics.
†Previously called EBS, Weber-Cockayne.
‡Includes patients previously classified as having EBS-Koebner.
TABLE 14-7  Junctional EB Subtypes

<table>
<thead>
<tr>
<th>Major JEB Subtype</th>
<th>Subtypes*</th>
<th>Targeted Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>JEB, Herlitz (JEB-H)</td>
<td>—</td>
<td>Laminin 5 (Laminin-332)</td>
</tr>
<tr>
<td>JEB, other (JEB-O)</td>
<td>JEB, non-Herlitz, generalized (JEB-nH gen)†</td>
<td>Laminin 5 (Laminin-332); type XVII collagen</td>
</tr>
<tr>
<td></td>
<td>JEB, non-Herlitz, localized (JEB-nH loc)</td>
<td>Type XVII collagen</td>
</tr>
<tr>
<td></td>
<td>JEB with pyloric atresia (JEB-PA)</td>
<td>α 6β4 Integrin</td>
</tr>
<tr>
<td></td>
<td>JEB, inversa (JEB-I)</td>
<td>Laminin 5 (Laminin-332)</td>
</tr>
<tr>
<td></td>
<td>JEB, late onset (JEB-lo)‡</td>
<td>?</td>
</tr>
</tbody>
</table>

*Rare variants shown in italic type.
†Formerly known as generalized atrophic benign EB (GABEB).
‡Formerly known as EB progressive.

TABLE 14-8  Dystrophic EB Subtypes

<table>
<thead>
<tr>
<th>Targeted Protein</th>
<th>All Subtypes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDEB</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>DDEB, generalized (DDEB-gen)</td>
<td></td>
</tr>
<tr>
<td>DDEB, acral (DDEB-ac)</td>
<td></td>
</tr>
<tr>
<td>DDEB, pretibial (DDEB-Pt)</td>
<td></td>
</tr>
<tr>
<td>DDEB, pruriginosa (DDEB-Pr)</td>
<td></td>
</tr>
<tr>
<td>DDEB, nails only (DDEB-na)</td>
<td></td>
</tr>
<tr>
<td>DDEB, bullous dermolysis of the newborn (DDEB-BDN)</td>
<td></td>
</tr>
<tr>
<td>DDEB</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>DDEB, generalized (DDEB-gen)</td>
<td></td>
</tr>
<tr>
<td>DDEB, acral (DDEB-ac)</td>
<td></td>
</tr>
<tr>
<td>DDEB, pretibial (DDEB-Pt)</td>
<td></td>
</tr>
<tr>
<td>DDEB, pruriginosa (DDEB-Pr)</td>
<td></td>
</tr>
<tr>
<td>DDEB, nails only (DDEB-na)</td>
<td></td>
</tr>
<tr>
<td>DDEB, bullous dermolysis of the newborn (DDEB-BDN)</td>
<td></td>
</tr>
<tr>
<td>DDEB</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>DDEB, generalized (DDEB-gen)</td>
<td></td>
</tr>
</tbody>
</table>

*DDEB, Dominant dystrophic EB; RDEB, recessive dystrophic EB.
* Rare variants in italic type.
Recessive Dystrophic Epidermolysis Bullosa (RDEB)
• Absent anchoring fibrils (Type VII collagen)
• Subepithelial split below lamina densa
• RDEB mitis: involves acral areas and nails, localized form
• Severe generalized (Hallopeau-Siemens type): generalized lesions and clubbing of the digits, pseudoanomaly of fingers and toes (mitten hand deformity), flexion contractures, esophageal strictures and webs, stenosis of urethra and anal canal, phimosis, corneal scarring, squamous cell carcinoma can develop in non-healing wounds; glomerulonephritis, renal amyloidosis; IgA nephropathy; chronic renal failure (CRF); cardiomyopathy; delayed puberty; osteoporosis most severe type
• Generalized other (non-Hallopeau-Siemens type): blisters present at birth, GI abnormalities
• RDEB inversa: onset at birth, distribution of blistering is intertriginous, acral, lumbosacral, axial; esophageal strictures, anal strictures and fissures, oral erosions, partial fusion of the digits with contractures, females with vaginal involvement and scarring.
• RDEB centripetalis: initial acral distribution of blisters with centripetal spread, milia, atrophic scarring, nail dystrophy

Other Dystrophic EB Subtypes
• Acral:
  • Dominant dystrophic EB (DDEB) or recessive dystrophic EB (RDEB):
  • Blisters located on hands and feet, dystrophic or absent nails; develops during infancy
• Pretibial:
  • DDEB and RDEB: blisters develop during birth or infancy, located on pretibial area, hands and feet; nails (fingers and toes), lichen planus like lesions, dystrophic or absent nails
• DEB pruriginosa:
  • Rare variant of DEB due to COL7A1 dominant and recessive mutations, which is characterized by severe itching and lichenoid or nodular prurigo-like lesions, mainly involving the extremities
• DDEB nails only: onset at birth or infancy
• Kindler syndrome:
  • Autosomal recessive
  • Combination of features of dystrophic epidermolysis bullosa and congenital poikiloderma (e.g., Rohman Thompson)
  • Due to a mutation in the gene KIND 1 encoding for kindlin-1: component of focal contacts in basal keratinocytes: multiple cleavage planes (intraepidermal, junctional, or sublamina densa)
  • Generalized blistering, onset at birth, poikiloderma; photosensitivity; mental retardation (rare);

Diagnosis of Epidermolysis Bullosa
• Electron microscopy on biopsy at the edge of a fresh blister, include both unblistered and blistered skin
• Immunofluorescent studies to detect abnormal protein antigens and serial monitoring of the patient
• Skin biopsy
• Upper GI series or endoscopy
• DNA mutation analysis
• Treatment: symptomatic care

DISORDERS OF PIGMENTATION

Neurofibromatosis I (Von Recklinghausen Disease)
• Autosomal dominant disease
• Defect of NF1 gene (chromosome 17q11.2) codes for neurofibromin: tumor suppressor; down-regulates activity of RAS (associated with increased cell proliferation and possible tumor formation)
• Neurofibromin, also positively regulates intracellular cyclic adenosine monophosphate (cAMP) levels, which modulate cell growth and differentiation in the brain.
• Diagnosis: requires two or more of the following features:
  - > 6 Café-au-lait macules
  - 1.5 cm or larger in postpubertal individuals
  - 0.5 cm or larger in prepubertal individuals
  - Two or more neurofibromas or one plexiform neurofibroma (Fig. 14-2)
  - Most common tumor seen in patients with NF1
  - Axillary (Crowe’s sign) or inguinal freckling
  - Optic glioma: tumor of the optic pathway
  - Two or more lisch nodules: pigmented spots that are hamartomas of iris
  - Distinctive bony lesion: dysplasia of the sphenoid wing, dysplasia or thinning of long bone cortex
  - First-degree relative with NF-1
• Clinical features
  - Café-au-lait spots (CALs): often present at birth; flat, evenly pigmented macules or patches, may fade as patient ages, in which case, Wood’s lamp may aid in diagnosis
  - Skinfold freckling: usually not apparent at birth but appears later in childhood
  - Lisch nodules are asymptomatic, raised, pigmented hamartomas of the iris; diagnosis by slit lamp. They are present in most adult NF1 patients.
  - Discrete neurofibromas: benign peripheral nerve sheath tumors, develop during adolescence. They are composed of a mixture of cell types including

bone abnormalities (rare), gingival hyperplasia, cutaneous atrophy, colitis (may be severe); esophagitis, urethral strictures
Schwann cells, fibroblasts, mast cells, and vascular elements.

- **Plexiform neurofibromas**: may diffusely involve nerve, muscle, connective tissue, vascular elements, and overlying skin. Since they can remain clinically silent for many years, diagnosis may be incidental by imaging studies or by the effects of the tumor on associated organs or structures.

- **Optic pathway gliomas**: typically arise in young children, second most common tumor in NF1 patients, low-grade pilocytic astrocytoma that typically arises in the optic nerve and chiasm, hypothalamus, brainstem, and/or cerebellum

- **Increased risk of malignancy**: neurofibrosarcoma, astrocytoma, rhabdomyosarcoma, myelogenous leukemia, malignant peripheral nerve sheath tumor

- **Other neurological complications**: macrocephaly, hydrocephalus, cognitive impairment, headaches, seizures, and cerebral ischemia

- **Learning disabilities**: common in children with NF1, but frank mental retardation (IQ <70) is uncommon

- **Skeletal abnormalities**: kyphoscoliosis

- **Endocrine disease**: (acromegaly, cretinism, hypothyroidism, hyperparathyroidism, precocious puberty)

- **Variants of NF-1**:
  - **Segmental or mosaic NF1**: when one of the two NF1 genes sustains a mutation during fetal development; a localized area of the developing fetus is affected.
  - **Watson’s syndrome**: multiple café au lait spots, dull intelligence, short stature, pulmonary valvular stenosis, and only a small number of neurofibromas, and lisch nodules

---


**TABLE 14-9 Age-Dependent Manifestations and Management of NF1**

<table>
<thead>
<tr>
<th>Age</th>
<th>Manifestations and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2 years</td>
<td>- Café-au-lait macules&lt;br&gt;- Plexiform neurofibromas&lt;br&gt;- Tibial Dysplasias (anterolateral bowing of lower leg): may require orthopedic referral</td>
</tr>
<tr>
<td>3–5 years</td>
<td>- Skinfold Freckling&lt;br&gt;- Lisch nodules&lt;br&gt;- Optic Pathway Gliomas: requires serial neurologic, ophthalmologic, and MRI scans once detected. Further management is warranted if there is tumor progression.&lt;br&gt;- Learning disabilities: requires planning with parents and teachers and early intervention if detected.&lt;br&gt;- Precocious puberty: requires endocrinologic and radiographic evaluation&lt;br&gt;- Plexiform Neurofibromas: requires regular follow-up</td>
</tr>
<tr>
<td>Late childhood and early adolescence</td>
<td>- Dermal Neurofibromas&lt;br&gt;- Plexiform Neurofibromas: requires regular follow-up&lt;br&gt;- Scoliosis: requires orthopedic evaluation for possible bracing and/or surgery</td>
</tr>
<tr>
<td>Lifelong</td>
<td>- Neurofibromas&lt;br&gt;- Pain&lt;br&gt;- Plexiform Neurofibromas: requires regular follow-up&lt;br&gt;- Malignant Peripheral Nerve Sheath Tumor (MPNST)&lt;br&gt;- Other Malignant Neoplasms</td>
</tr>
</tbody>
</table>
• Neurofibromatosis-Noonan syndrome (NFNS): children with NF1 also display the following features (similar to Noonan’s syndrome): pectus excavatum, hypertelorism, short stature

• Management (Table 14-9)
  • Requires a multidisciplinary approach.
  • Abnormalities on the visual examination should prompt MRI evaluation (“screening” or “baseline” MRI evaluations, as they are not predictive)
  • Serial ophthalmologic and neurologic exams.

Neurofibromatosis II (Bilateral Acoustic Neurofibromatosis)
• Autosomal dominant disease
• Defect of NF2 gene coding for schwannomin or merlin (chromosome 22q11)
• Diagnosis: requires either of the following:
  • Bilateral cranial nerve eight masses (acoustic neuromas)
  • First-degree relative with NF-2 plus either unilateral eighth nerve mass or two of the following: neurofibroma, schwannoma, optic glioma, meningioma, juvenile posterior subcapsular opacity

• Clinical
  • Unilateral hearing loss with or without tinnitus, dizziness or imbalance
  • Mononeuropathy, mainly affects the facial nerve, resulting in a Bell’s-like palsy
  • Spontaneous malignant transformation of schwannomas to malignant peripheral nerve sheath tumours (MPNST); more than 10 times as likely to occur following radiation treatment
  • CNS tumors: meningiomas, the second most common tumor in NF2 patients, occur supratentorially in the falk and around the frontal, temporal, and parietal regions. Ependymomas and gliomas usually located in the cervical spine or brain stem.
  • Ophthalmic involvement: cataracts, optic nerve meningiomas and retinal hamartomas may cause visual loss
  • Cutaneous tumors: schwannomas with occasional neurofibromas

• Diagnosis
  • Magnetic resonance imaging (MRI) scan with gadolinium enhancement
  • Pathology: schwannomas, encapsulated tumors of pure Schwann cells, grow around the nerve; may contain blood vessels and have areas of sheets in intertwining fascicles (Antoni A) and looser arrangements (Antoni B). S-100 protein and vimentin positive.

• Treatment
  • Management by a multidisciplinary team

• Microsurgery and radiation treatment for patients with aggressive tumors
• Visual and audiological testing

VON HIPPEL-LINDAU SYNDROME

Von Hippel-Lindau Syndrome
• Autosomal dominant
• VHL gene (chromosome 3); tumor suppressor gene
• VHL gene affects the VCB-CUL2 complex, which targets a protein called hypoxia-inducible factor (HIF). HIF is involved in cell division and the formation of new blood vessels.
• Presents by fourth decade
• Diagnostic criteria: (1) more than one hemangioblastoma in the CNS, (2) one CNS hemangioblastoma and visceral manifestations of VHL, or (3) one manifestation and a known family history of VHL.
• Clinical findings
  • Common tumors: cerebellar, medullary, or spinal cord hemangioblastomas with increased intracranial pressure, spinal cord compression; retinal hemangioblastomas with visual impairment, and renal cell carcinoma (RCC)
  • Endocrine tumors: pheochromocytoma (usually intra-adrenal), adrenal carcinoma, pancreatic islet cell cancers
  • Cysts: renal and pancreatic
  • Phenotypic variability (types of presentation of VHL patients):
    - Type 1: retinal or CNS hemangioblastomas and RCC but not pheochromocytoma
    - Type 2: at least one affected individual has pheochromocytoma in the family; Type 2A: retinal and CNS hemangioblastomas are present, but rarely RCC occur; Type 2B hemangioblastomas, RCC and phaeochromocytoma
  • Other clinical features: polycythemia secondary to increased erythropoietin, capillary malformation on head and neck, endolymphatic sac neoplasm, cardiac rhabdomyoma, hepatic cyst, adenoma, and/or angioma, carcinoid of the common bile duct, bone cysts or hemagiomas, café-au-lait spots

Ataxia-Telangiectasia (Louis-Bar Syndrome)
• Autosomal recessive
• Mutation in ATM gene (ataxia-telangiectasia mutated/located on chromosome 11q22–23); codes for protein kinase, involved in cellular responses
to DNA damage and cell cycle control; defective DNA repair with increased sensitivity to ionizing radiation

- Clinical findings
  - Progressive ataxia, presenting symptom when a child begins to walk; affects the extremities first and then speech; due to depletion of granular and Purkinje cells in cerebellum
  - Oculocutaneous telangiectasias by ages 3 to 6 years
  - Respiratory infections owing to decreased humoral and cellular immunity; decrease in the total number of CD4+ cells
  - Decreased development of thymus gland
  - Malignancies: 40% non-Hodgkin’s lymphomas, 25% leukemias, 25% (most leukemias and lymphomas are of T-cell origin); assorted solid tumors (adenocarcinoma of the stomach, dysgerminoma, gonadoblastoma and medulloblastoma) and 10% Hodgkin’s lymphomas.
  - Hypogonadism
  - Diagnosis (Table 14-11)
  - Treatment, symptom based

<table>
<thead>
<tr>
<th>Type of Patient</th>
<th>Recommended Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected asymptomatic patient</td>
<td>• Annual physical examination and urine test</td>
</tr>
<tr>
<td></td>
<td>• Annual direct and indirect ophthalmoscopy</td>
</tr>
<tr>
<td></td>
<td>• Annual fluorescein angiography or angiography</td>
</tr>
<tr>
<td></td>
<td>• Annual renal ultrasonographic examination</td>
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<tr>
<td></td>
<td>• MRI or CT scan of the brain every 3 years to age 50 years then every 5 years thereafter</td>
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<tr>
<td></td>
<td>• Abdominal CT scanning every 3 years (more often if multiple renal cysts are present)</td>
</tr>
<tr>
<td></td>
<td>• Annual 24-hour urine collection for vanillylmandelic acid (VMA) levels</td>
</tr>
<tr>
<td>At-risk relatives – same protocol as above with additional age based exams</td>
<td>• Annual direct and indirect ophthalmoscopy from age 5 years</td>
</tr>
<tr>
<td></td>
<td>• Annual fluorescein angiography or angiography from age 10 years until age 60 years</td>
</tr>
<tr>
<td></td>
<td>• MRI or CT scan of the brain every 3 years from ages 15–40 years, then every 5 years until age 60 years</td>
</tr>
<tr>
<td></td>
<td>• Abdominal CT scanning every 3 years from ages 20–65 years</td>
</tr>
</tbody>
</table>

| Table 14-11 Laboratory Evaluation of A-T Patients |
|----------------------------------|---------------------------------|
| Alpha-fetoprotein                | Elevated                        |
| Radiation response               | Hypersensitive                  |
| p53 stabilization                | Defective                       |
| ATM mutations                    | Yes                             |
| ATM protein                      | Absent/Detectable               |
| ATM kinase activity              | Absent                          |
| ATM signalling pathways          | Defective                       |

Hereditary Hemorrhagic Telangiectasia (HHT/Osler-Weber-Rendu Syndrome)

- Autosomal dominant
- Mutation of:
  - HHT1 gene containing endoglin (chromosome 9q33–34); it encodes a membrane glycoprotein found on human vascular endothelial cells
  - HH2 gene contains the activin-like receptor kinase (ALK-1) on chromosome 12q; it encodes transforming growth factor-β receptors
- Presents in childhood to early adulthood
- Diagnosis
  - Based on the Scientific Advisory Board of the HHT Foundation International Inc. consensus on clinical diagnostic criteria—Curaçao Criteria for HHT:
    - Definite: three criteria are present
    - Possible or suspected: two criteria are present
    - Unlikely: fewer than two criteria are present
VASCULAR-RELATED DISORDERS

Diagnostic criteria (Table 14-12)

Clinical findings

- Asymmetric overgrowth of tissues and neoplasms
  - Cutaneous involvement: cerebriform connective tissue nevi, epidermal nevi, vascular malformations, lipomas, lipohypoplasia, and dermal hypoplasia
  - Extracutaneous manifestations: skeletal overgrowth (macrocephaly, frontal bossing), visceral overgrowth (pharyngeal or vocal cord), tumors (epibulbar dermoid of the eye, ovarian cystadenoma), pulmonary and intracranial cysts, hernias, hydrocele, and undescended or absent testes, venous and lymphatic malformations
  - May be associated with neurofibromatosis 1

Treatment: multidisciplinary approach

Klippel-Trenaunay Syndrome

- Sporadic inheritance
- Triad of capillary vascular malformation (port wine stain), varicose veins and/or venous malformation, and soft tissue and/or bony hypertrophy

Clinical findings

- Usually affects one limb; most commonly leg, then arm, and trunk
- Capillary, venous, and lymphatic malformations
- Soft tissue and bony hypertrophy (Fig. 14-3)
- Other features: phleboliths, deep venous thromboses, pulmonary emboli, thrombophlebitis, cellulitis, intraosseous vascular malformations

Treatment: multidisciplinary approach

Proteus Syndrome

- Sporadic inheritance
- PTEN gene mutation

### TABLE 14-12 Diagnostic Criteria for Proteus Syndrome

<table>
<thead>
<tr>
<th>Mandatory General Criteria</th>
<th>Mosaic Distribution of Lesions, Progressive Course, Sporadic Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific criteria (A, or 2 from group B, or 3 from group C)</td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>Connective tissue nevus</td>
</tr>
</tbody>
</table>
| Group B | Epidermal nevus
| | Disproportionate overgrowth (1 or more)
| | Limbs, skull, external auditory meatus, vertebra, viscera (spleen and/or thymus)
| | Specific tumors before the end of the 2nd decade (either one): bilateral ovarian cystadenomas, parotid monomorphic adenoma |
| Group C | Dysregulated adipose tissue (either one): lipomas, regional absence of fat
| | Vascular malformations (1 or more): capillary, venous, and/or lymphatic
| | Facial phenotype: dolichocephaly, long face, low nasal bridge, wide or anteverted nares, open mouth at rest |

Clinical findings

- **Facial port-wine stain** (Fig. 14-4)
  - Presents at birth and is typically unilateral (85%), involving the ophthalmic \((V_1)\), maxillary \((V_2)\), and/or mandibular \((V_3)\) divisions of the trigeminal nerve.
  - Occurs with ipsilateral leptomeningeal vascular anomalies (capillary, venous, and AV malformations) and/or choroidal vascular lesions with glaucoma (unilateral)
  - Involvement of the entire \(V_1\) distribution may indicate underlying neurological and/or ocular disorders
  - **Roach classification scale**:
    - Type I – Both facial and leptomeningeal angiomomas (LA); may have glaucoma
    - Type II – Facial angioma alone (no CNS involvement); may have glaucoma
    - Type III – Isolated LA; usually no glaucoma
- **Sturge-Weber Syndrome (Encephalotrigeminal Angiomatosis)**
  - Sporadic inheritance
  - Neural crest defect
  - Neurologic complications: seizures, psychomotor delay in infancy, headaches and migraines, hemiparesis
  - Tram-track calcification in cortex
CONNECTIVE TISSUE DISORDERS

Kyphoscoliosis (type VI or ocular-scoliotic type)
- Autosomal recessive
- Lysyl hydroxylase deficiency (LH1 gene)
- Clinical findings: generalized joint laxity with severe hypotonia, progressive scoliosis; unable to ambulate by early adulthood, scleral fragility, prone to global rupture, retinal hemorrhage and detachment, glaucoma, discolored sclera, arterial rupture, marfanoid habitus, osteopenia, osteoporosis
- LH can be measured in the amniotic fluid

Arthrochalasia (formerly VIIA and B)
- Autosomal dominant
- Deficiency of proA1 or proA2 chains of collagen type I
- Clinical findings: congenital bilateral hip dislocations, joint hypermobility with subluxations, kyphoscoliosis, mild osteopenia, skin laxity with bruising, atrophic scars, muscle hypotonia, short stature

Dermatosparaxis (type VIIC)
- Autosomal recessive
- N-terminal peptidase of type I collagen I (ADAMTS2 gene)
- Clinical findings: severe skin fragility, redundant sagging skin (resembles cutis laxa), easy bruising, large hernias, premature rupture of membranes at delivery, no impairment of wound healing

Other types
- X-linked form (formerly type V)
- X-linked recessive pattern
- Clinical findings: skin laxity, orthopedic abnormalities
- Periodontal (formerly type VIII)
- AD
- Clinical findings: gingival inflammation and resorption with loss of permanent teeth; variable presentation of skin laxity, joint hyperextensibility, and bruising
- X-linked cutis laxa (formerly type IX)
- X-linked recessive
- Clinical findings: occipital bony prominences, poor healing with scarring, intracellular copper-dependent enzymes, chronic diarrhea with orthostatic hypotension
- Fibronectin (formerly type X) and benign hypermobile joint syndrome (formerly type XI)

Osteogenesis Imperfecta (OI)
- Characterized by increased bone fragility and low bone mass.
Chapter 14  GENODERMATOSIS

Diagnosis: based on clinical criteria (Ghent nosology). Major and minor criteria of the following organ systems are evaluated in the patient: ocular, skeletal, integumental, respiratory, and cardiovascular. Major criteria in two systems with involvement of a third system are needed to make an unequivocal diagnosis.

Criteria include:
- Skeletal system (two of the components comprising the major criterion, or one component comprising the major criterion plus two of the minor criteria)
  - Major criteria: presence of at least four of the following manifestations: pectus carinatum, pectus excavatum requiring surgery, reduced upper to lower segment ratio or arm span to height ratio > 1.05, positive wrist and thumb signs, scoliosis of > 20° or spondylolisthesis, reduced extension of the elbows (< 170°), medial displacement of the medial malleolus causing pes planus, protrusio acetabulae of any degree (ascertained on x-ray)
  - Minor criteria: pectus excavatum of moderate severity, joint hypermobility, highly arched palate with dental crowding, facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
- Ocular system (two of the minor criteria)
  - Major criterion: ectopia lentis
  - Minor criterion: abnormally flat cornea (as measured by keratometry), increased axial length of globe (as measured by ultrasound), hypoplastic iris or hypoplastic ciliary muscle causing a decreased miosis
- Cardiovascular system (major criterion or only one of the minor criteria)
  - Major criteria: dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva, or dissection of the ascending aorta
  - Minor criteria: mitral valve prolapse with or without mitral valve regurgitation, dilatation of main pulmonary artery, in absence of valvular or peripheral pulmonic stenosis or any other obvious cause, under the age of 40 years, calcification of the mitral annulus below the age of 40 years, or dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years
- Pulmonary system (one of the minor criteria must be present)
  - Major criteria: none
  - Minor criteria: spontaneous pneumothorax, or apical blebs (ascertained by chest radiography)

### TABLE 14-13 Characteristics of Osteogenesis Imperfecta (OI)

<table>
<thead>
<tr>
<th>OI Subtype</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Thin skin, blue sclera</td>
</tr>
<tr>
<td></td>
<td>Lax joints, kyphosis, abnormal dentition</td>
</tr>
<tr>
<td></td>
<td>Aortic valve disease, mitral valve prolapsed, long bone fractures, vertebral compression fractures</td>
</tr>
<tr>
<td>II</td>
<td>In utero fractures, limb avulsion at delivery</td>
</tr>
<tr>
<td></td>
<td>Perinatal death common due to respiratory insufficiency following rib fractures</td>
</tr>
<tr>
<td></td>
<td>Aortic valve disease, blue sclera</td>
</tr>
<tr>
<td>III</td>
<td>In utero fractures</td>
</tr>
<tr>
<td></td>
<td>Progressive scoliosis, limb bowing, crippling deformity</td>
</tr>
<tr>
<td></td>
<td>Blue sclera, triangular facies, short stature</td>
</tr>
<tr>
<td>IV</td>
<td>Fractures at birth, abnormal teeth</td>
</tr>
<tr>
<td></td>
<td>Improvement with age</td>
</tr>
</tbody>
</table>

- Majority of patients (about 90%) have a mutation in COL1A1 or COL1A2, the genes encoding collagen type I (found in bone)
- Patients have low trabecular bone mineral density and thin cortices, and also small, slender bones.
- Mostly autosomal dominant
- Four main subtypes with different mutations resulting in varying severity of disease (Table 14-13)
- Other subtypes: non-collagen related defects
  - Type V: autosomal dominant (genetic defect unknown) moderate to severe bone fragility, irregular mesh-like appearance of lamellar bone
  - Type VI: autosomal recessive. Moderate to severe skeletal fragility; bone biopsy shows lamellae with fish like appearance and excessive osteoid.
  - Type VII: autosomal recessive. rhizomelia, coxa vera, reduction is expression of cartilage-associated protein (CRTAP)
- All characterized by osseous fragility
- May develop hearing loss due to otosclerosis

**Marfan’s Syndrome**
- Autosomal dominant; mutation in fibrillin-1 (*FBN1*), chromosome 15; main component of extracellular microfibrils associated with elastin within elastic fibers

- Diagnosis: based on clinical criteria (Ghent nosology). Major and minor criteria of the following organ systems are evaluated in the patient: ocular, skeletal, integumental, respiratory, and cardiovascular. Major criteria in two systems with involvement of a third system are needed to make an unequivocal diagnosis.
  - Major criteria: presence of at least four of the following manifestations: pectus carinatum, pectus excavatum requiring surgery, reduced upper to lower segment ratio or arm span to height ratio > 1.05, positive wrist and thumb signs, scoliosis of > 20° or spondylolisthesis, reduced extension of the elbows (< 170°), medial displacement of the medial malleolus causing pes planus, protrusio acetabulae of any degree (ascertained on x-ray)
  - Minor criteria: pectus excavatum of moderate severity, joint hypermobility, highly arched palate with dental crowding, facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
- Ocular system (two of the minor criteria)
  - Major criterion: ectopia lentis
  - Minor criterion: abnormally flat cornea (as measured by keratometry), increased axial length of globe (as measured by ultrasound), hypoplastic iris or hypoplastic ciliary muscle causing a decreased miosis
- Cardiovascular system (major criterion or only one of the minor criteria)
  - Major criteria: dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva, or dissection of the ascending aorta
  - Minor criteria: mitral valve prolapse with or without mitral valve regurgitation, dilatation of main pulmonary artery, in absence of valvular or peripheral pulmonic stenosis or any other obvious cause, under the age of 40 years, calcification of the mitral annulus below the age of 40 years, or dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years
- Pulmonary system (one of the minor criteria must be present)
  - Major criterion: none
  - Minor criterion: spontaneous pneumothorax, or apical blebs (ascertained by chest radiography)
• Skin and integument (major criterion or one of the minor criteria)
  - **Major criterion**: lumbosacral dural ectasia by computed tomography or magnetic resonance imaging
  - **Minor criteria**: striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress, or recurrent or incisional herniae

• Family history (one of the major criteria must be present)
  - **Major criteria**: having a parent, child, or sibling who meets the diagnostic criteria listed below independently, presence of a mutation in FBN1 known to cause the Marfan syndrome, or presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family
  - **Minor criteria**: none

• Requirements for the diagnosis of Marfan’s syndrome
  - **For the index case**: major criteria in at least two different organ systems and involvement of a third organ system
  - **For a family member**: presence of a major criterion in the family history and one major criterion in an organ system and involvement of a second organ system

• Course: premature death secondary to cardiovascular defects
• Treatment: surgery, beta-blockers

**Cutis Laxa (Generalized Elastolysis)**

• Categorized by mode of inheritance and phenotypes: autosomal dominant, autosomal recessive (CL type I, CL type II, and type III-de Barsey syndrome), X-linked recessive (occipital horn syndrome), or acquired

• Characterized by redundant, loose and inelastic skin.

• Genetic defects: AD- ELN gene (elastin), autosomal recessive- fibulin-5 gene (FBLN5), or x-linked recessive-ATP7A

• Acquired cases: associated with penicillin, penicillamine, complement deficiency, lupus, amyloid, erythema multiforme, contact dermatitis, and Sweet’s syndrome

• Clinical findings
  - **Autosomal recessive**:
    - *Cutis laxa, type I*: perinatal form, presents with pulmonary and other internal manifestations, leading to premature death
    - *Cutis laxa type II*: (also called *cutis laxa with joint laxity and developmental delay*); presents with sagging jowls, epicanthic folds, antimongoloid slant, maxillary hypoplasia, blue sclera, depressed nasal bridge, apparent ocular hypertelorism, and long philtrum, growth retardation, developmental delay, microcephaly, wrinkling of skin on the abdomen, hernia, joint laxity, and dislocation
    - *de Barsey syndrome*: rare type, associated with cutis laxa, retarded psychomotor development and corneal clouding due to degeneration of the tunica elastica of the cornea, growth retardation, may be pseudoathetoid movements
  - **Autosomal dominant**: benign course; primarily, skin involvement, infrequent systemic complications, normal life expectancy
  - **X-linked recessive**: skin laxity, skeletal and genitourinary tract abnormalities

• Histology: special elastin specific stains (Verhoeff–van Gieson and orcein) show loss, fragmentation, or both, or decreased number of elastic fibers

**Pseudoxanthoma Elasticum (Grönblad–Strandberg Syndrome) (Fig. 14-5)**

• Autosomal recessive more common than autosomal dominant

• **ABCC-6** gene, chromosome 16p; encodes multidrug resistance associated protein 6 (MRP6), which belongs to the ABC (ATP binding cassette) transmembrane transporter family of proteins.

• D-Penicillamine implicated in drug-associated cases

• Progressive fragmentation and calcification of elastic fibers in skin, blood vessels, and Bruch’s membrane of the eye

• Clinical findings
  - Redundant intertriginous skin

**FIGURE 14-5** Pseudoxanthoma elasticum. (Reprinted with permission from Wolff K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)
• “Plucked chicken” or “gooseflesh” appearing skin with yellow papules typically developing on the neck and may coalesce into plaques; other areas affected include antecubital and popliteal fossae, axillae, inguinal, and periumbilical areas. Mucosal membranes may also be affected. Lesions are asymptomatic.
• Affected skin may become lax and wrinkled.
• Perforating PXE: occurs with extrusion of calcium deposits
• Ocular manifestations: angiod streaks in Bruch’s membrane (seen in 85% of patients): irregular, reddish-brown, or grey lines that radiate from the optic disc. They are due to degenerated and calcified elastic fibers of the retina that causes breaks in Bruch’s membrane. The earliest eye finding is a peau d’orange appearance (yellowish mottled pigmentation) of the retina. Other findings: colloid bodies, macular degeneration, optic nerve head drusen (whitish-yellow irregularities of the optic disc), and “owl’s eyes” (paired hyperpigmented spots).
• Cardiovascular manifestations
  - Claudication, hypertension, myocardial infarction (MI), cerebrovascular accident (CVA), coronary artery disease (CAD), renovascular hypertension, congestive cardiac failure, renal failure
• Gastrointestinal bleeds: (seen in 10% of patients) due to calcified submucosal vessels
• Diagnostic criteria
  • Major: characteristic skin lesions: cobblestone lesions in flexural areas, characteristic eye findings: angiod streaks, peau d’orange retinal appearance, maculopathy, characteristic histologic findings seen with elastic tissue and calcium stains.
  • Minor: characteristic histologic findings of non-lesional skin; family history of PXE in first degree relatives
• Histology: hematoxylin-eosin stains—elastic fibers are basophilic because of the calcium deposition; fibers fragmented, swollen, and clumped in the middle and deep reticular dermis
• Course: decreased lifespan owing to cardiovascular disease
• Management: regular eye exams, cardiology assessment, laboratory tests- CBC, ferritin, serum lipids, urinalysis; aspirin for high risk patients

Tuberous Sclerosis (Bourneville’s Syndrome, Epiloia)
• Autosomal dominant or spontaneous mutation
• Hamartin (TSC1, chromosome 9q34); protein function: Together with tuberin, hamartin regulates mTOR-S6K, and cell adhesion through interaction with ezrin and Rho
• Tuberin (TSC2, chromosome 16p13.3); protein function: together with hamartin, tuberin regulates mTOR-S6K and GTPase-activating proteins. Tuberin has a role in cell cycle.
• Clinical findings
  • Triad of epilepsy, low intelligence, adenoma sebaceum (epiloia)
  • Epilepsy: begins during the first year of life
• Cutaneous manifestations
  • Hypomelanotic macules: most common cutaneous manifestation (90% to 98% of patients)
  • Bilateral facial angiofibromas: hamartomatous nodules of vascular and connective tissue, in a butterfly pattern over the malar eminences and naso labial folds (80% of children)
  • Shagreen patch: connective tissue nevi, usually found on lumbosacral flank
  • Forehead fibrous plaque: yellow–brown or flesh-colored plaque, histology shows angiofibroma
  • Ungual fibroma: Koenen tumor, connective tissue hamartoma, adjacent to or below nail plate
• Other manifestations
  • Brain lesions: cortical tubers (proliferation of glial and neuronal cells), subependymal nodules (hamartomas), subependymal giant-cell tumours, and white matter abnormalities
  • Dental abnormalities: dental pits (90% of patients)
  • Renal manifestations: bilateral angiomyolipomas (70% to 90% of patients), renal cell carcinoma, renal cysts, smooth muscle cell carcinoma
  • Ocular manifestations: retinal hamartomas (40% to 50% of patients), mulberry lesions are composed of glial and astrocytic fibers
  • Pulmonary manifestations: lymphangiomatosis (alveolar smooth-muscle proliferation with cystic destruction of lung)
  • Hepatic manifestations: rare angiomyolipomas
• Diagnosis requires the presence of two major features, or one major and two minor criteria
• Diagnostic criteria for tuberous sclerosis:
  • Major features
    ▲ Non-traumatic ungual or periangual fibroma; Koenen’s tumor (Fig. 14-6)
    ▲ Shagreen patch (connective tissue nevus) migration lines (Fig. 14-7)
    ▲ Hypomelanotic “ashleaf” macules (three or more) (Fig. 14-8)
    ▲ Facial angiofibromas or forehead plaque pits in dental enamel (Fig. 14-9)
    ▲ Multiple retinal nodular hamartomas
CONNECTIVE TISSUE DISORDERS

Cortical tuber
Subependymal nodule
Subependymal giant-cell astrocytoma
Cardiac rhabdomyoma, single or multiple
Lymphangioleiomyomatosis, renal angiomyolipoma, or both

Minor features
Multiple, randomly distributed
Hamartomatous rectal polyps
Bone cysts
Cerebral white matter radial
Gingival fibromas
Non-renal hamartoma

FIGURE 14-6 Koenen tumors in tuberous sclerosis complex. (Reprinted with permission from Wolff, K et al: Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)

FIGURE 14-7 Shagreen patch in tuberous sclerosis. (Reprinted with permission from Wolff K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)

FIGURE 14-8 Ash-leaf macules. (Reprinted with permission from Wolff K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)

FIGURE 14-9 Facial angiofibromas. (Reprinted with permission from Wolff K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)
Chapter 14    GENODERMATOSIS

Lipoid Proteinosis (Urbach-Wieth Syndrome, Hyalinosis cutis et mucosae)
- Autosomal recessive
- ECM1
- Clinical findings
  - Dental anomalies and loss of teeth early
  - Cutaneous manifestations: eyelid with beaded papules (appear as a string of pearls), yellow waxy papules on skin, lips, palate, generalized skin thickening, hyperkeratosis at sites of trauma (hands, elbows, knees), pock-like or acneiform scars, infiltration of mucous membranes (pharynx, tongue, soft palate, lips) leading to difficulty in breathing, hoarseness
  - CNS manifestations: temporal and hippocampal sickle or bean-shaped calcifications
- Histology: dermal deposition of diastase-resistant PAS positive hyaline material
- Treatment: CO₂ laser treatment of vocal cords and eyelid papules; etretinate, penicillamine

Buschke-Ollendorf Syndrome (Dermatofibrosis Lenticularis)
- Autosomal dominant
- LEMD3 gene
- Increased desmosine and elastin in skin
- Clinical findings
  - Dermatofibrosis lenticularis disseminata: symmetrical skin colored to yellowish grouped papules and nodules forming plaques; localized on the trunk: sacrolumbar region and extremities
  - Osteopoikilosis: radiopaque round or oval spots in the epiphyses and the metaphyses of the long bones, pelvis and the bones of hands and feet, no increased fracture risk
- Histology: thickened collagen fibers in the dermis; fragmented elastic fibers
- Prognosis: normal lifespan

Focal Dermal Hypoplasia (Goltz Syndrome)
- X-linked dominant (lethal in males)
- Mutations in PORCN and Wnt signaling may be implicated
- Clinical findings
  - Cutaneous anomalies: atrophic, linear hypo- or hyperpigmented patches, telangiectatic streaks in Blaschko’s lines, fat herniations through dermal defects (focal dermal hypoplasia), papillomas on lips, perineum, axilla, absent/dystrophic fingernails, sparse, brittle hair
  - Skeletal anomalies: syndactyly with “lobster claw” deformity, ectrodactyly, polydactyly, absence or hypoplasia of digits, scoliosis, skeletal asymmetry, clavicular dysplasia, spina bifida occulta, osteopathia striata (linear striations primarily in the long bones)
  - Dental anomalies: hypodontia, oligodontia, microodontia, enamel fragility, dysplasia, malocclusion
  - Eye findings: micophthalmia, bilateral coloboma of the iris, ectopia lentis, strabismus, anophthalmia
  - Other manifestations: mild mental retardation, hearin defects, horse shoe kidneys, hernias: inguinal, umbilical, epigastric
  - Cardiac anomalies: cardiac tumors, congenital heart disease (truncus arteriosus)
- Course: normal lifespan

Retinal achromic patch
Confetti-like skin lesions
Multiple renal cysts
- Management: electroencephalography, cranial MRI, genetic testing, echocardiography, renal ultrasonography, chest computed tomography, ophthalmic examination

PREMATURE AGING AND PHOTOSENSITIVE DISORDERS

Progeria (Hutchinson-Gilford Progeria Syndrome)
- Autosomal dominant
- Lamin A defect (LMNA): produces some normal lamin A and some mutated lamin A (progerin).
- Clinical findings
  - Premature signs of aging: alopecia (including scalp and eyebrows), prominent scalp veins

Aplasia Cutis Congenita
- Autosomal dominant, autosomal recessive, or sporadic
- Clinical findings
  - Localized absence of epidermis, dermis, subcutis, bone or dura
  - Well-demarcated erosions/ulcerations; 65% occur on scalp, 25% of cases are found on the trunk or limbs
  - May present as an isolated defect or be combined with congenital malformations (abnormal limbs, dysraphism, facial cleft, abnormalities of the eyes, digestive tract, heart, neurological malformations), chromosome anomalies (Down’s syndrome, 4 p-syndrome), or other disorders such as bullous epidermolysis and pyloric stenosis.
  - Adams-Oliver syndrome (AOS): most commonly of the scalp and skull, and terminal transverse limb defects, congenital heart disease.
- Treatment: wound care, most lesions heal with scar formation
and forehead, classical facial features including micrognathia (small jaw), prominent eyes and a convex nasal profile (beak-like nose), and circumoral cyanosis
- High-pitched voice
- Loss of subcutaneous fat, muscle wasting
- Cutaneous: mottled hyperpigmentation, scleroderma-like changes on lower extremities
- Dystrophic teeth
- Skeletal manifestations: frequent osteolysis, limited joint mobility (contractures), coxa valga, and shortened clavicles, short stature
- Cardiovascular and cerebrovascular diseases: myocardial ischemia and infarction as well as stroke; angina, chronic congestive heart failure, or transient ischemic attacks
- Course: premature death in teens owing to atherosclerotic complications (angina, MI, CHF, CVA)

**Cockayne Syndrome**
- Autosomal recessive
- Type 1: CSA (also called CNK1 or excision-repair cross-complementing group 8, ERCC8 gene); chromosome 5q12-q13
- Type 2: CSB (also called ERCC6 gene); chromosome 10q11, 80% of cases
- Deficiency in transcription-coupled nucleotide excision repair (TC-NER)
- Increased sister chromatid exchanges
- Clinical findings
  - Cutaneous manifestation: photosensitive skin eruption (may affect any sun-exposed area). Pruritus, no increased risk of cutaneous or visceral malignancy
  - Typical features: progeroid, with sparse, dry hair, facial lipoatrophy, large ears, and a thin nose
  - Ocular findings: poor pupillary dilatation, enophthalmos (due to loss of subcutaneous fat), optic nerve hypoplasia, and retinal pigmentation, “salt and pepper,” retinal pigmentation, cataracts (15% of patients)
  - Musculoskeletal, central nervous, and genitourinary systems: kyphoscoliosis and flexion deformities of the hips, knees, and ankles; abnormal gait, developmental delay and mental retardation, microcephaly, large hands and feet
  - Sensorineural hearing impairment
- Genitourinary: Approximately one-third of boys have undescended testes and girls frequently exhibit menstrual irregularities
- Cockayne syndrome I (CS-I), classic Cockayne syndrome, symptoms begin after the first year of life, survive into adolescence and early adulthood
- Cockayne syndrome II (CS-II)/Pena-Shokeir type: exhibit intrauterine growth retardation, poor postnatal growth, congenital cataracts or early structural eye abnormalities, and severe and more rapidly progressive neurologic impairment.
- CS is frequently associated with xeroderma pigmentosum (XP) and trichothiodystrophy (TTD): these disorders exhibit sensitivity to ultraviolet (UV) light and defects in nucleotide excision repair (NER)
• Treatment: supportive: photoprotection, physical therapy, and optimizing nutrition; genetic counseling

**Bloom Syndrome**
• Autosomal recessive
• BLM gene (RECQL3) encodes a DNA helicase, chromosome 15
• Chromosomal instability, increased rate of sister chromatid exchange
• Increased incidence in Ashkenazi Jews
• Clinical findings
  - Onset in infancy
  - Cutaneous findings: erythema, telangiectasias in butterfly distribution, chelitis, café au lait macules
  - Short stature; characteristic facies
  - High-pitched voice, hypogonadism, infertility
  - Malignancy: 20% have leukemia, lymphoma, or colon cancer
  - Other medical problems: type 2 diabetes mellitus, chronic lung disease, immune deficiency with recurrent gastrointestinal and respiratory infections, abnormal liver function tests

**Seckel Syndrome (Microcephalic Primordial Dwarfism)**
• Autosomal recessive
• Mutation of pericentrin (PCNT) gene, functions to anchor both structural and regulatory proteins in the centrosome
• Clinical findings
  - Bird-headed dwarfism: growth retardation, microcephaly, micrognathia, beak-like nose, dwarfism
  - Other manifestations: mental retardation, trident hands, skeletal defects, hypodontia, hypersplenism, premature graying

**SYNDROMES WITH MALIGNANCY**

**Dyskeratosis Congenita (Zinsser-Engman-Cole Syndrome)**
• X-linked recessive (xq28), gene mutation DKC1; encodes dyskerin- a nucleolar protein found in small nucleolar RNA protein complexes.
• Autosomal dominant: milder spectrum of disease; gene mutation of human telomerase RNA component (hTERC); responsible for synthesizing telomeric DNA repeats; the mutation results in genomic instability and widespread cell death
• Autosomal recessive: unknown genetic mutation
• Hoyerall-Hreidearsson syndrome: severe variant of DC, multisystem disorder that develops in the neonatal period and infancy; severe growth retardation of perinatal onset, bone marrow failure, immunodeficiency, cerebellar hypoplasia and microcephaly.
• Clinical findings
  - Triad of nail dystrophy, increased skin pigmentation, and mucosal leukoplakia
  - **Mucocutaneous features:**
    - Poikiloderma neck, face, chest and arms (90% of patients)
    - Dystrophic nails (90% of patients) with longitudinal ridging and splitting with complete nail loss.
    - Mucosal leukoplakia (80% of patients): lingual mucosa, buccal mucosa, palate, and tongue (most commonly affected). Increased risk of malignancy at leukoplakia sites (35% of patients)
    - Other findings: cutaneous atrophy, hyperhidrosis of the palms and soles, telangiectasias, cracking, fissuring, bullae formation, loss of dermal ridges, hair tufts with keratotic plugs on the limbs and keratinized basal cell papillomas, alopecia, amyloidosis
  - **Non-mucocutaneous features:**
    - Pulmonary disease (20% of patients)
    - Ophthalmic manifestations: epiphoria due to nasolacrimal duct blockage, conjunctivitis, blepharitis, pterygium formation, ectropion, strabismus, cataracts and optic atrophy.
    - Skeletal manifestations: (20% of patients): mandibular hypoplasia, osteoporosis, abnormal bone trabeculation, avascular necrosis and scoliosis
    - Dental abnormalities: leukoplakia, hyperpigmentation, periodontal disease, hypocalcified teeth, taurodontism
    - Genitourinary abnormalities: hypoplastic testes, hypospadias, phimosis, urethral stenosis, horseshoe kidneys
    - Gastrointestinal abnormalities: esophageal webs causing dysphagia, hepatomegaly, cirrhosis
    - Neurological abnormalities: altered mental status, learning difficulties, peripheral neuropathy
    - Other abnormalities: microcephaly, intracranial calcification, deafness, , and chonael atresia. Bone marrow failure resulting in peripheral cytopenias (75% of patients develop pancytopenia, responsible for death in 70% of patients).
• Course: death in third to fourth decade due to malignancy (usually SCC), gastrointestinal bleed, or infection

**Xeroderma Pigmentosa**
• Multigenic, multiallelic, autosomal recessive disease
• Ocular symptoms (80% of patients) include photophobia, conjunctivitis, corneal vascularization, and opacification; malignant tumors may also arise
• Mucocutaneous manifestations (Fig. 14-10): skin appears prematurely aged, increased incidence of actinic keratosis, keratoacanthoma, squamous cell carcinoma, basal cell carcinoma, melanoma beginning in childhood; poikiloderma
• Neurologic manifestations: progressive cognitive deterioration mainly in complementation groups A, D and G: sensorineural deafness, spasticity, ataxia, hyporeflexia
• DeSanctis-Cacchione syndrome: subtype mainly associated with XPA, distinguished by severe neurologic disease, dwarfism, and immature sexual development
• Prognosis: two-thirds die by third decade
• Treatment
  • Aggressive avoidance of sun exposure
  • High-dose oral isotretinoin
  • Excision of cutaneous malignancies
  • Imiquimod 5% cream, 5-fluorouracil cream
  • Skin screenings every 3 months
  • Ophthalmologic evaluation

Muir-Torre Syndrome (Fig. 14-11)
• Autosomal dominant disorder characterized by the combination of sebaceous gland tumors of the skin and internal malignancies
• Subtype of hereditary nonpolyposis colorectal cancer syndrome (HNPCC, also called Lynch syndrome)
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Internal malignancies: adenocarcinoma of the colon is most common cancer; other sites include genitourinary tract, hematologic and breast malignancies have also been reported.

Treatment: sebaceous adenoma and epithelioma—excision or cryotherapy; sebaceous carcinoma—excision, radiotherapy or Mohs surgery; keratoacanthoma—excision.

Cowden Syndrome (Multiple Hamartoma Syndrome)

- Autosomal dominant
- PTEN defect (phosphate and tensin homolog, also called MMAC1), located on 10q23; the gene defect is also found in Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome.
- Presents in second to third decade
- Diagnostic criteria
  - Mucocutaneous lesions alone if
    - > 6 facial papules with >3 trichilemmomas
    - Cutaneous facial papules and oral mucosal papillomatosis
    - Oral mucosal papillomatosis and acral keratoses
    - 6 or more palmar/plantar keratoses, or
  - 2 major criteria but one must include macrocephaly or Lhermitte-Duclos disease, or
  - 1 major and 3 minor criteria, or
  - 4 minor criteria
- Pathognomonic criteria
  - Facial papules (facial trichilemmomas and papillomatous papules), acral keratoses and oral papillomatosis
- Major criteria:
  - Breast cancer, thyroid cancer, macrocephaly, hamartomatous outgrowths of cerebellum (Lhermitte-Duclos disease)
- Minor criteria:
  - Thyroid lesions (goiter, adenoma), hamartomatous intestinal polyps, fibrocystic disease of the breast, lipomas, fibromas, genitourinary tumors or malformations, mental retardation (IQ < 75)

Clinical findings
- Mutocutaneous lesions: facial trichilemmomas, acral keratoses, oral papillomas—found mainly on the buccal and gingival mucosa, where coalescent lesions lead to a characteristic cobblestone-like pattern; other cutaneous lesions: lipomas, xanthomas, vitiligo, neuromas, hemangiomas, lentigines, acanthosis nigricans
- Extracutaneous findings
  - Breast abnormalities: fibrocystic breast changes, fibroadenomas
  - Thyroid abnormalities: (60%) goiter, benign adenoma, thyroglossal duct cyst, hyper- or hypothyroidism, thyroiditis

Defect in DNA mismatch repair (MMR) genes
- Most often MSH2 located on chromosome 2p
- Sometimes MLH1 located on chromosome 3p
- Presents in fifth to sixth decade

Diagnostic criteria
- Group A: sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma, keratoacanthoma
- Group B: visceral malignancy
- Group C: multiple keratoacanthomas, multiple visceral malignancies, family history of Muir-Torre syndrome
- Diagnosis requires: criterion from group A and group B, or all three from group C

Clinical findings
- Cutaneous tumors: sebaceous tumors: adenomas, hyperplasia, epitheliomas, sebaceous carcinomas; may also present with keratoacanthomas

Defect in DNA mismatch repair (MMR) genes
- Most often MSH2 located on chromosome 2p
- Sometimes MLH1 located on chromosome 3p
- Presents in fifth to sixth decade

Diagnostic criteria
- Group A: sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma, keratoacanthoma
- Group B: visceral malignancy
- Group C: multiple keratoacanthomas, multiple visceral malignancies, family history of Muir-Torre syndrome
- Diagnosis requires: criterion from group A and group B, or all three from group C

Clinical findings
- Cutaneous tumors: sebaceous tumors: adenomas, hyperplasia, epitheliomas, sebaceous carcinomas; may also present with keratoacanthomas
- **Gastrointestinal abnormalities**: polyps have low malignant potential, diverticula, hepatic hamartomas
- **Urogenital abnormalities**: ovarian cysts, uterine leiomyomas, hydrocele and varicocele in males, hypoplastic testes, vulvar and vaginal cysts
- **Ocular abnormalities**: cataracts, angiod streaks, myopia
- **Nervous system abnormalities**: neuromas, neurofibromas, meningiomas
- **Skeletal abnormalities**: adenoid facies, bone cysts, craniomegaly, high arched palate, kyphoscoliosis, pectus excavatum, rudimentary sixth digit, syndactyly
- **Internal malignancy**: breast adenocarcinoma (at least 20% of cases); follicular thyroid adenocarcinoma (7%), endometrial cancer, adenocarcinoma of the colon, hepatocellular carcinoma
- **Lhermitte-Duclos disease**: variant with cerebellar hamartomas and ataxia
- **Diagnosis and evaluation**
  - Baseline studies: thyroid function tests, thyroid scanning, complete blood count, urinalysis, mammography and chest radiography.

**Gardner Syndrome**
- Autosomal dominant; 25% of cases occur due to spontaneous mutations.
- Adenomatosis polyposis coli (APC) gene, a tumor suppressor gene; linked to 5q21-q22
- Defect also found in familial adenomatous polyposis (FAP)
- Promotes destruction of β-catenin: component of a transcription factor complex
- **Clinical findings**
  - **Gastrointestinal manifestations**: polyposis of colon by second to fourth decade; most develop colon or rectal cancer
  - **Skeletal manifestations**: osteomas of the skull and jaw (50% of patients), supernumerary teeth
  - **Cutaneous manifestations**: epidermoid cysts of head and neck (66% of patients), fibromas, neurofibromas, lipomas, leiomyomas, pigmented skin lesions.
  - **Tumors**: desmoid, fibromas, hepatoblastoma
  - **Ocular manifestations**: congenital hypertrophy of the retinal pigment epithelium (CHRPE)
  - **Other manifestations**: papillary thyroid cancer, menigiomas, hepatoma, hepatoblastoma, fibromas, leiomyomas, lipomas, biliary and adrenal neoplasms, osteosarcoma, chondrosarcoma
- **Diagnosis**: DNA analysis
- **Treatment**: colonoscopies, prophylactic colectomy, high fiber diet, screen family members with large bowel and upper GI surveillance, as well as thyroid and possibly hepatic surveillance.

**Peutz-Jeghers Syndrome (Periorificial Lentiginosis)** (Fig. 14-12)
- Autosomal dominant or sporadic
- **STK11** gene (serine/threonine protein kinase, LKB1) tumor suppressor gene; mapped to chromosome 19p13.13
- Presents in childhood
- **Clinical findings**
  - **Cutaneous findings**: lentigines on mucosa, periorificial skin, palms, digits; present at birth; lesions on the skin and lips often fade after puberty, while intraoral lesions persist
  - **Gastrointestinal findings**: hamartomatous polyps (more common in small intestine) may cause bleeding, pain, intussusception, obstruction; adenocarcinoma
  - **Genitourinary findings**: ovarian neoplasm-most common sex cord tumor with annular tubules (SCTAT), mucinous epithelial ovarian tumor, serous tumor and ovarian mature hamartoma; endometrial adenocarcinoma, and adenoma malignum of the cervix
  - **Endocrine findings**: gynecomastia due to calcified Sertoli cell testicular tumors
  - **Other findings**: breast cancer (usually ductal), pancreatic cancer
- **Diagnosis**: monitor with colonoscopy, polypectomy
- **Course**: normal lifespan if malignancy detected early
Multiple Endocrine Neoplasia IIa (Sipple Syndrome)
- Autosomal dominant
- Receptor tyrosine kinase (RET) protooncogene; activation of Ret protein and results in hyperplasia of target cells—such as C cells (clear large cells in a peri- or parafollicular location; precursor lesion for medullary thyroid carcinoma [MTC]) in the thyroid gland and chromaffin cells in adrenal glands.
- Clinical findings
  - Macular or lichen amyloidosis
  - Hyperparathyroidism with parathyroid hyperplasia (20% of cases) or adenoma
  - Thyroid hyperplasia or medullary thyroid carcinoma (MTC)
  - Pheochromocytoma, bilateral in 70% of cases; age at onset is approximately 40 years; patients present with hypertension, sweating, palpitations and tachycardia, nausea, vomiting, polyuria, polydipsia
- Diagnosis: RET germline mutation testing
- Laboratory work up: calcitonin levels, urine catecholamine; plasma free and urinary fractionated metanephrines
- Imaging studies: pheochromocytomas: CT scan, MRI, metaiodo-benzylguanidine (MIBG) scanning; OctreoScan imaging, positive emission tomography (PET).
- Treatment: total thyroidectomy with radical lymph-node dissection (patients 5 years or older with RET mutation); pheochromocytomas: surgical excision

Multiple Endocrine Neoplasia IIb (Multiple Neuroma Syndrome)
- Autosomal dominant
- Receptor tyrosine kinase (RET) mutations; protooncogene
- Chromosomal locus 10q11
- Clinical findings
  - Mucosal neuromas may result in thickened lips, eyelid eversion
  - Medullary thyroid carcinoma; aggressive, occurs in childhood
  - Pheochromocytoma
  - Marfanoid habitus
  - Adrenomedullary hyperplasia; multifocal and often bilateral
  - Gastrointestinal ganglieneuromatosis with megacolon; constipation or diarrhea
- Laboratory work up: calcitonin levels, urine catecholamine; plasma free and urinary fractionated metanephrines
- Imaging studies: pheochromocytomas: CT scan, MRI, metaiodo-benzylguanidine (MIBG) scanning; OctreoScan imaging, positive emission tomography (PET).
- Course: normal lifespan with early detection and treatment of thyroid carcinoma
- Treatment: total thyroidectomy with radical lymph-node dissection (patients 5 years or older with RET mutation); pheochromocytomas: surgical excision

Carney Complex
- Autosomal dominant; mutations in the PRKAR1A gene; encodes the R1a regulatory subunit of protein kinase A.
- The following syndromes are now included under Carney complex:
  - LAMB (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi)
  - NAME (nevi, atrial myxoma, myxoid neurofibroma, and ephelides)
- Clinical findings: pituitary adenoma, Sertoli-cell tumors, thyroid nodules, cardiac myxomas (accounts for 7% of all cardiac myxomas)
- Cutaneous findings: skin myxomas, melanotic schwannomas, lentigines (common areas: face, trunk, lips)
- Imaging studies: echocardiography
- Treatment: surgical excision of intracardiac myxomas

DISORDERS ASSOCIATED WITH IMMUNODEFICIENCY

Wiskott-Aldrich Syndrome (WAS)
- X-linked recessive
- WAS gene, Xp11; genetic defect in Wiskott-Aldrich syndrome protein (WASp)
- Decreased sialophorin (CD43) on surface of lymphocytes
- Impaired T- and NK-cell function
- Clinical findings
  - Atopic dermatitis with secondary infection, allergies, asthma
  - Recurrent bacterial infections
  - Thrombocytopenia, petechiae, bloody diarrhea
  - Increased IgA, IgD, and IgE, but decreased IgM
- Course: death from infection, hemorrhage, or lymphophoreticular malignancy
- Laboratory studies
  - serum immunoglobulin levels, complete blood cell count
- Imaging studies
  - Computed tomography: splenomegaly, rule out malignancy. Evaluation of intracranial bleeding, sinus or pulmonary infections.
DISORDERS WITH CHROMOSOME ABNORMALITIES

Leukocyte Adhesion Deficiency (LAD)
- Autosomal recessive
- CD18 gene (part of an integrin)
- Impaired leukocyte mobilization
- Clinical findings
  - Gingivitis can lead to loss of teeth
  - Poor wound healing, so wounds become large ulcers
  - Delayed separation of umbilical cord
  - Differentiate this from Type II LAD which also has mental retardation and short stature; defect in GDP-fucose biosynthesis

Chronic Granulomatous Disease
- X-linked recessive, sometimes autosomal recessive
- Mutations in nicotinamide dinucleotide phosphate (NADPH) oxidase subunits (eg. gp91phox subunit of cytochrome b, or p47phox)
- Deficient killing of phagocytised organisms
- Clinical findings
  - Pyoderma, perianal abscesses, and perioral ulcers
  - Pneumonia and emphyema
  - Osteomyelitis with Serratia
  - Hepatosplenomegaly with granulomas
  - Nitroblue tetrazolium assay abnormal (abnormal leukocytes unable to reduce dye and make blue color)
- Treatment includes interferon-gamma

Hyper-immunoglobulin E Syndrome
- Autosomal dominant
- Chromosome 4q
- Increased levels of IgE
- Clinical findings
  - Eczematous rash
  - Cold abscesses with Staphylococcus, Streptococcus or Candida
  - Sinopulmonary infections with Staphylococcus, H. Influenza, or fungus
  - Osteopenia with bone fractures and scoliosis
  - Retention of primary teeth and other dental anomalies
  - Job syndrome is a subgroup with hyperextensible joints.

Severe Combined Immunodeficiency
- X-linked recessive, sometimes autosomal recessive
- Defect in γ chain of IL-2 receptor, adenosine deaminase, or JAK 3 pathway
- Impaired T-cells, may also affect NK- and B-cells
- Clinical findings
  - Absent thymus on x-ray, lack tonsillar buds
  - Recurrent infections with Candida, Staphylococcus, and Streptococcus
  - Pneumonias with Pneumocystis carinii, Parainfluenza, or Cytomegalovirus
  - Chronic viral diarrhea, malabsorption, and failure-to-thrive
  - Graft-versus-host reaction to in utero maternal lymphocytes
  - Must irradiate blood products before transfusion and avoid live vaccines
  - Omenn syndrome: severe variant with failure-to-thrive, alopecia, and erythroderma; secondary to RAG 2 gene mutation

Down Syndrome (Trisomy 21)
- Mainly sporadic secondary to nondisjunction at chromosome 21
- Presents at birth
- Clinical findings
  - Single palmar crease
  - Nuchal skin folds
  - Syringomas
  - Elastosis perforans serpiginosa
  - Xerosis and lichenification with age
  - Alopecia areata
  - Flat nasal bridge, short broad neck, epicanthal folds, small mouth with protruding scrotal tongue
  - Mental retardation and seizures
  - Congenital heart disease
  - Duodenal atresia
  - Acute myelogenous leukemia
- Course: increased infant mortality secondary to congenital heart defects and neoplasms

Turner Syndrome (Gonadal Dysgenesis, Ullrich–Turner)
- Sporadic loss of one X chromosome (XO monosomy)
- Some cases demonstrate mosaicism
- Clinical findings
  - Dermatologic findings: melanocytic nevi, koilonychia, increased keloids, webbed neck
  - Low-set hairline, patchy alopecia
  - Triangular facies, short stature, shield chest with wide-set nipples, cubitus valgus
  - Primary amenorrhea, infertility
  - Mental retardation
  - Horseshoe kidneys
  - Coarctation of aorta
- Treatment: estrogen replacement, treatment of congenital anomalies
Noonan Syndrome

- Autosomal dominant
- PTPN11 gene encoding protein tyrosine phosphatase SHP2, recently SOS1 and RAF1 mutations reported
- Clinical findings
  - Resemble Turner syndrome with short stature, webbed neck, low posterior hairline, cubitus valgus
  - Cryptorchidism
  - Cardiac malformations (pulmonic stenosis)
  - Lymphedema
  - Tendency for keloid formation
- Treatment: correction of cardiac defects

Klinefelter Syndrome

- 47,XXY
- Decreased serum testosterone
- Clinical findings
  - Hypogonadism, gynecomastia
  - Tall with low hairline
  - Sparse body hair
  - Mental retardation, psychiatric problems in one-third of patients
  - Thrombophlebitis, leg ulcers
  - Risk of gonadal tumors, breast cancer
- Treatment: testosterone replacement and wound care

Questions

1. Type VIIC (dermatospraxis) Ehlers-Danlos syndrome is caused by a problem with collagen formation at which site?
   A. Nucleus
   B. Ribosome
   C. Golgi lumen
   D. Extracellular space

2. Lamellar ichthyosis is characterized by which of the following?
   A. Widespread bullae at birth, palmoplantar keratoderma later
   B. Superficial blistering and molting, followed by flexural hyperkeratosis
   C. Collodion baby followed by large platelike scales
   D. Migratory geographic patches of erythema that stabilize after puberty

3. The defect in Louis-Bar syndrome involves:
   A. DNA repair
   B. Tumor suppressor
   C. Developmental error
   D. TGF-beta receptor

4. The defect in the syndrome marked by clumped melanosomes in the fetal hair shaft, silvery hair, abnormal platelets, and recurrent infections involves:
   A. Tyrosinase
   B. P gene
   C. Melanosome transfer
   D. C-kit

5. Aplasia cutis congenital can be associated with all of the following EXCEPT:
   A. Otherwise healthy newborn
   B. Limb hypoplasia
   C. Lung hypoplasia
   D. Epidermolysis bullosa

6. Your patient presents with telangiectasias, photosensitivity, acral keratoses, alopecia, and cataracts since age 5. You counsel your patient that he has risk for:
   A. Squamous cell carcinoma and sarcoma
   B. Leukemia and frequent infections
   C. Hypertension and vascular malformations
   D. Neurologic degeneration including deafness

7. If you suspect a patient has Neimann-Pick disease, you might examine the skin to look for what lesion?
   A. Melanoma
   B. Café-au-lait macules
   C. Xanthomas
   D. Cherry red spots

8. Some porphyrias can have acute attacks precipitated by various drugs, infections, alcohol, dieting, and pregnancy. What symptoms suggest an acute attack?
   A. Photosensitivity and fluorescent urine
   B. Abdominal pain and confusion
   C. Gallstones and blisters
   D. Hemolytic anemia and liver cancer

9. Because rapamycin inhibits mTOR activity, it has been used to shrink tumors associated with which syndrome?
   A. Gorlin’s syndrome
   B. Familial cylindromatosis
   C. Neurofibromatosis
   D. Tuberculous sclerosis

10. Coloboma is associated with all of the following EXCEPT:
    A. Goltz’s syndrome
    B. Bloch-Sulzberger’s syndrome
    C. CHIME (neuroectodermal) syndrome
    D. Urbach-Wiethe syndrome
Answers

1. D. This type of Ehlers-Danlos syndrome involves a mutation in the ADAM-TS2 gene, or N-peptidase gene. N-peptidase cleaves the N-terminus of collagen Type I in the extracellular space, where tropocollagen is formed to then be incorporated into mixed fibrils.

2. C. Unlike many other ichthyoses, lamellar ichthyosis persists and remains severe past childhood. Characteristic large, squarish, “dry riverbed” scales are most prominent in the flexures.

3. A. The ATM gene encodes a phosphatidyl inositol-3-kinase-like protein that is involved in DNA repair. Ataxia-telangiectasia, or Louis-Bar syndrome, is neurodegenerative and immune system disorder associated with infections and malignancies, particularly lymphomas and leukemias.

4. C. Chediak-Higashi syndrome is caused by a mutation in the LYST gene, which encodes a trafficking protein. Decreased melanosomes transfer results in clumped melanosomes visible in the medulla of fetal hair shafts, useful for diagnosis.

5. C. Aplasia cutis congenital (ACC) is associated with multiple abnormalities listed above except for lung hypoplasia. The association of epidermolysis bullosa with ACC is called Bart’s syndrome. The association of ACC with cutis marmorata telangiectatica congenita and limb abnormalities is called Adams-Oliver syndrome.

6. A. Rothmund-Thomson syndrome (poikiloderma congenitale) patients have acral verrucous keratoses that can evolve into squamous cell carcinomas. Patients also have rare osteosarcoma and fibrosarcoma. The above findings are related to the RecQL4 helicase defect.

7. C. Xanthomas on the face and upper extremities can be seen in Neimann-Pick disease. Cherry red spots are located in the fovea and would not be visible on the skin.

8. B. Acute attacks occur when hemoglobin or cytochromes, the end products of the porphyrin pathway, are depleted. Acute attacks manifest with abdominal pain, peripheral neuropathy, confusion, seizure, tachycardia, and hypertension. Treatment includes glucose, hematin, carbohydrates, and hormones.

9. D. Normally, hamartin and tuberin associate with each other to inhibit Rheb. Rheb in turn increases mTOR signaling which results in cell growth. Tuberous sclerosis 1 and 2 result from defects in hamartin or tuberin, respectively. Patients with tuberous sclerosis have increased mTOR, which can be inhibited by the drug rapamycin.

10. D. Coloboma is a gap in a structure of the eye due to incomplete development, and is associated with Goltz’s syndrome, Bloch-Sulzberger’s syndrome, and CHIME syndrome. Sickle-shaped beanbag calcifications in the hippocampus and eyelid (“string of pearls”) are associated with Urbach-Wiethe syndrome (lipoid proteinosis).

REFERENCES

Epidermolysis Bullosa


Disorders of Pigmentation


**Disorders of Vascularization**


**Connective Tissue, Premature Aging, and Photosensitive Disorders**


**Immunodeficiency**


**Chromosomal Abnormalities**


Nguyen D, Turner JT, Olsen C, Biesecker LG, Darlington TN: Cutaneous manifestations of proteus syndrome:


**DISORDERS OF PIGMENTATION**

**Mongolian Spot (Fig. 15-1)**
- Presentation
  - Blue-gray patches present at birth or early infancy
  - Usually buttocks, lumbosacral back
  - Common in black, Hispanic, and Asian races
  - Color due to Tyndall effect (scattering of light as it strikes dermal melanin)
- Course
  - Usually resolves by early to late childhood
  - Extensive Mongolian spots (dermal melanocytosis) with dorsal/ventral distribution, indistinct borders, and persistent and/or “progressive” behavior may be a sign of underlying lysosomal storage disease (most commonly GM1 gangliosidosis type 1 and Hurler disease)

**Nevus of Ota (Fig. 15-2)**
- Also known as oculodermal melanocytosis, nevus fusoceruleus ophthalmomaxillaris
- Presentation
  - Unilateral bluish gray discoloration of facial skin
  - Affects region supplied by trigeminal nerve V₁ and V₂ ± ipsilateral sclera
  - Congenital or acquired by second decade
  - More common in black or Asian races, females
- Treatment: pigmented lesion lasers
- Course
  - Persists; both this and nevus of Ito may increase in size/intensity over time
  - Ocular involvement: risk of glaucoma

**Nevus of Ito (Fig. 15-3)**
- Also known as nevus fusoceruleus acromiodeltoides
- Presentation: similar to nevus of Ota but localized to unilateral shoulder, lateral neck, scapula, and/or deltid
- Course: persists
- Treatment: pigmented lesion lasers

**Mosaic Hypopigmentation (Fig. 15-4)**
- Includes hypomelanosis of Ito (incontinentia pigmenti acromians), nevus depigmentosus (achromic nevus)
- Presentation
  - Benign, hypopigmented oval or round patches, bands, or swirls
  - May be localized or extensive
  - Arranged along one or more Blaschko lines
  - No preceding vesicular or inflammatory stages
  - Incidence of systemic manifestations highest with most extensive lesions
  - Most commonly CNS, musculoskeletal, and eyes depending on particular chromosome defect and level of mosaicism
- Course: persists

**VASCULAR DISORDERS**

**Blueberry Muffin Baby (Fig. 15-5)**
- Presentation
  - Multiple, dark blue to magenta, small, nonblanching papules and macules
  - Present at birth or by first day of life
- Etiology
  - Extramedullary hematopoiesis
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Differential
- Includes neoplastic-infiltrative disease (lesions typically larger, more nodular, and fewer in number)
- Neuroblastoma, rhabdomyosarcoma, Langerhans’ cell histiocytosis (especially congenital self-healing histiocytosis, also known as Hashimoto-Pritzker disease), congenital leukemia (especially myelogenous)

Course
- Skin lesions involute spontaneously in 2 to 6 weeks

FIGURE 15-1  Mongolian spot. (Courtesy of Dr. Adelaide Herbert.)

FIGURE 15-2  Nevus of Ota. (Courtesy of Dr. Adelaide Herbert.)


FIGURE 15-4  Hypomelanosis of Ito. (Courtesy of Dr. Adelaide Herbert.)

- Associated with congenital infections (TORCH viruses, most commonly cytomegalovirus), hemolytic disease of the newborn, hereditary spherocytosis, twin-twin transfusion syndrome
VASCULAR DISORDERS

Fever, edema, and targetoid purpuric lesions on face, ears, distal extremities
Children generally appear well despite alarming appearance of skin lesions
Systemic symptoms: renal, joint, gastrointestinal (GI) involvement exceptional (important difference from adult Henoch-Schonlein purpura)
Course: clinical improvement in 1 to 3 weeks

Henoch-Schonlein Purpura (Anaphylactoid Purpura) (Fig. 15-7)
- Presentation
  - Triad: characteristic skin lesions, abdominal pain, and hematuria
  - Children and young adults
  - Often preceding upper respiratory infection
  - Pink or erythematous papules that become purpuric on extensor extremities, buttocks
  - Develop in crops
- Systemic signs and symptoms
  - Abdominal pain
  - Arthralgias
  - Hematuria
  - Nephritis; rare progressive glomerular disease
- Course
  - Most resolve in 6 to 16 weeks
  - May recur
  - Severe/prolonged disease more common in older children/adolescents
  - Nephritis may manifest up to 3 years after initial onset; important to monitor urinalyses (UAs)
- Treatment: supportive care

Nevus Anemicus (Fig. 15-8)
- Presentation
  - Congenital vascular abnormality, asymptomatic
Destructive options include cantharidin, curettage, cryotherapy, and topical irritants (retinoic acid, imiquimod).

Eczema Herpeticum (Kaposi’s Varicelliform Eruption) (Fig. 15-10)

Presentation
- Herpes simplex virus (HSV) infection within preexisting dermatitis (atopic dermatitis, severe seborrheic dermatitis, scabies, bullous disorders)

Sudden onset of grouped, uniformly sized vesicles and/or pustules that evolve into crusted erosions

Fever, lymphadenopathy, malaise

Diagnosis
- Tzanck smear
- Biopsy
- Rapid HSV immunofluorescence

INFECTIONS

Molluscum Contagiosum (Fig. 15-9)

Presentation
- Skin-colored, umbilicated papules
- Children commonly affected
- Contagious, with autoinoculation

Causative organism
- Pox virus (large DNA virus, 200–300 nm)

Diagnosis
- Usually clinical
- Histology: Henderson-Patterson bodies (cytoplasmic viral inclusion bodies) on path

Course: Individual lesions last weeks to months; total course may last several months to years

Treatment
- Not required because lesions will resolve spontaneously

FIGURE 15-8 Nevus anemicus. (Courtesy of Dr. Denise Metry.)

FIGURE 15-9 Molluscum contagiosum. (Courtesy of Dr. Denise Metry.)

FIGURE 15-10 Eczema herpeticum. (Courtesy of Dr. Denise Metry.)
• Treatment
  • First episode most serious because of risk of systemic involvement
  • Oral or intravenous acyclovir
• Prognosis
  • Estimated 20% incidence of minor recurrence

Unilateral Laterothoracic Exanthem (Asymmetric Periflexural Exanthem of Childhood)
• Presentation
  • Erythematous papules develop close to a flexure (typically axilla)
  • Papules coalesce and spread to involve the adjacent trunk and extremity
  • Lymphadenopathy common
  • Contralateral involvement occurs occasionally
  • Typically affects children younger than 10 years of age
• Causative organism
  • Etiology unknown
  • Viral cause suspected owing to high incidence of preceding upper respiratory infection or gastroenteritis
• Diagnosis
  • Mainly clinical
  • Histology: lymphocytic infiltrate around eccrine ducts
• Treatment: resolves spontaneously in 2 to 6 weeks

Scabies (Fig. 15-11)
• Presentation
  • Pruritic papules, vesicles, burrows of web spaces, flexures, genitals
  • Often excoriated, impetiginized
  • Spread by close contact
  • Norwegian scabies (Fig. 15-12)
    – Heavily crusted lesions with many mites
    – Immunodeficient, debilitated patients
  • Nodular scabies (Fig. 15-13)
    – Persistent red nodules; represents hypersensitivity to mites
• Causative organism
  • Sarcoptes scabei
  • Female mite burrows and deposits eggs in stratum corneum
• Diagnosis
  • Clinical
  • Microscopic examination of mite, ova, or feces (scutula) on skin scraping
• Treatment
  • Topical 5% permethrin is treatment of choice (approved down to 2 months of age)
  • For newborn infants or pregnant/nursing women, 6% to 10% sulfur in petrolatum (permethrin is pregnancy category factor B)
Greasy, salmon-colored patches on face (central forehead, glabella, eyebrows, nasolabial folds), retroauricular, intertriginous areas

Blepharitis may be present

Etiology: possible role of *Pityrosporum ovale* (*Malassezia furfur*)

Course

Generally resolves by 1 year of age

Postinflammatory hypopigmentation characteristic of darker-skinned infants

Treatment

Low-potency topical corticosteroids

Antiseborrheic shampoos

Topical antifungals

**Gianotti-Crosti Syndrome (Papular Acrodermatitis of Childhood) (Fig. 15-16)**

Presentation

Greasy, salmon-colored patches on face (central forehead, glabella, eyebrows, nasolabial folds), retroauricular, intertriginous areas

Blepharitis may be present

Etiology: possible role of *Pityrosporum ovale* (*Malassezia furfur*)

Course

Generally resolves by 1 year of age

Postinflammatory hypopigmentation characteristic of darker-skinned infants

Treatment

Low-potency topical corticosteroids

Antiseborrheic shampoos

Topical antifungals

**DERMATOSES**

**Seborrheic Dermatitis (“Cradle Cap”) (Fig. 15-15)**

Presentation

Yellowish, scaling dermatitis of scalp
Erythema Toxicum Neonatorum (ETN) (Fig. 15-18)

- Presentation
  - Common; affects half of full-term newborns
  - “Flea-bitten rash” of few to hundreds of erythematous macules, wheals, papules, and pustules
  - Occurs in the first 24 to 48 hours of life
  - Both TNPM and ETN almost always spare the palms and soles (important distinguishing clinical feature from congenital candidiasis)

Acropustulosis of Infancy (Infantile Acropustulosis) (Fig. 15-17)

- Presentation
  - Crops of pruritic vesiculopustules on the hands and feet of infants/young children
  - Occurs in crops every 2 to 4 weeks
  - Scabies prep negative
- Etiology: may be reactive to previous scabies exposure
- Pathology: subcorneal and intraepidermal neutrophilic abscesses
- Treatment
  - Potent topical steroids
  - Oral antihistamines
  - Oral erythromycin
  - Dapsone for exceptionally severe cases
- Course: resolves in 1 to 2 years

Transient Neonatal Pustular Melanosis (TNPM)

- Presentation
  - Very superficial vesicles, sterile pustules
  - Seen at birth in up to 4% of healthy, term newborns
  - Rupture with desquamation leaves characteristic residual hyperpigmented macules generally within first 2 days of life
- Pathology: intracorneal and subcorneal neutrophilic spongiosis (few if any eosinophils)
- Treatment
  - Self-limited
  - Postinflammatory pigmentation fades in weeks to months

Constitutional symptoms: low-grade fever, lymphadenopathy, splenomegaly
- Pathology: associated with viral infections: Epstein-Barr virus (most common association in the United States), hepatitis B virus, cytomegalovirus (CMV), respiratory syncitial virus (RSV)
- Course: resolves spontaneously in 3 to 8 weeks
- Treatment: symptomatic
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- Histology: folliculitis with eosinophils (few neutrophils, no spongiosis)
- Treatment: resolves within 1 to 2 weeks

Lichen Striatus (Fig. 15-19)
- Presentation
  - Linear band of erythematous to flesh-colored papules
  - Develops over several weeks

- Follows Blaschko’s lines
- Affects children and young adults
- Resolves within 1 to 2 years with postinflammatory hypopigmentation that improves slowly
- Initially may be mildly pruritic

Pathology
- Spongiotic or lichenoid dermatitis with necrotic keratinocytes
- Lymphocytic infiltrate around eccrine coils
- Treatment: topical anti-inflammatories may be useful for pruritus; may hasten resolution of inflammatory lesions

CUTANEOUS NEOPLASMS AND MALFORMATIONS

Epstein’s Pearls (Bohn’s Nodules)
- Presentation: white to yellow mobile papules at the hard palate (Epstein’s pearls) or gum margin (Bohn’s nodules) of newborns
- Etiology/pathology: milia
- Treatment
  - No treatment required
  - Resolves within weeks

Pseudoverrucous Papules and Nodules (Fig. 15-20)
- Presentation: shiny, moist, flat-topped erythematous papules of diaper area or surrounding urostomy/colostomy sites
- Etiology/pathology: form of severe irritant contact dermatitis resulting from incontinence, encopresis, severe diaper dermatitis
- Treatment: protection of skin by barrier creams

FIGURE 15-19 Lichen striatus. (Courtesy of Dr. Denise Metry.)

FIGURE 15-20 Pseudoverrucous papules and nodules. (Courtesy of Dr. Denise Metry.)
Schimmelpenning’s Syndrome
- Presentation: large nevus sebaceous associated with ocular lesions, intracranial masses, mental retardation, seizures, skeletal and/or pigmentary abnormalities

Linear Epidermal Nevus (Fig. 15-23)
- Presentation
- Verrucous pink to brown papules following Blaschko’s lines
- Generally presents at birth or within first year of life, sometimes later in childhood or adolescence
- Subtypes
  - Systematized epidermal nevus (Fig. 15-24): extensive, bilateral lesions
  - Ichthyosis hystrix/nevus unius lateris: extensive unilateral lesions
  - Inflammatory linear verrucous epidermal nevus (ILVEN)
    - Inflammatory variant with erythema, pruritus
    - Often on an extremity or perineum in girls
- Etiology/histology
  - Hyperplasia of epidermal structures with hyperkeratosis, acanthosis, papillomatosis, some with epidermolytic hyperkeratosis
  - Accompanying parakeratosis and inflammation (with ILVEN)
- Course/therapy
  - Destruction by excision, laser ablation, cryotherapy, dermabrasion, chemical peels, topical retinoids
  - Recurrence is common
  - Pruritus with ILVEN often refractory to treatment

Nevus Sebaceous of Jadassohn (Fig. 15-22)
- Presentation
  - Congenital hairless, yellow to orange plaque on the scalp (usually round), face, or neck (usually linear)
  - Pebbly, velvety, or cerebriform surface, although often flat at birth
- Etiology/pathology
  - Early: increased numbers of immature sebaceous glands and hair follicles
  - Postpubertal: papillomatosis, hyperkeratosis, and hypergranulosis accompany lobules of sebaceous glands and ectopic apocrine glands
- Course/therapy
  - Prepubertal excision often considered due to low risk of secondary tumor growth later in life
  - Most commonly associated malignant neoplasm: basal cell carcinoma (BCC)
  - Most common benign neoplasm: trichoblastoma

Perianal (or Perineal) Pyramidal Protrusion (Fig. 15-21)
- Presentation
  - Triangular-shaped, flesh-colored to erythematous nodule on the perineal median raphe, anterior to the anus
  - More than 90% of cases occur in female infants
  - Average age at presentation: 14 months
- Etiology/pathology: related to constipation, possibly lichen sclerosus et atrophicus
- Course: resolves spontaneously over several months to 1 to 2 years
- Treatment: treating associated constipation may hasten resolution
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Most commonly on vertex
Seventy percent solitary
Rare association with other developmental abnormalities
  - Irregular, large, stellate defects of the scalp associated with trisomy 13 and underlying cerebrovascular malformations
  - Large, bilateral, truncal stellate defects associated with fetus papyraceus (placental infarction after the death of a twin fetus) and gastrointestinal atresia

Etiology/pathology
  - Sporadic or autosomal dominant inheritance with variable penetrance
  - Localized absence of the epidermis, dermis ± subcutis

Course/therapy
  - Protection from trauma and infection
  - Most heal within several months, leaving scar
  - MRI/MRA and radiographs for large scalp defects; abdominal imaging for large truncal defects

MASTOCYTOSIS

Solitary Mastocytoma (Fig. 15-26)

- Presentation
  - One to several yellowish to brown nodule(s)
  - Presents within first 6 months of life
  - Often on trunk, upper extremities, neck
  - Darier’s sign: when stroked, lesion urticates
  - May develop bullae in infancy
  - Spontaneous regression over several years
Widespread spontaneous blistering with erosions and crusts, erythroderma, pruritus

Etiology: systemic involvement in up to 10% of children (greater in adults)

Systemic Mastocytosis

Presentation
- Rare mast cell accumulation in one or more organs other than the skin, especially bone marrow
- The presence of systemic symptoms does not make the diagnosis of systemic mastocytosis
- Invasive diagnostic procedures for
  - Patients with hematologic abnormalities
  - Persistent, localized bone pain and severe gastrointestinal symptoms
  - Evidence of hepatic insufficiency
- Signs and symptoms
  - Flushing
  - Osteoporosis or sclerosis
  - Lymph node involvement
  - Hepatomegaly, splenomegaly, may have increased bleeding with heparin
  - Pancytopenia
  - Heart, kidneys, GI tract, or lung may be affected
  - Mast cell leukemia (rare) portends poor prognosis
  - Other leukemias or lymphomas may develop
- Diagnosis (of cutaneous mastocytosis)/etiology
  - Histology
    - Accumulation of mast cells in skin
    - Dense dermal aggregate of mast cells
    - Mast cells stains: Leder, toluidine blue, Giemsa
  - Mutation of c-kit protooncogene receptor that codes for transmembrane tyrosine kinase (also in piebaldism)
  - Serum tryptase: useful screening test for systemic mastocytosis

Urticaria Pigmentosa

Presentation
- Most common form of mastocytosis
- Develops between 3 and 9 months of life
- Persistent, pruritic red-brown-yellow macules, papules, or nodules
- Lesions most common on the trunk
- Positive Darier’s sign
- Pruritus induced by rubbing, exercise, heat, mast-cell degranulators (EtOH, opiates)

Etiology: Hymenoptera stings or histamine-releasing drugs may rarely cause severe symptoms, anaphylaxis

Treatment
- $H_1$ antagonists for pruritus, urticaria, flushing
- $H_2$ antagonists for gastrointestinal symptoms
- Diarrhea may be controlled with cromolyn (disodium chromoglycate)
- Calcium channel blockers may inhibit mast cell degranulation
- Epi-Pen for patients with a history of anaphylaxis
- Seventy percent of patients markedly improved by adolescence

Diffuse Cutaneous Mastocytosis

Presentation
- Rare
- Presents at birth or within first few weeks of life
- Skin diffusely infiltrated with mast cells
- Leathery, orange-peel appearance (peau d’orange), especially in flexures
- Widespread spontaneous blistering with erosions and crusts, erythroderma, pruritus

Etiology: systemic involvement in up to 10% of children (greater in adults)

Systemic Mastocytosis

Presentation
- Rare mast cell accumulation in one or more organs other than the skin, especially bone marrow
- The presence of systemic symptoms does not make the diagnosis of systemic mastocytosis
- Invasive diagnostic procedures for
  - Patients with hematologic abnormalities
  - Persistent, localized bone pain and severe gastrointestinal symptoms
  - Evidence of hepatic insufficiency
- Signs and symptoms
  - Flushing
  - Osteoporosis or sclerosis
  - Lymph node involvement
  - Hepatomegaly, splenomegaly, may have increased bleeding with heparin
  - Pancytopenia
  - Heart, kidneys, GI tract, or lung may be affected
  - Mast cell leukemia (rare) portends poor prognosis
  - Other leukemias or lymphomas may develop
- Diagnosis (of cutaneous mastocytosis)/etiology
  - Histology
    - Accumulation of mast cells in skin
    - Dense dermal aggregate of mast cells
    - Mast cells stains: Leder, toluidine blue, Giemsa
  - Mutation of c-kit protooncogene receptor that codes for transmembrane tyrosine kinase (also in piebaldism)
  - Serum tryptase: useful screening test for systemic mastocytosis

Questions

1. An 18-month-old boy presents with large, progressively extending, blue-gray patches over his anterior and posterior trunk. What diagnosis should be considered?
   A. Nevus of Ota
   B. Nevus of Ito
   C. Mosaic hypopigmentation
   D. Neurofibromatosis
   E. Lysosomal storage disease

   2. A newborn is found to have multiple, dark blue, non-blanching papules in a generalized distribution. Each of the following diagnoses could be causative, EXCEPT:
A. CMV infection  
B. Rubella  
C. Hemolytic disease of the newborn  
D. Tuberous sclerosis  
E. Hereditary spherocytosis

3. Which of the following features distinguish Finkelstein’s disease from Henoch-Schonlein purpura?  
A. Purpuric skin lesions that are targetoid or “cockade”  
B. Edema of the face and distal extremities  
C. Rapid resolution within 1–3 weeks  
D. Rare renal, joint or gastrointestinal involvement  
E. All of the alone

4. Histologic examination of a nevus anemicus shows:  
A. Presence of melanocytes around blood vessels  
B. Absence of melanocytes  
C. Smooth muscle hamartoma  
D. Collections of mast cells  
E. Normal skin

5. A 6-month-old infant is diagnosed with scabies. The treatment of choice is:  
A. 10% sulfur in petrolatum  
B. Topical 5% permethrin  
C. Topical 1% permethrin  
D. Oral ivermectin  
E. Topical lindane

6. In staphylococcal scaled skin syndrome, the bacterial toxin that is produced cleaves:  
A. Desmoglein 3  
B. Desmoglein 1  
C. Bullous pemphigoid antigen 180  
D. Alpha-6 beta-4 integrin  
E. Plectin

7. In the United States, Gianotti-Crosti syndrome is most commonly due to:  
A. Hepatitis B virus  
B. Group A Streptococcus  
C. Cytomegalovirus (CMV)  
D. Epstein-Barr virus (EBV)  
E. Varicella-zoster virus

8. A 2-day-old, otherwise healthy newborn presents with multiple erythematous papules and pustules. Microscopic examination of the contents of a pustule shows numerous eosinophils. The most likely diagnosis is:  
A. Transient neonatal pustular melanosis  
B. Erythema toxicum neonatorum  
C. Acropustulosis of infancy  
D. Impetigo  
E. Contact dermatitis

9. An 18-month-old girl with a history of constipation presents with a 3-month history of a triangular-shaped, soft, flesh-colored nodule on her perineal median raphe. The most likely diagnosis is:  
A. Verruca  
B. Histiocytosis  
C. Perianal pyramidal protrusion  
D. Lichen sclerosus et atrophicus  
E. Pseudoverrucous papules and nodules

10. A 4-year-old male presents with a linear clustering of verrucous, brown papules on his posterior leg that have been present since birth. The most likely diagnosis is:  
A. Nevus sebaceous of Jadassohn  
B. Lichen striatus  
C. Linear epidermal nevus  
D. Flat warts  
E. Incontinentia pigmenti

Answers

1. E. Extensive Mongolian spots (dermal melanocytosis) with dorsal/ventral distribution, indistinct borders, and persistent and/or “progressive” behavior may be a sign of underlying lysosomal storage disease (most commonly GM1 gangliosidosis type 1 and Hurler disease).

2. D. Multiple, dark blue to magenta, small, non-blanching papules and macules, present at birth or by the first day of life, are a sign of extramedullary hematopoiesis. This is associated with congenital infections (TORCH viruses, most commonly cytomegalovirus), hemolytic disease of the newborn, hereditary spherocytosis, and twin-twin transfusion syndrome. It is NOT associated with tuberous sclerosis.

3. E. Finkelstein’s disease is an acute form of leukocytoclastic vasculitis. It affects children under 2 years of age, has a rapid onset; often follows a preceding infection, and is accompanied by fever, edema, and targetoid purpuric lesions on the face, ears, and distal extremities. Children generally appear well despite alarming appearance of skin lesions. Renal, joint, and GI involvement is exceptional (important difference from adult Henoch-Schonlein purpura).

4. E. Histologic examination of a nevus anemicus shows normal skin.
5. B. Topical 5% permethrin is the treatment of choice (approved down to 2 months of age). For newborn infants or pregnant/nursing women, 6% to 10% sulfur in petrolatum is the recommended treatment (permethrin is pregnancy category B).

6. B. Staphylococcal scalded skin syndrome occurs due to the epidermolytic toxin of *Staphylococcus* phage group II which cleaves desmoglein 1.

7. D. Gianotti-Crosti syndrome is associated with viral infections: Epstein-Barr virus (most common association in the United States), hepatitis B virus, cytomegalovirus (CMV), and respiratory syncitial virus (RSV).

8. B. Erythema toxicum is a common newborn rash, affecting half of full-term newborns. It appears as a “flea-bitten rash” of few to hundreds of erythematosus macules, wheals, papules, and pustules. Microscopic examination of the contents of a pustule will show numerous eosinophils. It occurs in the first 24 to 48 hours of life and resolves during the first 1–2 weeks of life.

9. C. Perianal pyramidal protrusion is a triangular-shaped, flesh-colored to erythematous nodule on the perineal median raphe, anterior to the anus. More than 90% of cases occur in female infants. The average age at presentation is 14 months. It is related to constipation and possibly lichen sclerosus et atrophicus. Perianal pyramidal protrusion resolves spontaneously over several months to 1 to 2 years. Treating the associated constipation may hasten resolution.

10. C. Linear epidermal nevus contains verrucous pink to brown papules following Blaschko’s lines. It is generally present at birth or within first year of life, but sometimes later in childhood or adolescence.

**REFERENCES**


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PARASITE

- An organism that lives on or within another organism (host)
- A parasite causes harm to the host. This distinguishes parasitism from commensalism, in which the host derives no benefit but is not injured, and mutualism, where the relationship benefits both organisms
- Host, in addition to providing a steady food source, provides warmth and shelter
- Definitive host: parasite becomes sexually mature and undergoes reproduction
- Reservoir hosts are those in which parasites that are pathogenic to other animals or to humans
- Vector: agent by which a parasite is transmitted to the host (e.g., arthropod, mollusk)

ARTHROPODA

- Bites usually result in localized, cutaneous reactions and pruritus
- Some of these organisms are medically important: Fleas, lice, and ticks can transmit lethal epidemic disorders
- Many of these vector-transmitted diseases are endemic in various regions of the world
- Four classes of arthropods are of dermatologic interest and are covered in this chapter:
  - Chilopoda: including centipedes
  - Diplopoda: including millipedes
  - Insecta: including caterpillars, moths, bedbugs, lice, flies, mosquitoes, beetles, bees, wasps, hornets, fire ants, and fleas
  - Arachnida: including ticks, mites, scorpions, and spiders
- Organisms from the arthropod classes Arachnida and Insecta have a hard-jointed exoskeleton and paired, jointed legs
- Class Insecta: a group of organisms with six legs and three body segments: head, thorax, and abdomen. Includes the following orders:
  - Siphonaptera: fleas
  - Anoplura: head and body lice
  - Pthiridae: crab louse
  - Diptera: two-winged flies, mosquitoes, midges
  - Hemiptera: true bugs
  - Lepidoptera: butterflies, moths, and their caterpillars
  - Hymenoptera: ants, wasps and bees
- Class Arachnida: a group of organisms with eight legs and two body segments: cephalothorax and abdomen
  - Ixodidae: hard ticks
  - Argasidae: soft ticks
  - Araneae: spiders
- Centipedes and millipedes

INSECTA

Siphonaptera (Fleas)

- Wingless, laterally compressed insects with a hard, shiny integument
- The body has three regions: head, thorax, and abdomen
- Mouthparts are modified (paired maxillary palpi) for piercing and sucking
- Survive months without feeding
- Order Siphonaptera contains two flea families of medical importance
  - Pulicidae: (human, cat, dog, and bird fleas)
  - Sarcopsyllidae (also called Tungidae): the sand flea
- Fleas jump, on average, about 20 cm
One flea can bite two to three times over a small area. Bites produce irregular, pruritic, red wheals up to 1 cm in diameter. Patients may present with a surrounding halo with a central papule, vesicle, or bulla or with hemorrhagic macules, papules, vesicles, or bullae.

1. *Pulex irritans* (human flea) (Fig. 16-1)
   - Farms, urban areas, predominant flea on dogs in portions of the Carolinas
2. *Tunga penetrans* (chigoe flea)
   - Tropical and subtropical regions of North and South America, Africa
   - Intense itching and local inflammation
   - Causes tungiasis
     - Female sand flea, which burrows into human skin at the point of contact, usually the feet
     - Head is down into the upper dermis feeding from blood vessels
     - Caudal tip of the abdomen is at the skin surface
     - Nodule (usually on the foot) that slowly enlarges over a few weeks
   - Treatment
     - Occlusive petrolatum suffocates the organism.
     - Lindane, dimethyl phthalate, or dimethyl carbamate
3. *Xenopsylla cheopis* (Oriental rat flea)
   - Plague (*Yersinia pestis*)
   - Endemic (murine) typhus (*Rickettsia typhi*)
4. Cat flea (*Ctenocephalides felis*)
   - Endemic (murine) typhus (*Rickettsia felis*)

The will die of starvation if kept off the body for more than 10 days. They are also killed by washing in water at 53.5°C for 5 minutes. Life span of a louse is about 30 to 45 days.

1. *Pediculus humanus corporis* (body louse)
   - Up to 5 mm long
   - Vector for
     - Epidemic typhus (*Rickettsia prowazekii*)
     - Trench fever, bacillary angiomatosis, bacillary peliosis (*Bartonella quintana*)
     - Relapsing fever (*Borrelia recurrentis, Borrelia duttoni*)
   - Crowded, unsanitary conditions
   - Lives in clothing and moves to body to feed
   - Pyoderma involving areas covered by clothing, most notably the trunk, axillae, and groin; erythematous macules, papules, and wheals, as well as excoriations, also may be seen
   - Treatment: malathion 1% powder, permethrin spray
2. *Pediculus humanus capitus* (head louse) (Fig. 16-2)
   - Whitish in color and up to 3 mm long
   - Confined to the scalp
   - Lice and their eggs can withstand vigorous washing and combing
   - Nits: cementing of white eggs to the hair; usually found in the warm areas of the scalp such as behind the ears and on the posterior neck
   - Eggs hatch in approximately 7 to 9 days
   - Treatment: requires that both the adult lice and the nits be killed

**Anoplura**

**Pediculidae**

After attaching to the skin, these flattened, wingless insects feed on human blood and can cause intense itching.
All require a blood meal at some time in their development
- Bites can manifest as immediate urticarial papules, delayed erythematous papules, or both

**FLIES**
- Number of infectious diseases can be transmitted by biting flies
- A variety of flies commonly bite humans
- Common housefly does not bite but rather feeds on the surface of the skin
- Wound myiasis: eggs are deposited on an open wound
- Furuncular myiasis: solitary furuncle-like lesions often transferred by a mosquito vector
- Plaque myiasis: grouped boil-like lesions caused by eggs laid on wet laundry

**DERMATobia hominis (Botfly)**
- Most common cause of furuncular myiasis
- Occurs when fly larvae (maggots) invade tissue
- Raised, erythematous papule develops at the site of the bite, most frequently on the distal extremity or scalp
- Enlarges to become an indurated nodule with a central punctum, which is the breathing hole for the larva
- Treatment
  - Surgical excision; occlusion

**Sand Flies (Phlebotomus and Lutzomyia)**
- Vectors for bartonellosis (Bartonella bacilliformis-Oroya fever, Carrion’s disease) and leishmaniasis
- Leishmaniasis
- Leishmania: protozoan infection
- Leishmania transform to the promastigote (or flagellate) form in the gut of the vector
  - Promastigote is a slender organism with a flagellum
  - After replicating, the promastigotes migrate to the sandfly’s proboscis, from which they are regurgitated into the next host as the sandfly feeds
- Located within reticuloendothelial cells of infected tissues, Leishmania exist in an amastigote (nonflagellate) form
- Vector: sand fly (Phlebotomus and Lutzomyia species)
- Clinical
  - Cutaneous
    - Nontender, firm, red papule at bite
    - Lesion widens with central ulceration, serous crusting, and granulomas
    - Lesions may be wet or dry and become fibrotic or hyperkeratotic with healing

**Pthiridae**
- *Pthirus pubis* (Fig. 16-3)
  - Pubic louse, crab louse
  - Short, broad body with rather stout claws on the middle and hind legs
  - Reddish brown in color
  - Often sexually transmitted
  - Rarely involves facial (eyelashes), chest, or axillary hair
  - Patients can remain asymptomatic for up to a month before pruritus develops; nits, similar to those in pediculosis capitis, are seen
  - Blue macules (maculae ceruleae) are often seen on the surrounding skin and are believed to be produced by louse saliva acting on blood products
  - Treatment: lotions or shampoos containing 1% lindane, 0.3% pyrethrins, or 5% permethrin, asphyxiating agents
  - Infestation of the eyelashes: petrolatum or fluoroscein

**Diptera**
- Two-winged, biting insects
Trypanosomes are ingested during a blood meal by the tsetse fly from a human reservoir, develop into epimastigotes, and are reinfected into human hosts. Extensive antigenic variation of parasite surface glycoproteins.

- West African (T. brucei gambiense)
  - Slow progression
- East African (T. brucei rhodesiense)
  - Rapid progression (within a week)

**Stage 1**
- Chancre
- Hypersensitivity reaction: urticaria, pruritus, facial edema, fever, arthralgias, Winterbottom’s sign (posterior cervical lymphadenopathy)
- Kerandel’s sign: delayed sensation to pain or a sensation of hyperesthesia

**Stage 2: central nervous system (CNS) changes**
- Headaches, behavioral changes, seizures in children

**Laboratory studies**
- Anemia, hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), thrombocytopenia, and hypoalbuminemia
- Wet smear of unstained blood, bone marrow, spinal fluid, skin lesions: parasite is visualized
- Card agglutination test for trypanosomiasis (CATT)

**Treatment**
- Early stages: suramin, pentamidine
- CNS stage: intravenous melarsoprol B, eflornithine

**CHRYSOPS (DEER FLY)**
- Vector for loaisis (see below)

**MOSQUITOES**
- Belong to the family Culicidae
- Delicate winged insects with long proboscises and long, thin legs
- Require water to mature through the larval and pupal stages
- Can be the vector for filariasis, yellow fever, dengue fever, encephalitis and malaria
- Cutaneous reactions to bites include urticarial wheals, delayed papules, bullous lesions, hemorrhagic necrotic lesions, excoriations, eczematous patches, and granulomatous nodules

**CULEX**
- Vector for
  - Japanese encephalitis
  - Murray Valley encephalitis virus
  - Rift Valley fever
  - Ross River virus
  - Sindbis virus
Transform into amastigotes after ingestion by macrophages; *T. cruzi* burst from the macrophages as trypomastigotes and disseminate widely to invade most human tissues

Lymphatic spread then carries the organism to regional lymph nodes

Chagoma: red nodule at site of bite; lasts only a few days to a couple of weeks

Ramaña’s sign: bite near the eye causes unilateral periorbital conjunctivitis and edema

Hematogenous dissemination: acute phase with fever to 104°F, vomiting, diarrhea, cough, hepatosplenomegaly, edema, myocarditis, seizures, and meningoencephalitis

Latent phase: myocardial heart disease, with fibrosis, conduction defects

Cardiac involvement: congestive heart failure

Gastrointestinal system affected: dysphagia and abdominal pain, constipation secondary to megacolon (owing to destruction of the parasympathetic ganglion)

Sequelae of myocardial damage, megacolon, megaesophagus

Diagnosis: parasites are relatively numerous initially and easily demonstrable on peripheral blood smear

Treatment: benzimidazole, nifurtimox

Lepidoptera (Caterpillars)

1. *Automeris io* (family Saturniidae)
   - Io moth
   - East of the Rocky Mountains from Canada to Mexico
   - Feed on deciduous (broadleaf) trees and herbaceous plants
   - Yellow-green with red and white lateral stripes
   - Urticating spines

2. *Megalopyge opercularis* (puss caterpillar, asp caterpillar) (Fig. 16-4)
   - Broad and flat
   - Dense covering of long, silky, gray to reddish brown hairs
   - Urticating spines dispersed among the hairs

3. *Sibine stimulea* (saddleback caterpillar)
   - Brown at both ends
   - Green around the middle “saddle blanket”
   - Purple-brown oval-spot “saddle”
   - Urticating spines along the sides and at the front and rear of the body

4. Hagmoth: brown with nine pairs of variable-length lateral processes with urticating hairs

5. Buck moth
   - Purple-black with a reddish head
   - Pale-yellow dots scattered over the body with reddish to black branches
   - Stinging spines arising from tubercles
Chapter 16  CUTANEOUS INFESTATIONS

Solenopsis
- Alkaloid venom contains phospholipase and hyalurinidase
- May be red or black and live in ground colonies
- Sting by first biting the victim with their powerful set of pincer jaws and then swiveling and stinging in a circular pattern
- Pustules, burning itch

2. Vespidae: yellowjackets, hornets, paper wasps
- Paper wasps build hives under the eaves of buildings
- Yellow jackets are ground-nesting
- Hornets reside in shrubs and trees

3. Apoidea family
- Bumble bees and honey bees
- Honeybees feed on flowering plants
- Stinger contains a barb, causing it to be left on the victim along with the venom sac
- This act eviscerates and kills the bee

ARACHNIDA

- Adult forms have four pairs of legs, six-legged larvae common among ticks and mites; may cause human injury by biting, burrowing in, and feeding on skin, stinging, and delivering toxic venom

Ticks
- Tick-bite alopecia
- Wells’ syndrome, consisting of erythematosus, edematous plaques composed histologically of eosinophilic granulomatous dermatitis
- Systemic toxic venom
- From multiple stings
- Constitutional symptoms
- Systemic allergic
- Immunoglobulin (Ig) E antibodies cause degranulation and the release of vasoactive substances: urticaria and angioedema
- Other: serum sickness, acute renal failure, possible Guillain-Barré syndrome

Suborder: Apocrita—Ants, Wasps and Bees

1. Formicidae: ants

Most ticks fast for long periods because they cannot live on vegetable matter; blood meal is acquired mostly by chance.

Feeding is usually complete within 6 to 7 days, but the tick can remain attached to the host for an unspecified period.

Ticks require a blood meal before they can lay eggs.

Body of mites and ticks:
- Divided into two regions
  - Anterior: cephalothorax (or prosoma)
  - Posterior: abdomen (or opisthosoma)

**Mites**

*Cheyletiella*
- “Walking dandruff”: caused by movement of mite under scales
- Live on keratin layer of small mammals (dogs, cats, rabbits)
- Pruritic dermatitis in humans who handle pets

*Liponyssoides (Formerly Allodermanyssus) sanguineus*
- House mouse mite
- Rickettsial pox (*Rickettsia akari*)

*Ornithonyssus sylviarum*
- Found in birds and domestic fowl
- Bird handlers are bitten most commonly

*Dermatophagoides (Family Pyroglyphidae)*
- House dust mite
- Tiny, translucent mites, generally less than 0.2 mm long
- Cause severe asthma and other allergic complaints in humans
- Humidity levels below 60% appear to support fewer mites

**Family Demodicidae**

*Demodex folliculorum (Fig. 16-5)*
- Elongate, microscopic mites
- Live in hair follicles and sebaceous glands
- Generally asymptomatic
- May cause folliculitis
- Associated with rosacea

**Harvest Mites (Family Trombidiidae)**

*Trombiculidae (Chigger, “Red Mite”)*
- Only the six-legged larval form parasitizes other animals
- Attach to a host, feed for 2 to 3 days, molt to the nymphal stage, and then leave the host
Skin lesions develop 3 to 24 hours later when an allergic reaction to mite saliva develops
- Pruritic red papules grouped about the waist, thighs, and legs
- Can persist for several weeks
- Eutrombicula alfredugesi most common variety in the United States
- Neotrombicula autumnalis most common variety in Europe
- Scrub typhus (Rickettsia tsutsugamushi)

Scabies or Itch Mites (Family Sarcoptidae)

**Sarcoptes scabei (Fig. 16-6)**
- Globular, semitranslucent mites, less than 0.3 mm long
- Adult mites copulate on the skin, after which the female will burrow, laying her eggs along the way
- Six-legged larvae hatch and take 10 to 14 days before becoming adults
- They survive off the human body for only 2 to 3 days
- Symptoms take 30 days after an immune response develops to the mites or their excrement (scybala)
- Spread by close personal contact
- Hands and wrists are affected most often
- Burrows, which are produced by the adult female mite, and erythematous papules
- In adult patients, the scalp and face are uninvolved
- Pruritus of scabies generally is severe and most noticeable at night
- Diagnosis: mites, eggs, larvae, or scybala on microscopic examination of lesional skin scrapings
- Nodular scabies
  - Erythematous, firm nodules that persist for weeks to months after treatment
- Norwegian scabies
  - Seen in immunocompromised or debilitated patients

Thick, scaling, crusted plaques that are found most commonly on the hands, feet, and scalp but may be generalized in distribution
- Lesions contain thousands of mites

**Treatment**
- 5% permethrin
- Lindane: avoid in young children and pregnant women owing to reports of neurotoxicity
- 5% to 10% precipitated sulfur in petrolatum
- 25% crotamiton
- Oral ivermectin
- Nodular scabies: topical or intralesional injection of a corticosteroid

Hard or Shield Ticks (Family Ixodidae)

- Wingless arthropods
- Eight-legged as adults, six-legged larva
- Flattened dorsoventrally
- Often teardrop-shaped from dorsal view
- Scutum (shield) on the dorsal surface
- **1. Ixodes tick**
  - *I. scapularis*: eastern United States
  - *I. pacificus*: in California
  - *I. ricinus*: in Europe
  - Vector for
    - Lyme disease (*Borrelia burgdorferi*)
    - Babesiosis
    - Anaplasmosis
- **2. Amblyoma americanum** (lone star tick) (Fig. 16-7)
  - Prominent white dot on the back of the adult female
  - Primarily found in the southern United States, although the range is expanding
  - Vector for
    - Rocky Mountain spotted fever (*Rickettsia rickettsii*)
    - Ehrlichiosis (*Ehrlichia chaffeensis*)

**Figure 16-6** Sarcoptes scabei. (Reprinted with permission from Wolff and Johnson: Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 6th Ed. New York: McGraw-Hill; 2009.)
Adults are generally brown but become slate gray when engorged
- Commonly involved with tick paralysis
- Female: dark reddish brown with a white shield covering the front third of the body
- Male: grayish-white shield area on top of the body
- Tick paralysis
- *D. variabilis*
  - Dog tick
  - Eastern United States
  - Tick paralysis

**Soft or Leathery Ticks (Family Argasidae)**
- *Ornithodoros hermsi, O. parkeri, O. turicata*
  - Light gray and leathery in appearance
  - Mouthparts are hidden underneath the body
  - Transmits relapsing fever: *Borrelia duttoni, B. recurrentis*

**Araneae (Spiders)**
- All spiders have a cephalothorax from which extend eight legs and an abdomen
- A pair of jaws (chelicerae) are found at the anterior end of the cephalothorax
- Jaws terminate in sharp, chitinized fangs from which venom is ejected

**Lactrodectus mactans (Black Widow) (Fig. 16-9)**
- Eastern and central regions of the United States
- Black with a globose abdomen that has the characteristic red hourglass-like marking on the ventral surface
Phospholipase (sphingomyelinase D) causes platelet aggregation, thrombosis, and massive neutrophil infiltration.

Initial bite is often painless and unnoticed by the patient; central papule and associated erythema

Flag sign
- Central blue-gray area due to thrombosis
- Blanched halo from arterial spasm
- A large surrounding area of reactive erythema

Systemic: hematuria, anemia, constitutional symptoms, rash, cyanosis, and severe intravascular hemolysis

Treatment
- Tetanus toxoid
- Rest, ice and elevation
- Antibiotics if superficial infection develops
- Data are mixed concerning triamcinolone and dapsone. A delay of even 1 hour may negate any effect of dapsone

Scorpions
- Large arachnids with an elongated abdomen that terminates in a stinger
- Abdominal glands that release both neurotoxic and hemolytic venom into the stinger
- Nocturnal and hide during the daytime in dark places
- Pain and swelling at the site of sting
- Neurotoxin can result in: localized numbness, fasciculation, lacrimation, salivation, profuse sweating, urinary urgency, nausea, tongue paresthesia, restlessness, convulsions, and an increase in extraocular muscle activity
- Centruroides sculpturatus most toxic in United States, although it rarely results in death
- Highly dangerous scorpions include Parabuthus, Uroplectes and Tityus species
- Treatment
  - Remove the stinger
  - Cool the site with ice; antivenin
  - Barbiturates or diazepam for the central nervous system hyperactivity
  - Atropine for cholinergic side effects of the neurotoxin

Centipedes and Millipedes

American Centipedes
- Slender, segmented body that ranges in color from yellow to green to brown or black and may vary in length from 1 to 30 cm
SOIL-MEDIATED HELMINTHIC INFECTIONS

- Nocturnal carnivores and prefer a dark, moist environment like that found under rocks and logs
- *Scutigera* species
  - Found in the eastern United States
  - Does not sting humans
- *Scolopendra* species
  - Western United States and Hawaii
  - Can inflict a painful sting
  - Immediate reaction consists of local burning pain
  - Chevron-shaped bite
  - Occasionally, local necrosis, regional lymphangitis, and lymphadenopathy
- Treatment
  - Cleanse the wound
  - Inject a local anesthetic into the wound
  - Tetanus prophylaxis
  - Systemic antihistamines

**Millipedes**

- Multisegmented, with a hard, often brightly colored exoskeleton
- Nocturnal vegetarians that prefer dark, moist environments
- When disturbed, some millipedes will coil into a tight spiral and then secrete a toxic liquid from repugnatorial glands located on the sides of each segment
- Causes an immediate burning sensation when it contacts human skin
- Skin then becomes yellow-brown and in 24 hours develops intense erythema and often vesiculation
- Treatment: immediate lavage of the area with alcohol or water

**PROTOZOA**

**Cutaneous Amebiasis**

- *Entamoeba histolytica*
- Humans are the major reservoir
- Clinical presentation includes an acute dysenteric form and a less symptomatic nondysenteric intestinal form
- Life cycle: cysts travel to the small intestine after ingestion from fecally contaminated food or water
- Trophozoites are released
- They reencyst and produce asymptomatic infection (resolves spontaneously within 12 months) or parasite causes symptomatic amebiasis
- Intestinal disease: acute proctocolitis (dysentery)
- Extraintestinal disease: brain and liver amebic abscesses, peritonitis, pericarditis, cutaneous lesions of amebiasis seem to be extremely rare (direct extension of intestinal disease): with painful ulcerations that may enlarge rapidly
- Diagnosis: indirect hemagglutination, immunofluorescence, and ELISAs
- Treatment: metronidazole, iodoquinol, paromomycin

**HELMINTHIC INFECTIONS**

- *Helminth* is derived from the Greek word *helmins*, meaning “worm”
- Categorized as
  - Annelids (i.e., phylum Annelida, the segmented worms)
  - Nematodes (i.e., phylum Nematoda, the roundworms)
  - Platyhelminths (i.e., phylum Platyhelminthes, the flatworms)
  - Trematodes (i.e., flukes) and cestodes (i.e., tapeworms)

**SOIL-MEDIATED HELMINTHIC INFECTIONS**

**NEMATODES (ROUNDWORMS)**

- Hookworm: *Ancylostoma* and *Necator*
- Strongyloidiasis
- Ascariasis
- Enterobiasis
- Trichinosis
- Dracunculiasis
- Filariasis: loiasis, onchocerciasis
- Hookworms: caused by the roundworms

**ANCYlostOMA DUODENALe, NECATOR AMERICANUS**

- Ground itch
- Life cycle: female worms, residing in the host’s small intestine, release eggs that are passed in the feces
- Larvae in the soil penetrate foot and migrate to lungs through the venous system
- Larvae are then coughed up and swallowed, and they end up in the intestine and mature into adults
- Pruritic, erythematous, edematous, linear, threadlike tracts marking larval migration in the skin
- Gastrointestinal bleeding, iron-deficiency anemia, hypoproteinemia
- Treatment: mebendazole, albendazole

**CUTANEOUS LARVA MIGRANS (CREEPING ERUPTION) (FIG. 16-11)**

- *Ancylostoma braziliensis*, hookworm of wild and domestic dogs and cats
- Most common cause of cutaneous larva migrans; human is a dead-end host
• Larvae can penetrate skin of the host (quick migration rate of 5 to 10 cm/h) and then penetrate basement membrane to affect lungs and the gastrointestinal tract
• Larvae subsequently are swallowed and reach the small intestine
• Intense pruritus, purpura, serpentine urticarial streaks
• Autoinfection: transformation of noninfective larvae (rhabditiform) into infective larvae (filariform)
• Chronic strongyloidiasis
• Serpiginous wheals beginning perianally and extending to the buttocks, upper thighs, and abdomen
• Hemorrhagic pneumonia can result
• Stool for ova and parasites
• Enterotest (string test) or duodenal aspiration to examine duodenal fluid
• Blood cultures
• Enzyme immunoassay (EIA), indirect fluorescent antibody (IFA)
• Chest radiograph to reveal possible patchy alveolar infiltrate
• Sputum examination
• Loefler’s syndrome: eosinophilia, pneumonitis
• Treatment: thiobendazole, albendazole, ivermectin

**ASCARIASIS**

*Ascaris lumbricoides*

• Adult worms live in the small intestine; eggs are laid and then passed out in the feces
• Eggs may remain viable in soil up to 17 months
• Larvae develop within the eggs
• Eggs are ingested or inhaled from soil; larvae hatch and move to heart, lungs, and pharynx
• Swallowed larvae mature into adults in intestine
• Urticaria
• Gastrointestinal symptoms/obstruction
• Cough, dyspnea, asthma, and chest pain
• Stool examination for ova and parasites
• Treatment: mebendazole, pyrantel pamoate

**ENTEROBIASIS (PINWORM DISEASE)**

*Enterobius vermicularis*

• Most common helminth infection in industrialized countries
• After ingestion, eggs usually hatch in the duodenum within 6 hours
• Female worm migrates to the rectum after copulation and, if not expelled during defecation, migrates to the perineum (often at night)
• Pruritus ani, bruxism
• Diagnosis
  • Transparent tape is pressed against the perineum at night

**STRONGYLOIDES (LARVA CURRENS, “RACING LARVA”)**

*Strongyloides stercoralis* (known as threadworm)

• Nematodes live in the small intestine
• Eggs hatch into larvae (rhabditiform), which are passed in the feces
• Eggs are passed from animal feces into warm, moist, sandy soil, where the larvae hatch
• Larva penetrate skin directly but cannot penetrate basement membrane
• Larvae migrate slowly (2 cm/day) in skin, lack the ability to invade further, and complete their life cycle
• Produce raised, threadlike, serpiginous, pruritic, erythematos tracks
• Treatment: topical thiabendazole, ivermectin, albendazole

SOIL-MEDIATED HELMINTHIC INFECTIONS

• Identify eggs under the low-power lens of microscope (Fig. 16-12)
• Treatment: pyrantel and mebendazole

TRICHINOSIS
• *Trichinella spiralis*
• Larval cysts ingested from undercooked meat (usually pork)
• Acidity and enzymatic activity of the human digestive system disrupt the cyst, releasing large numbers of newborn larvae that penetrate the gut wall, enter the systemic circulation, and migrate to various tissues
• Larvae usually persist only in striated skeletal muscle cells, transformed into nurse cells
• Calcified cysts in muscle, elevated muscle enzymes
• Fever, myalgias, and periorbital edema (increased interstitial fluid)
• Vasculitis: splinter hemorrhages in nails and eyes
• Diagnosis
  • Enzyme immunoassay (EIA) or the bentonite flocculation (BF) test
  • Elevated creatine kinase (CK) and lactate dehydrogenase (LDH)
  • Stool examination: Charcot-Leyden crystals from eosinophils may be found in stools
• Treatment
  • Trichinosis is usually a self-limited illness
  • Prednisone
  • Mebendazole and albendazole
  • Proper cooking of meat is the most effective method to prevent infection

FIGURE 16-12 Enterobius eggs under the microscope. (From Freedberg IM et al. *Fitzpatrick’s Dermatology in General Medicine, 6th Ed. New York: McGraw-Hill; 2003, p. 2239.)

DRACUNCULIASIS
• *Dracunculus medinesis*, guinea fire worm; nematode
• Ingested larvae reside in an intermediate host, a tiny freshwater crustacean or copepod
• Migrates from the gastrointestinal tract to a location in the lower extremity (most commonly the foot), causing a bulla that ruptures to release the larvae back into water
• Clinical: presence of the adult worm in the subcutaneous tissue, usually lower extremity
• Constitutional symptoms
• Treatment
  • Slowly wind worm around stick
  • Metronidazole, thiabendazole may case aberrant migration of worms, and should be used with caution.

FILARIAE
• Eight species of roundworm belonging to the family Filarioidea develop to adulthood in humans
• Larvae or microfilariae are ingested by a feeding insect vector
• Larvae are then inoculated into the vertebral host for the final stages of development
• Cutaneous group (listed below)
  • *Loa loa*
  • *Onchocerca volvulus*
  • *Mansonella streptocerca*
• Lymphatic group
  • *Wuchereria bancrofti*: causes Bancroftian filariasis
    – Genital disease: edema of scrotal skin, funiculitis, epididymitis, orchitis, and hydrocele
    – Distinctive lymphangitis of the arms or legs characterized by a unique retrograde spread or extension
    – Starting in a single node, erythematous patches of subcutaneous edema or diffuse erythema and edema develop and progress distally
    – Treatment: diethylcarbamazine, ivermectin
  • *Brugia malayi*: causes Malayan filariasis
  • *Brugia timori*: causes Timorian filariasis
    – Clinical manifestations of Malayan filariasis and Timorian filariasis:
    – Axillary or inguinal lymphadenitis, lymphangitis, and fever are common
    – Lymphatic abscesses and resulting scarring
• Body cavity group
  • *Mansonella streptocerca*: causes streptocerciasis
  • Central and West Africa
  • Transmitted by the midge *Culicoides grahami*
  • Adult worms are found in the dermis of the patient’s upper trunk
  • Microfilariae are found in the dermis and lymph nodes
  • Treatment: diethylcarbamazine

TRICHINOSIS
• *Trichinella spiralis*
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• Acidity and enzymatic activity of the human digestive system disrupt the cyst, releasing large numbers of newborn larvae that penetrate the gut wall, enter the systemic circulation, and migrate to various tissues
• Larvae usually persist only in striated skeletal muscle cells, transformed into nurse cells
• Calcified cysts in muscle, elevated muscle enzymes
• Fever, myalgias, and periorbital edema (increased interstitial fluid)
• Vasculitis: splinter hemorrhages in nails and eyes
• Diagnosis
  • Enzyme immunoassay (EIA) or the bentonite flocculation (BF) test
  • Elevated creatine kinase (CK) and lactate dehydrogenase (LDH)
  • Stool examination: Charcot-Leyden crystals from eosinophils may be found in stools
• Treatment
  • Trichinosis is usually a self-limited illness
  • Prednisone
  • Mebendazole and albendazole
  • Proper cooking of meat is the most effective method to prevent infection

FIGURE 16-12 Enterobius eggs under the microscope. (From Freedberg IM et al. *Fitzpatrick’s Dermatology in General Medicine, 6th Ed. New York: McGraw-Hill; 2003, p. 2239.)
TOXOCARIASIS
- Visceral larva migrans
- Caused by the roundworm of the dog and cat: *Toxocara canis* and *T. catis*
- Eggs ingested from soil; larvae penetrate bowel and lodge in organs and blood vessels
- Hemorrhage, necrosis, urticaria
- Ocular larva migrans: penetrating larva can become encysted, leading to the formation of a large granuloma

GNATHOSTOMIASIS (WANDERING SWELLING, YANGTSE RIVER EDEMA)
- *Gnathostoma spinigerum*
- Humans eat fish that contain larvae, or larvae penetrate the skin directly
- Migrating erythematous swelling, pain, pruritus
- Treatment: surgery, ivermectin, albendazole

TREMATODES (FLUKES)
- Phylum Platyhelminthes contains the dorsoventrally flattened worms
- Schistosomiasis (bilharziasis)
- Life cycle
  - Eggs passed in urine (*S. haematobium*) or feces (*S. japonicum* and *S. mansoni*), hatch in water
  - From eggs, miracidia hatch into the water, where they penetrate into snails; in the snails they develop into cercariea that penetrate the host skin
  - Enter the portal venous system of the liver and travel to heart, lungs, and finally the bladder or the mesenteric vessels
- Schistosomiasis organisms (blood flukes)
  - *S. mansoni* – South America
    - Portal hypertension, found in large intestine and liver, eggs shed in stool
    - Location of spine on ova: lateral
  - *S. japonicum* – Asia
    - Portal hypertension; found in small intestine and liver; eggs shed in stool
    - Location of spine on ova: no spine
  - *S. haematobium* – Africa, Middle East
    - Found in bladder, pelvic/urogenital venules; eggs shed in urine
    - Location of spine on ova: apical
- Clinical
  - Cercarial dermatitis (swimmer’s itch):
    - Pruritus, dermatitis
    - Skin exposure to fresh or salt water
    - Macular eruption, pruritic
    - Spares clothing-covered skin
Sparganosis
- *Spirometra* species
- Larvae from undercooked fish are ingested
- Enlarging subcutaneous nodule
- Treatment: surgical excision

Coenurosis
- *Taenia* species (multiceps, serialis, brauni)
- Eggs in host feces (dogs, fox, wolf)
- Ingested by herbivores (cows) and penetrate bowel to enter muscle, brain, and eyes, where they develop into larvae
- Seizures, mass lesions, subcutaneous nodules
- Treatment: surgical excision

Reptiles

Snakes
- United States: rattlesnake, cottonmouth moccasin, and copperhead (family *Crotalidae*) account for the vast majority of bites

Elapidae Family
- Coral snake
  - Round eyes
  - Red and yellow or white bands (“red on yellow kills a fellow” helps distinguish from milk snake)
  - Neurotoxic
  - Muscle fasciculations, later flaccid paralysis
- Viperidae family (pit viper)
  - Copperhead, rattlesnake, cottonmouth (water moccasin)
  - Triangular head distinct from the body
  - Elliptical “cat’s eye” pupils
  - Venom with hydrolases; anticoagulant in the venom causes hemolysis and capillary leakage
  - Pain, edema, ecchymosis, vesiculation, petechiae, and tissue necrosis can develop at the site of the bite
  - Damage to vascular endothelium, hypotension

Questions
1. Endemic typhus is carried by:
   A. *Ctenocephalides felis*
   B. *Tunga penetrans*
   C. *Pulex irritans*
   D. *Xenopsylla cheopis*
   E. Both A and D
2. Body lice carry:
   A. Epidemic typhus
   B. Trench fever
   C. Relapsing fever
   D. Bacillary angiomatosis
   E. All of the above

3. Leishmaniasis is carried by:
   A. Sandflies
   B. Mosquitoes
   C. Deer flies
   D. Ticks
   E. Mites

4. The first stage of sleeping sickness is characterized by a (an):
   A. Chancre
   B. Buboe
   C. Lymphadenitis
   D. Persistent fever
   E. Enlargement of the spleen

5. Mosquitoes carry:
   A. Filariasis
   B. Yellow fever
   C. Dengue
   D. Encephalitis
   E. All of the above

6. Reduviid bugs transmit:
   A. Chagas disease
   B. Leishmaniasis
   C. Dengue
   D. Malaria
   E. Sleeping sickness

7. Tick paralysis in North America is most closely associated with:
   A. Dermacentor ticks
   B. Rhipicephalus ticks
   C. Ornithodoros ticks
   D. Amblyomma ticks
   E. Ixodes ticks

8. *Liponyssoides* mites carry:
   A. Rickettsial pox
   B. Typhus
   C. Typhoid
   D. Rocky Mountain spotted fever
   E. Relapsing fever

9. *Cheyletiella* mites are associated with:
   A. Walking dandruff in dogs
   B. Mange in dogs
   C. Alopecia in hedgehogs
   D. Cat scratch disease
   E. Endemic typhus

10. *Ornithodoros* ticks are associated with:
    A. Relapsing fever
    B. Rickettsial pox
    C. Typhoid
    D. Typhus
    E. Colorado tick fever

**Answers**

1. E. While *Xenopsylla cheopis* has been considered the classic vector of endemic typhus, in recent years *Ctenocephalides felis* has been recognized as a major vector. The disease has emerged as more common in South Texas, where the vector is *C. felis* and oppossums serve as a disease reservoir.

2. E. While head and pubic lice are not clearly linked to the spread of disease, body lice are important disease vectors, especially in refugee populations. They carry epidemic typhus, trench fever, relapsing fever, and the bacillary angiomatosis organism. When transmitted by a louse, the latter organism is more likely to cause endocarditis.

3. A. Leishmaniasis is carried by sandflies, *Phlebotomus* sp. in the old world and *Lutzomyia* species in the new world. Sandfly bites correspond to the site of ulcer or nodule formation.

4. A. The organisms that cause sleeping sickness are related to those that cause leishmaniasis. Both produce chancriform lesions. Sleeping sickness also causes urticaria, pruritus, facial edema, fever, and arthralgias, central nervous system manifestations occur in the second phase of illness.

5. E. Mosquitoes cause more human morbidity and mortality than any other group of arthropods. Among the many diseases they spread are filariasis, yellow fever, dengue, and viral encephalitis.

6. A. Chagas disease is transmitted by reduviid bugs. Bedbugs may represent a secondary vector. Leishmaniasis and sleeping sickness are spread by biting flies and malaria and dengue are spread by mosquitoes.

7. A. In North America, Dermacentor ticks are the most important cause of tick paralysis. The ticks attach to the head and neck region and are often hidden by hair, contributing to the significant mortality associated with tick paralysis. Ixodes ticks cause tick paralysis in Australian dogs.
8. A. Liponyssoides mites carry rickettsial pox. Typhus is carried by lice, relapsing fever by lice and ticks, and Rocky Mountain spotted fever by ticks. Most typhoid is food-borne.

9. A. Cheyletiella mites affect cats, dogs and rabbits. They produce eczematous “hot spots” referred to as walking dandruff.

10. Ornithodoros ticks carry relapsing fever. Relapsing fever may also be louse-borne. Rickettsial pox is transmitted by a mite, typhus by a louse, and Colorado tick fever by Dermacentor ticks. Typhoid is most commonly food borne.

REFERENCES


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DNA VIRUSES

1. Pox viruses
2. Papillomaviruses
3. Herpes viruses
4. Parvoviruses
5. Hepadnavirus

**Pox Viruses**
- Large, enveloped, double-stranded, linear DNA viruses
- Belong to the Poxviridae family
- Replicate in the cytoplasm, except for the adenovirus
- Poxviruses of clinical importance include: smallpox, vaccinia, monkeypox, molluscum contagiosum, orf and milker’s nodules

**Molluscipox (Molluscum Contagiosum; MCV)**
- Common, benign, self-limiting skin disease
- Generally affects pediatric age group
- Virus commonly acquired by skin to skin contact (non-sexual)
- Incubation period is from 2 weeks to 6 months
- Four different strains have been identified (based on restriction endonuclease digestion pattern). Two main subtypes: MCV I, responsible for the majority of infections in the United States, and MCV II (more prevalent in HIV patients); both are genital/nongenital
- Clinical
  - 3- to 6-mm erythematous or skin-colored, dome-shaped, umbilical papules distributed over the trunk and face. The lesions may persist for six to eight weeks or more (Fig. 17-1)
  - In immunocompromised patients, especially HIV-infected individuals, thousands of papules distributed on the body and face. High risk of bacterial infection and treatment resistance
  - Genital papules: usually sexually transmitted, most common in adults (Fig. 17-2)
  - Positive Koebner reaction
  - Free virus cores found in all layers of epidermis
- Diagnosis
  - Clinical
  - Confirmatory biopsy in some cases. Henderson-Paterson bodies (molluscum bodies) = viral particles in infected keratinocytes, eosinophils
- Treatment
  - Resolution is often preceded by inflammation, uncomplicated lesions heal without scaring
  - Physical destruction (salicylic acid, liquid nitrogen, cantharidin, lactic acid, CO2, trichloroacetic acid)
  - Immune modulation: imiquimod
  - Manual extrusion (curettage) of the lesions
  - Cidofovir in immunocompromised patients

**Smallpox**
- Caused by variola virus; variola minor also known as alastrim
- Serious, contagious, and sometimes fatal infectious disease
- Eradicated after a successful worldwide vaccination program
- Face-to-face contact is not required to be infected, direct contact with infected body fluids or contaminated objects
Humans are the only natural host

Clinical
- Incubation 12 to 13 days, fever, malaise, backache, body aches and exanthem that appears after 2 to 4 days
- Two clinical forms: Variola major, most common and severe form with a 30% incidence of mortality (secondary to pulmonary edema from heart failure) four clinical types: ordinary, modified (by previous vaccination), flat, and hemorrhagic and Variola minor, less severe and 1% mortality
- Early rash appears as small red spots in the mouth; macules → papules → vesicles → pustules; all lesions exist in the same stage
- Complications: corneal ulceration, laryngeal lesions, encephalitis, hemorrhage
- Progressive vaccinia related to immunosuppression, malignancy, radiation therapy, or AIDS
- Vaccination: rare postvaccinal encephalitis and progressive vaccinia; high level immunity for 3 to 5 years and decreasing immunity thereafter

Diagnosis
- Clinical
  - Histology: balloon and reticular degeneration with hemorrhage inclusion bodies, polymorphonuclear cells
- Treatment
  - No antiviral treatment for smallpox; cidofovir suggested

Vaccinia (Figs. 17-3 and 17-4)
- Laboratory virus used to vaccinate against smallpox and monkeypox
- Infection occurs primarily in laboratory workers
DNA VIRUSES

**ORF (ECTHYMA CONTAGIOSUM, SCABBY MOUTH)**
- Large ovoid virus, 250 × 160 nm with surface tubules, resistant to drying
- Endemic among sheep and goats, oxen; infection from animals or fomites: barn doors, troughs
- Uncommon dermatosis resulting from cutaneous infection with sheep pox virus. Sheep farmers, veterinarians mainly affected
- **Clinical**
  - 4 to 7 days incubation followed by 36-day period with six clinical stages: each lasts 6 days
  - Lesions progress through several stages. They occur at sites of contact with infected animals or fomites
  - Papular stage: red elevated lesion
  - Target stage: nodule with red center, white ring, red halo
  - Acute stage: weeping surface
  - Regenerative stage: thin, dry crust with black dots
  - Papillomatous stage: small papillomas over surface of lesion
  - Regressive: thick crusts heal with scarring
- Systemic symptoms include lymphangitis, lymphadenitis, malaise and fever
- **Diagnosis**
  - Based on typical clinical skin lesion and a history of sheep exposure. It is confirmed by histological study with or without electron microscopy
  - Histology varies depending on the stage of the lesion. Epidermal necrosis is prominent with vacuolization of cells in the upper third of the stratum spinosum. Eosinophilic inclusion bodies in the cytoplasm and nucleus of infected cells and mixed infiltrate in the dermis
  - **Treatment**
    - Vaccinia immune globulin (VIG) or surgical removal of massive lesions followed by VIG

**MONKEYPOX**
- Occasionally infects humans; predominantly residents of western and central Africa; vaccinia infection may confer protection
- Reported cases in the United States were related to direct contact with infected exotic or wild mammalian pets (prairie dogs)
- **Clinical**
  - Differs from the cases of monkey pox in Africa and the United States
  - Red erosion progresses to a white vesicle to an umbilicated pustule with a central hemorrhagic crust and satellite lesions
  - Dissemination may occur

**COWPOX**
- Infects cows, but more commonly seen in cats
- Cow/cat teats: sites of injury
- Lymphadenopathy, fever

**MILKER’S NODULES (PARAVACCINIA)**
- Paravaccinia virus is a 140 × 310 nm, double stranded DNA poxvirus
- It is resistant to desiccation, cold and heat
- Endemic to cattle, on cow teats
- Occupational disease affects mainly milkers, farm workers and veterinary surgeons
- **Clinical**
  - Incubation period varies from 4 days to weeks
  - Lesions usually found on the fingers, the hand or the forearm
  - One single lesion or few lesions (in burned areas), 0.5–1.5 cm in diameter, firm, dome-shaped, movable, red or purplish red papules or nodules, some may have a target like appearance and central ulceration may occur
Chapter 17  VIRAL DISEASES

HPV may cause genitomucosal lesions, nongenital cutaneous lesions, epidermodysplasia verruciformis (EV) and Heck’s disease

Anti-viral treatments exist (Interferon, imiquimod—indirect action and cidofovir), but most therapies aim to destroy the clinical lesions

Nongenital Cutaneous Diseases (Table 17-1)

Occur in 10% of children, peak incidence between 12 and 16 years old, adults are also affected but less commonly

The clinical lesions can be classified as:

- Verruca palmaris or plantaris (myrmecia or palmoplantar wart) (Fig. 17-5)
  - Clinical
    ▲ “Anthill” HPV1
    ▲ Volar aspects of palms/soles, tips of fingers/toes
    ▲ Thick, endophytic papules with a central depression
    ▲ Pain with pressure when walking
  - Diagnosis
    ▲ Histology: ortho- and parakeratosis, acanthosis and extensive papillomatosis. Rete ridges extend further into the dermis. Higher power intracytoplasmatic, eosinophilic, keratohyalin-like granules within the epithelial cell in the low stratum of malpighii

- Verruca vulgaris (common warts)
  - HPV 1, 2 or 4
  - Clinical (Fig. 17-6)
    ▲ Verrucous papules
    ▲ The lesions can be hyperkeratotic, exophytic and dome-shaped papules

Human Papillomaviruses (HPV)

- Non-enveloped, double-stranded, circular DNA viruses with approximately 8000 base pairs
- HPV genome encodes early proteins (E1–E7) and late proteins (L1–L2)
- Proteins E6 and E7 are involved in oncogenesis. E6 inactivates the tumor suppressor protein p53 blocking cell apoptosis. E7 inactivates the Rb-family proteins inducing cell proliferation
- Clinical
  - Infect epithelia or skin or mucosa and mostly causes benign papillomas or warts
  - Most infections are transient; however, lesions may recur, persist or become latent (especially in immunocompromised individuals)
  - Main risk factor is close personal contact, the lesions spread by direct skin to skin or skin to mucosa contact. Other factors involved are the quantity of HPV in the lesion, the type of contact, the immune status of the individual and the lesion location
  - Lesions may koebnerize

TABLE 17-1  Nongenital Cutaneous Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>HPV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common warts (verrucae vulgaris)</td>
<td>1, 2, 4, 26, 27, 29, 41, 57, 65</td>
</tr>
<tr>
<td>Plantar warts (myrmecia)</td>
<td>1, 2, 4, 63</td>
</tr>
<tr>
<td>Flat warts (verrucae plana)</td>
<td>3, 10, 27, 28, 38, 41, 49</td>
</tr>
<tr>
<td>Butcher’s warts (common warts of people who handle meat, poultry, and fish)</td>
<td>7</td>
</tr>
<tr>
<td>Mosaic warts</td>
<td>2, 27, 57</td>
</tr>
<tr>
<td>Ungual squamous cell carcinoma</td>
<td>16</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis (benign)</td>
<td>2, 3, 10, 12, 15, 19, 36, 46, 47, 50</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis (malignant or benign)</td>
<td>5, 8, 9, 10, 14, 17, 20, 21, 22, 23, 24, 25, 37, 38</td>
</tr>
</tbody>
</table>
or nodules with punctuate black dots
(thrombosed capillaries and capillary bleeding)
- Treatment
  ▲ Salicylic acid, 50% tricholoacetic acid, cantharidin, cryotherapy with liquid nitrogen, electrodesiccation, combination therapy using cryodestruction or surgery and imiquimod
- Verrucae plana (flat warts) (Fig. 17-7)
  - HPV 3 or 10
  - Clinical
    ▲ Slightly elevated flat flesh-colored papules that may be smooth or slightly hyperkeratotic
    ▲ Located on dorsal hands, arms or face, often in a linear array
  - Treatment: retinoic acid 0.05% applied daily until desquamation occurs; mild irritation may occur, imiquimod or a combination of the treatment options
- Butcher’s warts
  - HPV7
  - Proliferative hand warts
  - Histology: same as common warts
- Epidermodysplasia verruciformis (EV)
  - Very rare chronic disease
  - Autosomal recessive pattern
  - Unique susceptibility to cutaneous infections by a group of phylogenetically related HPV types (mainly types 5 and 8)
  - Manifest at childhood
  - Clinical
    ▲ Lesions are polymorphic, verruca plana-like, red-brown plaques
  ▲ Actinic keratoses arise after the age of 30 years and transform into Bowenoid or squamous cell carcinomas (50% of patients)
- Diagnosis
  ▲ Clinical confirmed by biopsy
  ▲ Histology: stratum corneum with a basketweave appearance, uneven keratohyaline granules; large, course granules in the epidermis; koilocytes; gray cytoplasm; increase in amount of cytoplasm. Dysplasia and actinic keratoses may be evident
Bowenoid papulosis
• Rare manifestation of HPV infection – HPV16, -18, and -33 (oncogenic) – Young, sexually active adults; cervix in females
• Premalignant disease –
• Clinical – Red or hyperpigmented, multiple groups of well-demarcated, 2 to 3 mm papules on the external genitalia
• Diagnosis – Clinically confirmed by histology
• Histology: full-thickness dysplasia, dysplastic keratinocytes
• Treatment – Cryotherapy, laser, excision, topical retinoids, 5-fluorouracil 5% solution, imiquimod 5% cream (studies show this treatment has a lower recurrence rate than other treatments)

**TABLE 17-2 Anogenital Diseases Associated With HPV**

<table>
<thead>
<tr>
<th><strong>HPV Type</strong></th>
<th><strong>Condyloma acuminata</strong></th>
<th><strong>Bowenoid papulosis</strong></th>
<th><strong>Bowen’s disease</strong></th>
<th><strong>Giant condyloma (Buschke-Löwenstein tumors)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6, 11, 30, 42, 43, 44, 45, 51, 52, 54</td>
<td>16, 18, 34, 39, 42, 45</td>
<td>16, 18, 31, 34</td>
<td>6, 11</td>
</tr>
</tbody>
</table>

**FIGURE 17-8** Anogenital disease. (Courtesy of Dr. Stephen Tyring.)
• Premalignant and malignant diseases. Verrucous carcinoma (giant condyloma acuminata of Buschke and Lowenstein tumor)
  – Low grade squamous cell carcinoma
  – Infection with HP6, HP11 (types not usually associated with malignancy)
  – Clinical
    ▲ Large exophytic tumors up to several centimeters in diameter
    ▲ Locally invasive and destructive
    ▲ Rarely metastasize
  – Treatment
    ▲ Local excision
• Bowen’s disease
  – Some cases associated with human papilloma virus
  – Clinical
    ▲ Insidious onset, lesions have a slow rate of growth and are minimally symptomatic
    ▲ Slightly raised plaque (sometimes misdiagnosed as eczema) with an irregular border and the surface can be fissured with adherent scales
  – Diagnosis
    ▲ Histopathology: full thickness dysplasia of squamous epithelium
  – Treatment
    ▲ Excision, curettage, cryosurgery, topical 5-fluorouracil and/or imiquimod
• Erythroplasia of Queyrat
  – Penile Bowen’s disease
  – A squamous cell carcinoma in situ
  – Located on the glans under the foreskin of the uncircumcised penis
  – Clinical
    ▲ Red plaques with a moist surface
    ▲ Metastasis occur in 10% to 30%
  – Diagnosis
    ▲ Histopathology: same as Bowen’s above
  – Treatment
    ▲ Excision, curettage, cryosurgery, topical 5-fluorouracil and/or imiquimod

**Nongenital Mucosal Disease (Table 17-3)**

- Oral focal epithelial hyperplasia (Heck’s disease)
  - A rare disease
  - HPV types 13 and 32
  - Mostly affects the aboriginal population (i.e., Native American, Greenland, etc.)
  - Focal epithelial hyperplasia
  - Clinical
    - It affects the labial, lingual and buccal mucosa
    - Multiple flat-topped or dome-shaped pink-white papules, 1 to 5 mm, some lesions coalesce into plaques

<table>
<thead>
<tr>
<th>TABLE 17-3 Nongenital Mucosal Disease</th>
<th>HPV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral focal epithelial hyperplasia (Heck’s disease)</td>
<td>13, 32</td>
</tr>
<tr>
<td>Oral carcinoma</td>
<td>16, 18</td>
</tr>
<tr>
<td>Oral leukoplakia</td>
<td>16, 18</td>
</tr>
</tbody>
</table>

- Diagnosis
  - Histology: hyperplastic mucosa with thin parakeratotic stratum corneum, acanthosis, blunting and anastomosis of rete ridges, pallor of epidermal cells as a result of intracellular edema
- Treatment
  - Surgical excision
  - Cryotherapy
  - Imiquimod 5% cream
  - Sulfonamides
  - Oral vitamin A

**Treatments for HPV**

- Topical agents
  - Salicylic acid
    - Over-the-counter treatment
    - Removes surface keratin
  - Cantharidin
    - Dried extract of the blister beetle
    - Causes epidermal necrosis and blistering
  - Dinitrochlorobenzene (DNCB)
    - Powerful sensitizing agent
    - Induces an allergic contact dermatitis
    - Causes local inflammation and an immune response
    - Reported mutagen
  - Dibutyl squaric acid
    - Contact sensitizer
    - Unlike DNCB, it is not a mutagen and therefore may be a safer alternative
  - Trichloroacetic acid
    - Caustic compound
    - Causes immediate superficial tissue necrosis
    - Concentrations up to 80%
    - May require weekly applications
  - Podophyllotoxin
    - Derived from the roots of the Indian podophyllum plant
    - Binds to tubulin and prevents microtubule assembly
- Genital wart treatment: application twice daily for three consecutive days per week for up to 4 weeks
  - Fluorouracil (5FU)
  - Used primarily to treat actinic keratoses
  - Antimetabolite: fluorinated pyrimidine
  - Active form inhibits DNA synthesis by inhibiting the normal production of thymidine
  - Effective in treating warts when used under occlusion daily for up to 1 month
  - Teratogenic
  - Imiquimod 5% cream
  - Topical cream approved for treating genital warts; used for other HPV infections
  - Anogenital warts: treat at night, three times a week
  - Common warts: treat nightly under occlusion
  - Palmoplantar warts: treat nightly under occlusion, alternate with a keratolytic
  - Potent stimulator of proinflammatory cytokine release
  - Works best as part of combination therapy for nonanogenital warts
- Cidofovir
  - Nucleotide analogue of deoxycytidine monophosphate
  - Used for refractory condyloma acuminata and recurrent genital herpes
  - Cidofovir gel applied once or twice daily
  - Must be compounded
- Tretinoin
  - Disrupts epidermal growth and differentiation, thereby reducing the bulk of the wart
- Systemic agents
  - Cimetidine
  - Type 2 histamine receptor antagonist
  - Immunomodulatory effects
  - Variable results
  - 25 to 40 mg/kg tid × 3 months
- Intralesional injections
  - Bleomycin
    - Cytotoxic polypeptide that inhibits DNA synthesis in cells and viruses
    - Side effects of bleomycin include pain with injection, local urticaria, Raynaud phenomenon, and possible tissue necrosis
    - If used periungually, bleomycin may cause nail dystrophy or nail loss
  - Interferon-alpha
    - Recombinant version of naturally occurring cytokine with antiviral, anticancer, and immunomodulatory effects
    - Intralesional administration is more effective than systemic administration and is associated only with mild flu like symptoms.
    - Treatments may be required for several weeks to months before beneficial results are seen. Use for warts that are resistant to standard treatments or use in combination therapy with surgery
  - *Candida* antigen
    - Stimulates the acquisition of HPV immunity
    - Its application causes trauma and inflammatory reaction
  - Cryosurgery: liquid nitrogen (−196°C) is the most effective method of cryosurgery
- Lasers
  - Carbon dioxide
    - Procedure can be painful and leave scarring
    - Risk of nosocomial infection also exists in health care workers because HPV can be isolated in the plume
  - Flashlamp-pumped pulse dye laser
    - Mixed results in treating warts
    - Decreased risk of scarring and transmission of HPV in the plume smoke
    - Electrodesiccation and curettage
    - May be more effective than cryosurgery
    - Painful
    - More likely to scar
    - HPV can be isolated from the plume
- Surgical excision: avoid using because of the risks of scarring and recurrence (or follow with interferon)

**Human Herpes Viruses (HHV)**
- Most herpes viruses measure approximately 200 nm in diameter
- Enveloped, linear, double-stranded DNA virus
- Biological features unique to herpes viruses are latency and reactivation
- Transmission: direct exposure of mucous membranes or abraded skin to the lesions or mucosal secretions of an infected individual or respiratory droplets
- Eight main types
  - HHV 1: herpes simplex 1 (HSV-1): herpes labialis > genitalis
  - HHV 2: herpes simplex 2 (HSV-2): herpes genitalis > labialis
  - HHV 3: varicella-zoster virus (VZV): chickenpox/herpes zoster
  - HHV 4: Epstein-Barr virus (EBV): mononucleosis, Gianotti Crosti, Burkitt’s lymphoma, oral hairy leukoplakia
  - HHV 5: cytomegalovirus (CMV): retinitis in AIDS patients
  - HHV 6: roseola infantum (exanthem subitum)
  - HHV 7: possible pityriasis rosea
  - HHV 8: Kaposi’s sarcoma

**Herpes Simplex Virus (HSV)**
- **Herpes simplex 1 (HSV-1)**
  - Belongs to the family Herpesviridae
  - Humans are the only natural reservoirs, and no vectors are involved in transmission
• Eighty percent of U.S. adults are infected, 85% of adults infected worldwide
• Ninety percent orofacial, 10% genital
• Mode of transmission is by close personal contact
• Viral properties
  – Neurovirulence: capacity to invade and replicate in the nervous system
  – Latency
    ▲ Establishment and maintenance of latent infection in nerve cell ganglia
    ▲ HSV-1 infection: trigeminal ganglia are involved most commonly
    ▲ Primary infection is subclinical (90%), gingivostomatitis (10%)
    ▲ In 40% of HSV-1 seropositive persons recurrent herpes labialis usually recur one to four times per year
    ▲ Accounts for 30% of primary but less than 5% of recurrent genital HSV
• Reactivation
  – Induced by a variety of stimuli: fever, trauma, emotional stress, sunlight, menstruation
  – Recurrent infection and peripheral shedding of HSV
  – Occurs more frequently in the perioral rather than the genital region
  – More frequent and severe in immunocompromised patients
• Clinical
  – Gingivostomatitis
    ▲ Abrupt onset
    ▲ Children aged 6 months to 5 years
    ▲ High fever (102–104°F)
    ▲ Anorexia and listlessness
    ▲ Gingivitis is the most striking feature
    ▲ Vesicular lesions develop on the oral mucosa, tongue, and or lips and later rupture and coalesce, leaving ulcerated plaques
    ▲ Regional lymphadenopathy
    ▲ Acute herpetic pharyngotonsillitis
    ▲ Acute disease lasts 5 to 7 days
    ▲ Viral shedding may continue for 3 weeks
• Herpes labialis (Fig. 17-9)
  – Most common manifestation of recurrent HSV-1
  – Prodrome of pain, burning, and tingling often occurs at the site where lesions develop
  – Clinical
    ▲ Erythematous papules develop rapidly into tiny, thin-walled, intraepidermal vesicles that become pustular and ulcerate
    ▲ Maximum viral shedding is in the first 24 hours of the acute illness but may last 5 days
• Diagnosis
  – Histology: acantholysis, intraepidermal vesicle, ballooning and reticular degeneration, intranuclear eosinophilic inclusion bodies, multinucleated keratinocytes (not specific)
  – Viral culture
  – Polymerase chain reaction (PCR) techniques: detection of HSV DNA
  – Immunofluorescent staining of the tissue culture cells or of smear can quickly identify HSV and can distinguish between types 1 and 2
  – Antibody testing
    ▲ Tzanck smear: multinucleated giant cells → nucleus divides but not cell; nuclear molding; does not distinguish between HSV2 and VZV
• Treatment: see HSV-2 below
• Herpes simplex 2 (HSV-2) (Figs. 17-10, 17-11, and 17-12)
  – Primary genital herpes; asymptomatic in most patients
  – Causes 70% of primary, >95% of recurrent genital herpes
  – Women have 45% higher risk of infection compared to men
  – Primary infection asymptomatic: 75%
  – Ninety-five percent of asymptomatic females and males actively shed virus at some point in time
  – Eighty percent of transmission is secondary to asymptomatic shedding
  – Ninety percent have recurrences
  – Clinical
    ▲ Incubation period is 3 to 7 days
    ▲ Cervical vesicles resulting in ulcers; can recur with or without external lesions
    ▲ Ulcerative lesions persist from 4 to 15 days
    ▲ Viral shedding lasts approximately 12 days
Clinical – Recurrent HSV may last much longer compared with immunocompetent hosts (>30 days)
Chronic ulcerative HSV: persistent ulcers and erosions starting on the face or perineal region

Systemic complaints in > 70% of primary HSV: fever, dysuria, malaise, lymphadenopathy, females greater than males
Spread by sexual contact (1% to 2% days/year male, 6% to 8% female: asymptomatic transmission)

• Treatment
  – Acyclovir:
    ▲ First episode: 200 mg five times daily or 400 mg tid for 7 to 10 days
    ▲ Recurrences: 200 mg PO five times daily or 400 mg tid for 5 days
    ▲ Chronic suppressive therapy: 400 mg bid or 200 mg three to five times daily
  – Valacyclovir (Valtrex)
    ▲ First episode 1 g bid for 10 days
    ▲ Recurrences: 500 mg twice daily for 3 days or 2 g bid for one day
    ▲ Suppressive dosing for HSV: 500 mg to 1 g/d
  – Famciclovir (Famvir)
    ▲ First episode: 250 mg tid for 10 days
    ▲ Recurrences: 125 mg twice daily for 5 days or 1 gm (for genital herpes) or 1.5 once for herpes labialis
    ▲ Suppression: 250 mg bid

• Herpes simplex virus in immunosuppressed patients
  – HIV: 95% coinfected with HSV-1/HSV-2 or both
  – Fifty-two percent of HIV infections are among people who also have herpes simplex virus type 2

Clinical
  ▲ Recurrent HSV may last much longer compared with immunocompetent hosts (> 30 days)
  ▲ Chronic ulcerative HSV: persistent ulcers and erosions starting on the face or perineal region
Generalized acute mucocutaneous HSV: dissemination and fever after localized vesicular eruption

Systemic HSV: follows oral or genital lesions; areas of necrosis in the liver, adrenals, pancreas

- Treatment of genital ulcers caused by HSV-2 with specific antivirals has been previously shown to reduce HSV-2 and HIV shedding
- Acyclovir-resistant HSV in HIV patients (5–8%)
  ▲ 1% Cidofovir (compounded)
  ▲ Foscarnet
     △ Reversibly inhibits viral DNA polymerase
     △ Does not need thymidine kinase
     △ Side effects: penile ulcers, nephrotoxicity

Other herpes manifestations
- Herpetic whitlow
  - HSV of the fingers, occurs at or near the cuticle or at other sites associated with trauma
  - HSV-2 > HSV-1
- Herpes gladiatorum (Fig. 17-13)
  - Due to direct skin-to-skin contact among wrestlers
  - Scattered cutaneous HSV-1 lesions
- Herpes-associated erythema multiforme (EM)
  - 80% of recurrent EM are thought to be associated with HSV reactivation
  - Multiple outbreaks of EM often associated with herpes reactivation
  - Pathogenesis may represent a delayed-type hypersensitivity reaction
  - Patients experience an average of 6 attacks annually, each episode lasting nearly 2 weeks
- Self-limited
- Herpetic keratoconjunctivitis
  - Recurrent erosions of the conjunctiva and cornea that can lead to blindness
- Lumbosacral herpes simplex virus
  - Infection is typically asymptomatic but can cause sciatica
- Eczema herpeticum (Fig. 17-14)
  - Widespread HSV infection in patients with skin disorders such as atopic dermatitis, Darier’s disease, pemphigus, thermal burns or Sézary syndrome
- HSV encephalitis (usually HSV-1)
  - Most common cause of sporadic encephalitis
  - Sudden onset of fever, headache, confusion, temporal lobe involvement
  - Seventy percent mortality if not treated
- Ramsay Hunt (usually VZV or HSV-1)
  - Infection of the facial nerve

- Symptoms on the affected side typically include facial weakness and a painful herpes-type skin eruption on the pinna of the ear, and there is frequently vestibulocochlear disturbance
- Recovery of facial movement occurs in about 50% of treated patients

Congenital herpes simplex virus
- One in 3500 vaginal births
- Transmission:
  - Perinatal: 90%; congenital: 5% to 8%; few postnatal
Lesions: “dewdrops on a rose petal”; begin on face, scalp, trunk, with relative sparing of the extremities.

Lesions start as red macules and pass through the stages of papule, vesicle, pustule, and eventually crust. Lesions are pruritic.

Different stages of the rash are present simultaneously.

Complications:
- Young immunocompetent individuals: secondary bacterial infection (Staphylococcus aureus or Streptococcus pyogenes) and scarring.
- Adults and immunocompromised: myelitis, large vessel granulomatous arteritis, encephalitis, varicella pneumonia or varicella hepatitis.

- If lesions on infant in first 10 days, mortality is 20%.
- Mortality rate (if no treatment) is 65% transplacental, 80% HSV-2, 20% HSV-1.
- Treatment / prevention
  - Pregnancy
    ▲ In infected females, initiate treatment at week 36 and continue until delivery:
      ▲ Valacyclovir 1 g qd or
      ▲ Famciclovir 250 mg bid or
      ▲ Acyclovir 400 mg bid tid or 200 mg three to five times daily
  - IV acyclovir for neonates: 30 mg/kg per day

- Risk of transmission: 50% if mother has primary infection, 3% to 5% if mother has recurrent disease.
- Birth canal transmission: lesions usually on scalp, face; associated encephalitis, hepatorenal necrosis, pneumonia, death.
- If transmission in first 8 weeks, severe defects result.
- If lesions on infant in first 10 days, mortality is 20%.
- Mortality rate (if no treatment) is 65% transplacental, 80% HSV-2, 20% HSV-1.
- Treatment / prevention
  - Pregnancy
    ▲ In infected females, initiate treatment at week 36 and continue until delivery:
      ▲ Valacyclovir 1 g qd or
      ▲ Famciclovir 250 mg bid or
      ▲ Acyclovir 400 mg bid tid or 200 mg three to five times daily
  - IV acyclovir for neonates: 30 mg/kg per day

- Varicella-zoster virus [human herpes virus 3 (HHV 3)]
  - 98% of the adult population in the United States have serological evidence of previous infection.
  - Causes chickenpox and herpes zoster.
  - Chickenpox (Fig. 17-15)
    - Transmitted to others from the skin and respiratory tract.
    - VZV remains dormant in sensory nerve ganglia after primary infection.
    - Low-grade fever precedes skin manifestations by 1 to 2 days.
    - Incubation period of about 2 weeks.
  - Clinical
    ▲ Prodromal symptoms include headache, myalgias, anorexia, nausea and vomiting.
  - Lesions: “dewdrops on a rose petal”; begin on face, scalp, trunk, with relative sparing of the extremities.
  - Lesions start as red macules and pass through the stages of papule, vesicle, pustule, and eventually crust. Lesions are pruritic.
  - Different stages of the rash are present simultaneously.
  - Complications
    ▲ Young immunocompetent individuals: secondary bacterial infection (Staphylococcus aureus or Streptococcus pyogenes) and scarring.
    ▲ Adults and immunocompromised: myelitis, large vessel granulomatous arteritis, encephalitis, varicella pneumonia or varicella hepatitis.
  - Congenital varicella syndrome
    - First 20 weeks of pregnancy: 2% risk of complications.
- Leads to intrauterine growth retardation, microcephaly, cortical atrophy, limb hypoplasia, microphthalmia, cataracts, chorioretinitis, cortical atrophy and cutaneous scarring (areas of hypertrophic scarring with indurations and erythema located primarily on the extremities)
- Perinatal infection occurs within 10 days of birth
- If female gets VZV five days before or two days after delivery, the rate of mortality is 30%

- **Infantile zoster**
  - Manifests within the first year
  - Maternal varicella infection after the twentieth week of gestation
    ▲ Neonatal varicella
  - Any infant with clinical or laboratory-confirmed varicella
  - Onset in the first month of life
    ▲ Without features of varicella embryopathy
    ▲ Infection may result from peripartum maternal infection or postnatal exposure
  - Treatment
    ▲ Healthy children do not necessarily require acyclovir, but treatment allows them to return to school sooner
    ▲ Acyclovir: 20 mg/kg; given orally four times daily for 5 to 7 days
    ▲ Avoid aspirin to prevent Reye’s syndrome
    ▲ Symptomatic care
    ▲ Adults
      △ Acyclovir, famciclovir, valacyclovir at herpes zoster doses
      △ Most effective if it is started within the first 72 hours after development of vesicles
  - Varicella vaccine
    ▲ Two doses, at 12 months and 4–6 years of age
    ▲ Seroconversion: adolescents and adults have a 78% conversion rate after the first dose and 99% after the second dose

- **Zoster (shingles)** (Fig. 17-16)
  - Due to reactivation of latent VZV in sensory ganglion (20% incidence unless immunocompromised)
  - Incidence: 66% of cases occur in patients older than 50 years
  - Clinical
    ▲ Rash preceded by prodrome: fever, malaise, headache, localized pain in the involved dermatome
    ▲ Constitutional symptoms develop initially
  - Rash is in a unilateral dermatomal distribution with erythema, vesicles, pustules, & crusting
  - Contagious until crusted
  - Hutchinson sign: zoster on tip of nose (ophthalmic nerve, nasociliary division), could result in herpetic keratitis
  - Complications
    ▲ Postherpetic neuralgia (PHN)
    ▲ Pain following resolution of skin

**FIGURE 17-16** Zoster (shingles). (Courtesy of Dr. Adriana Motta.)
lesions; occurs in 10% to 15% of patients; Resolution rate is 50% by 3 months, 75% by 1 year
△ Occurs in 60% of patients over age 60
△ Zoster sine herpete: segmental pain without lesions
△ Ophthalmic zoster: ocular disease (20% to 70% of cases with V-1 Zoster), cicatricial lid retraction, ptosis, keratitis, scleritis, uveitis, secondary glaucoma, oculomotor palsies, chorioretinitis, optic neuritis, panophthalmitis
△ CNS zoster: has asymptomatic cerebrospinal fluid (CSF) changes
△ Primary varicella pneumonia: 14%, higher rate in adults and immunocompromised patients
△ Reye’s syndrome: acute fetal encephalopathy associated with fatty degeneration of the liver, associated with aspirin treatment
△ Bacterial superinfections: usually due to Staphylococcus aureus
△ Acute cerebellar ataxia: unsteady gait 11 to 20 days following rash
△ Guillain-Barré syndrome
   △ Acute idiopathic polyneuritis
   △ Encephalitis with headache, fever, photophobia, nausea, vomiting, nerve palsies
   △ Motor paralysis (1% to 5%), extension from sensory ganglion to anterior horn, first 2 to 3 weeks
   △ Ramsay Hunt: facial palsy second- ary to herpes-zoster infection of facial (VII) and auditory (VIII) nerves; affects external ear, tympanic membrane; causes tinnitus, vertigo, deafness, otalgia, loss of taste
- Diagnosis
  △ Nonspecific tests
    △ Tzanck smear: multinucleated giant cells, nuclear molding
    △ Histology: intraepidermal vesicles, balloon degeneration, reticular degeneration, inclusion bodies, margination of chromatin, vascular involvement (75% VZV)
  △ Specific tests
    △ Viral culture
    △ PCR
- Treatment
  △ Acyclovir: 800 mg five times daily for 7 days
  △ Valacyclovir: 1 g three times daily for 7 days
  △ Famciclovir: 500 mg three times daily for 7 days
△ Pain and pruritus: analgesics, oral antipruritics, calamine lotion, cool compresses
- Treatment of PHN
  △ Non-narcotic or narcotic analgesic
  △ Capsaicin cream
  △ Topical lidocaine gel or patch
  △ Tricyclic antidepressants: (amitriptyline, maprotiline, desipramine)
  △ Anticonvulsants: carbamazepine, gabapentin, pregabalin
  △ Sympathetic nerve blockade
  △ Steroids: methylprednisolone
  △ Transcutaneous electrical stimulation
- Vaccine: to increase immunity in persons seropositive for VZV in order to decrease risk of zoster. FDA approved for 60 years and older
- Epstein-Barr virus [human herpes virus 4 (HHV 4)]
  △ Double-stranded DNA virus
  △ Replicates in the nucleus
  △ Primarily infects B-lymphocytes
  △ After acute infection, EBV persists as a latent infection for life
- Clinical
  △ Infectious mononucleosis (IM)
    △ Delayed primary infection with EBV
    △ Young adults are typically affected and a small percentage of children and older adults contract the disease
  △ Clinical
    △ IM can be asymptomatic or have nonspecific symptoms; the incubation period varies from 4 to 6 weeks
    △ More frequent symptoms are a triad of fever, sore throat, lymphadenopathy (5% to 15%)
    △ Rash: maculopapular (3% to 15% of patients)
    △ Eighty percent of patients have rash if treated with amoxicillin or ampicillin
    △ The resolution of the illness occurs between week 5 and 10
- Diagnosis: see diagnosis of EBV on p. 300
- Treatment: supportive care, antipyretics, analgesics, topical steroids for cutaneous manifestations. Prednisone for complications such as hemolytic anemia, thrombocytopenia, or lymphadenopathy that compromises the airway
  △ Gianotti-Crosti (infantile papular acrodermatitis)
  △ Self-limited cutaneous response to viral infections with worldwide distribution
▲ Most often in young children (between 6 months and 14 years of age)
▲ Clinical
  △ Upper respiratory syndrome
  △ Mild systemic compromise such as low-grade fever
  △ Inguinal and axillary lymphadenopathy and hepatosplenomegaly
  △ Symmetric cutaneous lesions appear abruptly: exanthem with monomorphic, edematous, pink-red papules or papulovesicles, slightly pruritic and can become confluent lichenoid papules that spare the trunk
  △ Located on cheeks, buttocks and extensor surface of the extremities
  △ Also associated with hepatitis B, adenovirus, CMV
  △ Spontaneous resolution within three to four weeks
  △ Treatment: supportive measures

- Oral hairy leukoplaikia
  ▲ Benign EBV infection of oral mucosa epithelial cells
  ▲ Usually associated with immunocompromised patients
  ▲ Prevalence of the disease amongst immunocompromised patients varies between 3% and 11%
  ▲ Secondary nonmalignant hyperplasia of epithelial cells
  ▲ Clinical
    △ Location: lateral and dorsolateral parts of the tongue
    △ Flat lesion with white corrugate vertical folds or ridges that cannot be scraped off
    △ Self-limited course with resolution within months in immunocompromised persons
  ▲ Diagnosis
    △ Made clinically; confirmed with biopsy
    △ Histology: hyperplasia, parakeratosis, acanthosis and papillated epithelial surfaces. EBV detected within ballooned and nonballoned cells of the prickle cell layer and the keratinized cells of the superficial epithelium

- Kikuchi’s syndrome
  ▲ Benign, self-limiting disease that resolves spontaneously within 1 to 4 months of onset
  ▲ More common in Asia and usually affects young women in their late 20s and early 30s
  ▲ Pathology is suggestive of hyperimmune reaction to an infectious agent causing regional lymph node enlargement
  ▲ Clinical
    △ Fever and leukopenia (50%), cervical lymphadenopathy
    △ Mucocutaneous (16% to 40%) lesions: facial erythema, erythematous papules, plaques, nodules, cutaneous ulcers, and oral mucosal ulcers
  ▲ Diagnosis
    △ Histology: histiocytic aggregates, atypical lymphoid cells, karyorrhectic debris, and patchy necrosis

- Plasmablastic Lymphoma
  ▲ Recently discovered AIDS-related non-Hodgkin’s lymphoma associated with chronic EBV infection
  ▲ Usually affects the oral cavity, especially the gingival mucosa, hard palate, and soft palate
  ▲ Infiltrates the mucosal surface, the adjacent bone, and finally the bone marrow, which usually occurs during therapy
  ▲ Clinical
    △ Similar to Kaposi’s sarcoma: painful, purple red mass in the oral cavity, usually the gingival mucosa
    △ Prognosis is poor with death occurring between 1 and 24 months after diagnosis

- Burkitt’s lymphoma
  ▲ Highly aggressive and poorly differentiated B-cell lymphoma with a high proliferative rate
  ▲ EBV genome can be detected in tumor cells
  ▲ Two types described (i) the endemic, or African BL (most often associated with EBV infection), and (ii) the sporadic
  ▲ BL arises in the lymph nodes, nasopharyngeal mucosa, and the gastrointestinal tract
  ▲ Cutaneous involvement is rare, only a few cases reported
  ▲ Skin lesions include erythematous firm nodules in connection with the involved lymph node

- Nasopharyngeal carcinoma
  ▲ Lymphoepithelial carcinoma with distinct histological types characterized by either squamous, non-keratinizing, or undifferentiated epithelial cells
  ▲ Prevalent disease in southern China and Southeast Asia
Chapter 17  VIRAL DISEASES

• A threat to the fetus
• Congenital malformations: central nervous system injury, sensorineural hearing loss, growth retardation, microcephaly, cerebral atrophy, periventricular calcifications, chorioretinitis, thrombocytopenia and hepatosplenomegaly

• Cutaneous manifestations: jaundice, purpuric macules and papules (secondary to persistent hematopoiesis – “blueberry muffin baby”)
  - Immunocompromised patients
  • Retinitis, hepatitis and colitis
  • Skin lesions: vary from vesicles to verru- cous plaques, and ulcerations in the peria- nal area

• Complications
  - CMV pneumonia (19%)
  - Mononucleosis-like syndrome after treatment with ampicillin or amoxicillin
  - Guillain-Barré syndrome
  - Bone marrow transplant patients have highest mortality (85%) secondary to pneumonia
  - Four times higher mortality rate than for solid- organ transplant
• In pregnant women, after the first trimester, hepatitis, pneumonia, purpura, and DIC may occur
• HIV and CMV: retinitis is the most common symptom

• Diagnosis
  - Histology: vasculitis, “owl’s eyes”: basophilic intranuclear inclusions
  - CMV antibodies
  - Antigenemia
  - Shell vial assay

• Treatment
  - Most EBV infections are self-limited; treat symptomatically
  - Oral hairy leukoplakia: acyclovir 400 mg five times daily

• Cytomegalovirus (CMV) [human herpes virus 5 (HSV-5)]
  - Enveloped double-stranded DNA virus restricted to humans
  - Transmitted through infectious secretions
  - In developing countries, 100% of the population is seropositive, 50% in developed countries
  - Latent infection in the host occurs after infection

• Clinical
  - Primary infection
    - Usually asymptomatic in immunocompe- tent subjects
    - When symptomatic, it is called CMV mononucleosis syndrome
      △ Fever, fatigue and less commonly lymphadenopathy, sore throat and organomegaly
      △ One third have a maculopapular gener- alized rash
  - Primary infection in pregnant women
    - Occurs during the first trimester: rate of transmission is 40%
    - Most common congenital viral infection (1% of U.S. infants)
  - Monospot test: measures acute infectious mononucleosis heterophile antibodies in a rapid qualitative fashion

• EBV serology
  - Major viral antigens:
    - Latent = EBNA → EBV nuclear antigens
    - Early = EADR → early antigen, diffuse restricted
    - Late = VCA → viral capsid antigen, MA → membrane antigen

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• A threat to the fetus

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    - Occurs during the first trimester: rate of transmission is 40%
    - Most common congenital viral infection (1% of U.S. infants)
DNA VIRUSES

- Transmitted through saliva
- Diagnosis
  - Serology
  - Treatment
  - Symptomatic
- **Human herpes virus 8 (HHV 8):** Kaposi sarcoma (KS) (Figs. 17-18 and 17-19)
  - Malignancy of lymphatic endothelial cells associated with human herpes virus 8
  - Four types
    - Endemic African KS: 50% of all childhood soft tissue tumors, usually an aggressive course
    - Epidemic AIDS-related KS: patients with advanced HIV infection
    - Immunocompromised (iatrogenic) KS: patients receiving immunosuppressive therapy; visceral involvement
    - Classic KS: sporadic and slowly progressive in 50–70 year-old men of Mediterranean and Eastern European background
- Clinical
  - Brown, pink, red or violaceous macules/patches, papules/plaques, nodules. The lesions can vary depending upon the clinical variant
  - Mucous membrane, cutaneous and visceral involvement is common (lymph nodes, gastrointestinal tract and lungs)
- Diagnosis
  - Biopsy: spindle cells, prominent slitlike vascular spaces, and extravasated red blood cells
- Treatment
  - Antiretroviral therapy for epidemic AIDS-related KS

- Abrupt onset with high fever (102.2 to 105.8°F)
- Bulging anterior fontanelle, tonsillar and pharyngeal inflammation, tympanic injection, and lymph node enlargement
- Fever defervesces on the fourth day, coinciding with onset of a rash
- Rash: starts on trunk and may spread to neck and upper and lower extremities
- Pink macules: 2 to 5 mm
- May present with upper respiratory infection, adenopathy, central nervous system involvement, intussusception, thrombocytic purpura, palpebral edema (Berliner’s sign, “heavy eyelids”) and periorbital edema and mononucleosis like (as in adults). Seizures (6% to 15%) during the febrile phase
- Course: no sequelae generally observed
- HIV + HHV 6: tropism for CD4+ cells; upregulation of CD4 expression, which is needed by the gp120 unit of HIV to infect cells
- Bone marrow transplant patients: idiopathic bone marrow suppression secondary to virus
- Diagnosis
  - PCR
- Treatment
  - Symptomatic; a few case reports describe foscarin and/or ganciclovir to be successful, but dosages are not known
- **Human herpes virus 7 (HHV 7)**
  - Significant homology with HHV 6
  - No clinical disease has been definitively linked to HHV 7; with questionable relationship to pityriasis rosea
  - Eighty-five percent of adults are seropositive, and most infections develop within the first 5 years of life

![FIGURE 17-17 Roseola infantum. (Courtesy of Dr. Stephen Tyring.)](image1)

![FIGURE 17-18 Kaposi sarcoma (classic). (Courtesy of Dr. Stephen Tyring.)](image2)
Parvoviruses

PARVOVIRUS B19: “SLAPPED CHEEKS,” FIFTH DISEASE, ERYTHEMA INFECTIOSUM (FIG. 17-20)
- Single stranded DNA erythrovirus
- Tropism for rapidly dividing erythrocyte precursors
- Clinical
  - Twenty percent are asymptomatic
  - Headache, coryza, and low-grade fever about 2 days prior to the onset of the rash
  - Characterized by a “slapped cheek” appearance of the face on the first day
  - Erythematous, lacy macular eruption on the trunk and extremities
  - After rash fades, a lacy marble-like pattern to the skin appears: not contagious at this stage
  - Eruption can last 5 to 9 days and can recur for weeks or months with triggers such as sunlight, exercise, temperature change, bathing, and emotional stress
  - Headache, pharyngitis, fever, malaise, myalgias, arthralgias, coryza, diarrhea, nausea, cough, and conjunctivitis
  - Papular-pruritic “gloves-and-socks” syndrome: Erythematous exanthem of the hands and feet with a distinct margin at the wrist and ankle joints is present along with pain and edema
  - Complications: aplastic crisis in patients with increased red blood cell turnover, chronic anemia in immunocompromised persons, patients with chronic hemolytic anemia, fetal hydrops, sickle cell anemia, G6PD deficiency, and β-thalassemia

- Solitary KS lesions may be excised surgically or removed using laser surgery for patients with single lesions
- Radiation
- Combination of topical retinoids, intralesional vinblastine, interferon-α and chemotherapy: liposomal doxorubicin, liposomal daunorubicin, vincristine, vinblastine, bleomycin, and paclitaxel
- Herpes virus B: herpes simiae
  - Macaque herpes virus that is occasionally transmitted to humans from a bite, scratch, or open wound
  - Neurotropic: remains latent in ganglia
  - Clinical
    - In humans: initial local erythema, vesicular eruption with constitutional symptoms
    - Death secondary to encephalitis; very high mortality rate
- Treatment: nucleoside analogues (e.g., intravenous acyclovir)

FIGURE 17-19 Kaposi sarcoma (scrotal in patient with AIDS). (Courtesy of Dr. Stephen Tyring.)

FIGURE 17-20 Parvovirus B19. (“slapped cheeks”). (Courtesy of Dr. Stephen Tyring.)
Diagnosis
- Parvovirus serology (IgM and IgG) can be determined
- PCR
- Complete blood count (CBC): low reticulocyte count (0% to 1%)

Treatment
- Ibuprofen or acetaminophen for fever (to prevent Reye’s syndrome: aspirin use is contraindicated)
- Red blood cell (RBC) transfusions for aplastic crisis

**Hepadna Viruses**

**Hepatitis B**
- Hepadna virus
- Partially double-stranded circular DNA
- Encodes four overlapping open reading frames as follows:
  - S for the surface or envelope gene encoding the pre-S1, pre-S2, and S protein
  - C for the core gene, encoding for the core nucleocapsid protein and the e antigen
  - X for the X gene encoding the protein
  - P for the polymerase gene, encoding a large protein promoting priming, RNA-dependent and DNA-dependent DNA polymerase and RNase H activities
- Transmitted sexually, perinatally and through contact with body fluids
- Clinical
  - Incubation approximately 75 days
  - Prodromal or preicteric phase: serum sickness-like; develops in 20% to 30% of patients: arthralgia, proteinuria, hematuria
  - Icteric phase: jaundice (10 days after the appearance of constitutional symptomatology and lasts for 1 to 3 months), nausea, vomiting, and pruritus
  - Skin: urticaria/vasculitis secondary to perivascular deposition of immune complexes, hepatitis B + C3, IgM, or IgG
- Associated conditions
  - Transient hypocomplementemia associated with urticaria
  - Polyarthritis nodosa: associated with arthralgia, fever, malaise, renal disease, nodules
  - Globulinemia: associated with chronic HBV, purpura, arthralgia, renal disease, necrotizing vasculitis, with mixed IgG and IgM
  - Others: erythema nodosum, urticaria, lichen planus, leukocytoclastic vasculitis, Gianotti-Crosti
- Diagnosis
  - Active hepatitis B: high levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST); HBsAg (Australian antigen) and HBeAg (marker of infectivity) identified in the serum; HbcAb (IgM)
  - Chronic inactive hepatitis B: HBsAg, HBcAb of IgG type, and HBeAb also are present in the serum
  - Chronic active hepatitis B: mild to moderate elevation of the aminotransferases

**Treatment**
- Interferon-α
- Lamivudine
- Adefovir dipivoxil, entecavir, telbivudine, among others
- Hepatitis B vaccine available

**RNA Viruses**

1. Picornavirus
2. Paramyxovirus
3. Togavirus
4. Flavivirus
5. Retrovirus
6. Arenavirus: Lassa fever, Argentine hemorrhagic fever, and related viruses
7. Bunyavirus: ssRNA enveloped viruses, sandfly fever virus and Hantaan virus

**Picornaviruses**
- Nonenveloped (naked virions)
- Size range of 20 to 25 nm
- Capsids composed of four different proteins
- Genome is single-stranded (ss) RNA
- Size range of 7500 to 8500 nucleotides
- Three major human genera
  - Rhinoviruses
  - Hepatovirus: hepatitis A virus (HAV)
  - Enteroviruses
  - Poliovirus
  - Enterovirus
  - Coxsackie virus
  - Echovirus

**Enteroviruses**
- These are distinguished by other members of the Picornaviruses by its stability at low pH levels
  - Hand, Foot, and Mouth Disease (Fig. 17-21)
    - Etiology
      ▲ Coxsackie A-16 – most common
      ▲ Enterovirus 71 – causes CNS involvement
      ▲ Primarily affects children age 3–10
    - Transmission (highly contagious)
      ▲ Oral-oral
      ▲ Oral-fecal
Resolves spontaneously after 2–3 days without complications

- Diagnosis: isolation and identification of virus in cell culture
  - Histology:
    - Intraepidermal blister: neutrophils, monocytes, necrotic roof
    - Intercellular edema (reticular edema/balloon degeneration)
    - Edematous dermis
    - Intracytoplasmic particles in a crystalline array
  - Cell culture
    - Detection of Enterovirus RNA via PCR of blood, stool, and pharyngeal vesicles
    - Stool is least specific because children are able to excrete Enterovirus for up to eight weeks in feces from a previous infection
  - Treatment: symptomatic

- Herpangina
  - Transmission: fecal-oral route
  - Etiology
    - Coxsackieviruses A 1–10, 16, or 22
  - Clinical manifestations
    - Incubation period typically is 7 to 14 days
    - Mucus membrane lesions 1–2 mm, gray/white papulovesicular lesions, with an erythematous surrounding:
      - Location: soft palate tonsillar pillars, faucets, uvula
      - Sudden onset of fever, headache, sore throat, back/extremity pain
      - Exanthem: not distinctive in appearance for clinical diagnosis
    - Treatment – self limited

- Hepatovirus
  - Hepatitis A
    - Transmission: fecal – oral route
    - Affects children and adults—commonly seen in daycare, schools, and restaurants
    - Pathogenesis
      - Viral replication within the hepatocyte’s cytoplasm causes a non-cytopathic infection
      - CD 8+ T lymphocytes and natural killer cells that are HAV specific assist in destruction of the infected hepatocytes leading to hepatocellular injury
      - As a result, the host’s immune system ultimately causes damage to the liver
    - Clinical manifestations
      - Incubation period: 2 to 7 weeks
      - Children – acute infection is self limited
RNA VIRUSES

Initiated with viral entry via conjunctivae or respiratory mucosa
- Initial viremia—local replication and dissemination through lymphatic system and reticuloendothelial system
- Experience brief respiratory symptoms, or morbilliform rash, many are asymptomatic
- Length—10–14 days

Prodrome
- Second viremia occurs several days post-incubation period
- Three Cs of measles: cough, coryza, and conjunctivitis
- Low grade fever (101–103°F), malaise, anorexia
- Length: 2–8 days

Enanthem: pathognomonic
- Koplik spots—described as “grains of salt on a red background”
  △ 1–3 mm white, gray, bluish elevations with erythematous base located on buccal and labial mucosa, adjacent to the molars
- Appear 24 hours before exanthem

Exanthem
- Non-pruritic, erythematous maculopapular rash with cephalocaudal progression
- Rashes begin post auricular, progresses across face, down the trunk as upper rash fades
- Rarely involves palms and soles
- Erupts 5 days post-prodrome, improvement of symptoms within two days of onset
- Length: within 5 days, rash fades becoming non-blanching, copper-colored, followed by a fine desquamation
- Measles is highly contagious from 4 days pre-exanthem until 4 days post-exanthem

Complications—greater than 3 days post exanthema indicates a complication
- Thrombocytopenic purpura
- Tracheobronchitis— with involvement of upper respiratory tract
- Otitis media and pneumonia from the secondary bacterial infection,
- Reactivation of tuberculosis—secondary to effect on cellular immunity
- Neurological syndromes
  △ Subacute sclerosing panencephalitis (SSPE) — progressive degenerative disease of the CNS
  △ Presents 7–10 years post infection
  △ Risk factor (50%): development of measles before age 2
  △ Post-infectious encephalomyelitis — autoimmune related demyelinating disease that appears within weeks of exanthem

**Diagnosis**
- HAV RNA detection of stool, body fluids, and liver tissue
- **GOLD STANDARD** for acute disease: serum IgM anti HAV; the antibody is positive at onset of symptoms, peaks during the convalescent phase, and stays detectable for up to six months after
- Treatment: mild self limited disease
  △ Prophylactic treatment: hepatitis A vaccine now recommended for
    △ All kids 12–23 months of age
    △ All international travelers
    △ Patients with chronic liver disease
    △ Patients with clotting factor disorders
- Combination vaccine for the prevention of hepatitis A and hepatitis B virus has been approved

**Paramyxovirus**
- Spherical
- Enveloped virus
- ssRNA

**RUBEOLA/MEASLES**
- Most contagious virus known
- Responsible for almost 1 million deaths worldwide
- Clinical syndromes divided into three categories:
  △ Typical
  △ Modified—partially immune host, clinical signs are milder with longer incubation period
  △ Atypical – infection of host previously immunized with killed virus vaccine
- Suspected case of rubeola is reportable by law for outbreak prevention
- Clinical manifestations
  △ Incubation

**Symptoms include:** fever, malaise, vomiting, diarrhea, abdominal pain, mild hepatomegaly
- Jaundice is seen via serological detection one week after onset
- During prodrome period there is an elevation of aminotransferase levels
  △ Adults – symptomatic for several weeks up to six months
    △ 80% present with hepatomegaly
    △ 70% present with jaundice
    △ Less than one percent progress to fulminant hepatic failure, often in patients with underlying liver disease
    △ 11% of cases manifest as a transient, discrete, maculopapular, urticarial, or petechial rash
    △ Rarely, persistent hepatitis A develops into a globulinemia with cutaneous vasculitis
- Diagnosis
  - HAV RNA detection of stool, body fluids, and liver tissue
  - **GOLD STANDARD** for acute disease: serum IgM anti HAV; the antibody is positive at onset of symptoms, peaks during the convalescent phase, and stays detectable for up to six months after
- Treatment: mild self limited disease
  - Prophylactic treatment: hepatitis A vaccine now recommended for
    △ All kids 12–23 months of age
    △ All international travelers
    △ Patients with chronic liver disease
    △ Patients with clotting factor disorders
  - Combination vaccine for the prevention of hepatitis A and hepatitis B virus has been approved
- Complications—greater than 3 days post exanthema indicates a complication
  △ Thrombocytopenic purpura
  △ Tracheobronchitis – with involvement of upper respiratory tract
  △ Otitis media and pneumonia from the secondary bacterial infection,
  △ Reactivation of tuberculosis—secondary to effect on cellular immunity
  △ Neurological syndromes
    △ Subacute sclerosing panencephalitis (SSPE) — progressive degenerative disease of the CNS
      △ Presents 7–10 years post infection
      △ Risk factor (50%): development of measles before age 2
    △ Post-infectious encephalomyelitis — autoimmune related demyelinating disease that appears within weeks of exanthem

**Symptoms include:** fever, malaise, vomiting, diarrhea, abdominal pain, mild hepatomegaly
- Jaundice is seen via serological detection one week after onset
- During prodrome period there is an elevation of aminotransferase levels
  △ Adults – symptomatic for several weeks up to six months
    △ 80% present with hepatomegaly
    △ 70% present with jaundice
    △ Less than one percent progress to fulminant hepatic failure, often in patients with underlying liver disease
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**Paramyxovirus**
- Spherical
- Enveloped virus
- ssRNA

**RUBEOLA/MEASLES**
- Most contagious virus known
- Responsible for almost 1 million deaths worldwide
- Clinical syndromes divided into three categories:
  △ Typical
  △ Modified—partially immune host, clinical signs are milder with longer incubation period
  △ Atypical – infection of host previously immunized with killed virus vaccine
- Suspected case of rubeola is reportable by law for outbreak prevention
- Clinical manifestations
  △ Incubation
Chapter 17    VIRAL DISEASES

- Replication occurs in the cytoplasm of host cells of the nasopharynx and lymph nodes
- Hematogenous spread leads to infection of the skin and other organs. The virus is able to freely cross the placenta
- Host sheds the virus almost two weeks prior to the onset of the rash, and to a lesser degree, up to a week after onset of symptoms
- Incubation period: 2–3 weeks
- Transmission: via droplets or direct contact with nasal secretions
- Postnatal acquired rubella syndrome
  - Clinical manifestations
    - 25–50% of patients can be asymptomatic, symptoms are commonly more severe in adults than children
    - Generalized tender lymphadenopathy for up to a week: involves all nodes, most striking in the suboccipital, postauricular, and posterior cervical nodes
    - Low-grade fever and malaise lasting 1–2 days, begins two weeks after initial infection
    - Enanthem – “Forscheimer’s spots”

Togaviruses
- Enveloped
- ssRNA
- Rubella: German measles (Fig. 17-22)
  - Affects adult and children, predominant age of infection: children 5–9 years old
  - Known as “3-day measles”
  - Pathogenesis
    - Virus acquired via inhalation of droplets and infection of nasopharyngeal cells

FIGURE 17-22 Rubella. (Courtesy of Dr. Stephen Tyring.)
RNA VIRUSES

- Nonspecific pinpoint red macules and petechiae over the soft palate and uvula just before or along with the exanthem
- Exanthem – erythematous maculopapular rash, progresses cephalocaudally, and may be followed by desquamation, lasts 3–5 days (same distribution and appearance of measles rash, with milder symptoms)
- Myalgias and polyarthritis coincide with appearance of exanthem and can persist for a few weeks up to a month. It is most commonly found in young women
  - Complications
    - Post infectious encephalitis
    - Thrombocytopenic purpura
    - Arthritis/arthritis

- Congenital rubella syndrome
  - Affects the fetus of a pregnant woman without immunity to the virus
  - Greatest hazard if fetus infected during first trimester, up to eighty percent suffer complications

- Treatment
  - Congenital rubella syndrome: no treatment available, acetaminophen for fever, and supportive care
  - Postnatal rubella: no specific treatment, disease is usually self-limited
  - Contact isolation in patients for 7 days after exanthem onset
  - Contact isolation necessary for congenitally infected children for one year until cultures are negative

- Preventative measures
  - MMR vaccine given in 2 doses
    - Dose #1 between 12 and 15 months of age
    - Dose #2 recommended at 4 to 6 years of age
  - Contraindicated in pregnant women
  - Relative contraindication in patients allergic to eggs, the immunodeficient or immunocompromised population
  - Most effective prevention of congenital rubella syndrome is immunization of non-immune women before pregnancy or immunization immediately post-partum

Flaviviruses

- Enveloped
- ssRNA
- Flaviviruses of clinical importance: hepatitis C, yellow fever, Dengue fever, West Nile virus

Hepatitis C (HCV)

- Uses an RNA dependent RNA polymerase for viral replication which lacks proofreading ability and creates slightly mutated strands, leading to the difficulty in control of and development of a vaccine against the virus
- Transmission: percutaneous, body piercing and tattoos, inhaled cocaine, blood, sexual intercourse
- Population at risk: IV drug abusers, sexually active patients, health care workers, hemodialysis patients, blood transfusion recipients (especially before 1992)
- Incubation: 7–8 weeks
- Acute hepatitis C is self limited and rarely causes hepatic failure
  - 80% of cases persist greater than 6 months leading to chronic infection
• Chronic viral hepatitis is most commonly caused by HCV
  • Most patients with chronic HCV have chronic liver disease, which can progress to cirrhosis and hepatocellular carcinoma
  • Alcohol increases the clinical severity of chronic disease
• Diseases associated with chronic hepatitis C:
  • Immune complexes: skin, kidney (glomerulonephritis)
  • Sialadenitis
  • Autoimmune thrombocytopenic purpura
  • Lymphoma: increased antibodies to HCV in patients with non-Hodgkin’s B-cell lymphoma (20% to 40%)
  • Mixed cryoglobulinemia (types II and III)
  • Porphyrria cutanea tarda
  • Lichen planus
  • Polyarteritis nodosa (5%)
  • Pruritus (39%)
• Clinical course
  • Usually mild with no outward signs of infection
  • Symptoms indistinguishable from other types of acute viral hepatitis
  • Fever (60%), fatigue, malaise (67%), nausea and vomiting, anorexia
  • Jaundice (< 25%)
  • Hepatomegaly
  • Dark urine (84%)
  • mild right upper quadrant pain
  • Extrahepatic manifestation of HCV infection
    – Palmar erythema, spider nevi, asterixis, clubbing
    – Icteric sclera, temporal muscle wasting, enlarged parotid
    – Gynecomastia, scant body hair
    – Peri-umbilical hernia, ascities, caput medusae, abdominal bruit
    – Ankle edema
• Diagnosis
  • Bilirubin – unconjugated and conjugated can be markedly elevated
  • Alkaline phosphatase – mild elevation
  • Aminotransferases – elevated 6–12 weeks post exposure in acute HCV
  • Elevation of ALT levels for 6 months or greater define chronic hepatitis
    – These levels fluctuate so a normal value does not indicate eradication of disease
    – AST/ALT ratio > 1 is associated with cirrhosis in chronic HCV
  • HCV RNA becomes positive in acute cases within eight weeks post-exposure, confirmation of ongoing diseases are established via these markers
  • Hepatitis C antibody test (anti HCV serological screening) via enzyme immunoassay test (EIA), unable to distinguish acute from chronic infection
  • Recombinant immunoblot assay – detection of antibody against 2+ antigen
    ▲ Resolution of HCV infection is indicated by a positive immunoblot assay and two or more instances of undetectable HCV RNA
  • Quantitative assay to confirm HCV RNA, via PCR of the blood
    ▲ This can help predict host response to treatment, and changes in HCV RNA levels
• Positive results of EIA, RIBA, and PCR testing are diagnostic for active HCV infection, host should then be treated
  • If these markers persist for greater than six months, the disease is defined as chronic liver disease
  • Positive alpha fetoprotein in patients with chronic HCV may indicate hepatocellular carcinoma
• Histological findings
  • Lymphocytic infiltration, moderate degrees of inflammation and necrosis, and portal or bridging fibrosis are noted
  • Regenerative nodules are seen in patients with cirrhosis
• Treatment
  • Eradication of HCV is defined as absence of HCV RNA in serum for six months or greater secondary to antiviral therapy
  • Antiviral therapy should be considered if:
    – Elevated ALT levels; however up to 30% of patients with chronic HCV have normal ALT
    – Positive HCV antibody and serum HCV RNA
    – Liver biopsy shows portal or bridging fibrosis with moderate inflammation and necrosis
  • Acute HCV treatment
    – Interferon monotherapy
    – Pegylated interferon
    – Pegylated interferon + ribavirin (most effective) antiviral therapy is highly effective if given for 12–24 weeks
  • Chronic HCV treatment
    – Pegylated interferon + ribavirin. Weekly injections of PEG-IFN alfa combined with twice daily doses of ribavirin (most effective).
      Two types of pegylated interferon use
        ▲ Peg-IFN alfa 2b 1.5 mcg/kg SC weekly or
        ▲ Peg-IFN alfa 2a 180 mcg SC weekly
    – Ribavirin: 400–600 mg taken by mouth twice daily
    – Combination therapy: Treatment individualized via genotype

Chronic viral hepatitis is most commonly caused by HCV

Most patients with chronic HCV have chronic liver disease, which can progress to cirrhosis and hepatocellular carcinoma.

Alcohol increases the clinical severity of chronic disease.

Diseases associated with chronic hepatitis C:

- Immune complexes: skin, kidney (glomerulonephritis)
- Sialadenitis
- Autoimmune thrombocytopenic purpura
- Lymphoma: increased antibodies to HCV in patients with non-Hodgkin’s B-cell lymphoma (20% to 40%)
- Mixed cryoglobulinemia (types II and III)
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This can help predict host response to treatment, and changes in HCV RNA levels.

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If these markers persist for greater than six months, the disease is defined as chronic liver disease.

Positive alpha fetoprotein in patients with chronic HCV may indicate hepatocellular carcinoma.

Histological findings:

- Lymphocytic infiltration, moderate degrees of inflammation and necrosis, and portal or bridging fibrosis are noted
- Regenerative nodules are seen in patients with cirrhosis.

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- Antiviral therapy should be considered if:
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  - Pegylated interferon.
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- Chronic HCV treatment:
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    Two types of pegylated interferon use
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      ▲ Peg-IFN alfa 2a 180 mcg SC weekly.
  - Ribavirin: 400–600 mg taken by mouth twice daily.
  - Combination therapy: Treatment individualized via genotype.
RNA VIRUSES

- HCV Genotype 1—high dose medication for 48 weeks
- HCV Genotype 2 or 3—medication given for 24 weeks
  - Pegylated interferon monotherapy
  - Interferon monotherapy
- Combination therapy is most effective against genotype 2 and 3, leads to 80% eradication of HCV RNA
  - Treatment has a better outcome in patients < 40 years old, absence of cirrhosis, and shorter duration of infection
  - Treatment precaution
- Interferon therapy aggravates autoimmune disorders, and is contraindicated in patients with platelet levels < 50,000
- Interferon therapy poses increased risk of depression and suicidal ideation and should be used with caution in certain patient populations
- Use of corticosteroids has been linked with increased mortality
- Ribavirin can induce hemolytic anemia and has strong association with birth defects and should be avoided during pregnancy

Retroviruses

- Enveloped
- ssRNA
- Use a reverse transcriptase

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

- Estimated 1.1 million people in US infected with HIV, affecting predominately young adults between ages 25–44 years
- Targets and destroys CD4+ T lymphocytes leaving the body in state of severe immunodeficiency open for opportunistic infections and malignancies
- Viral structure
  - Diploid genome – 2 molecules of RNA, p24 nucleocapsid core protein, envelope proteins: gp41 and gp120; reverse transcriptase
- Route of infection
  - HIV enters CD4 lymphocytes via adherence of envelope proteins to the cell. Reverse transcriptase converts single stranded viral RNA to double stranded DNA which is inserted into the hosts DNA. Virions are released and the lymphocytes are destroyed, eventually leading to an immunodeficient state
- HIV can infect: CD4+ T cells, macrophages, thymic cells, astrocytes and dendritic cells
- Stages of HIV infection
  - Viral transmission
    - Sexual activity (70%)
  - Coexistence of a sexually transmitted disease with genital ulceration has four times higher rate of transmission
  - Increased risk in homosexual population
- Blood and body fluids
  - Needles
  - IV drug abusers
  - Accidental needle sticks
  - Perinatal transmission in HIV infected women
  - Transmission has been reduced with HIV testing of pregnant women and treatment with antiretroviral drugs
  - Breastfeeding post-partum
  - Recipients of blood transfusions (especially between 1975–85)
  - Organ transplantation
  - Genetics
    - Patients with a homozygous CCR5 gene mutation for a cell surface protein and co receptor of the virus are immune to the HIV virus. Those with a heterozygous gene mutation have a slower course of disease. Patients with a CXCR1 gene mutation have a rapid progression of HIV to AIDS
  - Primary HIV infection
    - Predominant percentage of HIV infections transmitted during this time because of increased level of viremia and very nonspecific symptoms
    - Presence of acute symptoms for greater than 14 days correlates with increased risk of progression to AIDS in 3 years
    - 6 months post infection—CD8 T cells allow viremia to level out and prevent further destruction of CD4 count
  - Seroconversion
    - After 4–10 weeks post exposure, patient will have positive HIV serology
    - 95% of patients seroconvert within 6 months
  - Mononucleosis like symptoms:
    - Headache, retro-orbital pain, muscle aches, fever, pharyngitis, fatigue, lymphadenopathy, weight loss, night sweats, fine morbilliform rash and mucutaneous ulcers
  - Clinical latent period
    - Period of time with no signs of virus except lymphadenopathy
    - From seroconversion to six months after transmission
    - During this time there is an increased rate of viral replication and CD4 cell destruction
    - Viral load – measures rate of disease progression and antiviral therapy response in early stage of disease. Stable at 6 months, can increase very slowly without treatment
• Early symptomatic HIV infection
  − These diseases are most severe in association with the HIV infection. Cutaneous manifestations include:
    ▶ Thrush
    ▶ Oral hairy leukoplakia
    ▶ Herpes (2+ episodes)
    ▶ Bacillary angiomatosis

• AIDS
  − Defined as a CD4+ count of < 200 cell/mm³
  − CD4+ count measures degree of immunosuppression
  − Also defined by diseases which have their onset in the setting of severe immunosuppression
    ▶ Pneumocystis carinii pneumonia
    ▶ Candidiasis of the upper respiratory system
    ▶ Kaposi’s sarcoma
    ▶ Mycobacterium avium
    ▶ Disseminated mycobacterium tuberculosis
    ▶ Cytomegalovirus
    ▶ Dementia secondary to HIV infection
    ▶ Invasive cervical anal cancer
    ▶ Toxoplasmosis of internal organ
    ▶ Burkitt’s lymphoma
  − Advanced HIV with CD4 < 50 cell/mm³. Patients will survive only 1 year without antiviral therapy once their disease has become so advanced

• Clinical manifestations
  − Acute retroviral syndrome—presents four weeks after patient infected with the virus (70% of HIV + patients)
  − Primary symptoms (resembles symptoms of mononucleosis)
    − Headache, retro-orbital pain, muscle aches, fever, pharyngitis, fatigue, lymphadenopathy, weight loss, and a fine morbilliform rash, mucutaneous ulcers

• Diagnosis
  − ELISA – detects antibodies in blood to virus, 3–7 weeks after infection [high sensitivity, moderate specificity]
  − Western blot assay – confirmatory test (low sensitivity, high specificity)
  − Viral load measured by PCR
  − Baseline testing: CD4+ cell count, chest x-ray, PPD, VDRL/RPR, serology for CMV, VZV, hepatitis, and toxoplasmosis; HIV antibody test, and HIV viral load
  − Acute HIV infection diagnosed with:
    − Positive p24 antigen
    − High viral load (>100,000)
    − Negative serology test
    − Mild clinical symptoms

• Antiretroviral therapy (Table 17-4)
  − Without antiviral therapy patient progresses into a stage of acquired immunodeficiency within ten years of transmission, when CD4 count reaches < 200 cells/mm³
  − Since development and use of highly active antiretroviral therapy (HAART), there has been a decline in the trend of newly infected HIV and AIDS patients
  − Treatment should be initiated if
    − Patient diagnosed with AIDS or has symptomatic HIV
    − CD4 count is below 350 cells/mm³,
    − HIV RNA levels are greater than 50,000 copies/mL
  − Combination regimen
    − A non-nucleoside reverse transcriptase inhibitor + 2 nucleoside reverse transcriptase inhibitors

Table 17-4 Seven Classes of Antiretroviral Drugs

| Nucleoside Reverse Transcriptase Inhibitors (NRTIs) |
|-----------------|-----------------|-----------------|
| **Drug**        | **Dose**        | **Side Effects** |
| Zidovudine [Retrovir] | 200 mg three times daily | Bone marrow suppression, Myopathy |
| Lamivudine, 3TC [Epivir] | 150 mg twice daily | Hepatitis B exacerbation, Hepatomegaly with steatosis, Peripheral neuropathy, Rhabdomyolysis, Anaphylaxis, Myalgia/arthritis, Abnormal dreams |

(Continued)
### TABLE 17-4 (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stavudine</td>
<td>40 mg tablet twice daily</td>
<td>Discontinue if peripheral neuropathy occurs</td>
</tr>
<tr>
<td>[Zerit]</td>
<td></td>
<td>Hyperlactatemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe motor weakness</td>
</tr>
<tr>
<td>Didanosine</td>
<td>100 mg</td>
<td>Fatal and nonfatal pancreatitis</td>
</tr>
<tr>
<td>[Videx]</td>
<td>2 tablets twice daily</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaphylactoid reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>Discontinued in America</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>[Hivid]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>300 mg twice daily</td>
<td>Fatal anaphylaxis</td>
</tr>
<tr>
<td>[Ziagen]</td>
<td></td>
<td>Liver failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200 mg tablet once daily</td>
<td>Adult respiratory distress syndrome</td>
</tr>
<tr>
<td>FTC [Emtriva]</td>
<td></td>
<td>Respiratory failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe hypotension</td>
</tr>
<tr>
<td>Combivir</td>
<td>Zidovudine 300 mg Abacavir 300 mg twice</td>
<td>Zidovudine associated hematologic toxicity and myopathy</td>
</tr>
<tr>
<td></td>
<td>daily</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myositis</td>
</tr>
<tr>
<td>Triziv</td>
<td>Zidovudine 300mg Lamivudine 150mg</td>
<td>Not for use if weight &lt; 40 kg</td>
</tr>
<tr>
<td></td>
<td>Abacavir 300 mg</td>
<td>Fatal anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Twice daily</td>
<td>Liver failure</td>
</tr>
<tr>
<td></td>
<td>Has good viral suppression, should be</td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td>used in cases when Efavirenz is</td>
<td>Severe hypotension</td>
</tr>
<tr>
<td></td>
<td>ineffective</td>
<td>Adult respiratory distress syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory failure</td>
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<tr>
<td></td>
<td></td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythema multiforme</td>
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<tr>
<td></td>
<td></td>
<td>Toxic epidermal necrolysis</td>
</tr>
</tbody>
</table>
### TABLE 17-4 (Continued)

#### Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atripla</strong></td>
<td>Efavirenz 600 mg Emtricitabine 200 mg Tenofovir 300 mg One tablet at night on empty stomach</td>
<td>Associated with dizziness, drowsiness, impaired concentration Not recommended for patients younger than 18 yrs old. Sudden discontinuation of drug can severely exacerbate HBV infection</td>
</tr>
<tr>
<td><strong>Epzicom</strong></td>
<td>Abacavir 600 mg Lamivudine 300 mg Once daily</td>
<td>Lactic acidosis FDA pregnancy category C Increased thirst, urination Seizures, mood changes Do not take if hypersensitivity to Abacavir</td>
</tr>
<tr>
<td><strong>Truvada</strong></td>
<td>Emtricitabine 200 mg Tenofovir 300 mg Once daily on an empty stomach</td>
<td>Pancreatitis Lactic acidosis Severe heptomegaly with steatosis</td>
</tr>
</tbody>
</table>

#### Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

**Commonly Seen Side Effects: Cytochrome P450 Inducers, Rash**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine [Viramune]</td>
<td>200 mg daily X 14 days</td>
<td>Hepatotoxicity in women with reduced T-cell levels Fatal hypersensitivity reaction Steven-Johnson syndrome Rhabdomyolysis Granulocytopenia Angioedema Severe stomatitis</td>
</tr>
<tr>
<td>Delavirdine [Rescriptor]</td>
<td>200 mg three times daily in 3 oz water</td>
<td>Mild rash resolves in 3–14 days Angioedema Granulocytosis, leukopenia, pancytopenia GI bleed Cardiomyopathy Rhabdomyolysis Acute renal failure</td>
</tr>
<tr>
<td>Etravirine TMC-125 [Interlence]</td>
<td>100 mg 2 tablets twice daily after meals</td>
<td>Used for multi-resistant strains, do not use in naïve patients or children Tablet must be swallowed whole with liquids Severe skin rash, extremity tingling, high blood pressure</td>
</tr>
<tr>
<td>Efavirenz [Sustiva]</td>
<td>600 mg at bedtime on empty stomach</td>
<td>CNS symptoms: confusion, depression, hallucinations, seizures, memory loss, suicidal thoughts Exfoliative dermatitis False positive marijuana drug testing Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td>Side Effects</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>500 mg 2 tablets twice daily with food Given with Norvir 100 mg once daily</td>
<td>Hepatotoxicity, Diabetes mellitus, Pancreatitits, Seizures, Steven-Johnson syndrome, Thrombocytopenia, Portal hypertension, Thrombophlebitis, Intestinal obstruction</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>300 mg 2 tablets twice daily</td>
<td>Hepatotoxicity, Diabetes mellitus, Pancreatitits, Seizures, Steven-Johnson syndrome, Thrombocytopenia, Portal hypertension, Thrombophlebitis, Intestinal obstruction</td>
</tr>
<tr>
<td>Indinavir</td>
<td>400 mg Two tablets every 8 hours without food</td>
<td>Nephrolithiasis, Lipodystrophy, Anemia</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>750 mg three times daily with food</td>
<td>Avoid mixing with acidic food/juice, Diarrhea, Leukopenia, Suicidal ideation, Hepatitis, Jaundice, Don’t treat pregnant patients due to ethyl methanesulfonate</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>Discontinued in the United States</td>
<td></td>
</tr>
<tr>
<td>Kaletra</td>
<td>200 mg Lopinavir + 50 mg Ritonavir Two tablets twice daily (used in pediatric and naïve population)</td>
<td>Pancreatitis, Neutopenia, Thrombocytopenia (peds), Exfoliative dermatitis, Hemarthrosis in hemophiliacs</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>700 mg Two tablets twice daily without food – for naïve patients 700 mg Fosamprenavir two tablets/daily + 100 Ritonvair once daily without food – for resistant patients</td>
<td>Increased liver enzymes, Severe skin reactions, Neutopenia, Fat redistribution, Hemolytic anemia</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>250 mg co-administered with 100 mg Ritonavir Two tablets, twice daily with food</td>
<td>Hypercholesterolemia, hyperlipidemia, Intracranial hemorrhaging, Platelet aggregation and coagulation, rash, Contraindicated in: treatment naïve patients, potent CYP 3A inducers, Child-Pugh class B or C</td>
</tr>
</tbody>
</table>

(Continued)
### Protease Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir</td>
<td>Prezista 300 mg 2 tables twice daily with food</td>
<td>Severe skin rashes</td>
</tr>
<tr>
<td>[Prezista]</td>
<td>Taken with Ritonavir 100 mg 1 tablet twice daily with food for resistant patients</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>** Must be taken with Ritonavir to keep Prezista level high in blood</td>
<td>Fat redistribution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inflammation nose and throat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>**Contains sulfa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid if hepatic impairment</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>200 mg Two tablets once daily with food (naïve patients)</td>
<td>1st or 2nd degree AV block</td>
</tr>
<tr>
<td>[Reyataz]</td>
<td>300 mg Atazanavir + 100 mg Ritonavir One daily with food – resistant patients</td>
<td>PR prolongation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe hyperglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysuria, hematuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immune reconstruction syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated CK</td>
</tr>
</tbody>
</table>

### Nucleotide Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>300 mg daily</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>[Viread]</td>
<td></td>
<td>Severe hepatomegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypophosphatemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fanconi syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute renal tubular necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteomalacia with renal tubulopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspnea</td>
</tr>
</tbody>
</table>

### Fusion Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide, T-20</td>
<td>90 mg subcutaneous injection twice daily for resistant strains</td>
<td>Injection site reactions: redness, swelling, itching</td>
</tr>
<tr>
<td>[Fuzeon]</td>
<td></td>
<td>Increased risk of bacterial pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guillain-Barrè syndrome</td>
</tr>
</tbody>
</table>
### CCR5 Co-receptor Antagonist

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc [Selzentry]</td>
<td>300 mg twice daily ** only effective against CCR5-tropic HIV</td>
<td>Myocardial ischemia or infarction Orthostatic hypotension Hepatotoxicity Infection Malignancy</td>
</tr>
</tbody>
</table>

### Integrase inhibitor

To Be Used in Combination With Other Antiretroviral Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir [Isentress]</td>
<td>400 mg twice daily Used in multi-drug resistant strains</td>
<td>Diarrhea, nausea, headache Skin rash Myopathy Rhabdomyolysis Elevated levels of creatinine kinase Gastritis Myocardial infarction</td>
</tr>
</tbody>
</table>

- Protease inhibitor + 2 nucleoside reverse transcriptase inhibitors
- 3 nucleoside reverse transcriptase inhibitors (least effective)
- Goal: to reduce viral load, and increase CD4 counts

### Quiz

#### Questions

1. A 28-year-old pregnant (2 months) woman from Iran has an erythematous rash that started on the head and spreads to the trunk. She has had three days of fever associated with pain in the back of her neck, joint pain, and headache. The probability that the baby will be infected is:
   - A. 85% to 90%
   - B. 100%
   - C. The baby will not be infected
   - D. 10%
   - E. 40% to 60%

2. Which of the following serologic markers is the most important to determine newborn infection with hepatitis B?
   - A. HBsAG
   - B. HBeAG
   - C. HBcAG
   - D. HBSAb
   - E. HAAg

3. A college student does not go to her scheduled class. She has fever, sore throat, malaise, fatigue and a bump in the right side of the neck. Her abdominal exam showed a increased liver size. The microscopic exam of the epithelial cells revealed a giant nuclei surrounded by clear zones. The cause of the infection is:
   - A. Cytomegalovirus
   - B. HIV
   - C. Herpes virus type 1
   - D. Herpes virus type 2
   - E. Papilloma virus

4. A 3-year-old infant is taken by his mother to the doctor. She says he has had fever, malaise and abdominal pain for the last 4 days, today he presents with erythematous macules with a gray center and vesicles surrounded by erythema. The lesions are distributed on hands, feet and buttocks. The infectious virus is:
A. ssRNA enveloped virus  
B. dsRNA non enveloped virus  
C. ssRNA nonenveloped virus  
D. dsDNA noneveloped virus  
E. dsDNA enveloped virus

5. A pregnant woman has small (1 to 3 mm), discrete, smooth-surfaced, flesh-colored papules. Some may coalesce into larger plaques. The lesions started 2 months ago, and they have been increasing in size and number. She visits her doctor and asks for treatment. Which of the following options would be the best for her?  
A. Podophyllin  
B. Podophyllotoxin  
C. 5-Fluorouracil  
D. Imiquimod  
E. Cryotherapy

6. A 6-year-old girl presents with a rash that started on the trunk and spread to the face and extremities. At physical exam she presented with vesicles, pustules and crusts on her skin. Her mother had the infection 5 years ago and she had a new baby 1 month ago. Which immunoglobulin will protect the 1-month-old baby from getting the infection?  
A. IgM  
B. IgG  
C. IgE  
D. IgD  
E. IgA

7. A 12-year-old boy is brought in by his mother with the complaint of a rash that began 4 days ago. She states she believed her son had the flu about a week before the rash onset. He suffered from cough, runny nose, watery eyes, and was very lethargic. She treated him with over-the-counter decongestants and children’s Tylenol for his fever, which she said reached 101 degrees Fahrenheit. Just 3 days ago she noticed a non-pruritic erythematous rash had appeared behind his ears, and now had spread down to his trunk and upper extremity. Physical examination of the patient reveals an erythematous maculopapular rash across his face and on the anterior aspect of his trunk. Two-mm blue-gray papules with erythematous base are visualized adjacent to his lower molars. The patient appears alert and oriented to time and place, and is able to follow the commands of the doctor. The papules visualized adjacent to his molars are commonly known as:

8. An 8-year-old black male with sickle cell anemia complains for two days of malaise and his mother noticed an erythematous, lacy macular eruption on the cheeks, trunk and extremities. His doctor is concerned that this viral infection will cause an aplastic crisis. The virus related to this association is:
A. Varicella zoster virus  
B. Herpes simplex virus  
C. Coxsackie A-16  
D. Coxsackieviruses A 1–10  
E. Parvovirus B19

9. A 16-year-old high school student presents to the nurse with complaints of problems swallowing, extreme fatigue and a pruritic erythematous rash. Physical examination of the girl shows swollen erythematous tonsils, tender and enlarged cervical lymph nodes with mild hepatosplenomegaly. The patient’s mother has been administering ampicillin to the child for the past 2 days. Blood tests of this patient would reveal:
A. Hyperlipidemia  
B. An increase concentration of IgM antibodies to EBV  
C. Leukopenia  
D. Microcytic anemia  
E. A decrease concentration of IgG antibodies to HCV

10. A 33-year-old male presents to a local clinic by his ski lodge with complaints of low grade fever, headaches, muscle aches, and a vesicular rash of the upper extremity for the past 5 days. Closer examination of the rash reveals vesicles shaped as teardrops mounted on an erythematous base intermixed with resolving crusted lesions along his trunk, face, and mucus membranes. Scrapings of the vesicles are expected to reveal:
A. Eosinophils  
B. Owl’s eyes inclusion bodies  
C. Hyphae  
D. Multinucleated giant cells  
E. None of the above

Answers
1. E. The greatest danger from rubella is to the fetus. If the infection occurs during the first 2 months of gestation the risk varies from 40% to 60%. If
the infection occurs during the fourth month the risk to infection will drop to 10%. A and B do not represent the risk during the pregnancy period described. C. Rubella has a vertical transmission. D. 10% is the risk that the fetus will be infected if the mother gets infected during the fourth month of pregnancy.

2. D. HBeAg is an important indicator of transmissibility and virus replication A. HBsAg is found on the surface of HBV; it is positive during acute disease. The continued presence indicates carrier stage. B. HbcAg is positive during the window phase; IgM HbcAb is an indicator of recent disease. C. HBsAb is the antibody to HBsAg; provides the immunity to hepatitis B. E. HA Ag is the antigen for HAV.

3. A. Cytomegalovirus produces the owl’s eye nuclei (giant nuclei surrounded by clear zones). B. Epithelial cells do not show HIV. C and D. Herpes histology will show ballooning of the infected cells, intranuclear inclusions and multinucleated giant cells. E. Papilloma virus is characterized by the presence of abnormal cells that have a vacuolated with clear cytoplasm or perinuclear halos and nuclear pyknosis.

4. C. The virus infecting this infant is a coxackie A-16. It is a picornavirus and is an ssRNA non-enveloped virus. A. HCV is an ssRNA enveloped virus. C. HEV is an ssRNA non-enveloped virus. D. HBV is a dsDNA nonenveloped virus.

5. E. Cryotherapy is a destructive method that does not cause any harm to the fetus when it is used as therapy for genital warts. A, B and C are teratogenic drugs. D. Does not have studies that support its use in genital warts in pregnancy.

6. B. IgG is the only immunoglobulin that diffuses into fetal circulation. It will provide protection during the first 4 to 6 months of life. A. IgM is a pentamer and is the first antibody detected in serum after exposure to an antigen. C. IgE is involved in hypersensitivity and allergic reactions. It leads to mast cell degranulation and the release of leukotrienes. D. It does not reach appreciable plasma concentrations. Functions as a cell surface receptor. E. IgA is found in tears, Colostrum, saliva and other secretions.

7. B. Koplik spots are pathognomonic for measles, which commonly affects children. They can be described as “grains of salt on a red background.” The spots are 1–3mm blue-gray elevations with an erythematous base. They are often found on the buccal mucosa, adjacent to the lower molars. The Koplik spots surface about 24 hours before the rash appears on the patient’s face. Commonly, within 5–6 days the rash, fever and Koplik spots fade with no further complications. A. Nikolsky sign is described as the result of the loss of epithelial cell-to-cell adhesion of the skin. In patients suffering from an autoimmune skin disorder such as pemphigus, if pressure is applied to the skin an extension of the blister to the adjacent area of skin is seen. D. Herpangina manifests itself on the mucous membrane as 1–2 mm slight elevated gray-white papulovesicular lesions with an erythematous surrounding. They are often seen on the soft palate, uvula, and posterior pharynx. This disease is caused by the coxsackieviruses. E. The oral ulcerative lesions of hand-foot-mouth disease are often located on the palate, tongue, as well as the buccal mucosa. They are caused by the coxsackieviruses, and are small rapidly ulcerating lesions, and are on an erythematous base.

8. E. Parvovirus infection is associated with aplastic crisis in sickle cell anemia patients. Varicella zoster virus is associated with encephalitis or pneumonia when its infection results in chickenpox. Herpes simplex virus is not associated with aplastic crisis but type 1 can cause Ramsay hunt. Coxsackie A-16 produces hand-foot-mouth disease. Coxsackie A-1 to -10 produce herpangina.

9. B. This patient is suffering from infectious mononucleosis, which commonly affects patients in their late teens through their twenties. This patient presents with classic clinical symptoms such as extreme fatigue, cervical adenopathy, and hepatosplenomegaly. Since this patient is suffering from an acute disease it is expected that the patient will have an increase in IgM antibodies against Epstein-Bar virus (EBV). A, D. An elevated lipid count or a microcytic anemia is incorrect. An acute EBV infection has no affect on lipid levels or red blood cells. C. Usually with an infection it is expected that the total white blood cell count will increase by 20%, not decrease. E. This patient is suffering from acute infectious mononucleosis, not hepatitis C. You would expect to see elevated titers of IgM in an acute infection, not IgG.

10. D. Patients suffering from herpes zoster will initially present with an erythematous maculopapular rash that rapidly evolves into a grouped vesicular rash within three to four days and resolves two weeks later. Scraping of the vesicular rash are expected to show multinucleated giant cells, when are visualized on a Tzanck smear. Eosinophils are expected to be found in scraping of erythema toxicum vesicles of the newborn. Owl eye inclusion bodies are pathognomonic for CMV infections and not expected to be seen in this patient. Hyphae are normally obtained from vesicular scrapings of children suffering from candidial diaper dermatitis.
These are commonly due to infrequent diaper change or use of antibiotics.

REFERENCES


Shafran SD, Tyring SK, Ashton R, et al: Once, twice, or three times daily famciclovir compared with acyclovir for the oral treatment of herpes zoster in immunocompetent


**Impetigo (Fig. 18-1)**

- Superficial nonfollicular infection most often due to *Staphylococcus aureus* or group A *Streptococcus* occurs more commonly in children
- Clinical:
  - Lesions can begin as an erythematous papules that evolves into a vesicle or pustule. The pustules may rupture leaving contagious honey-colored crusts
- Treatment: topical mupirocin
- Bullous impetigo is a toxin-mediated erythroderma (Fig. 18-2) is caused only by *Staphylococcus aureus*
- Separation of the epidermis is due to exotoxin produced by staphylococci
- Toxin cleaves desmoglein 1
- Sharply demarcated flaccid bullae without surrounding erythema
- Seen most frequently in newborns
- Treatment: dicloxacillin or first-generation cephalosporin, topical mupirocin
- Glomerulonephritis may follow up to 5% of cases of impetigo

**Ecthyma**

- Differs from impetigo in that the dermis is ulcerated
- Usually caused by group A beta-hemolytic streptococci
- Clinical:
  - Most commonly affects the lower extremities of children, persons with diabetes, and neglected elderly patients
  - Often occurring with lymphadenitis
  - Thick crusted ulcer that heals slowly and may produce a scar
  - Histology: ulceration to dermis with bacteria, crusting and an acute inflammatory infiltrate
  - Treatment: usually dicloxacillin or first-generation cephalosporin, parental antibiotics may be needed for widespread infection.

**Bacterial Folliculitis (Fig. 18-3)**

- Most cases caused by *S. aureus*
- Clinical:
  - Superficial infection: (facial involvement is called Bockhart’s folliculitis): red papules/pustules, follicularly-centered
  - Deep infection: (facial involvement is termed sycosis barbae); erythematous, fluctuant nodules
  - Lupoid sycosis: chronic form of sycosis barbae associated with scarring
  - Treatment: topical antibiotics, systemic antibiotics may be indicated

**Furuncles/Carbuncles (Fig. 18-4)**

- *S. aureus* most commonly found
- Clinical:
  - Deep-seated nodules around hair follicle (inflammation involves the subcutis)
  - Multiple furuncles make a carbuncle, evolve from preceding folliculitis
  - Treatment: topical mupirocin and dicloxacillin; if large, then also need drainage

**Abscess (Fig. 18-5)**

- Cutaneous abscesses represent a collection of purulent debris in the skin
- Usually *Staphylococcus aureus* (including possibly methicillin-resistant strains)
- Inguinal and perineal area may involve gram-negative flora
- Clinical:
  - Deep-seated nodules around hair follicle (inflammation involves the subcutis)
  - Fully-formed lesions are fluctuant
May be accompanied by fever, cellulitis, lymphangitis, lymphadenopathy, or leukocytosis
• Culture (useful when MRSA suspected)
• Treatment: warm compresses (to “ripen”), incision and drainage, systemic antibiotics

**Lymphangitis**

• Infection and inflammation of the lymphatic channels

Variety of causal bacteria – group A *Streptococcus*, *S. aures*, even *Pasteurella multocida* (cat-scratch fever)

• Clinical
  • Erythematosus and irregular appearing linear streaks in the skin
Staphylococcal Scalded-Skin Syndrome (Ritter’s Disease)

- Typically seen in children younger than 4 years of age
- Can occur in adult patients with renal insufficiency (cannot clear exotoxin)
- Exotoxins A or B; elaborated by bacteria, disseminated systemically
- Exotoxins cleave desmoglein 1 (similar mechanism to localized bullous impetigo); these toxins are serine proteases that actually cleave the desmoglein rather than simply binding to it.
- S. aureus: phage group II (types 3A, 3B, and 3C) (types 55 or 71) (exfoliative variants)
- S. aureus originates from a focus of infection other than the skin (differs from localized bullous impetigo)

Clinical
- Superficial blistering owing to disruption of the epidermal granular cell layer
- Sparing of mucous membranes
- Nikolsky’s sign present (extension of a blister resulting from lateral pressure to the border of an intact blister)
- Periorificial and flexural accentuation may be observed

Diagnosis:
- Frozen section tissue analysis to exclude toxic epidermal necrolysis (TEN) by level of blister formation:
  - SSSS – subcorneal separation
  - TEN – subepidermal separation
- Cultures of bullae are typically negative, but cultures from other sites (oral/nasal cavities, throat, axillary/genital/umbilical regions, blood) may demonstrate staphylococcus
  - Gram’s stain and/or culture from the remote infection site

Treatment: intravenous penicillinase-resistant penicillin, supportive measures

Prognosis: mortality rate less than 4% in children, greater than 50% in immunosuppressed patients

Cellulitis

- Acute bacterial infection of skin and soft tissues
- Often follows an introduction via fissuring, laceration, puncture or insect bite
- Vast majority of cases caused by Staph aureus
- May rarely be caused by Streptococcus pneumoniae or marine vibrio species

Clinical:
- Characterized by expanding edema, erythema, warmth, pain, tenderness
- The lesions are not sharply circumscribed
- Fever is common, and lymphangitis or lymphadenopathy may accompany the disease
- Epidermal necrosis or disproportionate pain may indicate necrotizing fasciitis

Treatment: mild cases treated with first-generation cephalosporins or dicloxacillin, more severe cases may be hospitalized for parenteral antibiotics

Staphylococcal Toxic Shock Syndrome (TSS)

- Toxins produced by S. aureus, many that act as superantigens, lead to pro-inflammatory cytokine cascades involving tumor necrosis factor, interleukin-1, M protein, and interferon-γ
- Toxin-1 (TSST-1) causes most menstrual-related cases
- Many in the population have protective antibodies for these toxins and are not predisposed to the disease
- TSS may be associated with non-rayon tampons, surgical packings, nasal packing

Criteria for staphylococcal toxic shock syndrome:
- Prodromal period of 2 to 3 days
Chapter 18  BACTERIAL DISEASES

Treatment: intravenous penicillinase-resistant penicillin clindamycin, fluid therapy, and supportive measures

**Blistering Distal Dactylitis**
- Group A beta-hemolytic streptococci
- Clinical:
  - Tense purulent blister of distal finger or toes, volar pad
  - Common in children, more rare in adults
  - Can be confused with herpetic whitlow
- Treatment: dicloxacillin or first-generation cephalosporin

**Erysipelas (Fig. 18-6)**
- Group A beta-hemolytic streptococci
- Clinical:
  - Febrile illness
  - Brightly erythematous, indurated plaque, often on face or legs with sharp margins
  - Lymphedema and chronic tinea pedi may predispose
- Diagnosis: antistreptolysin (ASO) may have some utility
- Treatment: penicillin, cephalosporins or macrolides (azithromycin or erythromycin)

**Scarlet Fever**
- Toxin-producing group A beta-hemolytic streptococci (GABHS)
- Fever, hypotension
- Skin findings: diffuse rash, occasionally patchy and erythematous, with desquamation occurring approximately 1 to 2 weeks later
- Involvement of three or more organ systems:
  - Gastrointestinal: vomiting or diarrhea
  - Muscular: myalgia, increased creatine phosphokinase level
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: increased blood urea nitrogen or creatinine, urinary sediment with pyuria (without evidence of urinary tract infection)
  - Hepatic: increased total bilirubin, serum glutamic-oxaloacetic transaminase (AST, SGOT), or serum glutamic-pyruvic transaminase (ALT, SGPT)
  - Hematologic: platelets <100,000/mm³
  - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent
- Negative results on the following tests
  - Rocky Mountain spotted fever
  - Leptospirosis
  - Measles
  - Hepatitis B
  - Antinuclear antibody
  - False-positive Venereal Disease Research Laboratory (VDRL) test results
  - Antibodies to Monospot testing
- Treatment: penicillinase resistant penicillin, clindamycin, intravenous gamma globulin, fluid replacement

**Streptococcal Toxic Shock Syndrome**
- *S. pyogenes* exotoxin A (SPEA) and *S. pyogenes* exotoxin B (SPEB): produced by group A beta-hemolytic streptococci
- Criteria for streptococcal TSS:
  - Isolation of group A *Streptococcus* from a normally sterile site (e.g., blood, cerebrospinal fluid, surgical wounds) or a non-sterile site (e.g., throat)
  - Hypotension (as defined earlier)
  - Involvement of two or more organ systems:
    - Renal: increased blood urea nitrogen or creatinine
    - Hematologic: coagulopathy
    - Hepatic: increased liver enzymes
    - Respiratory: acute respiratory distress syndrome
    - Cutaneous: tissue necrosis, (i.e., necrotizing fasciitis), erythematous rash
    - Desquamating rash

- **FIGURE 18-6** Erysipelas. (Reprinted with permission from Connor DH et al. Pathology of Infectious Diseases. Stamford, CT: Appleton & Lange; 1997, p. 819.)
- Produces erythrogenic exotoxin
- Clinical:
  - Fever and pharyngitis
  - Mucous membrane changes: white strawberry tongue turns into red strawberry tongue after 4 days
  - Skin changes: 2 to 4 days after initiation of fever, sandpaper-like rash starting on trunk then becomes more generalized; desquamates after 4 to 5 days
  - Circumoral pallor
  - Pastia’s lines: linear petechial rash over skin folds (axillary/antecubital)
- Diagnosis: antistreptolysin O (ASO) titers
- Treatment: penicillin or erythromycin

### Erythrasma (Fig. 18-7)

- *Corynebacterium minutissimum* a lipophilic gram-positive aerobic diphtheroid
- Clinical:
  - Superficial infection of the intertriginous areas (axillae, groin, digital web-spaces)
  - White maceration between fourth and fifth webspace
  - Inner thighs have reddish brown plaques without central clearing
- Diagnosis: fluoresce “coral red” with Wood’s lamp (owing to production of coproporphyrin III by the bacteria)
- Treatment: erythromycin or benzoyl peroxide

### Trichomycosis Axillaris

- *Corynebacterium tenuis* (gram-positive diphtheroid)
- Clinical:
  - White concretions on hair shaft, usually in axillae
  - Occasionally affects pubic hair (trichomycosis pubis)
  - Often seen with hyperhidrosis, usually asymptomatic; however, patients may complain of malodorous sweat
- Treatment: shave affected hair; use topical clindamycin or erythromycin

### Pitted Keratolysis (Fig. 18-8)

- *Kytococcus sedentarius* (previously *Micrococcus sedentarius*)
- Bacteria proliferate and produce proteinases: destroy the stratum corneum, creating shallow pits on soles
- Clinical:
  - Seen with sweaty feet
  - Malodor owing to the production of sulfur-compound by-products
- Treatment: reduce hyperhidrosis, topical clindamycin or erythromycin

### Erysipeloid

- *Erysipelothrix rhusiopathiae* (gram-positive bacillus)
- Direct contact with infected meat, fish, or animal products
- Three clinical forms
  - Localized cutaneous form (erysipeloid of Rosenbach): purplish raised plaque, well demarcated on hand (common in fishermen and butchers)
  - Diffuse cutaneous form: Multiple lesions appear on various parts of the body.

---

**FIGURE 18-7** Erythrasma. *(Courtesy of Dr. Steven Mays.)*

**FIGURE 18-8** Pitted keratolysis. *(Courtesy of Dr. Ronald Rapini.)*
• Generalized or systemic infection associated with endocarditis
• Treatment: penicillin, ciprofloxacin, third-generation cephalosporin

**Anthrax**

• *Bacillus anthracis* (gram-positive bacillus)
• Exposure to sick animals or contaminated wool, hair, or animal hides
• Two virulence factors: (1) D-glutamyl polypeptide capsule; (2) pair of toxins: edema toxin and lethal toxin
• Clinical:
  • 1- to 12-day incubation period, followed by a low-grade fever and malaise
• Pulmonary anthrax (woolsorter’s syndrome):
  • Five percent of anthrax cases
  • Inhalation of anthrax spores
  • Nonspecific symptoms: low-grade fever and a nonproductive cough
  • Hemorrhagic mediastinal infection
  • Can result in septicemic anthrax
  • Chest x-ray: widened mediastinum with hemorrhagic pleural effusions
  • Usually fatal
• Gastrointestinal anthrax
  • Ingestion of infected meat products
  • Mainly affects the cecum
• Cutaneous anthrax
  • Occurs 1 to 7 days after skin exposure
  • “Malignant pustule”: central area of coagulation necrosis (ulcer with eventual eschar), edema and vesicles filled with bloody or clear fluid (actually not pustular)
  • Ruptures to leave a black eschar and scar
  • Regional lymphadenopathy may persist
  • Most cases of simply zoonotically acquired cutaneous anthrax are not fatal (<20% fatality untreated, <1% fatality treated)
  • Anthrax meningitis may occur after bacteremic seeding from any form of anthrax
• Diagnosis:
  • Stain exudates from ulcer with methylene blue or Giemsa
  • Culture on blood agar: from skin, pleural fluid, cerebrospinal fluid (CSF)
  • Serologic diagnosis (ELISA)
  • Blood cultures
  • Skin biopsy: organisms can be seen within capillaries
• Treatment
  • Pencillin, doxycycline
  • Quinolones if patient is unable to take pencillin, doxycycline
  • Postexposure prophylaxis to prevent inhalation anthrax for 60 days
• Vaccine exists but is not readily available
• Do not incise and drain secondary to dissemination
• Considered by the CDC to be a viable weapon of bioterrorism (Category A)

**Necrotizing Fasciitis (NF)**

• Life-threatening soft tissue infection, needs urgent care and consultation
• Group A beta-hemolytic streptococci or caused by *Clostridium perfringens*
• Type I: polymicrobial
• Type II: group A streptococcal (“flesh-eating” strep)
• Type III: gas gangrene or clostridial myonecrosis
• Can occur as a complication of a number of surgical procedures
• Clinical
  • In early stages, pain out of proportion to physical findings
  • Begins with erythema progressing to vesication or bullae formation
  • Spreads from the subcutaneous tissue along the superficial and deep fascial planes
  • Ischemia and tissue necrosis due to thrombosis
  • Crepitus present with gas-forming aerobes
  • Septicemia
  • Fournier’s gangrene
    • Localized variant of type I NF involving gentitocrural areas (usually men but can be women)
• Diagnosis
  • Standard radiographs or computed tomography (CT) to visualize free air
  • Deep incisional biopsy will demonstrate bacteria, thrombos and tissue necrosis
  • Culture
  • Tissue biopsy
  • Gram stain
• Treatment
  • Aerobes: (usually gram-negative organisms), ampicillin, and gentamicin
  • Anaerobes: clindamycin, or metronidazole
  • Intravenous immunoglobulin
  • Surgical debridement

**Actinomycosis**

• Caused by *Actinomyces israelii*, a filamentous, anaerobic, gram-positive bacteria
• Cutaneous disease includes cervicofacial disease (lumpy jaw) or cutaneous mycetoma (Madurosis)
• Clinical:
  • Cervicofacial – abscess with draining sinus, usually at the angle of the jaw or in submandibular area, sulfur granules may be seen in the exudate
• Madurosis – cutaneous pyoderma with characteristic purulent draining with discharged “sulfur granules” (aggregates of filamentous bacteria)
• Diagnosis:
  - Complete blood count: mild leukocytosis
  - Culture
  - Gram-stained smear: branched, gram-positive filamentous rods
• Treatment: penicillin, tetracyclines are alternatives; Madurosis often requires surgical intervention or even amputation

GRAM-NEGATIVE BACTERIAL DISEASES

Ecthyma Gangrenosum
• Bacteremia with skin lesions
• Pseudomonas aeruginosa (gram-negative rods)
• Clinical
  - Hemorrhagic bullae that develop into black eschars
  - Gluteal or perineal region (57%), extremities (30%), trunk (6%)
  - Most often in immunocompromised patients (neutropenic or those with HIV infection)
• Diagnosis:
  - Gram stain
  - Blood cultures
  - Histology: vascular necrosis with inflammatory cells and surrounding bacteria
• Treatment: penicillins, aminoglycosides, fluoroquinolones, third-generation cephalosporins, or aztreonam

Green Nail Syndrome
• P. aeruginosa
• Greenish discoloration in areas of onycholysis due to pigment production: —pyocyanin: blue, fluorescein: yellow/green, pyomelinin: black
• Seen in people who chronically have their hands in water
• Treatment: acetic acid solution and/or thymol 4% solution

Pseudomonas Folliculitis
• Hot tub folliculitis
• P. aeruginosa
• Clinical:
  - Exposure to whirlpools, swimming pools, and hot tubs
  - Pustular eruption in follicular distribution on trunk (underneath swim-wear)
• Treatment: self-limited, acetic acid soaks, quinolones in severe cases

Gram-Negative Folliculitis
• Proteus, Klebsiella, Escherichia, and Serratia spp.
• Complication in patients with acne vulgaris and rosacea who have received systemic antibiotics for prolonged periods of time
• Clinical
  - Acne that has not been responding to antimicrobial therapy or other therapy: 80% of patients
  - Patient’s acne suddenly flares: 20% of patients
  - Superficial pustular lesions without comedones
  - Deep, nodular, and cystic lesions
• Laboratory studies: Gram stain and culture
• Treatment: isotretinoin, systemic antibiotics

Malakoplakia
• Commonly due to Escherichia coli
• Seen mainly in immunocompromised patients
• Mainly affects genitourinary tract but may occasionally involve the skin
• Clinical
  - Yellow to pink papules, nodules, or ulcerations
  - Draining abscesses/sinuses
  - Common areas of presentation; perianal or inguinal areas, the buttocks, and the abdominal wall
• Diagnosis:
  - Histology: foamy histiocytes with basophilic inclusions containing calcium and iron - referred to as Michaelis-Gutmann bodies (stain with von Kossa for calcium and Perls Prussian blue for iron, also stain with periodic acid–Schiff and are diastase resistant); histiocytes with fine eosinophilic cytoplasmic granules (von Hansemann cells) can also be seen
  - Culture fluid from sinuses: check for bacterial (aerobic and anaerobic), fungal, and mycobacterial pathogens
• Treatment: quinolone antibiotics and sulfonamides, excise skin lesions and drain abscesses

Rhinoscleroma
• Klebsiella rhinoscleromatis (gram-negative coccobacillus)
• Chronic granulomatous condition of the nose and upper respiratory tract
• Inhalation of droplets or contaminated material
• Clinical
  - Three stages:
    - rhinitic: purulent rhinorrhea,
    - proliferative,
      ▲ Affects nose most often: intranasal rubbery nodules or polyps
      ▲ Epistaxis (bloody nose)
Chapter 18  BACTERIAL DISEASES

Pustules, bullae, and hemorrhagic lesions with central necrosis
- Stellate purpura with a central gunmetal-gray hue
- Fulminant meningococcemia
  - Can present as purpura fulminans
  - Waterhouse-Friderichsen syndrome: symmetric peripheral gangrene, cyanosis, hypotension, and profound shock
- Meningitis
  - Headache and a stiff neck
  - Lethargy or drowsiness
- Chronic meningococcemia: one week to as long as several months with recurrent fever and variable rash usually occurring on pressure areas or around painful joints

Diagnosis
- Blood and throat cultures on blood agar
- Lumbar puncture
- Gram stain of lesional skin biopsy or aspirate specimens
- Histology: acute vasculitis with meningococci seen in thrombi of dermal vessels

Prevention: a new, longer-acting, conjugated vaccine exists for types A, B, C, W135, and Y that can be administered to patients 11 to 55 years of age

Treatment: penicillin G, third-generation cephalosporin

Meningococcal Disease (Fig. 18-9)
- Neisseria meningitides (obligate aerobic, encapsulated gram-negative diplococcus)
- Serogroups A, B, C, W135, X, Y, and Z
- Transmitted from person to person via respiratory secretions
- 20–40% of young adults are carriers of the bacteria
- Persons with deficiencies of terminal complement components C5 to C9 or properdin, immunoglobulin deficiency, asplenia, and HIV infection are most susceptible
- Direct invasion of endothelial cells and indirect damage from endotoxin release

Clinical
- Cutaneous findings:
  - Petechiae

Bartonella Species
- Cat-scratch disease, oroya fever, verruga peruana, bacillary angiomatosis, trench fever
- Aerobic gram-negative organisms

Cat-Scratch Disease (Benign Lymphoreticulosis)
- Mainly caused by Bartonella henselae (gram-negative bacillus)
- Vector: cat flea (Ctenocephalides felis): maintains infection in cats

Clinical
- Infection spread by bite or scratch from cats (particularly kittens), incubation of 3–12 days
- Fever in 25% to 75% of patients
- Constitutional symptoms: anorexia, myalgias
- Red papules appear at the site of scratch (develops over 3 to 10 days)
- Lymphadenopathy (develops 1 week to 2 months after exposure)
  - Fifty percent have involvement of a single node
  - May last 6 weeks to 2 years
- Parinaud oculoglandular syndrome: unilateral conjunctivitis and regional lymphadenitis
- CNS changes 1 to 2%: headaches, mental status changes, seizures, encephalitis, cerebrospinal fluid usually normal

Hebra nose: nasal enlargement, deformity, and destruction of the nasal cartilage
- Fibrotic: sclerosis and fibrosis with possible stenosis

Diagnosis
- Culture
- CT scan: soft-tissue masses of variable sizes

Histology
- Mikulicz cells: parasitized histiocytes
- Silver stains (Warthin-Starry) can be used to highlight the bacteria
- Russel body: eosinophilic bodies inside and outside plasma cells secondary to increased IgG

Treatment
- Surgery combined with antibiotic therapy
- Tetracycline, ciprofloxacin, and rifampin

FIGURE 18-9 Meningococcal disease. (Courtesy of Dr. Asra Ali.)
• Diagnosis:
  - Indirect fluorescent antibody (IFA) for Bartonella (cross-reactivity between B. henselae and B. quintana)
  - Brown-Hopp tissue Gram stain and Warthin-Starry silver staining show small, curved, gram-negative bacilli
  - Fourfold rise in IgG antibody levels
  - Lymph node biopsy: necrotizing granulomas
• Treatment
  - Immunosuppressed patients: azithromycin, erythromycin, doxycycline, septa, rifampin, ciprofloxacin, gentamycin
  - Immunocompetent patients: supportive care since CSD is a self-limiting disease

**Bacillary Angiomatosis (Fig. 18-10)**

- Etiologic agents are *B. henselae*, *B. Quintana*
- Typically occurs in HIV (with CD4 counts <200/μL) or in other immunocompromised patients
- Adheres to and invades red blood cells (RBCs)
- Makes an endothelial cell–stimulating factor: proliferation of both endothelial cells and blood vessels
- Clinical
  - Four cutaneous patterns
    - Erythematous papules and nodules that are non-blanching
    - Violaceous nodule (similar to Kaposi’s sarcoma)
    - Violaceous lichenoid plaque
    - Subcutaneous nodule that may ulcerate

- Other areas of the body affected by BA: brain, bone, bone marrow, lymph nodes, gastrointestinal tract, respiratory tract, spleen and liver
- Peliosis hepatitis
  - Blood-filled cysts in liver of AIDS patients (occasionally are found in spleen)
  - Nausea, vomiting, diarrhea, and fever with hepatosplenomegaly

- Diagnosis:
  - Histology
    - Bacilli stain with modified Warthin-Starry stain (silver-based)
    - Vascular proliferation with small vessels arranged in clusters; epithelial collarette may be observed
  - Chest x-ray and CT: pulmonary nodules
- Treatment
  - Erythromycin, doxycycline
  - May get Jarisch-Herxheimer reaction:
    - Self-limited reaction to therapy
    - Seen after treatment of syphilis, borreliosis, brucellosis, typhoid fever, trichinellosis, leptospirosis, leprosy, Lyme disease, relapsing fever (epidemic)
    - Fever, malaise, nausea/vomiting
    - Exacerbation of secondary rash
    - Occurs 8 hours after the first injection
    - Resolves within 24 hours

**Trench Fever**

- Caused by *B. quintana* (aerobic, gram-negative bacillus)
- Incubation period of a few days to a month
- Clinical
  - Symptoms begin with chills and fever: relapsing fever every 5 days (also can have single febrile episode occurring for 3 to 5 days or persistent fever lasting 2 to 6 weeks)
  - Headaches, neck and back pain
  - Groups of erythematous macules or papules measuring 1 cm or less
  - Spread by human body louse (*Pediculus humanus corporis*)
- Diagnosis
  - Polymerase chain reaction (PCR)
  - Histology: perivascular infiltrate, organisms are not visible
- Treatment: doxycycline, erythromycin

**Oroya Fever (Carrion’s Disease) and Verruga Peruana**

- Caused by *B. bacilliformis*
- Vector: sand fly (*Lutzomyia verrucarum*)
- Clinical
Host response results in tissue granulomas and visceral microabscesses

Clinical
- Acute fever, malaise, arthralgias
- Cutaneous signs: rare granulomas, ulcerations, petechiae, purpura, and erythema nodosum
- Endocarditis
- Sacroilitis, epididymoorchitis in males
- Meningitis

Diagnosis:
- Agglutination titers for anti-O-polysaccharide antibody
- Culture (bone marrow culture much more sensitive than blood culture)
- Immunoglobulin G (IgG) by ELISA
- Anemia, thrombocytopenia, pancytopenia in 6% of patients
- Elevated liver enzymes
- Bone marrow: erythrophagocytosis
- CSF reveals pleocytosis, elevated protein levels
- Echocardiogram to evaluate for endocarditis

Treatment
- Doxycycline and rifampin or trimethoprim-sulfamethoxazole (TMP-SMZ) plus rifampin
- Drain pyogenic joint effusions or rare paraspinal abscesses

Leptospirosis (Weil Disease or Icteric Leptospirosis)

Leptospira interrogans (spirochete)
- Incubation period is usually 7–12 days
- Infects many types of mammals: cats, dogs, cattle, pigs, squirrels
- Transmitted via infected urine and then through contact with contaminated water and soil
- Over half of cases in the United States occur in Hawaii

Clinical
- Two distinct presentations
  - Septicemic: organism may be isolated from blood cultures, CSF, and most tissues; patients may have myalgias, weakness as well as meningitis like symptoms (headache, photophobia)
  - Immune: occurs after a few days of improvement following the septicemic stage.
  - Occurs as a result of an immune reaction to the infection
  - Circulating antibodies may be detected or the organism may be isolated from urine; it may not be recoverable from blood or CSF
- Subclinical meningitis with headaches, fever, petechiae
- Cutaneous lesions: macular or maculopapular eruption with erythematous, urticarial, petechial, or desquamative lesions, jaundice (90% of
TICK-BORNE BACTERIAL INFECTIONS

Typhoidal (10–15% of cases) severe form with pneumonia, fever, myalgias

Diagnosis:
- Blood cultures: usually normal
- Serologic testing: enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR)
- Treatment: aminoglycosides (streptomycin)
- Considered by the CDC to be a viable weapon of bioterrorism (Category A)

Lyme Disease (Fig. 18-12)
- Caused by the spirochete Borrelia burgdorferi
- Vector: Ixodes ticks (hard ticks)
- Eastern/midwestern United States: I. scapularis, I. dammini
- Northwestern United States: I. pacificus
- Europe: I. ricinus and I. persulcatus
- Clinical
  - Stage 1: early localized
    - Erythema migrans (EM) occurs in up to 80% of cases
    - Erythematous macule or papule at site of the tick bite, can have central clearing
    - Expanding figurate erythema occurs over days to weeks
    - Typically resolves in about one month

Tularemia (Ohara’s Disease, Deer Fly Fever)
- Francisella tularensis (gram-negative coccobacillus)
- Vectors: hard tick (Dermacentor andersoni) or deer fly (Chrysops discalis)
- Reservoir: rabbits (“rabbit fever” common in hunters)
- Incubation period of 3–4 days
- Clinical
  - Eight forms: depend on mode of transmission:
    - Ulceroglandular (most common), glandular, ocular, oropharyngeal, pulmonary, typhoidal, meningeal, chancroidal
    - Intracellular parasitism of reticuloendothelial system of humans
    - Infection common in hunters after infected animal exposure via vectors
  - Ulceroglandular (70–80% of cases)
    - Organism enters through a scratch or abrasion.
    - Tender papule that ulcerates with spirochoid spread
    - Regional lymphadenopathy

TICK-BORNE BACTERIAL INFECTIONS

FIGURE 18-12 Lyme disease. (Reprinted with permission from Connor DH et al. Pathology of Infectious Diseases. Stanford, CT: Appleton & Lange; 1997, p. 637.)
ROCKY MOUNTAIN SPOTTED FEVER

- *Rickettsia rickettsii* (obligate intracellular gram -coccobacilli)
- Disease commonly found in North Carolina and Oklahoma which account for one third of total cases reported; other areas outside of the United States include Canada, Mexico, Central America, Colombia, and Brazil
- Vectors
  - Eastern United States: wood tick (*Dermacentor andersoni*)
  - Western United States: dog tick (*Dermacentor variabilis*)
- Clinical
  - Triad: fever, headache, and rash (1 to 2 weeks after tick bite)
  - Multisystem involvement is common
  - Skin lesions
    - Appear two to four days following fever
    - Blanchable macular rash that starts on extremities and spreads to trunk (centripetal)
    - Face usually spared; involvement of the scrotum or the vulva and palms/soles
  - Neurologic changes (meningitis, encephalitis)
- Diagnosis
  - Antibody titer (antibodies take 4–6 weeks to develop and thus, are not usually present at the time of the rash)
  - Confirm positive ELISA antibody titers with PCR
  - False-positive results of IFA or ELISA can occur because of cross-reactivity with *Treponema pallidum*, and other spirochetal agents
  - Histology: presence of telangiectasias and cellular infiltrates of lymphocytes with admixed plasma cells; ACA demonstrates striking epidermal atrophy
- Treatment
  - Doxycycline or amoxicillin
  - Pediatric patients: erythromycin

Rickettsioses

- Obligate intracellular gram-negative coccobacilli
- Transmitted to humans by arthropods
- Spotted fever group
  - Rocky Mountain spotted fever
  - Rickettsialpox
  - Boutonneuse fever
- Typhus group
  - Louse-borne (epidemic) typhus
  - Brill-Zinsser disease (i.e., relapsing louse-borne typhus)
  - Murine (endemic or flea-borne) typhus
- Other rickettsial diseases
  - Tsutsugamushi disease (i.e., “scrub typhus”)
  - Q fever: *Coxiella burnetii*
  - Ehrlichia

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  - Tsutsugamushi disease (i.e., “scrub typhus”)
  - Q fever: *Coxiella burnetii*
  - Ehrlichia
Enzyme-linked immunosorbent assay (ELISA): detects antibodies to lipopolysaccharides (LPS) of *R. conorii*

Treatment: tetracyclines together with chloramphenicol and quinolones

**Typhus Group**

- Three main forms of typhus: epidemic typhus; rat-flea or endemic typhus, and scrub typhus.

Diagnosis:
- Actual isolation and culture of *rickettsiae* are difficult
- Serologic tests for antibodies
- Indirect immunofluorescence assay (IFA)
- Enzyme-linked immunosorbent assay (ELISA)
- Indirect immunoperoxidase
- Weil-Felix test
- Polymerase chain reaction (PCR): serum or skin biopsy
- Complement fixation (CF)

Treatment: doxycycline, chloramphenicol

**Epidemic Typhus**

- Caused by *R. prowazekii*
- Vector: human body louse (*Pediculus humanus corporis*)
- Incubation period of 7 to 14 days

Clinical:
- Fever, headache
- Erythematous macular eruption without becoming hemorrhagic or necrotic following fever

**Murine Typhus (Endemic Typhus)**

- Caused by *R. typhi*
- Vectors: rat or cat flea (*Xenopsylla cheopsis, Ctenocephalides felis*)
- Incubation of 6 to 18 days

Clinical:
- Erythematous macular eruption without becoming hemorrhagic or necrotic following fever

**Scrub Typhus (Tsutsugamushi Fever)**

- *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi*); it has a different cell wall structure and genetic composition than that of the rickettsiae
- Vector: trombiculid mite (larval stage of a chigger): *Leptotrombidium akamushi* and possibly *L. deliense*
- Incubation period is 5–20 days

Clinical
• Headaches, shaking chills, lymphadenopathy, conjunctival injection, fever
• Painless papule develops at site of bite, and then a central necrosis results with formation of an eschar
• Five to eight days after infection, dull red rash on trunk and extending to the extremities
• Pneumonitis or encephalitis can occur
• Hepatosplenomegaly
• Regional lymphadenopathy

**Ehrlichiosis**
- Due to gram-negative organisms that resemble *Rickettsia*
- Human monocytic ehrlichioses (HME): *Ehrlichia chaffensis*
- Human granulocytic ehrlichioses (HGE): *E. phagocytophilia*
- Vector: Lone Star tick (*Amblyoma americanum*) or deer tick (*Ixodes persulcatus*)
- Infects mononuclear cells and granulocytes
- Clinical
  - Rash is rare in ehrlichiosis; however, can develop maculopapular lesions following fever
  - Rare renal failure and encephalopathy
  - Lymphadenopathy may be present
- Diagnosis:
  - Histology: characteristic morulae in the cytoplasm of leukocytes
  - Neutropenia, lymphocytopenia, or thrombocytopenia
  - Elevated immunoglobulin G (IgG) immunofluorescent antibody (IFA) *Ehrlichia* titer
- Treatment: tetracyclines; chloramphenicol is not effective in ehrlichiosis

**SEXUALLY TRANSMITTED BACTERIAL INFECTIONS**

**Gonorrhea (Fig. 18-13)**
- *Neisseria gonorrhoeae* (gram-negative intracellular aerobic diplococcus)
- Clinical
  - Men: urethritis; women: dyspareunia, bleeding or discharge
  - Neonates: bilateral conjunctivitis (ophthalmia neonatorum) after vaginal delivery from an infected mother
  - Acute perihepatitis with hepatic capsular adhesions (Fitz-Hugh-Curtis syndrome)
  - Dissemination: arthritis dermatitis syndrome (1–3% of cases)
    - Septic arthritis: knee is most common site; polvarthralgia with pain, tenderness
- Five to eight days after infection, dull red rash on trunk and extending to the extremities
- Pneumonitis or encephalitis can occur
- Hepatosplenomegaly
- Regional lymphadenopathy

**Granuloma Inguinale (Fig. 18-14)**
- *Klebsiella granulomatis* (gram-negative rod), formerly *Calymmatobacterium granulomatis*
- Clinical
  - Four types of skin lesions:
    - **Ulcerative** (most commonly seen)
      - Painless, beefy red ulcers with clean, friable bases and distinct, raised/rolled margins
      - Autoinoculation is common
    - **Nodular**
      - Pruritic, soft, red nodules that ulcerate at the site of inoculation
    - **Pseudobubo**: nodule appears clinically as a lymph node
    - **Cicatricial**
      - Dry ulcers that progress into scarring plaques
      - Lymphedema may be present
  - **Hypertrophic or verrucous** (relatively rare)
  - Vegetating soft masses

**FIGURE 18-13  Gonorrhea. (Reprinted with permission from Connor DH et al. Pathology of Infectious Diseases. Stanford, CT: Appleton & Lange; 1997, p. 686.)**
Sexually Transmitted Bacterial Infections

- Immunofluorescent testing with monoclonal antibodies
- Treatment: doxycycline; alternative is erythromycin

Chancroid (Fig. 18-16)
- Caused by Haemophilus ducreyi (gram-negative bacillus)
- The bacteria secretes a cyto-lethal distending toxin (HdCDT): inhibits cell proliferation and induces cell death
- Clinical
  - Soft chancre
  - Painful ragged punched-out ulcers, undermined borders, covered by a grayish fibrinous membrane
  - Lymph node involvement mostly unilateral and can rupture
  - Bubo: tender, fixed, inguinal lymphadenopathy
- Diagnosis
  - Complement fixation test with titer of 1:64
  - Culture
  - Immunochromatography: monoclonal antibodies to the hemoglobin receptor of H. ducreyi, hgbA
- Treatment
  - Azithromycin 1 g PO single dose, ceftriaxone 250 mg IM single dose, erythromycin 500 mg PO qid for 7 days, or ciprofloxacin 500 mg PO bid for 3 days.
  - Buboes should be drained

Syphilis
- Caused by Treponema pallidum (microaerophilic spirochete)
Early latent: < 1 year’s duration
Late latent: ≥1 year’s duration or of unknown duration (seroreactivity, in the absence of symptoms, greater than 2 years after inoculation)

- **Tertiary**
  - Seroreactivity greater than 2 years with symptoms
  - Gummas: granulomas of skin and bone
  - Neurologic (neurosyphilis): may be asymptomatic or present as a subacute meningitis
  - **Tabes dorsalis**: demyelination of the posterior columns, dorsal roots, and dorsal root ganglia (e.g., ataxic wide-based gait and foot slap)
  - **Argyll-Robertson pupil**: small, irregular pupil, normal accommodation but abnormal light response (Romberg sign)
  - Cardiovascular: aortic aneurysm, aortitis

- **Congenital syphilis caused by transplacental transmission of spirochetes**
  - Early (< 2 years of age)
  - Late (> 2 years of age)

- Clinical
  - **Primary**
    - Occurs after incubation of approximately 3 weeks
    - Highly infectious painless chancre (ulcerated lesion with a surrounding red areola)
    - Lasts 10 to 14 days
    - Buboes
      - **Enlarged, nontender lymph nodes**
  - **Secondary**
    - Occurs usually one month after chancre presents
    - Hair: alopecia (“moth eaten”), caused by papular follicular syphilids, localized patches to total alopecia
    - Mucous membrane:
      - **Condyloma lata**: infectious papules and small plaques develop at the mucocutaneous junctions and intertriginous areas
      - **Pharyngitis**
      - **Mucous patches**: silver-gray erosions with a red areola
    - Skin: bilaterally symmetric discrete round macules on the trunk and proximal extremities (often affecting palms and soles); can become necrotic
    - Ocular: anterior uveitis
  - **Latent syphilis**
    - Follows resolution of the secondary stage
    - Only evidence is positive serologic test for syphilis
    - Categories
• Frontal bossing
• Higomenaki’s sign: unilateral sternoclavicular enlargement
• Bulldog jaw
• Clutton joints (arthritis of both knees)
  ▲ Recurrent arthropathy
  ▲ Cranial nerve VIII deafness
• Diagnosis
  • Histology: often with psoriasiform and lichenoid changes and perivascular infiltration, chiefly by lymphocytes, plasma cells, and macrophages; may see spirochetes with modified Steiner or Warthin-Starry stains (silver based)
  • Identification of *T. pallidum* in lesions on tissue:
    - Dark-field microscopy: immediate result
    - DFA-TP (direct fluorescence antibody test): direct fluorescent antibody *T. pallidum*, 1 to 2 days
    - Immunohistochemical stains for *T. pallidum*
• Nontreponemal serology screening
  - Venereal Disease Research Laboratory (VDRL) test: measures IgM and IgG antibody directed against a cardiolipin lecithin-cholesterol antigen; not specific for *T. pallidum*; used to follow response to therapy (lower titers with successful treatment)
• Prozone effect:
  - May cause a false-negative reaction
  - Occurs when the reaction is overwhelmed by antibody excess and may happen in late primary or secondary syphilis
  - Should dilute the serum to at least a 1/16 dilution
• Rapid plasma reagin (RPR)
  - Develops 1 to 4 weeks after chancre
  - Fourfold decline in titer by 3 months following treatment
  - False-positive RPR results occur in 1% to 2% of the normal population.
• Treponemal tests
  - FTA-ABS: fluorescent treponemal antibody absorption
    ▲ Reactive 4 to 6 weeks after infection
    ▲ Remains reactive for many years
    ▲ Does not indicate response to therapy
    ▲ Does not distinguish between syphilis and other treponematoses
    ▲ Antibody (IgM and IgG) directed against *T. pallidum*
  - MHA-TP: microhemagglutination assay
    *T. pallidum* test
    ▲ Remains reactive for life
    ▲ Not recommended for monitoring reinfection or the efficacy of treatment
• Chest x-ray for patients with tertiary syphilis to screen for aortic dilation
• Lumbar puncture: in patients with latent syphilis, if treatment has failed or the time course of disease is unknown and if the patient is known to also have HIV.
• Treatment
  • Penicillin 2.4 million units IM
  • Jarisch-Herxheimer reaction (see above)

## Leprosy (Hansen’s Disease)

• Chronic granulomatous infection that affects skin and nerves
• Causative organism is *Mycobacterium leprae* (intracellular acid-fast gram-positive bacillus)
• Transmission: respiratory, human to human, armadillos, and sphagnum moss
• Humans are the primary reservoir of *M. leprae*
• Bimodal age distribution, with peaks at ages 10–14 years and 35–44 years
• Incubation: up to 5 years and may be 20 years or longer
• Clinical
  • **Neurological**
    - Acral distal symmetric anesthesia
    - Palsies of cranial nerves V and VII
    - Nerve enlargement
    - Predilection for superficial nerves (bacteria prefers lower temperatures)
    - Great auricular, ulnar, median, superficial peroneal, sural, and posterior tibial nerves (most commonly affected)
    - Anesthetic skin lesions (sensation to temperature is lost first)
  • **Cutaneous**: varies based on type of infection
    - **Ocular**: lagophthalmos (inability to close the eye/involvement of cranial nerve [CN] VII branches), reduced corneal reflex and reduced blinking [ophthalmic branch of the trigeminal nerve (CN V2)]
  • **Classification of leprosy types**
    - **TT** (polar tuberculoid) ↔ **BT** (borderline tuberculoid) ↔ **BB** (borderline) ↔ **BL** (borderline lepromatous) ↔ **LLs** (subpolar lepromatous), **LLp** (polar lepromatous)
    - Levels are not static: patients can move through spectrum of disease through upgrading or downgrading reactions
• **Indeterminate leprosy (IL)**
  • Early form, usually no sensory loss
Chapter 18  BACTERIAL DISEASES

Granulomas with lymphocytes and foamy macrophages
Nerves with inflammatory cell infiltration; bacilli and globi (M. leprae within multinucleate Virchow giant cells from histiocytes)
Patients remain in this stage, improve, or regress

* **Lepromatous leprosy (LL)**
  - Multibacillary
  - Predominance of CD8+ cells
  - T_{H2} (anti-inflammatory) profile: IL-4 and IL-10
  - Lack of cell-mediated immunity permits progression of the infection
  - HLA-DQ1 and TLR2 gene mutations have been associated with LL
  - Clinical (Fig. 18-17)
    - Poorly defined symmetric skin-colored plaques and nodules, begin as pale macules
    - Anhidrosis
    - Diffuse dermal infiltration
    - Leonine facies: widening of the nasal root
    - Madarosis: lateral alopecia of the eyebrows and lashes
    - Slow and progressive nerve involvement, acral distal symmetric anesthesia
    - Testicular infection: invasion of the seminiferous tubules causing sterility
    - Ocular involvement: photophobia, glaucoma, blindness
    - Oral involvement: lepromas of the hard and soft palates
    - Aseptic necrosis and osteomyelitis

  - FIGURE 18-17  Lepromatous leprosy. (Courtesy of Dr. Steven Mays.)
Subpolar lepromatous (LLs): can develop reversal reactions and erythema nodosum leprosum

Polar lepromatous (LLp): develops erythema nodosum leprosum

Histoid leprosy (HL): clinical variant of LL, occurs as a result of resistance to monotherapy; multi-bacillary lesion with spindle-shaped cells resembling fibrocytes without globi

Histology: Grenz zone (upper area of dermis is spared), foamy macrophages with globi (Virchow cells)

Untreated LL is progressive, it does not revert to the less severe borderline or tuberculoid types

**Relapsing leprosy**

Multibacillary patients who are noncompliant or develop drug resistance

Early relapses (occurring within 3.5 years after stopping treatment) are probably due to insufficient treatment, and late relapses (occurring more than 3.5 years after stopping treatment) to persisting bacilli or to reinfection

Clinical
- Recurrence of initial presentation
- Florid dermatofibroma-like lesions (histoid leprosy)
- Develop a reactional state: destructive inflammatory processes

**Jopling’s type 1 reversal reaction** (lepra reaction)

Delayed-type hypersensitivity reaction, leading cause of neurological impairment in patients with leprosy

Affects 30% of patients with borderline leprosy

Patients either upgrade to a more resistant state, remain unchanged, or downgrade to a less resistant state

Clinical
- Abrupt conversion of previously quiescent plaques to tumid lesions and/or development of new tumid lesions in clinically normal skin
- Dusky purple erythematous plaques
- Iritis and lymphedema (elephantiasis graecorum)
- Neuritis

**Jopling’s type 2 reaction** (erythema nodosum leprosum)

Often in LL but also in BL before, during, or after therapy

Clinical
- Crops of tender bright pink nodules in clinically normal skin
- Fever, anorexia, and malaise
- Upper and lower extremities, facial lesions in 50%
- Arthralgias
- Neutrophilic leukocytosis
- Abrupt fall in hematocrit

**Lucio reaction**

- Occurs in untreated diffuse lepromatous leprosy and/or relapsing leprosy
- Seen in Mexico and the Caribbean
- Latapi’s lepromatosis: diffuse nonnodular lepromatous leprosy with hemorrhagic infarcts
- Telangiectases
- Nasal septum perforation
- Total alopecia of the eyebrows and lashes
- Acral distal symmetric anesthesia
- Crops of necrotic lesions
- Painful ulcerations of the skin
- Histology: ischemic necrosis secondary to endothelial parasitization by AFB; thrombosis in deep vessels

Treatment for Lucio reaction: rifampin

**Laboratory changes**

- Hyperglobulinemia
- False-positive serologic test for syphilis
- Anemia of chronic disease
- Mild lymphopenia
- Elevated serum lysozyme and angiotensin-converting enzyme
- Proteinuria due to focal glomerulonephritis in ENL
- Testicular involvement in LL males manifests as high serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) but low testosterone
- Lepromin skin testing (Mitsuda test): intradermal injection of *M. leprae*, positive reaction occurs if a 5 mm or greater nodule appears 2–3 weeks following injection (usually positive in TT and BT leprosy while BB through LLp are negative)
- Not useful in diagnosis, indicates host resistance
- Helps in classification

**Treatment**

- Treatment may last from 6 months to 2 years. After 1–2 weeks of treatment, patients are considered noninfectious

**Paucibacillary** (tuberculoid) disease
- Dapsone (bacteriostatic) 100 mg daily
- Supervised rifampin (bactericidal) 600 mg monthly for 6 months

**Multibacillary** (lepromatous) disease
- Dapsone 100 mg daily + supervised rifampin 600 mg monthly + clofazimine (bacteriostatic) 50 mg daily (unsupervised) and 300 mg monthly (supervised) for 2 years
- Alternative combination of minocycline (bactericidal) 100 mg daily + rifampin 600 mg daily for 2 to 3 years, followed by monotherapy

**Reversal reactions**
- Prednisone (0.5 to 1.0 mg/kg per day)
Painless, fluctuant, subcutaneous abscesses form singly or at multiple sites
- Miliary TB
  - Chronic infection
  - Hematogenous spread from the primary infection (usually in the lungs) to other tissues
  - Small red spots that develop into ulcers and abscesses
  - Immunocompromised patients, e.g., HIV, AIDS, cancer
- Tuberculid: hypersensitivity reactions to tubercle bacillus
  - Erythema induratum (Bazin disease): recurring subcutaneous nodules that may ulcerate and scar are seen in the posterior calves; tubercle bacilli are not seen; mycobacterial cultures usually are negative; histology shows a lobular panniculitis with vasculitis
  - Papulonecrotic tuberculid: crops of recurrent necrotic skin papules on knees, elbows, buttocks or lower trunk that heal with scarring after about 6 weeks
  - Lichen scrofulosorum: lichenoid eruption of small follicular papules in young persons with underlying TB
- Laboratory studies
  - Tuberculin skin test: good test for latent infection; intradermal injection of 5 units (0.1 mL) of purified protein derivative (PPD); induration of 5 mm or greater, 48–72 hours following injection; patients with BCG vaccination at birth (10-mm induration or more is a positive result), or if the vaccination was given as an adult (30-mm induration or larger is a positive result)
  - Whole blood assay based on interferon-gamma release (IGRA); tests for latent TB infection
  - Chest radiograph: patchy or nodular upper lobe infiltrates, calcified nodules indicate old infection, small nodular lesions indicate miliary TB
  - Ziehl-Neelsen staining and culture of sputum specimens (3 consecutive days)
  - Skin biopsy: caseating necrosis surrounded by lymphocytes, multi-nucleate giant cells and epitheloid macrophages (organisms may be present within)
- Treatment
  - Four drug regimen for 2 months
  - Isoniazid
  - Rifampin
  - Pyrazinamide
  - Ethambutol or streptomycin
  - Isoniazid plus rifampin for four more months

**TUBERCULOSIS**

- Caused by *Mycobacterium tuberculosis*
- Aerobic, intracellular, curved bacilli, acid fast
- Transmitted by airborne droplets
- Causes epithelioid granulomas with central caseation necrosis
- Clinical
  - Multiorgan infection:
    - Pulmonary: productive cough, fever, and weight loss, hemoptysis or chest pain
    - Meningitis: headache that is either intermittent or persistent, mental status changes
    - Skeletal: spine (Pott disease), arthritis: hip or knee
    - Genitourinary: flank pain, dysuria, or frequency
    - Gastrointestinal TB: nonhealing ulcers
- Cutaneous TB
  - Verrucosa cutis
    - Direct inoculation
    - Prior infection
    - Purplish or brownish-red warty growth
  - Lupus vulgaris
    - Hematogenous spread
    - Persistent and progressive
    - Sharply defined reddish brown papule, plaques with a gelatious consistency (apple-jelly color)
  - Cutis orificialis
    - Autoinoculation into the periorificial skin and mucous membranes
    - Yellow/red nodule on mucosa that results in ulceration
    - Patients with advanced TB
    - Tuberculin sensitivity is strong
  - Scrofuloderma
    - Direct extension of underlying TB infection of lymph nodes, bone, or joints
    - Associated with TB of the lungs
    - Firm, painless lesions that eventually ulcerate with a granular base
    - Tuberculin sensitivity is strong
  - Metastatic tuberculous abscess (tuberculous gumma)
    - Occurs following hematogenous spread of mycobacteria to skin in tuberculin-sensitive individuals

- Prevents permanent nerve damage
- Minimum of 6 months
- *Erythema nodosum leprosum*
  - Thalidomide is the treatment of choice
  - Prednisone + clofazimine 200 mg daily
• Rifampin, pyrazinamide, and ethambutol for the entire 6 months if patient is resistant to isoniazid

**Atypical Acid-Fast Mycobacterium (AFB)**

- Acid-fast facultative saprophytes and organisms that do not cause tuberculosis or leprosy
- Usually occur in patients that are immunocompromised
- Categorized according to their production of yellow or orange pigment and their rate of growth
- **Group 1**
  - Photochromogens (pigmentation on exposure to light)
  - *M. kansasii, M. marinum, M. simiae*
- **Group 2**
  - Scotochromogens (pigmentation formed in the dark)
  - *M. scrofulaceum, M. szulgai, M. gordanae*
- **Group 3**: nonchromogens (no pigmentation)
  - *M. malmoense, M. xenopi, M. avium-intracellulare*
- **Group 4**
  - Fast growers (groups 1, 2, and 3 listed above grow slowly)
  - Grow in three to five days (e.g., *M. fortuitum, M. cheloneae, M. abscessus*)

- **Clinical**
  - *M. marinum* (Fig. 18-18)
    - Clinical lesion is often called a “fish tank granuloma”
    - Infection occurs when contaminated water is exposed to traumatized skin
    - Usually an isolated nodule on the upper extremity, particularly the hand
    - Lymphangitic spread with several nodules (sporotrichoid spread)
  - *M. fortuitum* (rapidly growing mycobacteria) (also *M. cheloneae* and variety *abscessus*):
    - causes chronic abscesses in humans
    - Primary cutaneous inoculation with possible sporotrichoid spread (linear distribution)
    - Other clinical affects include: keratitis, corneal ulcerations, osteomyelitis, lymphadenitis, and endocarditis
    - May be resistant to treatment

- **Diagnosis**: stain with carbolfuchsin (basic dye, red in color)
  - Tissue culture
  - Skin biopsy: suppurative granulomas (most characteristic finding) diffuse inflammation with foamy histiocytes, panniculitis, cutaneous abscesses, and necrotizing folliculitis

- **Treatment**
  - Surgical drainage, debridement, and long term (>3 mo) treatment with a regimen of several antibiotics used in combination
  - Rifampin
  - Ethambutol
  - Minocycline
  - Trimethoprim and sulfamethoxazole
  - Clarithromycin

**FIGURE 18-18** *M. marinum.* (Courtesy of Dr. Asra Ali.)
7. Cutaneous anthrax is not typically _____________.
   A. Edematous
   B. Fatal
   C. Purulent
   D. B and C
   E. A, B, and C

8. Necrotizing fasciitis is characterized by:
   A. A need for a deep incisional biopsy for diagnosis
   B. Ischemia, thrombosis and tissue necrosis
   C. Pain “out of proportion” to physical findings
   D. Rapid spread
   E. All of the above

9. “Hot-tub folliculitis” is caused by:
   A. Erysipelothrix rhusiopathiae
   B. Group A Streptococcus
   C. Pseudomonas aeruginosa
   D. Staphylococcus aureus
   E. Staphylococcus epidermidis

10. Matching exercise:
    Part A—Match the following diseases with their corresponding etiological organism:
        A. Endemic typhus 1. R. akari
        B. Epidemic typhus 2. R. prowasekii
        C. Rickettsial pox 3. R. rickettsii
        D. Rocky Mountain spotted fever 4. R. tsutsugamushi
        E. Scrub typhus

    Part B—Match the following histopathologic findings with the corresponding disease:
        A. Donovan bodies 1. granuloma inguinale
        B. Michaelis-Guttman bodies 2. leprosy
        C. Mikulicz cells 3. malakoplaasia
        D. Rocha-Lima bodies 4. rhinoscleroma
        E. Virchow cells (globi) 5. verruga peruana

Answers
1. Of the answer choices, the chief difference between impetigo and eczema is the depth of involvement, with eczema yielding true epidermal ulceration. Impetigo also tends to involve young children and perioral locations, while eczema is more common in teens and adults and is often situated on the lower extremities.

2. In bullous impetigo, certain forms of Staphylococcus aureus (Phage Group 2) may elaborate a toxin which locally cleaves desmogleins, yielding subcorneal epidermal separation.

3. Cutaneous streptococcal infections may yield both post-streptococcal glomerulonephritis and scarlet fever, but they do not yield rheumatic fever.
4. C. Staphylococcal scalded skin syndrome (SSSS) is caused by the elaboration of toxins by the bacteria that are distributed systemically, and act to cleave desmogleins in the upper aspects of the epidermis yielding desquamation. Because the toxin is cleared by the kidneys, adults with pre-existing renal insufficiency are at a greater risk for the disease.

5. A. In comparison to ordinary cellulitis, erysipelas is distinguished by brighter (more red) erythema and sharp and well-dermarcated lesions. Erysiploid often demonstrates a more dusky and purple erythema. Bilateral lesions are uncommon in both classic cellulitis and erythema and often suggest the existence of a severe exacerbation of stasis dermatitis.

6. B. Corynebacterium, like *Corynebacterium minutissimum* that is involved in erythrasma, produced water-soluble coproporphyrin III, which fluoresces a “coral-red” color when examined using a Wood’s lamp. Care must be taken not to test recently washed skin, as this may remove the coproporphyrin resulting in a “false-negative” test.

7. A. The ancient name of “malignant pustulosis” to describe cutaneous anthrax is somewhat of a misnomer as lesions of cutaneous anthrax are rarely purulent. With the exception of potential bioterrorism using a “weaponized” strain, most cases of cutaneous anthrax represent an acquired zoonosis and are not fatal. “Edema factor,” a toxin elaborated by the organism, can cause significant localized, regional, and even systemic edema.

8. E. Necrotizing fasciitis is a medical emergency. The infection can result in a large degree of tissue loss and mortality, particularly when it is not diagnosed early. Often the first indication is pain out of proportion to physical findings and exceeding that of simple cellulitis. Tissue necrosis and hemorrhagic bullae often follow later. To make the diagnosis a deep incisional biopsy is needed.

9. C. Hot-tub folliculitis is a self-limited condition caused by the gram-negative organism, *Pseudomonas aeruginosa*. It most often occurs on the skin underneath swimwear and is a result of inadequate chlorination. All the other answer choices are gram-positive organisms.


REFERENCES


CHAPTER 19

FUNGAL DISEASE

ALY RAZA
MELISSA A. BOGLE
MARK LAROCCO

SUPERFICIAL MYCOSES

Tinea Versicolor (Fig. 19-1)
- Caused by Malassezia furfur; part of the normal flora, but can also act as an opportunistic pathogen
- Clinical: hypo-, hyperpigmented, or erythematous scaly macules on trunk, extremities; occasionally, an inverse form will affect flexural areas of the body
- Diagnosis
  - Wood’s lamp: coppery-orange fluorescence
  - Histology: round to oval yeast with septate hyphae in stratum corneum
- Potassium hydroxide (KOH): “spaghetti and meatballs” appearance of hyphae and spores
- Culture: Saboroud dextrose agar (SDA) with olive oil (fatty acids essential for growth)
- Treatment: topical selenium sulfide (2.5%), topical azole and allylamine antifungals, oral ketoconazole, fluconazole, and itraconazole

Tinea Nigra
- Hortaea werneckii, formerly known as Phaeoannellomyces werneckii
- Clinical: Brown-black, asymptomatic, nonscaly macules on the palms/soles
- Transmitted by traumatic implantation; incubation period is 2–7 weeks
- Histology: periodic acid-Schiff (PAS)–positive septate brown hyphae in stratum corneum, no tissue response
- KOH: branched brown hyphae with light brown septa
- Microscopic: large, dematiaceous hyphae
- Culture: SDA, brown-black colonies
- Treatment: topical keratolytics and antifungals; topical thiabendazole

Piedra
- Piedraia hortae (black piedra); Trichosporon beigeli (white piedra)
- Clinical:
  - Black piedra (BP): firmly adherent, pigmented hard nodules on scalp hair (most commonly); metallic sound when combing hair, common in areas with tropical climates
  - White piedra (WP): less adherent, light-brown to white nodules in beard, mustache, or pubic hair, common in temperate and semitropical climates
  - Both infections cause hair breakage
- Diagnosis:
  - KOH of hair shaft: BP: hyphae tightly attached to shaft; WP: hyphae loosely attached to hair shaft
  - Histology: BP – well-organized stroma; hyphae aligned regularly in periphery of nodule, WP – less organized; hyphae perpendicular to shaft
  - Culture: T. beigeli requires cyclohexamide-free media; wrinkled, creamy white colonies
  - P. hortae grows slowly; dark-brown to black colonies with reddish brown pigment on reverse
- Treatment: shaving, topical imidazoles, selenium sulfide, zinc pyrithione, precipitated sulfur in petrolatum, oral terbenafine for BP

CUTANEOUS MYCOSES

- Filamentous fungi, possessing keratinolytic enzymes, that infect superficial keratinized tissue (skin, hair, and nails)
- May be classified as dermatophytes or dermatomycoses (non-dermatophyte fungi)
- Three genera of dermatophytes (Tables 19-1 and 19-2)
  - Trichophyton: affects hair, nails, skin (Table 19-3)
  - Epidermophyton: affects hair, nails, skin
  - Microsporum: affects hair, skin
- Different species may show marked host preferences
- Humans (anthropophilic species)
- Animals (zoophilic species; Table 19-4)
- Soil (geophilic species)
Tinea Capitis

- Endothrix infection (growth and sporulation within hair shaft) (Fig. 19-2 and Table 19-5)
  - *Trichophyton tonsurans*: common isolate in the United States causes “black dot” presentation (weak hair shafts break at the skin surface). The clinical presentation may vary from minimal inflammation to diffuse scaling (Fig. 19-3)
  - *T. violaceum*: more common in Europe, North Africa, and Middle East, South Asia
  - *T. schoenleinii*: see below: tinea favosa
- Ectothrix infection (growth and sporulation around hair shaft); tend to fluoresce (see Table 19-6)
  - *Microsporum audouinii*: anthropophilic, causes epidemic tinea capitis, previously most common cause of tinea capitis

**FIGURE 19-1** Tinea versicolor. (Courtesy of Dr. Asra Ali.)

**TABLE 19-1** Key Morphologic Criteria for Identifying the Dermatophytes

<table>
<thead>
<tr>
<th>Microscopic Morphology</th>
<th>Epidermophyton</th>
<th>Microsporum</th>
<th>Trichophyton</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroconidia</td>
<td>Abundant, club-shaped, thick-walled, smooth, arranged in groups</td>
<td>Usually abundant, spindle-shaped, thick-walled, rough</td>
<td>Usually scarce, club-shaped, smooth, thin-walled</td>
</tr>
<tr>
<td>Microconidia</td>
<td>Absent</td>
<td>Usually scarce, elongate</td>
<td>Abundant, spherical, elongate, or pear shaped</td>
</tr>
</tbody>
</table>

**TABLE 19-2** Differentiating Characteristics of Dermatophytes

<table>
<thead>
<tr>
<th>Dermatophyte</th>
<th>Colony</th>
<th>Microscopic</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>T. rubrum</em></td>
<td>Fluffy white; red on reverse (no diffusion) (see Fig. 19-6)</td>
<td>Smooth, regular-shaped microconidia; “birds on a wire”; thin walled microconidia</td>
<td>Urease (−)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hair perforation (−)</td>
</tr>
<tr>
<td><em>T. mentagrophyte</em> var. <em>mentagrophytes</em> (zoophilic)</td>
<td>Tan, granular, brown-red color on reverse</td>
<td>Grapelike clusters of microconidia and spiral hyphae (see Fig. 19-7)</td>
<td>Urease (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hair perforation (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(+) Hair invasion: large spore ectothrix</td>
</tr>
<tr>
<td><em>T. mentagrophyte</em> var. <em>interdigitale</em></td>
<td>Cream fluffy; reverse yellow/brown</td>
<td>Few pyriform microconidia</td>
<td>(+) Hair invasion, large spore ectothrix; (+) Hair penetration, urease positive</td>
</tr>
<tr>
<td><em>M. gypseum</em> (geophilic)</td>
<td>Cinnamon, flat powdery with brown reverse color</td>
<td>Thin walled rough macroconidia, less than 6 septa, cucumber-z shaped</td>
<td>(+) Hair invasion: large spore ectothrix, hair fluorescence: none or dull green</td>
</tr>
</tbody>
</table>

(Continued)
### TABLE 19-2 (Continued)

<table>
<thead>
<tr>
<th>Dermatophyte</th>
<th>Colony</th>
<th>Microscopic</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. canis</em></td>
<td>White fluffy to yellowish with radiating edge, reverse yellow</td>
<td>Rough, canoe-shaped macroconidia; pointed tip (&quot;snout&quot;) with at least 6 septa. Note: <em>Epidermophyton</em> are smooth-walled</td>
<td>Grows on polished rice (+) hair invasion&quot; small spore ectothrix; green fluorescence</td>
</tr>
<tr>
<td><em>M. audoinii</em></td>
<td>Downy beige; salmon pink on reverse</td>
<td>Micro- and macroconidia rarely present</td>
<td>Does not grow on polished rice (+) Hair invasion: small spore ectothrix (yellow/green)</td>
</tr>
<tr>
<td><em>T. tonsurans</em></td>
<td>Brown, yellow, white suedelike; reddish brown on reverse</td>
<td>Smooth balloon-shaped macroconidia (rare); teardrop-shaped microconidia with varying sizes and arrangement</td>
<td>(+) Hair invasion, requires thiamin</td>
</tr>
<tr>
<td><em>T. schoenleinii</em></td>
<td>Cream-colored, cerebriform, (glaborous), heaped</td>
<td>Antler-shaped hyphae (favic chandeliers)</td>
<td>(+) Hair invasion: fluorescence green causes scutula</td>
</tr>
<tr>
<td><em>T. verrucosum</em></td>
<td>Cream wrinkled, heaped; cream color on reverse</td>
<td>Smooth-walled macroconidia (rare) with “tails”</td>
<td>(+) Hair invasion: large spore ectothrix, requires thiamin and/or inositol</td>
</tr>
<tr>
<td><em>T. violaceum</em></td>
<td>Glaborous, wrinkled; reverse violet red</td>
<td>Micro- and macroconidia not present</td>
<td>(+) Hair invasion: endothrix, requires thiamine</td>
</tr>
<tr>
<td><em>T. concentricum</em></td>
<td>White glaborous; white color reverse</td>
<td>Micro- and macroconidia not present; narrow branching hyphae</td>
<td>Causes tinea imbricata: “tokelau”</td>
</tr>
<tr>
<td><em>E. floccosum</em></td>
<td>Flat, granular, khaki color front and reverse</td>
<td>Large, thin club-shaped macroconidia</td>
<td>Produces chlamydoconidia</td>
</tr>
<tr>
<td><em>M. nanum</em></td>
<td>Tan granular; beige color reverse</td>
<td>Rough-walled two-celled macroconidia (&quot;pig snout&quot;)</td>
<td>(+) Hair invasion, large spore ectothrix, no fluorescence</td>
</tr>
</tbody>
</table>

### TABLE 19-3  Nutritional Requirements of *Tricophyton* Species

<table>
<thead>
<tr>
<th>Nutritional Requirement</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine</td>
<td><em>T. tonsurans</em>, <em>T. violaceum</em>, <em>T. verrucosum</em>, some <em>T. concentricum</em></td>
</tr>
<tr>
<td>Histidine</td>
<td><em>T. megninii</em></td>
</tr>
<tr>
<td>Niacin</td>
<td><em>T. equinum</em></td>
</tr>
<tr>
<td>Inositol and thiamine</td>
<td><em>T. verrucosum</em></td>
</tr>
</tbody>
</table>

### TABLE 19-4  Zoophilic Dermatophytes

<table>
<thead>
<tr>
<th>Dermatophyte</th>
<th>Natural Hosts</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. gallinae</em></td>
<td>Chickens/other birds</td>
</tr>
<tr>
<td><em>M. nanum</em></td>
<td>Pigs (snouts)</td>
</tr>
<tr>
<td><em>M. canis</em></td>
<td>Cats, dogs, horses</td>
</tr>
<tr>
<td><em>T. verrucosum</em></td>
<td>Cattle, sheep, horses</td>
</tr>
<tr>
<td><em>T. equinum</em></td>
<td>Horses</td>
</tr>
<tr>
<td><em>T. simii</em></td>
<td>Monkeys, chickens</td>
</tr>
<tr>
<td><em>T. mentagrophytes</em> var. <em>mentagrophytes</em></td>
<td>Cats, dogs, rabbits</td>
</tr>
</tbody>
</table>
TABLE 19-5 Endothrix Fungi

<table>
<thead>
<tr>
<th>Fungus</th>
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<tbody>
<tr>
<td>T. tonsurans</td>
</tr>
<tr>
<td>T. schoenleinii</td>
</tr>
<tr>
<td>T. soudanese</td>
</tr>
<tr>
<td>T. gourvilli</td>
</tr>
<tr>
<td>T. yaoundie</td>
</tr>
<tr>
<td>T. violaceum</td>
</tr>
</tbody>
</table>

- M. canis: zoophilic, can cause localized outbreaks, may be acquired from dogs and cats
- T. mentagrophytes: zoophilic

**Tinea Favosa (Favus)**
- Caused by *T. schoenleinii*; less commonly *T. violaceum* and *M. gypseum*
- Favus: formation of air spaces between hyphae within the infected hair
- Clinical: patients present with scutula: yellow crust ing that surrounds the hair shaft; later stages result in permanent loss of hair and scarring
- Diagnosis: microscopic: linear arrangement of hyphae along longitudinal axis of hair shaft, bubbling of KOH through the air spaces between hyphae creating characteristic antler “nail head” shaped hyphae
- Treatment: griseofulvin

**Kerion**
- Suppurative folliculitis
- Deep boggy red areas characterized by a severe acute inflammatory infiltrate
- Usually caused by *Trichophyton* spp.

**Tinea Barbae**
- Usually seen in animal workers (may be contracted from cattle, dogs)
- Caused by both zoophilic (more commonly) and anthropophilic dermatophytes
**TABLE 19-6** Small Spore Ectothrix That Fluoresce

<table>
<thead>
<tr>
<th>Name</th>
<th>Color</th>
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</thead>
<tbody>
<tr>
<td><em>M. distortum</em></td>
<td>Yellow/green</td>
</tr>
<tr>
<td><em>M. audouinii</em></td>
<td>Yellow/green</td>
</tr>
<tr>
<td><em>M. canis</em></td>
<td>Yellow/green</td>
</tr>
<tr>
<td><em>M. ferrugineum</em></td>
<td>Yellow/green</td>
</tr>
</tbody>
</table>

Note: *T. schoenleinii* (favic type); causes blue/green fluorescence

- Most commonly caused by *T. verrucosum*; may also be caused by *T. mentagrophytes* var granulosum, *M. canis*, *T. schoenleinii*, and *T. megninii*
- Clinical: inflammatory or kerion-like lesions; superficial or sycosiform type: resembles bacterial folliculitis
- Circinate, spreading type: active, vesiculopustular border with central scaling
- Diagnosis: potassium hydroxide preparation: hyphae with or without arthroconidia
- Treatment: oral antifungals: griseofulvin, terbenafine, itraconazole

**Tinea Corporis**

- *T. rubrum* (most common cause), *M. canis* (children), *T. mentagrophytes*, and *T. tonsurans* (children with tinea capitis)
- Zoophilic fungi:
  - *T. verrucosum* or *T. mentagrophytes*
  - Causes more inflammatory reactions than anthropophilic fungi
- Clinical: scaly erythematous patches with raised borders and central clearing, resulting in an annular shape; borders are scaly, crusted with papules or vesicles (Fig. 19-4)
- Variants:
  - Tinea imbricata or Tokelau
    - Caused by *T. concentricum*, found in the South Pacific, Southeast Asia, Central and South America
    - Concentric circles and polycyclic or serpiginous scaly plaques
  - Bullous tinea corporis: caused by *T. rubrum*
  - Majocchi’s granuloma (Fig. 19-5)
    - Deeper involvement of hair follicles with foreign-body granulomas
    - Erythematous patch with perifollicular pustules and nodules
    - *T. rubrum*, *T. violaceum*, *T. tonsurans*

- Tinea corporis gladiatorum: dermatophyte infection spread by direct contact between wrestlers; lesions usually found on head, neck and arms
- Tinea incognito: tinea corporis modified by corticosteroid application
- Diagnosis:
  - Histology: hyphae between orthokeratosis and compact hyperkeratosis or parakeratosis; spongiosis, superficial inflammatory infiltrate with neutrophils
• Potassium hydroxide (KOH) (Fig. 19-6) examination of skin scrapings reveal numerous septate branching hyphae
• Treatment: topical azoles, allylamines, and ciclopirox olamine; oral azoles, oral terbinafine

**Tinea Pedis**

- Dermatophyte infection that affects soles and interdigital spaces of the feet
- Interdigital type with maceration between the toes (often found between the fourth and fifth digits); commonly due to: *T. rubrum, T. mentagrophytes var. interdigitale*, and *E. floccosum*
- Chronic hyperkeratotic “moccasin type” (Fig. 19-9): erythema with slight scaling may extend to side of feet, caused by *T. rubrum* (most common cause)

- Diagnosis: see tinea corporis above
- Treatment: topical azoles, allylamines, and ciclopirox olamine; oral azoles, oral terbinafine

**Tinea Cruris**

- Commonly due to *Epidermophyton floccosum* (Fig. 19-7) or *T. rubrum* (Fig. 19-8)
- Clinical: erythematous patches with central clearing located in the inguinal creases and medial aspects of the thighs, may extend over buttocks and waist, typically spares the penis and scrotum (versus candidiasis)

- Potassium hydroxide (KOH) (Fig. 19-6) examination of hyphae. *(Courtesy of Dr. Mark LaRocco.)*

- **Figure 19-7** *Epidermophyton floccosum.* *(Courtesy of Dr. Mark LaRocco.)*
Vesicular/bullous type (Fig. 19-10): tender, vesicles or bullae with pruritus; usually seen on the instep or anterior plantar surface of the foot; maybe associated with dermatophytid type reaction (symmetric scaly patches usually found on the hands; thought to be a hypersensitivity reaction to the tinea on the foot, and does not contain fungal elements, caused by *T. mentagrophytes* var. *mentagrophytes* (Fig. 19-11)

Ulcerative: ulcers and erosions in the web spaces with secondary bacterial infection, usually found in immunocompromised and diabetic patients

Treatment: keep feet cool and dry, keratolytics with topical antifungals, oral treatment can be used in recalcitrant disease

*Tinea Manuum* (Fig. 19-12)

- Most commonly caused by *T. rubrum*
- Clinical:
  - Scaly, erythematous patches, pruritic
Id Reaction
- Host’s immune response to dermatophytosis
- Occurs at a distant site from the fungal infection
- Lesions are devoid of organisms
- Acute vesicular dermatitis of the hands and feet and evolves into a scaly eczematoid reaction

SUBCUTANEOUS MYCOSES
- Pathogen, involves dermis, subcutaneous tissues, muscle, and fascia
- Mainly occur in the tropics and subtropics; fungi are usually implanted from environmental sources such as plants or soil

Sporotrichosis
- Caused by Sporothrix schenckii: dimorphic fungus found on decaying vegetation; infection is acquired by traumatic implantation
- Infection spreads by lymphatic vessels
- Two clinical forms: cutaneous or extracutaneous (pyelonephritis, orchitis, mastitis, synovitis, meningitis, or osseous infection)
- Cutaneous subclassification:
  - Lymphocutaneous form (Fig. 19-14)
  - Nodules with sporotrichoid spread (follows lymphatics) on extremities
- Fixed cutaneous form: single site (where skin was inoculated), scaly, acniform, verrucous, or ulcerative nodule; local lymphadenopathy
Yeast phase (37°C) (Fig. 19-15) • Consists of elongated, cigar-shaped yeasts; rarely seen in histologic sections of tissue

Mold/mycelial phase (room temperature; 25°C) • (Fig. 19-16)
Consists of septate hyphae
Turn white to black with age
Delicate conidiophores bearing pyriform (pear-shaped) conidia in rosette clusters

Treatment
- Lymphocutaneous disease: itraconazole, saturated solution of potassium iodide (SSKI), terbinafine
- Disseminated or deep infection: IV amphotericin B
- Other clinical forms: ulcers, or infection associated with draining sinuses
- Pulmonary or disseminated disease: occurs after inhalation with disseminated lesions in joints, lungs, mucous membranes, seen in immunosuppressed individuals
- Diagnosis
  - Histology: asteroid bodies: yeast forms surrounded by refractile eosinophilic halo; yeast forms are sparse and rarely seen, pseudoepitheliomatous hyperplasia with non specific granulomatous inflammation
  - Culture: dimorphic fungus; growth inhibited by cycloheximide


FIGURE 19-15 Sporothrix schenckii yeast. (Courtesy of Dr. Mark LaRocco.)
**Chromoblastomycosis (Chromomycosis, Carrion Mycosis)**
- Localized, chronic infection of skin or subcutis by pigmented (dematiaceous) fungi that develop as muriform cells (sclerotic cells or Medlar bodies): small clusters of cells
- Most common agents include *Fonsecaea pedrosii, F. compactum, Cladophialophora carrionii, Rhinocladiella aquaspersa, Phialophora verrucosa,* and *Wangiella dermatitidis*
- Acquired by implantation of organisms from soil or decaying wood
- Clinical:
  - Lesions are usually painless, slow growing, verrucous plaques, spread by direct extention; lymphedema may occur locally
  - KOH: brown muriform fungal cells
- Diagnosis:
  - Histology:
    - Pseudoepitheliomatous hyperplasia with inflammatory infiltrate of neutrophils
    - “Sclerotic bodies” (also called Medlar bodies, copper penny bodies) (Fig. 19-17)
    - Transepidermal elimination of intracellular and clumped organisms with single or double septum
  - Culture: folded gray-green to black colonies
- Treatment: itraconazole, terbinafine, amphotericin B, surgical excision

**Subcutaneous Phaeohyphomycosis**
- Dematiaceous fungi that cause subcutaneous inflammatory cysts
- Causative organisms: *Exophiala jeaneselmei, Wangiella dermatitidis, Alternaria* spp., *Bipolaris* spp., *Curvularia* spp., *Phialophora* spp
- Clinical: solitary subcutaneous cyst/abcess; may drain
- Diagnosis:
  - Microscopic: branched, spetate dematiaceous hyphae
  - Histology: hyphae seen along cyst wall with macrophages
  - Culture: dark leathery or wooly colonies; microscopic evaluation varies with each species
- Treatment: surgery, itraconazole

**Mycetoma (Madura Foot, Maduromycosis)**
- Includes infections by both actinomycetomas (caused by bacteria) and eumycetomas (caused by fungi)
- Acquired from soil implantation
- Etiologic agents: classification of mycetomas made by examining grains grossly for color and texture (Table 19-7)
- Clinical
  - Lesions involve skin (most commonly on the foot), subcutaneous tissue, fascia, and bone
  - Painless edematous subcutaneous nodules, grow slowly and coalesce. Fistulas and sinus tracts with purulent exudates and extrusion of grains (may infect adjacent tissue), possible bone destruction (Fig. 19-18)
- Diagnosis
  - Culture: etiologic agents are identified according to their microscopic and macroscopic features
  - Serology: ELISA and immunodiffusion
  - Histology:
    - Formation of neutrophil rich granulomas and abscesses that surround filamentous fungal or bacterial grains; size and shape of grains visualized in histopathology may help in their precise identification of eumycetoma or
actinomycotic mycetoma with fine filaments (Fig. 19-19)
- Treatment: actinomycetomas: combination of sulphonamethoxazole-trimethoprim plus rifampin or dapsone and streptomycin. Amikacin or imipenem for recalcitrant Nocardia infections
- Eumycetoma: surgical excision

Rhinosporidiosis
- Chronic granulomatous infection caused by Rhinosporidium seeberi, controversy over taxonomy of the agent: considered to be an aquatic protozoan (Mesomycetozoa), previously thought to be a fungus
- Endemic in India and Sri Lanka with South America as the second most common source of infection; close contact with rivers and lakes may result in infection
Chapter 19  FUNGAL DISEASE

DIMORPHIC FUNGI

- See Table 19-8
- Different anamorphic forms or phases
- Regulated by several biologic and physical factors, the most important being temperature
- 25°C fungi grow as molds: soil saprophytes
- 35–37°C fungi grow as yeasts or yeastlike: tissue or parasitic phase
- Disease characteristics
  - Portal of entry: respiratory tract
  - Infection is acquired via inhalation of conidia produced by the mold phase
  - Primary infections occur most commonly in the respiratory tract
  - Can progress to serious pulmonary or disseminated disease with multiorgan involvement
  - Tissue phase not transmissible, no person-to-person spread of infection
  - Extent of disease is regulated by the immunologic response of the host
    - Humoral response
      - Minimal role in protection
      - Sometimes increases disease severity (hypersensitivity responses)
    - Measurement of antibody titers is useful occasionally for diagnosis and prognosis (see below)
    - Cell-mediated response (T cells, cytokines, activated macrophages)
    - Primary protective mechanism and major determinant of disease severity

Coccidioidomycosis (San Joaquin Valley Fever, Desert Rheumatism)
- Dimorphic fungi with saprophytic and parasitic phases
- Hosts: humans, dogs, horses
- Acquired by inhalation of arthroconidia of Coccidioides spp.
- Lower Sonoran desert, southwestern United States, a soil inhabitant

<table>
<thead>
<tr>
<th>TABLE 19-8  List of Dimorphic Fungi</th>
</tr>
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<tbody>
<tr>
<td>Coccidioides immitis</td>
</tr>
<tr>
<td>Histoplasma capsulatum and H. duboisii</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
</tr>
<tr>
<td>Paracoccidiodes brasiliensis</td>
</tr>
<tr>
<td>Sporothrix schenckii</td>
</tr>
<tr>
<td>Penicillium manerfeii</td>
</tr>
</tbody>
</table>
**DIMORPHIC FUNGI**

- **Coccidioides immitis** (commonly found in the San Joaquin Valley, California)
- **C. posadasii** (commonly found in southwest United States, Mexico, and South America)

**Clinical:**
- Lungs are usually the primary focus of the infection with subsequent dissemination to skin, meninges, bones and joints
- Extrapulmonary disease is rare (<5% of cases) but serious; usually involves central nervous system, skin, and pericardium
- Up to 60% of cases may be asymptomatic
- Another 35% present as mild flu-like illness with fever, chest pain, and arthralgia
- Increased risk of infection in immunosuppressed patients, Mexicans, blacks, pregnant women, and Filipinos

**Cutaneous disease**
- Lesions may be organism specific (organisms are identified in skin biopsy and result mainly from hematogenous spread) or a reactive response to the organisms (no viable organisms present)
- Reactive lesions often present early and include: erythema nodosum, erythema multiforme, Sweet’s syndrome, acute generalized exanthem, interstitial granulomatous dermatitis
- Organism specific lesions include: single or multiple papules, nodules, verrucous plaques, abscesses, pustules, sinus tracts, and/or ulceration

**Diagnosis:**
- Histology: pseudocarcinomatous hyperplasia, dermal and/or subcutaneous inflammation with eosinophils
- Serology: qualitative and quantitative techniques

**Mold phase (culture of tissue specimens)**
- **Culture:** white to tan fluffy colony matures in 5-10 days
- **Microscopic:** hyphae separate to form barrel-shaped arthroconidia (infectious, may cause lab-acquired disease), (Fig. 19-20) arthroconidia are very
- **Tissue phase (tissue specimen or cytologic smear)**

**FIGURE 19-20 Coccidioides immitis mold phase. (Courtesy of Dr. Mark LaRocco.)**

**FIGURE 19-21 Coccidioides immitis tissue. (Courtesy of Dr. Mark LaRocco.)**
Chapter 19    FUNGAL DISEASE

- Microscopic: multinucleated spherules filled with endospores (produced by repeated cleavage) (Fig. 19-21)
  - Chest radiograph: eggshell pulmonary cavities, pneumonia, pulmonary nodules, hilar or mediastinal lymphadenopathy, pleural effusions
- Treatment: not needed for asymptomatic pulmonary disease; extrapulmonary disease and immunosuppressed patients: itraconazole, fluconazole, amphotericin B

**Histoplasmosis (Darling’s Disease)**

- *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii* are pathogenic to humans
- Associated with soil containing bird and bat droppings; the organism is most commonly found in Central and North America; in the United States, it is endemic in the Mississippi and Ohio River valleys
- Clinical:
  - Infection begins after inhalation of microconidia – acute pulmonary: self limited illness, fever, chills, dry cough, pneumonia; 5% develop rheumatologic or dermatologic symptoms (erythema multiforme and erythema nodosum)
  - Chronic cavitary pulmonary histoplasmosis: fungal infection is sometimes adjacent to emphysematous bullae with necrosis and increasing fibrosis causing large persistent cavities
  - Disseminated histoplasmosis: develops in immunosuppressed patients: including treatment induced immunosuppression with tumor necrosis factor inhibitors
  - Patients present with fever, malaise, anorexia, and weight loss. On exam: hepatosplenomegaly, lymphadenopathy, pallor and petechiae (with pancytopenia). Cutaneous lesions: mucous membrane ulcerations, skin ulcers, nodules, or molluscum-like papules. If both adrenal glands are severely affected by the infection, Addison’s disease can occur
  - Endocarditis and vascular infection: rare manifestation
  - Central nervous system infection: most commonly presents with chronic meningitis
- African histoplasmosis
  - *H. duboisi*
  - Involves mucocutaneous, bone, lymph nodes, lungs
  - Skin lesions can resemble molluscum contagiosum
- Diagnosis:
  - Mycology
    - Mold (mycelial) phase
  - Culture: (incubation at 25°) white cottony colony after 2–4 weeks of incubation (Fig. 19-22)
  - Microscopic: septate hyphae, formation of microconidia (infectious) and tuberculated macroconidia (diagnostic) (Fig. 19-23)
- Tissue phase
  - Parasitized histiocytes: small (4–6 μm), oval yeasts, usually found in monocytes and macrophages of the blood, lungs, and reticuloendothelial system (Fig. 19-24)
  - Laboratory studies: elevated alkaline phosphatase levels, C-reactive protein levels, lactate dehydrogenase levels, and ferritin; pancytopenia
  - Histology: oval, narrow-based budding yeast with methenamine silver or periodic acid-Schiff stains; yeasts are usually found within macrophages
- Treatment: none needed for asymptomatic pulmonary disease; extrapulmonary disease and immunosuppressed patients: itraconazole, fluconazole, amphotericin B

** Blastomycosis (Gilchrist’s Disease)**

- Caused by *Blastomyces dermatitidis*, infections occurs through inhalation of the conidia of the mold form
- Endemic in the Mississippi River valley, southeastern United States
- Clinical:
  - Pulmonary disease occurs, but extrapulmonary presentation is more common with chronic infection of the skin and bones
Inoculation blastomycosis is a rare and mild form of cutaneous disease in lab workers. Diagnosis:

Mycology
- Mold/mycelial phase
  - Septate hyphae, white colony in 3–4 weeks
  - Formation of oval microconidia

Tissue phase
- Large, thick-walled yeast with broad-based bud (Fig. 19-25)

Cutaneous lesions:
- Characterized by microabscess formation, papulopustular well circumscribed nodules, and crusty verrucous granulomas of the hands, face and mucocutaneous areas, cribiform scars

Other manifestations: genitourinary tract infection, septic arthritis, osteomyelitis

Systemic blastomycosis
- Pulmonary spread to skin, bones (osteolytic lesions), genitourinary tract, and CNS
- Pulmonary disease is similar to tuberculosis

Inoculation blastomycosis is a rare and mild form of cutaneous disease in lab workers.

Diagnosis:
- Mycology
  - Mold/mycelial phase
    - Septate hyphae, white colony in 3–4 weeks
    - Formation of oval microconidia
  - Tissue phase
    - Large, thick-walled yeast with broad-based bud (Fig. 19-25)

Treatment: itraconazole, amphotericin B
Paracoccidioidomycosis (South American Blastomycosis)
- Caused by Paracoccidioides brasiliensis, thermally dimorphic; commonly found in South and Central America
- Chronic, insidious, granulomatous disease
- Clinical:
  - Begins as a pulmonary infection following inhalation of the fungi and then disseminates; patients with lung infection have a productive cough and fever
  - Forms ulcerative granulomata and mulberry-like erosions of buccal (Aguiar-Pupo stomatitis), nasal, and occasionally the gastrointestinal mucosa
  - Lymph node involvement (commonly cervical) with extension to cutaneous tissue
  - Systemic involvement of multiple organ systems is a rare complication: adrenal glands, long bones
  - Male-to-female ratio 8:1 (estrogen may inhibit the hyphae to yeast transformation)
- Diagnosis:
  - Mycology
    - Mold phase (25°C)
      - Culture: white to tan colony, growth in 2–4 weeks
      - Microscopic: septate hyphae, oval microconidia indistinguishable from Blastomyces dermatitidis (must observe tissue phase)
    - Tissue phase (37°C)
      - Thin-walled yeast with narrow points of attachment of buds to mother cells “ship’s wheel” configuration; (Fig. 19-26)

SYSTEMIC MYCOSES

Paracoccidioidomycosis
- Invade deep structures and spread through hematogenous route to other areas of the body (skin, and mucosa)
- Two forms exist: opportunistic and endemic respiratory mycoses

Systemic Opportunistic Mycoses
CANDIDIASIS
- Candidal infection that result in a heterogeneous group of infectious diseases including systemic, mucocutaneous, and vulvovaginal infections; risk factors for developing candidal infection (Table 19-9)
- Candida are unicellular yeasts with thin walled ovoid cells (3- to 6-μm) that reproduce by budding; they frequently exist as normal inhabitants in the oropharynx, skin, mucous membranes, lower respiratory tract, gastrointestinal, and genitourinary tracts
- Fifteen species exist as significant human pathogens:
  - Candida albicans (most common)
  - Examples of non C. albicans Candida spp.
    - C. glabrata (increasing in frequency), C. tropicalis, C. parapsilosis, C. krusei
- Infection is usually of endogenous origin and may occur when: 1) there is increased fungal burden or colonization, 2) there is a breakdown

- Treatment: itraconazole, ketoconazole, amphotericin B, sulfonamides (sulfamethoxypyridazine and sulfadimethoxine)
of normal mucosal and skin barriers, 3) immune dysfunction leads to dissemination

- Clinical:
  - Local disease
  - Oral candidiasis (thrush): creamy, white patches on the tongue and oral mucosa, can be removed by scraping, chronic atrophic disease seen in denture patients with atrophic mucosa, candidal leukoplakia presents with firm, white plaques of the cheeks, lips and tongue, angular chelitis (perlesche): affects the oral commissures with scale, erythema, and fissures

<table>
<thead>
<tr>
<th>TABLE 19-9 Risk Factors for Developing Candidiasis</th>
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<tbody>
<tr>
<td>Adults</td>
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<tr>
<td>Prolonged length of stay in an ICU</td>
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<td>High acute physiology and chronic health evaluation</td>
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<td>II score (e.g., &gt; 20)</td>
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<td>Renal failure</td>
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<td>Hemodialysis</td>
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<td>Broad-spectrum antibiotics</td>
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<td>Central venous catheter</td>
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<td>Parenteral nutrition</td>
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<td>Immunosuppressive drugs</td>
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<td>Cancer and chemotherapy</td>
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<td>Severe acute pancreatitis</td>
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<td>Candida colonization at multiple sites</td>
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<tr>
<td>Surgery</td>
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<td>Neonates and Children</td>
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<tr>
<td>In addition to the adult risk factors:</td>
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<tr>
<td>Prematurity</td>
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<tr>
<td>Low Apgar score</td>
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<tr>
<td>Congenital malformations</td>
</tr>
</tbody>
</table>

• **Candida esophagitis**: seen in immunosuppressed patients (it is an AIDS-defining illness); dysphagia, chest pain, nausea, vomiting

• **Vulvovaginal candidiasis**: predisposing factors: immunosuppression, antibiotics, contraceptive devices, elevated estrogen; pruritic, erythematous mucosa with thick, white discharge

• **Cutaneous candidal infection**:
  - Generalized cutaneous candidiasis: presents with diffuse pustular and erythematous eruptions worse in intertriginous areas
  - Erosio interdigitalis blastomycetica: a chronically denuded/macerated area seen in the web space (commonly seen in the third web space of the fingers)
  - *Candida* folliculitis: seen mainly in immunocompromised hosts and among intravenous drug users; pustules and nodules in hair bearing areas
  - *Candida* balanitis: more common in uncircumcised males; infection is acquired with sexual intercourse with an infected partner; burning and itching of the penis with generalized erythema of the glans and/or prepuce, with eroded white papules and white discharge; may spread to buttocks and/or scrotum
  - Intertrigo (Fig. 19-27): occurs in creases and folds of the skin with erosions, oozing, exudation, maceration
  - Candidal paronychia: associated with frequent hand immersion in water and diabetes mellitus, loss of cuticle with erythema and scaling; may present with dystrophic nails
  - Diaper rash (Fig. 19-28): exacerbated by moisture under diapers, erythematous, macerated patches with satellite lesions
  - Perianal candidiasis: skin maceration and pruritus are frequent with frequent extension to the perineum

• **Chronic mucocutaneous candidiasis**: infections of the skin, mucous membranes, hair, and nails, recalcitrant to treatment; seen in patients with T-cell dysfunction, may be related to autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy (APECED) syndrome
  - Invasive infection (isolation of *Candida* from a normally sterile body site)

• **Acute disseminated candidiasis**
  - Occurs most commonly among neutropenic patients; erythematous or hemorrhagic palpable rash

• **Chronic disseminated candidiasis**: seen in neutropenic patients; low-grade fever, right upper quadrant pain, associated with a palpable and tender liver, splenomegaly, and an elevated serum alkaline phosphatase

• **Congenital candidiasis**
  - Benign in first 24 hours of life; may have transient respiratory distress; associated with chorioamnionitis
  - Endocarditis: develops mainly in patients with a chronic indwelling catheter, also found in intravenous drug abusers; due to *C. tropicalis* and *C. parapsilosis*
Vertebral osteomyelitis: usually affects lumbo-sacral vertebral disks and vertebral bodies; chronic progressive local back pain
Candida endophthalmitis: retinal lesions associated with untreated candidemia

Diagnosis:
- microscopic examination of skin or mucosal scrapings using potassium hydroxide smear or Gram stain
- 1, 3 b-glucan assay: high sensitivity and specificity
- Microscopic: pseudohyphae or true septate hyphae (Fig. 19-29)
- Culture: colonies are white and creamy on Sabouraud dextrose agar after 24–48 hours of incubation at 35°C (Fig. 19-30)

Treatment
- Topicals (nystatin, miconazole, clotrimazole) for uncomplicated cutaneous disease
- Amphotericin B (AMB), liposomal AMB, fluconazole, voriconazole, caspofungin for invasive and/or disseminated disease

CRYPTOCOCCOSIS
- Cryptococcus neoformans is the major human pathogen (United States and Europe)
- Four differing serotypes(A–D): C. neoformans var grubii (serotype A) and C. neoformans var neoformans C. neoformans var gattii (serotype B)
- Pigeons are a major reservoir for the fungus
- C. neoformans is found in bird droppings
- C. gatti (tropics including Africa)
- Found in leaf and bark debris from red gum trees
- Clinical:
  - Respiratory route of entry but primary infection is usually subclinical, can have hematogenous spread to lungs, bones, and viscera
  - Predilection for the central nervous system
  - Skin lesions: widespread papules, acneiform pustules around the nose and mouth, subcutaneous abscesses may ulcerate and form granulomatous, eroded areas, AIDS patients with mollusciform lesions

Diagnosis:
- Mycology
  - Slimy mucoid colony on Sabourand agar at 37°C
  - Encapsulated 4- to 8-μm yeast that produces by single or double buds surrounding clear halo; no pseudohyphae formed (Fig. 19-31)
  - Polysaccharide capsule: serves as a virulence trait of the fungus
  - Stains with mucicarmine; best seen with PAS or GMS
  - India ink smear for CSF

FIGURE 19-29 Candida albicans, microscopic view. (Courtesy of Dr. Mark LaRocco.)

• Treatment: amphotericin B, amphotericin B + 5-fluorocytosine, fluconazole

**Aspergillosis**

• Ubiquitous mold found in most environments
• *Aspergillus flavus*
  - Most common primary cutaneous pathogen; affects intravenous sites in immunosuppressed patients
• *A. fumigatus*
  - Most common pathogen overall, affecting primarily the lung
• *A. niger*
  - Associated with burn wounds

**Clinical:**
• Infection acquired by inhalation of conidia
• Allergic bronchopulmonary aspergillosis:
  - Hypersensitivity response to conidiospores; no tissue invasion
  - Aspergilloma (fungus ball); cavities in lungs (tuberculosis, sarcoidosis)
• Invasive pulmonary aspergillosis
  - Parenchymal invasion with hyphal progression along vascular pathways
• Disseminated aspergillosis
  - Involvement of two or more non-contiguous organ systems
• Mycotoxicoses
  - Ingestion of food contaminated with toxins produced by some aspergilli (aflatoxins)
• Invasive and/or disseminated aspergillosis
  - Often fatal disease in immunosuppressed patients; predisposing factors or conditions include: neutropenia, neoplasm, organ transplantation, chemotherapy, steroids

• Cutaneous infection: presents as necrotic ulcers or embolic lesions with black eschar

**Diagnosis:**
• Mycology
  - Rapidly growing monomorphic molds
  - Mycelium consists of septate hyaline hyphae
  - Conidiophores with terminal vesicle and phialides produce chains of conidia; different species have different conidial color, size and spatial arrangements (Fig. 19-32)
• Microscopic examination of tissue
  - GMS, PAS, or calcofluor stains: septate hyphae with 45-degree angle branching (Fig. 19-33)
• Culture: growth of hyaline mold in 1–2 days on routine fungal media incubated at 25°C. (Fig. 19-34)
  - Conidial pigmentation differs according to species (*A. fumigatus* = green)
• Serologic tests
  - Antibody tests available for allergic disease and aspergillosis, not good for invasive disease (patients often can’t produce antibodies)
  - Galactomannan antigenemia test available; results variable

**Treatment**
• Allergic disease: steroids
• Aspergilloma: none, surgical resection
• Invasive disease: amphotericin B, itraconazole, voriconazole, caspofungin

**Zygomycosis**

• Mainly saprophytic fungi

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**FIGURE 19-31** Cryptococcus neoformans, India ink preparation. (Courtesy of Dr. Mark LaRocco.)
The medically important orders and genera include:
- Mucorales, causing subcutaneous and systemic zygomycosis (Mucormycosis) – *Rhizopus, Absidia, Rhizomucor, Mucor, Cunninghamella, Saksenaea, Apophysomyces, Cokeromyces and Mortierella*
- Entomophthorales, causing subcutaneous zygomycosis (Entomophthoromycosis) – *Conidiobolus* and *Basidiobolus*
- Order Mucorales
  - Clinical presentations
    - Rhinocerebral infection (most common): rapidly progressive infection of sinuses, orbits, and brain, with infarction and necrosis, associated with ketoacidotic diabetes, sinus pain, proptosis, unilateral palsy, facial edema, purulent drainage, meningitis
    - Thoracic infection: pleural disease produces chest pain, cough
    - Abdominal, gastric infection: more common in children and malnourished patients
    - Skin infection: can affect burn and diabetic patients, local trauma of skin is portal of entry; may present with plaques, pustules, abscesses, or ulceration
Basidobolus infections: oral treatment with potassium iodide, ketoconazole or itraconazole

**PENICILLIOSIS**
- *Penicillium marneffei*: endemic in Southeast Asia
  - Thermally dimorphic fungus; infection occurs after inhalation of conidia
  - Clinical
    - Fever, weight loss, hepatomegaly, umbilicated papules (molluscum-like) with occasional necrosis; occurs on upper half of the body including the oral mucosa
    - Prominent lymphadenopathy, localized pulmonary lesions in disseminated disease
  - Diagnosis:
    - Mycology
    - Histology: histiocytes with intracellular yeastlike cells divided by a septum
    - Culture: green or gray mold with diffusible apricot red pigment
    - Microscopic: hyphae have paintbrush or broom look
  - Treatment: itraconazole, amphotericin B

**FUSARIUM**
- Common in soil and dead or living plants
- Most common of these are *Fusarium solani*, *F. oxysporum*, and *F. chlamydosporum*
- Immunocompromised hosts, particularly in neutropenic and transplant patients
  - Clinical:
    - Infection begins after trauma
    - Can present as central venous catheter infections, septic arthritis, disseminated infections, keratitis, endophthalmitis, endocarditis, peritonitis and fungemia
  - Cutaneous infections include: onychomycosis (superficial white onychomycosis, proximal subungual onychomycosis, and distal and lateral subungual presentation), tinea pedis, localized abscesses or disseminated lesions following hematogenous dissemination (widespread annular lesions often with a central dark or even hemorrhagic area), infection of burn wounds
  - Neutropenic or burn patients are at high risk for infection
  - Diagnosis:
    - Culture: colonies are usually fast growing, pale or brightly colored (depending on the species), and may or may not have a cottony aerial mycelium
    - Microscopic: sickle-shaped “banana” multiseptated macroconidia
  - Treatment:
    - Very drug-resistant fungi
• Intrinsically resistant to the novel glucan synthesis inhibitors, caspofungin, anidulafungin, and micafungin; can try amphotericin B, voriconazole, and natamycin

OTHER

Protothecosis
• Prototheca wickerhamii
• Achloric algae in stagnant, brackish water; spherical unicellular organisms ranging from 3 to 30 μm in diameter
• Ubiquitous in nature; may infect humans through contact with potential sources, such as contaminated soil or water
• Low virulence; risk factor is cellular deficiency
• Clinical
  • Cutaneous lesions: most common site of infection, ill-defined plaque or nodule that may have a verrucous surface
  • Olecranon bursitis
  • Disseminated or systemic infections: in severely immunocompromised patients, organs most commonly affected in dissemination are the skin, subcutaneous tissue, gut, peritoneum, blood, and spleen
• Diagnosis
  • Histology: “morula”; sporangia with a central rounded endospore surrounded by a corona of molded endospores
  • Culture: creamy yeast-like colonies at 30°C, inhibited by cycloheximide
• Treatment: medical and surgical approaches; ketoconazole, itraconazole, fluconazole, conventional amphotericin B, and liposomal amphotericin B

QUIZ

Questions

1. On Sabouraud medium at 25°C, tuberculate macroconidia developed. The organism is thermally dimorphic. Which of the following is true?
A. The disease is transmitted from person to person
B. The organism is Histoplasma capsulatum
C. The organism is Blastomyces dermatidis
D. The organism is Trichophyton rubrum

2. On microscopic examination septate hyphae with barrel-shaped arthroconidia are seen. The fungus is dimorphic. Which of the following is true?

3. Small black nodules up to one mm in size developed along the hair shaft of the scalp. The colonies were brown to black in color. Which of the following is true?
A. The etiologic agent is Piedraia hortae
B. The etiologic agent is Phaeoannelomysis werneckii
C. The disease is found in temperate climates
D. The etiologic agent also causes tinea versicolor

4. The organism is a thermally dimorphic fungus. Microscopic examination of the culture grown at 25°C demonstrated septate branching hyphae-bearing rosette-like clusters of conidia. What is your diagnosis?
A. Histoplasmosis
B. Sporotrichosis
C. Coccidioidomycosis
D. Cryptococcosis

5. Which of the following is true about Trichophyton tonsurans?
A. The organism is zoophilic
B. The organism causes eotothrix infection
C. The organism grows best if thiamine is present
D. Commonly causes scutula

6. A slimy, mucoid colony was grown on Sabouraud agar at 37°C. Budding yeast cells with distinct capsules were observed on microscopic examination. What is this organism?
A. Candida tropicalis
B. Cryptoccus neoformans
C. Candida glabrata
D. Histoplasma capsulatum

7. A lactophenal preparation of a dermatophyte revealed grape-like clusters of microconidia. Which of the following is true about this fungus?
A. This is Trichophyton rubrum
B. The organism is anthropophilic
C. It is urease positive
D. This is Trichophyton tonsurans

8. The colony is fluffy, white to yellow. Microscopic examination revealed thick-walled macroconidia with more than six septa. Which of the following is true?
A. The organism is *Micrococcus canis*
B. The organism is *Micrococcus audouinii*
C. It causes endothrix infection
D. It causes scutula

9. The colony was white fluffy with red pigment on reverse. The microscopic morphology showed smooth peg-shaped conidia. Which of the following is true?
   A. This is *Trichophyton mentagrophyte*
   B. This is *Trichophyton rubrum*
   C. It is usually associated with tinea capitis
   D. This is *Epidermophyton floccosum*

10. This bullous type tinea pedis is generally associated with a dermatophyte. Which of the following is true?
    A. *Trichophyton mentagrophytes* is usually associated with this type of tinea pedis
    B. *Trichophyton rubrum* is usually associated with this type of tinea pedis
    C. This is the most common form of tinea pedis
    D. *Trichophyton tonsurans* is associated with this type of tinea pedis

11. A PAS shows histiocytes filled with yeasts. On Sabouraud medium at 25°C, a slow-growing white fungus colony developed. What is your diagnosis?
    A. Coccidioidomycosis
    B. Blastomycosis
    C. Histoplasmosis

12. Microscopic examination from a dimorphic fungus colony revealed large thick-walled yeast with broad-based bud. What is your diagnosis?
    A. Sporotrichosis
    B. Coccidioidomycosis
    C. Blatamycoysis

**Answers**

1. B. *Histoplasma capsulatum* produces tuberculate macrocanidia when grown at 25°C. The disease is acquired by inhalation of microconidia and is not transmitted from person to person.
2. B. Hyphae of mycelial forms of *Coccidioides immitis* fragments into arthroconidia with alternating empty spaces. Once inhaled arthroconidia undergo dimorphism and are transformed into spherules containing endospores. The lower Sonoran life zone is ideal for the growth of *C. immitis*; the fungus flourishes in hot, dry environment with minimal rainfall and alkaline soil. The skin test is a useful diagnostic tool. Latex particle agglutination and immunodiffusion test are positive in 90% of cases in early phase of the disease. The CF is very useful and is last to become positive.
3. A. Black piedra is a hair disease of the tropics, caused by *Piedraia hortae*. The disease is also known as phaeohyphomycosis. Phaeohyphomycosis is a new concept and includes diseases caused by dematiaceous fungi – sclerotic bodies are not present. Sclerotic bodies (“copper penny”) are associated with chromoblastomycosis.
4. B. These are microscopic features of *Sporothrix schenckii*. Conidiophores bear rosette-like clusters of small round or pyriform conidia. Sporotrichosis is caused by thermally dimorphic fungus. At 37°C, oval, round or fusiform budding cells are produced. The fusiform cells are also called “cigar-shaped bodies.”
5. C. The most frequently isolated colony of *T. tonsurans* shows flat growth initially, becomes folded with a suede-like surface. The organism is anthropophilic and is a common cause of tinea capitis in the United States and northern Europe. The infection is endothrix and Wood’s light is not useful. The organism grows best if thiamine is included.
6. B. This is mucoid colony of *Cryptococcus neoformans* on Sabouraud agar at 37°C. India ink preparation shows yeast cell surrounded by large capsule prepared from culture or spinal fluid.
7. C. The colony is wooly or silky white (*T. mentagrophytes var. interdigitale*) to powdery form (*T. mentagrophytes var. mentagrophytes*). Globose (round microconidia in grape-like clusters and sometimes spiral hyphae are noted. The macroconidia when present have thin walls. *T. rubrum* is urease negative and most strains of *T. mentagrophytes* are urease positive.
8. A. The colony of *Micsorum canis* is wooly white to yellowish in color. The macroconidia are produced in abundance. They have thick walls with six or more septa. It causes ectothrix infection.
9. B. *T. rubrum* produces peg-shaped macroconidia that are uniform in size. Occasionally thin-walled pencil-shaped macroconidia are produced. *T. rubrum* is the major etiological agent of tinea pedis and onychomycosis.
10. A. Vesiculobullous type tinea pedis is most often caused by *T. mentagrophytes*. The eruptions occur typically with vesicle and bullae in clusters. This form is often responsible for the production of id reaction on the hands. During primary infection a brisk T-cell response develops, which produces and allergic reaction to the fungus.
11. C. In histoplasmosis, yeasts appear in the cytoplasm of histiocytes and giant cells as numerous
small spherical or oval-shaped yeast form (1 to 5 μm in diameter).

12. C. Blastomyces dermatitidis (a yeast form). In tissue, the fungus forms large, round, budding yeast cells, characterized by thick cell walls and broadly attached daughter yeast cells. The fungus is thermally dimorphic.

REFERENCES

VITAMIN DEFICIENCIES

Vitamin B₃ (Niacin/Nicotinic Acid) Deficiency

- Deficiency results in clinical findings of pellagra from the Italian “pelle agra” for “rough skin”
- Niacin, a B vitamins, can be synthesized from a precursor molecule, tryptophan
  - Deficiency may either be from a niacin or tryptophan deficiency
- Two coenzyme forms of niacin: nicotinamide adenine dinucleotide (NAD) and NAD phosphate which participate in a variety of redox reactions
- Found in animal proteins, bran, peanuts, legumes, seeds
- Risk factors for development of pellagra
  - Primary (inadequate intake): poverty, restrictive diets, prolonged intravenous supplementation, untreated maize
  - Secondary (inadequate absorption or conversion):
    - Crohn’s disease, GI surgery, intestinal parasites, chronic alcoholism
    - Medications: 6-mercaptopurine, sulfapyradine, 5-flourouracil, phenobarbitol, ethionamide, pyrazinamide, hydantoins, isoniazid therapy (pyridoxine deficiency secondary to isoniazid treatment could cause pellagra because pyridoxine is required for the conversion of tryptophan to niacin)
    - Carcinoid syndrome: tryptophan diverted to serotonin
    - Hartnup disease: inborn error (autosomal recessive) of tryptophan metabolism
- HIV
- Clinical
  - Classically described as three Ds: (1) dermatitis, (2) dementia, (3) diarrhea
    - Skin
  - Four types of dermatitis:
    - Photosensitive eruption: affecting dorsal hands, feet, forearms, legs, malar region, forehead, tip of nose and “V” of neck (referred to as Casal’s necklace)
    - Perineal lesions
    - Thickening and pigmentation over bony prominences
    - Seborrheic-like dermatitis on the face
  - Gastrointestinal tract
    - Glossitis: atrophy of the papillae of the tongue
    - Acute inflammation of the small intestine and colon
  - Neurologic
    - Deficiency causes patchy demyelination and degeneration of the various affected parts of the nervous system
    - Depression, anxiety, irritability, poor concentration, tremor, delusions progressing to encephalopathy
- Diagnosis
  - Made in part by response to niacin supplementation
  - Urinary N-methyl nicotinamide and 2-pyridone are the best measurement of niacin status
- Treatment: nicotinamide 100 mg PO q6h for several days or until resolution of major acute symptoms, followed by 50 mg PO q8-12h until all skin lesions heal

Vitamin B₂ (Riboflavin) Deficiency

- Isolated deficiency is rare and is usually associated with other vitamin B complex deficiencies
- Riboflavin is needed as a coenzyme for the activity of flavin adenine dinucleotide (FAD)
- Riboflavin found in milk, organ meat, eggs, leafy green vegetables
Sensitive to UV radiation
Deficiency may be primary or secondary
  - Secondary causes: alcoholic cirrhosis, hypothyroidism, neonatal phototherapy, chlorpromazine, imipramine, doxorubicin, quinacrine use, acute boric acid ingestion, malabsorptive states
Clinical
  - Oro-oculo-genital syndrome:
  - Genital dermatoses: often earliest manifestation of deficiency: patchy redness with scaling or fine powdery desquamation, chronic cases result in lichenification
  - Oral changes: angular stomatitis
  - Seborrheic-like scaling of nasolabial folds, ears, outer canthi of the eyelids
  - Rarely corneal vascularization and interstitial keratitis
  - Associated findings: anemia, neurologic dysfunction
Diagnosis: erythrocyte glutathione reductase level
Treatment: 5–10 mg riboflavin daily by mouth until corrected

Vitamin B<sub>12</sub> (Cyanocobalamin) Deficiency
- Needed by all DNA synthesizing cells including those of hematopoietic and nervous system
- Cyanocobalamin/hydroxocobalamin found in animal products
- Absorption occurs through binding with gastric intrinsic factor (IF), produced by gastric parietal cells
- In states of achlorhydria, IF secretion is reduced, leading to cyanocobalamin deficiency
- Absorption occurs in distal ileum
- Deficiency usually related to poor absorption states
  - Pernicious anemia (defect in IF)
  - Diseases of terminal ileum (Crohn’s disease, short bowel syndrome)
- Since body stores are large it takes 3 to 6 years to develop deficiency
Clinical
  - Cutaneous findings: generalized hyperpigmentation with accentuation in the flexural areas
  - Glossitis
  - Neuropathy: tingling/numbness in extremities, motor disturbances, cognitive changes, and in extreme cases paralysis
  - Megaloblastic anemia
Diagnosis
  - Serum cobalamin level
  - Test for pernicious anemia by measuring antibodies against IF
- Schilling test: used to test for malabsorptive states
- Treatment—parenteral cyanocobalamin 1000 μg/d IM/SC for 5 days or 1000 μg IM two times per week for 2 weeks, then 1000 μg/wk IM/SC for 5 weeks, then 100 to 1000 μg IM/SC every month

Vitamin C (Ascorbic Acid) Deficiency (Fig. 20-1)
- Clinical deficiency causes scurvy
- Symptoms develop 1 to 3 months after severe or total vitamin C deficiency
- Vitamin C needed for: antioxidant defense, collagen synthesis (cofactor for prolyl hydroxylase), fatty acid metabolism
- Sources of vitamin C: citrus fruits, berries, tomatoes, broccoli, bell pepper
- Usually a primary deficiency: elderly, alcoholics, psychiatric patients on restrictive diets, sailors (historically)
- Clinically presents with four “Hs”
  - Hemorrhagic signs: perifollicular hemorrhage, hemarthroses, subperiosteal hemorrhage, hemorrhagic gingivitis, epistaxis
  - Hyperkeratosis of hair follicles: leads to corkscrew hairs
  - Hypochondriasis: Cortical thinning, which is sometimes described as a “pencil-point cortex,” scurbutic rosary (resulting from abnormalities at the costochondral junction)
  - Hematologic abnormalities: anemia

FIGURE 20-1 Vitamin C (ascorbic acid) deficiency.
(Reprinted with permission from Wolff, K et al: Fitzpatrick’s Dermatology in General Medicine, 7th ed. New York: McGraw-Hill; 2008.)
VITAMIN DEFICIENCIES

Vitamin B1 (Thiamine) Deficiency
- Deficiency causes the condition beriberi
- Thiamine functions in body as part of thiamine pyrophosphate in energy metabolism, synthesis of neurotransmitters
- Thiamine is found in yeast, cereals, liver, meat, eggs, vegetables
- Primary deficiency: seen in strict polished-rice diet
- Secondary deficiency: much more common
  - alcohol related liver disease
  - increased depletion: hyperthyroidism, pregnancy, lactation, diarrhea, dialysis, diuretic use
- Clinical findings
  - Cutaneous: edema, glossitis
  - Neurologic
    - Peripheral neuropathy
    - Mental confusion and confabulation (Korsakoff’s syndrome)
    - Wernicke’s encephalopathy
  - Cardiovascular: congestive heart failure so called “wet” beriberi
  - Other: anorexia, weakness, constipation
- Diagnosis: most practical to assess response to thiamine replacement, whole blood or erythrocyte transketolase activity may be obtained
- Treatment: variable dosing of thiamine based on severity of symptoms

Pyridoxine (Vitamin B6) Deficiency
- Needed for the production of non-essential amino acids including aspartic acid and niacin and for production of serotonin
- Pyridoxine is found in animal products, whole-grain products, vegetables
- Usually occurs in association with other deficiencies
- Primary deficiency: alcoholics, elderly
- Secondary
  - Medications: cycloserine, hydralazine, isoniazid, D-penicillamine, pyrazinamide
  - Uremia, cirrhosis
- Clinical
  - Cutaneous: seborrhea-like changes around eyes, nose, mouth
  - May cause all findings seen in niacin deficiency since pyridoxine is a cofactor for niacin production; please see pellagra section for more details
  - Oral
    - Glossitis
    - Stomatitis
  - Neurologic
    - Depression, confusion, abnormal electroencephalogram
    - Seizures
    - Peripheral neuropathy
  - Anorexia, nausea, vomiting
  - Anemia
- Diagnosis: decreased serum levels of pyridoxine-5-phosphate
- Treatment: supplementation of pyridoxine 20–100 mg/day orally or 100 mg/day parenterally in adults

Vitamin D3 (Cholecalciferol) Deficiency
- Vitamin D regulates calcium and phosphorus metabolism, influences alkaline phosphatase levels
- Fat soluble vitamin found in butter, eggs, liver
- Vitamin D [cholecalciferol (vitamin D3), a steroid compound] is formed in the skin under the stimulus of ultraviolet light
- Other source of vitamin D: ergosterol (vitamin D2), which is contained in fish liver oil or as an irradiated plant steroid
- Synthesis
  - Cholecalciferol (vitamin D3) is formed in the skin from 5-dihydrotachysterol
  - Undergoes hydroxylation in two steps
    - First step: occurs at position 25 in the liver, producing calcidiol (25-hydroxycholecalciferol), which is the circulating reserve compound
    - Second step: occurs in the kidney at the 1 position, where it undergoes hydroxylation to the active metabolite calcitriol (1,25-dihydroxycholecalciferol), a hormone
  - Calcitriol [1,25(OH)2 D3] acts at three known sites:
    - Promotes absorption of calcium and phosphorus from the intestine
    - Increases reabsorption of phosphate in the kidney
    - Acts on bone to release calcium and phosphate
- Groups at risk for deficiency: breast fed newborns, dark skinned individuals, “excessive” use of sunscreens/sun avoidance, malabsorptive states, elderly, institutionalized, hospitalized
- Clinical:
  - Cutaneous: rarely alopecia
  - Bone abnormalities: osteomalacia in adults, rickets in children
Chapter 20  NUTRITION-RELATED DISEASES

Vitamin K found in green leafy vegetables, Vitamin K2 produced by bacteria in the gut

- At risk groups: newborns in the first two weeks of life, fat malabsorption states, certain antibiotics (cephalosporins, etc), liver disease, megadoses of vitamin A or E
- Clinical: secondary to decrease in vitamin K–dependent clotting factors. II, VII, IX, and X
  - Hemorrhage
  - Ecchymosis
  - Purpura
- Diagnosis
  - Elevated serum prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Treatment: oral or intramuscular phytonadione, risk of anaphylaxis with intravenous form
- Acute crisis: fresh frozen plasma

MINERAL DEFICIENCIES

Vitamin A Deficiency (Fig. 20-2)

- Major functions: vision, immunity, maintenance and differentiation of cells, growth
- Fat-soluble vitamin found in animal fats, liver, and milk
- Primary deficiency: common in developing countries
- Secondary deficiency: diseases of fat malabsorption: Crohn’s disease, celiac disease, cystic fibrosis, cholestatic liver disease
- Clinical
  - Cutaneous findings
    - Phrynoderma or toad skin: follicular hyperkeratosis, generalized xerosis
  - Ocular findings
    - Night blindness (nyctalopia), xerophthalmia, Bitot’s spots (foci of xerosis of conjunctiva), keratomalacia
  - Other: growth failure, mental retardation, increased susceptibility to measles
- Diagnosis: serum vitamin A level
- Treatment: vitamin A with dosing based on severity of ocular involvement

Vitamin K Deficiency

- Vitamin K is an essential lipid-soluble vitamin that plays a vital role in the production of coagulation proteins

MINERAL DEFICIENCIES

Zinc Deficiency

- Essential to the normal function of all cells
- Zinc found in nuts, whole grains, green leafy vegetables, shellfish
- Two types: genetic or acquired
  - Hereditary: acrodermatitis enteropathica (AE) (Fig. 20-3)
    - Autosomal recessive most common type
    - Defect in intestinal zinc specific transporter SLC39A4
    - Clinical signs occur 1 to 2 weeks after weaning from breast
      - Diarrhea, dermatitis with periorificial and acral distribution, alopecia

Vitamin A Deficiency (Fig. 20-2)


Vitamin K Deficiency

(Fig. 20-3) Acrodermatitis enteropathica.

MINERAL DEFICIENCIES

**Failure to thrive, lethargy, hypotonia, hypothermia, seizures, mental retardation, osseous alteration, anemia**

**Biochemical phenotype involves** (1) low levels of copper in plasma, liver, and brain because of impaired intestinal absorption, (2) reduced activities of numerous copper-dependent enzymes, and (3) paradoxical accumulation of copper in certain tissues (i.e., duodenum, kidney, spleen, pancreas, skeletal muscle, placenta)

**Diagnosis:** low copper and ceruloplasmin; decreased copper in cultured fibroblasts

**Treatment with copper histidine is usually unsuccessful**

**Folic Acid Deficiency**

**Involved in DNA synthesis**

**Found in liver, meat, milk, and green leafy vegetables**

**Supplementation in pregnant women recommended to prevent neural tube defects**

**Primary deficiency:** poor nutrition (alcoholism, elderly, restricted diet)

**Secondary causes of deficiency include:**
- Impaired absorption (celiac disease)
- Increased requirement (pregnancy, etc)
- Impaired metabolism (antimetabolites such as methotrexate, trimethoprim)
- Concomitant B12 deficiency
- Increased destruction by ethanol metabolite superoxide

**Clinical**
- Hyperpigmentation: patchy distribution
- Glossitis
- Cheilitis
- Megaloblastic anemia

**Diagnosis:** serum folate, must also rule out associated B12 deficiency

**Treatment:** folic acid

**Biotin Deficiency**

**Essential cofactor for several carboxylases**

**Found in liver, egg yolks, also produced by intestinal bacteria**

**Deficiency is rare but can occur in patients with short gut or excessive raw egg-white intake (egg whites contain avidin, a biotin antagonist)**

**Prolonged use of certain drugs, especially phenytoin, primidone, and carbamazepine; anticonvulsants inhibit biotin transport across the intestinal mucosa**

**Two rare inherited syndromes: both may be fatal if therapy not initiated early on**
- Holocarboxylase synthetase deficiency (neonatal type)
• Biotinidase deficiency (infantile type)
• Clinical
  • Cutaneous findings
    – Scaling eczematoid and xerotic lesions on arms, legs, and feet
    – Perioral and genital erosions
    – Cheilitis, waxy pallor to face
    – Alopecia
  • Conjunctivitis
  • Muscle pain
  • Neurologic findings: depression, lethargy, hallucinations, limb paresthesia
• Diagnosis: urine organic acid analysis may be performed
• Treatment:
  • For adults (acquired form) 60 micrograms/day
  • For inherited forms, 10 to 40 mg/day PO/IV/IM; adjust dose depending on severity of deficiency and response to therapy

Essential Fatty Acid Deficiency
• Unsaturated fatty acids that the body cannot synthesize
• Major EFAs are linoleic, linolenic, and arachidonic acids
• Functions include precursors to prostaglandins, reducing fluidity in phospholipids membranes, energy storage, lamellar granule formation
• Deficiency caused by: low-fat diet, severe malabsorption, long-term parenteral nutrition
• Clinical
  • Cutaneous findings
    – Xerotic, leathery skin with underlying erythema
    – Intertiginous erosions
    – Alopecia
    – Increase in transepidermal water loss
  • Systemic features
    – Growth failure, poor wound healing, neurologic damage
• Treatment: essential fatty acid replacement

PROTEIN-ENERGY MALNUTRITION

Marasmus
• Insufficient protein-calorie intake
• From Greek for “wasting”
• Clinical
  • Cutaneous findings
    – Dry, thin, pale skin
    – Ulcerations
    – Lanugo-like hair
    – Hair is thin, grows slowly and falls out readily
  – “Monkey facies” due to loss of subcutaneous fat and wrinkled skin
• Treatment: adequate protein-calorie intake, supplement with zinc and linoleic acid

Kwashiorkor
• From Ghana language meaning “sickness of the weanling”
• Insufficient protein intake but with adequate, sometimes excessive carbohydrate consumption
• Often associated with multiple nutritional disorders
• Clinical
  • Cutaneous findings
    – Dyschromia
    – Superficial desquamation in mild cases (“enamel paint spots”), in severe cases large areas of erosion (“flaky paint”)
    – Diffuse erythema that may progress to purpura
    – Hair is sparse, brittle
    – Flag sign bands of light and dark hair relating to periods of malnutrition
    – Nails soft and thin
    – Mucosal lesions, cheilosis, xerophthalmia, vulvovaginitis
  • Systemic features
    – Edema secondary to hypoalbuminemia
    – Anorexia, irritability, apathy
    – Failure to thrive
    – Superimposed bacterial and fungal infections
    – Bilateral parotitis, hepatomegaly, diarrhea, loss of muscle mass
• Treatment: fluid and electrolyte abnormalities and treatment for any infections

OTHER

Hypervitaminosis A
• May occur after single meal of liver of polar bear, bearded seal
• Clinical
  • Cutaneous
    – Loss of hair, coarseness of hair
    – Generalized exfoliation and pigmentation
    – Cheilitis
    – Pruritus
  • Lethargy, anorexia, weight loss
  • Bone fracture, bone pain
• Carotenoderma
  • Results from high intake of beta-carotene (natural provitamin of vitamin A) containing vegetables and fruits
  • Skin is yellow-orange, most prominent in areas of high sebaceous gland density (nasolabial folds, forehead)
3. A patient who follows a strict polished-rice diet may develop all of the following findings EXCEPT:
   A. Glossitis
   B. Phrynoderma
   C. Congestive heart failure
   D. Confusion
   E. Neuropathy

4. A hunter who eats the liver of a polar bear may develop which of the following findings?
   A. Cheilitis
   B. Hypertrichosis
   C. Genital dermatitis
   D. Peripheral neuropathy
   E. Anemia

5. An infant presents with yellow discoloration of the skin with accentuation in the nasolabial folds but no scleral icterus. Which investigation will lead to the correct diagnosis?
   A. Asking about recent diarrhea and weight loss
   B. Obtaining serum transaminases and liver ultrasound
   C. Asking about protein intake
   D. Asking about vegetable intake
   E. Asking about calcium intake

6. A patient who presents with follicular hyperkeratosis and growth failure should be assessed for all of the following EXCEPT:
   A. Cystic fibrosis
   B. Crohn’s disease
   C. Liver disease
   D. Pernicious anemia
   E. Celiac disease

7. A low serum alkaline phosphatase may be seen in association with:
   A. A periorificial rash
   B. Anemia
   C. Pili tori
   D. Generalized hyperpigmentation
   E. Peripheral neuropathy

8. Koilonychia, or spoon-shaped nail, may be seen most commonly with deficiency of which mineral?
   A. Calcium
   B. Zinc
   C. Iron
   D. Magnesium
   E. Selenium
9. A diet high in raw egg whites may cause a deficiency of:
   A. Biotin
   B. Zinc
   C. Pyridoxine
   D. Vitamin C
   E. Vitamin B₁₂

10. A child presents with significant edema, areas of eroded skin with a flaky paint appearance, and hair with bands of light and dark. Which disorder is he most likely to have?
   A. Marasmus
   B. Kwashiorkor
   C. Essential fatty acid deficiency
   D. Beri beri
   E. Scurvy

**Answers**

1. D. A diet high in untreated corn may result in niacin deficiency. The classic triad is that of dermatitis, dementia, and diarrhea. Hemorrhagic signs may be seen with vitamin C deficiency.

2. C. Vitamin C is a cofactor for prolyl hydroxylase. Deficiency leads to hemorrhagic signs, bony abnormalities, anemia and delayed wound healing.

3. B. A polished-rice diet may lead to a thiamine deficiency. Clinical findings include glossitis, neurologic problems including neuropathy, confusion, encephalopathy, as well as congestive heart failure. Phrynoderma or “toad skin” is associated with vitamin A deficiency.

4. A. The liver of the polar bear is very high in vitamin A. A single meal may result in vitamin A toxicity. Findings that may be seen include alopecia, generalized exfoliation, pruritus, chelitis as well as lethargy and bone pain.

5. D. Carotenoderma results from a high intake of beta-carotene (a natural provitamin of vitamin A) containing vegetables and fruits. The yellow color is often most prominent in areas of high sebaceous gland density. Unlike jaundice from liver disease, there is no scleral icterus.

6. D. Vitamin A is a fat soluble vitamin and deficiency may result from fat malabsorption. All disorders except pernicious anemia may lead to fat malabsorption. Vitamin A deficiency may result in generalized xerosis, follicular hyperkeratosis, ocular findings including night blindness and keratomalacia as well as growth failure. Deficiency has been associated with an increased susceptibility to measles.

7. A. A low serum alkaline phosphatase level is associated with zinc deficiency. Zinc deficiency may manifest with dermatitis in the perioroficial and acral distribution, alopecia, photophobia, stomatitis, and failure thrive.

8. C. Koilonychia is most commonly associated with iron deficiency. Other findings may include glossitis, stomatitis, and anemia.

9. A. Egg whites contain avidin, a biotin antagonist.

10. B. Kwashiorkor develops when there is insufficient protein intake but with adequate, sometimes excessive caloric intake. Edema often occurs secondarily to hypoalbuminemia.

**REFERENCES**


COMMON SKIN CHANGES RELATED TO PREGNANCY

- Hyperpigmentation of nipples, external genitalia
- Linea nigra: midline pigmentary demarcation line on abdomen
- Melasma: ill-defined pigmentation of cheeks, forehead
- Striae: start reddish, become whitish, redness may be improved faster by pulsed dye laser, but otherwise that and other treatments unproven to have long-term benefit
- Vascular lesions: varicosities, pyogenic granuloma
- Increased or changing nevi, melanoma: unclear if truly increased over controls
- Telogen effluvium typically starts 3 months after delivery

PRURITUS GRAVIDARUM

- This is itching without rash (up to 14% of all pregnancies)
- Potential intrahepatic cholestasis of pregnancy should be investigated in these patients, but this occurs in only 1–2% of all pregnancies, clinical jaundice in only 0.02% of pregnancies
- Elevated liver function tests and serum bile acid levels may occur
- Elevated glutathione S-transferase alpha (GSTA), a specific marker of hepatocellular integrity, identifies women with intrahepatic cholestasis and distinguishes them from those with benign pruritus gravidarum
- Reported increases in rates of premature delivery and perinatal mortality appear to be restricted to those in whom frank clinical jaundice develops
- Recurs in 50% of pregnancies
- Treatment: phenobarbital, cholestyramine, (ursodeoxycholic acid controversial but advocated by some)

PRURITIC URTICARIAL PAPULES AND PLAQUES OF PREGNANCY (PUPPP), POLYMORPHOUS ERUPTION OF PREGNANCY (PEP) (FIG. 21-1)

- The term PUPPP seems to be preferred in the United States and PEP in Europe
- Polymorphous eruption with papules, plaques, urticarial lesions
- The most common of the pregnancy rashes (0.6% of all pregnancies)
- Onset in abdominal striae is common, then commonly spreads to abdomen, buttocks, thighs
- Spongiosis may occur and cause confusion with pemphigoid gestationis, then immunofluorescence biopsy may be needed, since pemphigoid gestationis possibly may cause increased fetal morbidity or mortality, unlike PUPPP
- Intensely pruritic, like most of these pregnancy rashes
- Primagravids mostly, does not recur with subsequent pregnancies
- Increased incidence of twins, rapid maternal weight gain
- Usually third trimester
- Biopsy not very specific: perivascular lymphocytes with eosinophils, edema, sometimes with spongiosis or parakeratosis
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PENMICHOID GESTATIONIS (HERPES GESTATIONIS) (FIG. 21-2)

- The term pemphigoid gestationis is preferred by many because “herpes gestationis” causes confusion with herpes virus infection and its implications.
- Onset second or third trimester
- Papules, urticarial plaques, vesicles, bullae
- Often develops around umbilicus and extremities, later spreading to trunk, palms, soles. Usually spares face and mucous membranes
- Autoimmune disease similar to bullous pemphigoid (but linear C3 more often seen at dermal-epidermal junction zone than IgG)
- Increased HLA-DR3, DR4
- Circulating IgG1 autoantibodies in the blood are called herpes gestationis factor, avidly fixes complement to basement membrane zone of epidermis (in bullous pemphigoid, IgG4 is dominant over IgG1)
- Target antigen is most often the NC16a domain of 180kDa protein associated with basal keratinocyte hemidesmosomes (collagen XVII, formerly called bullous pemphigoid antigen 2). Bullous pemphigoid patients may have the same target antigen, but almost always have a second target: dystonin (DST), a 230kDa protein formerly designated BP antigen 1. The latter antigen is less commonly found in pemphigoid gestationis
- Maternal health not affected, but there may be increased fetal morbidity, small infant size. Less than 5% of infants have skin lesions, these spontaneously resolve

ATOPIC ERUPTION OF PREGNANCY (NEW TERM FOR PRURIGO GESTATIONIS)

- Often atopic diathesis
- Excoriated papules predominant
- Onset usually in second or third trimester
- No adverse maternal or fetal effects
- A variant known as papular dermatitis of Spangler is probably not a real entity: marked elevation of 24-hour urinary human gonadotropin (hCG) and decreased plasma estriol and cortisol was supposedly associated with fetal complications
**PUSTULAR PSORIASIS OF PREGNANCY**

**IMPETIGO HERPETIFORMIS**

(FIG. 21-3)

- Often no previous history of psoriasis
- Rarest of the pregnancy rashes mentioned here
- Papules, scaly plaques, pustules coalescing into lakes of pus
- Favors thighs, groin, trunk, extremities. Spares face, hands, feet
- Constitutional signs: fever, chills, nausea, vomiting, diarrhea, fatigue
- Leukocytosis, secondary hypoalbuminemia, hypocalcemia, tetany
- Often recurs in subsequent pregnancies, menses, oral contraceptives
- Increased morbidity of fetus possibly from placental insufficiency

**DISTINGUISHING POINTS**

- All of the rashes are most common in third trimester, but pemphigoid gestationis may occur in the second or third, and impetigo herpetiformis may occur in any trimester
- Pemphigoid gestationis is the only one with immunofluorescence findings
- Pemphigoid gestationis is the most likely one to recur in subsequent pregnancies
- The three with supposed increase fetal morbidity-mortality are pemphigoid gestationis, pruritus gravidarum (if cholestasis), and impetigo herpetiformis
- Most of these rashes, regardless of type, tend to resolve after delivery of the baby.

- All are treated with antihistamines (diphenhydramine is the most popular since it is FDA pregnancy class B). Cetirizine, cyproheptadine, and loratadine are also class B. Topical corticosteroids are often used but are class C. Prednisone is reserved for more serious cases, class B later in pregnancy

**QUIZ**

**Questions**

1. The most common rash of pregnancy is:
   - A. Pemphigoid gestationis
   - B. Impetigo herpetiformis
   - C. Pruritic urticarial papules and plaques of pregnancy (PUPPP)
   - D. Papular dermatitis of pregnancy
   - E. Autoimmune progesterone dermatitis

2. The eruption most characteristically beginning in the abdominal striae is:
   - A. Pemphigoid gestationis
   - B. Impetigo herpetiformis
   - C. Pruritic urticarial papules and plaques of pregnancy
   - D. Papular dermatitis of pregnancy
   - E. Autoimmune progesterone dermatitis

3. Prurigo gestationis has been re-named or considered to be in the same group with:
   - A. Pemphigoid gestationis
   - B. Atopic eruption of pregnancy
   - C. Impetigo herpetiformis
   - D. Pruritus gravidarum
   - E. Polymorphous eruption of pregnancy

4. Increased fetal mortality has been considered a significant feature according to some authorities in all except:
   - A. Pemphigoid gestationis
   - B. Impetigo herpetiformis
   - C. Papular dermatitis of pregnancy of Spangler
   - D. Pruritus gravidarum with jaundice
   - E. Pruritic urticarial papules and plaques of pregnancy

5. Hypoparathyroidism, hypocalcemia, hypophosphatemia, decreased vitamin D levels, elevated erythrocyte sedimentation rate, and leukocytosis are characteristic features that may occur in:

**FIGURE 21-3** Impetigo herpetiformis. Pustules are predominant. *(Courtesy of Dr. Asra Ali.)*
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3. Prurigo gestationis is now often considered to be within the spectrum of disease of the atopic eruption of pregnancy, though this terminology is new and may not be universally accepted. The same British group has long advocated using the term pemphigoid gestationis for herpes gestationis (to avoid confusion with herpes virus) and polymorphous eruption of pregnancy for what we usually call PUPPP in the United States.

4. The data for this are not great, as massive epidemiological studies have not been done, but PUPPP is the only one mentioned that has not been associated with increased fetal mortality.

5. It is important to watch the calcium level in impetigo herpetiformis. Leukocytosis in these sick patients can be confused with infection, so that blood cultures are sometimes needed if they are febrile.

6. Match the condition with an important finding:
   a. Pemphigoid gestationis  A. Elevated liver function tests
   b. Pruritus gravidarum B. Periumbilical accentuation
   c. PUPPP C. Psoriasis variant
   d. Progesterone dermatitis D. Last trimester in primagravidas
   e. Impetigo herpetiformis E. Skin test for diagnosis

7. The immunoprofile most characteristically found in pemphigoid gestationis is:
   A. Circulating IgG1 autoantibodies, target NC16a domain of 180-kD BP Ag2 (type XVII collagen)
   B. Circulating IgG4 autoantibodies, target 180-kD, BP Ag2
   C. Circulating mixed IgG autoantibodies, target 180-kD, BP Ag2
   D. Circulating IgG4 autoantibodies, target BP Ag1
   E. Circulating IgG1 autoantibodies, target BP Ag1

8. Which of the following pregnancy conditions characteristically does not recur with subsequent pregnancies?
   A. Impetigo herpetiformis
   B. Pemphigoid gestationis
   C. Pruritus gravidarum
   D. Pruritic urticarial papules and plaques of pregnancy

Answers
1. C. PUPPP is the most common pregnancy rash, which is fortunate since it has no known fetal complications. The others which are listed are relatively rare.
2. C. PUPPP often begins in the abdominal striae, and sometimes initially they just look red rather than like a rash. Pemphigoid gestationis often is prominent in the periumbilical area.
3. B. Prurigo gestationis is now often considered to be within the spectrum of disease of the atopic eruption of pregnancy, though this terminology is new and may not be universally accepted. The same British group has long advocated using the term pemphigoid gestationis for herpes gestationis (to avoid confusion with herpes virus) and polymorphous eruption of pregnancy for what we usually call PUPPP in the United States.
4. E. The data for this are not great, as massive epidemiological studies have not been done, but PUPPP is the only one mentioned that has not been associated with increased fetal mortality.
5. B. It is important to watch the calcium level in impetigo herpetiformis. Leukocytosis in these sick patients can be confused with infection, so that blood cultures are sometimes needed if they are febrile.

REFERENCES
dsDNA (double-stranded DNA or native DNA): 70% SLE, associated with lupus nephritis
- Histone: 50% to 70% SLE; also the antibody found in drug-induced SLE (but not in drug-induced subacute cutaneous lupus)
- Rim pattern: (fluorescence at edges of nucleus), anti-DNA, anti-histone and anti-laminin antibodies: SLE (most specific) but also may be seen in chronic active hepatitis
- Speckled pattern: (Fig. 22-2):
  - SS-A/Ro: 30% to 40% SLE; often with SCLE (subacute cutaneous lupus erythematosus), drug-induced SCLE, and neonatal LE; also seen in Sjogren’s syndrome (SS), dermatomyositis (DM)
  - SS-B/La: 15% SLE often with SCLE, drug-induced SCLE, neonatal LE
  - Anti-ribonucleoprotein (RNP): 30% SLE; associated with MCTD (mixed connective tissue disease)
- Nucleolar pattern (homogeneous, speckled, or clumpy staining of nucleolus):
  - RNA polymerase I (RNA pol 1): 4% to 23% SSc
  - U3 RNP/fibrillarin: SSc
  - Topoisomerase I (Scl-70): 22% to 40% of SSc, associated with diffuse SSc(Pm–Scl)
  - PM-Scl: SSc-polymyositis overlap
- Centromere pattern (antibodies to kinetochore proteins):
  - 22% to 36% of SSc patients
60% to 90% of limited SSc patients (e.g., CREST syndrome [calcinosis, Raynaud’s, esophageal dysmotility, sclerodactyly, telangiectasias])

- Extractable nuclear antigens (ENAs)
  - Soluble cytoplasmic and nuclear components that are bound by autoantibodies
  - Antibodies include Ro, La, Sm, RNP, Scl-70, Jo-1
  - ENA-4 test:
    - Identifies Ro, La, RNP, and Sm
    - Used to diagnose SLE, MCTD, and SS

Lupus Erythematosus
- Autoimmune disorder with a spectrum of presentations; may be cutaneous and/or systemic
- Cutaneous lupus subsets:
  - Acute cutaneous lupus erythematosus (ACLE)
  - Subacute cutaneous lupus erythematosus (SCLE)
  - Chronic cutaneous lupus erythematosus (CCLE)
  - Systemic lupus erythematosus (SLE)
- Acute cutaneous lupus (ACLE): most specific for SLE
  - Localized ACLE (malar rash): occurs in 20% to 60% of SLE patients
    - Lasts from days to weeks
    - Violaceous erythematous patches or plaques over the malar eminences, may involve entire face with sparing of the nasolabial folds
    - May heal with dyspigmentation or poikilodermia, but does not scar
    - Often is painful or pruritic
  - Associated with sun exposure; systemic disease flaring is common
  - Histologic findings: focal liquefactive degeneration of the basal cell layer; perivascular and periadnexal lymphocytes
  - Immunohistology (Fig. 22-4): IgG and C3 along dermal-epidermal junction in a continuous layer
Pleuritis: history of pleuritic pain or rub heard by physician or evidence of pleural effusion
Pericarditis: documented by electrocardiogram (ECG), rub, or evidence of pericardial effusion
- Renal involvement: proteinuria, cellular casts in urinalysis, elevated serum creatinine, and decreased albumin levels
- Hematologic disease: hemolytic anemia with reticulocytosis, leukopenia, lymphopenia, or thrombocytopenia
- Neurologic disorders: seizures or psychosis, in the absence of offending drugs or known metabolic disorders
- ANA (anti-nuclear antibody): 95% sensitivity
- Immunologic disorders: anti-ds DNA, anti-smith antibodies, antiphospholipid antibodies, biologic false positive serologic test for syphilis

Other associated manifestations of lupus that may be associated with disease flares
- Constitutional symptoms: fever, malaise, weight changes
- Leukocytoclastic vasculitis
- Urticaria, urticarial vasculitis (including hypocomplementemic urticarial vasculitis)
- Lupus panniculitis (can also occur without SLE)
- Livedo reticularis: especially in patients with antiphospholipid antibodies
- Raynaud’s phenomenon (20% to 30% of patients)
- Alopecia: patchy or generalized, nonscarring, similar to telogen effluvium; “lupus hairs” = whispy short hairs at anterior frontal hairline
- Arthralgias
- Headache
- Stroke, transient ischemic attacks (may be related to antiphospholipid antibodies)
- Myelopathy
- Abdominal pain: related to peritonitis, mesenteric vasculitis, and/or bowel infarction
- Libman-sacks endocarditis, accelerated cardiovascular disease with angina
- History of recurrent spontaneous abortions may indicate the presence of antiphospholipid antibodies

Laboratory tests
- Anti-phospholipid antibodies: (anticardiolipin immunoglobulin G or immunoglobulin M, or lupus anticoagulant); associated with livedo reticularis, arterial and venous thrombosis without vasculitis or active SLE, and increased incidence of fetal wastage
- Anti-dsDNA: high specificity; sensitivity is 70%, levels may correlate with disease activity (particularly with SLE nephritis)

Systemic Lupus Erythematosus (SLE)
- Multisystem autoimmune disorder
- Found commonly in women of child bearing age
- Associated with human leukocyte antigen (HLA): DR-2 and DR-3
- Diagnostic criteria for SLE (4 of 11 of these criteria must be met for diagnosis)
  - Mucocutaneous
    - Malar rash: see description above
    - Discoid rash (erythematous plaques with adherent keratotic scaling and follicular plugging with atrophic scarring in older lesions)
    - Oral (or nasal) ulcers
    - Photosensitivity: skin rash following exposure to UV-B radiation (ie: sunlight or fluorescent lights)
  - Systemic
    - Arthritis: two or more joints characterized by tenderness, swelling, or effusion; non-erosive
    - Serositis
- Generalized ACLE: characterized by erythematous macular or papular scaling, with or without edema; crusting and bullae can be present; spares the knuckles when it involves the hands (while dermatomyositis, involves the knuckles)
Etiologic agents
- Antiarrhythmics: procainamide and quinidine
- Antibiotics (minocycline, rifampin, voriconazole)
- Antitubercular: isoniazid
- Antifungal: griseofulvin
- Anticonvulsants (valproate, ethosuximide, carbamazepine, phenytoin and hydantoins)
- Hormonal therapy (leuprolide acetate, oral contraceptives)
- Antihypertensives (hydralazine, methyldopa, diltiazem and captopril)
- Anti-inflammatory (D-penicillamine and sulfasalazine)
- Antipsychotics (chlorpromazine)
- Cholesterol-lowering agents (lovastatin, simvastatin, and gemfibrozil)
- Antimalarial: hydroxychloroquine
- Others: glyburide, gold salts, interferon, amiodarone, docetaxel

Laboratory tests
- Positive ANA in 95%
- Anti-histone antibodies in >75%, homogenous pattern (50% to 70% of patients with classic SLE)
- Drugs with homogenous pattern: procainamide, isoniazid, timolol, hydralazine, and phenytoin
- In contrast, drug-induced subacute cutaneous lupus has a speckled pattern (anti-SSA/Ro), associated with thiazide diuretics, terbinafine
- Complement levels normal
- Treatment: not needed; symptoms usually clear within weeks of stopping the implicated drug

**Subacute Cutaneous Lupus Erythematosus (SCLE)**
- Associated with HLA-B8, HLA-DR3, HLA-DRw52, and HLA-DQ1
- Usually occurs in Caucasian females; seen in 9% to 27% of patients with SLE
- Clinical (Fig. 22-5)
  - Begins as erythematous papules or plaques
  - Annular lesions or scaling plaques (psoriasiform or lichenoid), usually on sun-exposed areas of the body but can be generalized
  - Knuckles are usually spared when lesions occur on the hands (rash of dermatomyositis typically involves the knuckles)
  - Photosensitivity to UVB, UVA, and rarely visible light
  - Waxing and waning course; may heal with transient hypopigmentation or even permanent leukoderma
- 50% of patients meet the ACR criteria for SLE, (most commonly: arthritis, leukopenia, positive ANA, and photosensitivity)
- Only 10% to 20% of patients develop severe SLE (e.g., nephritis, CNS disease)
- Drug-induced SCLE: most commonly hydrochlorothiazide, calcium channel blockers, angiotensin-converting
- Widespread: symmetric involvement of the trunk and extremities, more often progress to SLE compared to localized disease
- Lesions resolve with permanent scarring, including scarring alopecia
- Less photosensitive than other forms
- May involve mucous membranes

- Laboratory
  - ANA: 20%
  - Anti-Ro (SS-A): 1% to 3%
- Histology: similar to ACLE/SCLE, but with more marked periappendageal involvement and follicular plugging
- Direct immunofluorescence (DIF): 90% of patients on lesional skin

- Treatment
  - Corticosteroids (topical or intralesional)
  - Antimalarials (single or combination): hydroxychloroquine, chloroquine
  - Thalidomide
  - Oral retinoids
  - Azathioprine
  - Mycophenolate mofetil
  - Methotrexate
  - Enzyme inhibitors, griseofulvin, terbinafine, tumor necrosis factor antagonists

- Laboratory tests
  - Antinuclear antibody (ANA)
  - Anti-Ro (SS-A) in 70%, anti-La (SS-B) in 30%
  - May be associated with rheumatoid factor positivity, hypocomplementemia, and an elevated ESR
- Positive lupus band test: complement and/or immunoglobulin along dermal-epidermal junction
- Histology: similar to SLE
- Treatment
  - Sun-protection
  - Hydroxychloroquine, other antimalarials (chloroquine, quinacrine), thalidomide, azathioprine, acitretin, mycophenolate mofetil, dapsone, clofazimine

**CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS (CCLE)/DISCOID LUPUS (DLE)**
- Chronic, scarring and photosensitive disease
- Occurs in 15% to 30% of patients with SLE, 5% of patients with DLE progress to SLE
- Female to male of 3:1
- Clinical
  - Begin as erythematous papules or plaques
  - Progresses to plaques with follicular plugging, scale, central hypopigmentation, and peripheral hyperpigmentation
  - Localized: head and neck affected, usually with asymmetrical lesions on the face, ears, and scalp (Fig. 22-6)
Cutaneous Lupus Variants

- Tumid lupus erythematosus (TLE)
  - May be a variant of CCLE or SCLE
  - Low incidence of SLE
  - Non-scaling nodular lesion
  - Photosensitive
  - Histology shows mucin and interstitial lymphocytic infiltrate no epidermal involvement
  - Treatment: antimalarials

- Bullous systemic lupus erythematosus (BLE)
  - Subepidermal blistering disease that is seen in patients with SLE
  - Three types:
    - Antibodies to type VII collagen
    - Undetermined antigen location
    - Antigen in the epidermis
  - Clinical:
    - Patients must fulfill the criteria for SLE
    - Sudden onset of vesiculobullous lesions on an erythematous base, painful mucosal lesions
    - Most commonly affects upper trunk, proximal extremities, neck and face
    - Erosions result after rupture of the bullae which heal with hyper or hypopigmentation
  - Laboratory tests
  - Serologies: similar to SLE (see above)
    - Histology: subepidermal blister with neutrophils in the dermis
    - DIF: granular IgG, IgA, IgM and C3 at the dermal-epidermal junction
    - IIF: antibodies to collagen type VII
  - Treatment: dapsone

- Lupus erythematosus panniculitis/profundus (LEP) (Fig. 22-7):
  - Primarily affects deep dermis and subcutaneous fat
  - Occurs in SLE and CCLE patients, or as an isolated phenomenon
  - Clinical:
    - Chronic recurrent course
    - Tender, firm, subcutaneous nodules, often heal with prominent fat atrophy
    - Most commonly on proximal extremities, trunk, breasts, buttocks, and face (vs. erythema nodosum, which involves the calves)
  - Histology: dermal perivascular and periappendageal lymphocytic inflammation that extends into the subcutaneous fat; lobular panniculitis with lymphocytes, lymphoid nodules with germinal centers, plasma cells, and histiocytes, hyalinized fat necrosis possible epidermal atrophy and hydropic degeneration of the basal cell layer
  - IF: IgM at the basement membrane
  - Treatment: similar to other forms of cutaneous LE

- Hypertrophic discoid lupus erythematosus:
  - Rare variant of DLE with markedly hyperkeratotic or verrucous lesions
  - Often seen on the extensor extremities and face
  - Mimics squamous cell carcinoma, clinically and histologically
  - Chilblain lupus erythematosus (CHLE):
    - Red-purple papules and plaques on the fingers, toes, heels, elbows, knees, and nose precipitated by cold
    - Lesions develop scale and frequently scar
    - Usually occurs in patients with DLE

- Neonatal lupus erythematosus (NLE):
  - Caused by mother’s antibodies (anti-Ro (95%), anti-La, or U1-ribonucleoprotein) in the fetus
  - Mothers are usually asymptomatic at the time of childbirth, but may have numerous autoimmune conditions (i.e., SLE, Sjogren’s syndrome)
  - Maternal HLA-B8 and HLA-DR3
  - Affects 1% to 5% of infants with positive maternal anti-Ro antibodies
  - Mothers with an infant with NLE have a 25% incidence of having a subsequent affected child
  - Ro52 protein cardiac 5-HT4 serotoninergic receptor affected by maternal autoantibodies resulting in inhibition of serotonin activated L-type calcium currents \((I_{Ca})\)
  - Clinical (Fig. 22-8):
    - Cutaneous SCLE-like lesions in 50% with well-demarcated, annular, erythematous, scaling plaques
      - Frequently periorbital (“owl-eye”)
      - Photosensitive, with lesions on the scalp, neck, and face
Diagnosis of antiphospholipid syndrome requires the presence of one clinical criterion and one laboratory criterion.

Clinical criteria:
- Vascular thrombosis:
  - Arterial thrombosis
  - Venous thrombosis
  - Small vessel thrombosis of any organ/tissue confirmed by Doppler
- Pregnancy morbidity:
  - Spontaneous abortion of a normal fetus at or after the 10th week of gestation
  - Premature birth of normal neonate at or before 34th week gestation due to severe preeclampsia, eclampsia, or placental insufficiency
  - Three or more unexplained consecutive miscarriages before ten weeks gestation

Laboratory criteria (2 or more occasions 6 weeks or more apart):
- IgG, IgM or anticardiolipin antibody (aCL) in medium or high titer
- Anti-beta 2 glycoprotein
- Lupus anticoagulant

Other clinical findings (not included as part of criteria):
- Cutaneous findings: superficial phlebitis, leg ulcers, distal ischemia, blue toe syndrome
- Neurologic: transient ischemic attack, ischemic stroke, chorea, seizures, dementia, transverse myelitis, encephalopathy, migraines, pseudotumor cerebri, cerebral venous thrombosis, mononeuritis multiplex
- Cardiac: myocardial infarction, valvular vegetations, intracardiac thrombi, atherosclerosis
- Renal: renal vein/artery thrombosis, renal infarction, acute renal failure, proteinuria, hematuria, nephritic syndrome
- Gastrointestinal: Budd-Chiari syndrome, hepatic/gallbladder/intestinal/splenic infarction, pancreatitis, ascites, esophageal perforation, ischemic colitis
- Venous thrombosis: extremities/adrenal/hepatic/mesenteric/splenic vein/vena cava thrombosis
- Endocrine: adrenal/testicular/pituitary infarction
- Obstetric complications: spontaneous abortion, intrauterine growth retardation, hemolytic anemia, elevated liver enzymes, thrombocytopenia
- Hematologic: thrombocytopenia, hemolytic anemia, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura
- Ophthalmic: retinal vein/artery thrombosis, amaurosis fugax (temporary loss of vision in one

Antiphospholipid Syndrome (APS)
- Autoimmune disorder of unknown etiology, characterized by increased thrombosis and/or increased incidence of spontaneous abortions. Subgroups of APS patients—those with and those without the presence of other risk factors for arterial or venous thrombosis.

Figure 22-8 Neonatal lupus erythematosus (NLE). (Courtesy of Dr. Robert Jordon.)
eye caused by decreased blood flow [ischemia] to the retina

- SNAP syndrome: clinical manifestations of APS, without the presence of antibodies
- Conditions associated with the presence of aPL antibodies:
  - Autoimmune diseases: SLE, Sjogren’s syndrome, rheumatoid arthritis
  - Infections: syphilis, hepatitis C, human immunodeficiency virus, malaria, leprosy, parvovirus B19, cytomegalovirus
  - Medications: procainamide, quinidine, propanalol, hydralazine, phenytoin, chlorpromazine, interferon alpha, quinine, amoxicillin, sulfadoxine/pyrimethamine (fansidar), and cocaine
- HLA associated with aPL antibodies: DRw53, DR7, DR4
- Catastrophic antiphospholipid syndrome (CAPS): acute onset, criteria include: evidence of involvement of ≥3 organ systems, and/or tissue development of manifestations simultaneously or in <1 week, confirmation by histopathology of small-vessel occlusion in at least one organ/tissue laboratory confirmation of the presence of aPL (lupus anticoagulant and/or aCL an/or anti-B-2-GP I)
- Laboratory studies: (presence of antibodies on 2 or more occasions at least 12 weeks apart)
  - Antiphospholipid (aPL) antibodies
  - Anticardiolipin (aCL) antibodies
  - Anti-β2-glycoprotein I antibodies
  - Other antibodies to phosphatidylserine, phosphatidylthreonine (membrane phospholipids)
  - Activated partial thromboplastin time (aPTT)
  - Lupus anticoagulant (LA) test such as dilute Russell viper venom time (DRVVT)
  - False-positive serologic test result for syphilis
  - Complete blood cell count (thrombocytopenia, Coombs-positive hemolytic anemia)
  - Proteinuria and renal insufficiency from thrombotic microangiopathy
  - 45% of patients have a positive ANA
  - Ultrasound (evaluate for DVT); CT or MRI of chest (evaluate for pulmonary embolism), brain (evaluate for cerebral vascular accident), abdomen (evaluate for Budd-Chiari syndrome)
- Treatment
  - Following thrombosis: anticoagulation with intravenous heparin, followed by warfarin, heparin or low-molecular-weight (LMW) heparin
  - Recurrent spontaneous abortions: treated with subcutaneous heparin 7,500 to 12,000 units twice daily along with aspirin 81 mg daily
  - Thrombocytopenia: prednisone

**Sjögren’s Syndrome (SS)**
- Autoimmune disease that mainly affects the exocrine glands
- HLA-DR3 and HLA-DR52 in patients with primary SS
- Primary SS has xerophthalmia and xerostomia only
- Secondary SS has xerophthalmia and xerostomia and occurs with rheumatoid arthritis, SLE, SSc, DM, and MCTD
- SS criteria
  - Presence of four out of six criteria, as long as either the histopathology or serology is positive:
    - Ocular symptoms of dryness
    - Oral symptoms of dryness
    - Ocular signs—a positive result for at least one of the following two tests:
      - Schirmer’s test
      - Rose Bengal score or other ocular dye score
    - Histopathology: focal lymphocytic sialoadenitis, with a focus score of 1 per 4 mm² of glandular tissue
    - Salivary gland involvement—a positive result for at least one of the following diagnostic tests:
      - Unstimulated whole salivary flow (<1.5 mL in 15 min)
      - Parotid sialography showing the presence of diffuse sialectasias, without evidence of obstruction in the major ducts
      - Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
    - Autoantibodies: presence in the serum of the following autoantibodies: Ro(SSA) or La(SSB), or both
- Clinical findings
  - Keratoconjunctivitis sicca: xerophthalmia
  - Bilateral parotid swelling (most common sign in children)
  - Unstimulated salivary flow less than 1.5 mL/min
  - Positive Schirmer’s test showing decreased tear film for eyes
  - Xerostomia (Fig. 22-9): signs of reduced salivary flow, associated with angular chelitis, dental caries, oral candidiasis with resulting erythema and atrophy of the dorsum of the tongue or a white, cheesy curd that bleeds when wiped off
  - Extraglandular symptoms
    - Hepatitis (13%): also increased incidence of primary biliary cirrhosis
    - Arthritis (42%)
**Mixed Connective Tissue Disease (MCTD)**

- Disease syndrome with overlapping features of systemic sclerosis, systemic lupus erythematosus (SLE) and polymyositis
- Associated with HLA-DR4 or HLA-DQB1
- Controversy exists as to whether MCTD constitutes a distinct clinical entity

**Alarcon-Segovia and Villareal classification**
- Serologic criterion is a positive anti-RNP at a titer of 1:1600 or higher
- Clinical criteria; presence of at least 3 of the following:
  - Edema of the hands
  - Raynaud’s phenomenon
  - Acrosclerosis
  - Synovitis
- Kusukawa diagnostic criteria for mixed connective tissue disease (MCTD)
  - Requirement for diagnosis: at least one common symptom, with positive U1 RNP antibodies and one or more findings in at least two of the three categories A, B, and C from the mixed findings list
  - Common symptoms
    - Reynaud’s Phenomenon
    - Swollen fingers or hands
    - Presence of Anti U1 RNP
- Mixed findings
  - Systemic lupus erythematosus (SLE)–like
    - Polyarthritis
    - Pericarditis/pleuritis
    - Lymphadenopathy
    - Facial erythema
    - Leukopenia/thrombocytopenia
  - Scleroderma–like
    - Sclerodactyly
    - Pulmonary fibrosis
    - Esophageal dysmotility

**Histopathology:**
- B-lymphocyte infiltration (20% to 25%) and CD4+ T-cell infiltration (70% to 80%) localized in the salivary glands
- Positive Schirmer’s test (Fig. 22-10): measures lacrimation response in the eye; filter paper strip placed in lower conjunctival sac and the wetting length achieved in 5 minutes is measured; greater than 8 mm in 5 minutes is abnormal
- Treatment: symptom control; no curative agent exists
  - Topical cyclosporine A (Restasis): 0.05% to 0.1% ophthalmic drops
  - Pilocarpine HCl (Salagen): 5 mg tablets, cholinergic agonist
  - Cevimeline HCl (Evozac): 30 mg tablets, cholinergic agonist binding to muscarinic receptors
  - Plaquenil (hydroxychloroquine)

**FIGURE 22-9** Sjögren syndrome (SS). (Courtesy of Dr. Bela B. Toth.)

**FIGURE 22-10** Positive Schirmer test. (Courtesy of Dr. Robert Jordon.)
Classic DM with associated connective tissue disease
- Clinically amyopathic DM (CADM)
  - Amyopathic DM (ADM)/dermatomyositis sine myositis: no clinical or lab evidence of myositis for 6 months without treatment
  - Hypomyopathic DM (HDM): no clinical evidence of myositis, but lab evidence of subclinical disease

Polymyositis (PM), similar clinical feature to DM: inflammatory myopathy with symmetric muscle weakness
- Juvenile DM (JDM)
  - Classic JDM
  - Clinically amyopathic JDM

Cutaneous findings:
- Occur 2 to 3 months prior to muscle weakness
- Primary lesion: pruritic erythematous-violaceous patches and plaques with or without scale. Poikiloderma may be present.
- Lesions frequently involve scalp, anterior/posterior neck, photoexposed areas and extremities, but can involve any body area
- Heliotrope rash: first cutaneous sign: periorbital, symmetric, violaceous patches with or without edema
- Gottron's papules: violaceous papules overlying the following joints of the dorsal hands: metacarpophalangeal, distal interphalangeal, and/or proximal interphalangeal
- Gottron's sign: violaceous symmetric macular erythema over bony prominences of hands and elsewhere (e.g., elbows, knees, medial malleoli)
- Tendon streaking: linear violaceous erythema along extensor tendons of hands/feet
- Nailfold capillary changes: correlated with disease severity; capillary telangiectasia, infarcts, capillary loop dropout (whitish areas of avascularity—not seen in LE), Samitz sign cuticular dystrophy
  - V-sign: macular erythema and poikiloderm of V-area of neck and chest
  - Shawl sign: macular erythema and poikiloderm of upper back and shoulders
  - Holster sign: erythematous patches/plaques on bilateral hips
  - Malar rash: erythema of the central face but unlike ACLE, usually does not spare nasolabial folds
  - Mechanics hands: hyperkeratosis of the palm and lateral surfaces of the fingers, associated with interstitial lung disease
  - Calcinosus cutis: cutaneous calcium deposition, usually in areas of trauma, associated with

Laboratory studies
- CBC
- Muscle enzymes: creatine kinase, aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase
- Anti-RNP, anti-Smith, anti-Ro(SSA), anti-La(SSB), anti-Scl-70, phospholipids, anti-cardiolipin and histone, complement: C3, C4,
- High-titer ANA in a speckled pattern
- Antibodies against U1—70-kDa small nuclear ribonucleoprotein (snRNP) at titer > 1:1600
- Histology: myositis
- Other tests: chest x-ray, barium swallow (evaluate esophageal motility)
- Echocardiography: (evaluate myocardial function and pulmonary artery pressure)

Treatment
- Corticosteroids, hydroxychloroquine, Cyclophosphamide, azathioprine, methotrexate

Dermatomyositis (DM)
- Idiopathic inflammatory myopathy with characteristic cutaneous lesions with or without muscle inflammation and weakness
- Diagnostic criteria: (3 criteria plus the rash)
  - Symmetrical muscle weakness: limb girdle muscles and anterior neck flexors
  - Muscle biopsy: evidence of muscle fiber necrosis, inflammatory exudate, often perivascular
  - Elevated muscle enzymes: CPK, aldolase, LDH
  - EMG triad: small polyphasic action potentials, positive sharp waves and insertional irritability and bizarre high frequency repetitive discharges
  - Cutaneous changes: heliotrope rash with periorbital edema; scaly dermatitis

Classification
- Adult dermatomyositis:
  - Classic DM
  - Classic DM with malignancy
increased disease activity, 10% of adult DM patients

- Extracutaneous findings
  - Proximal symmetric muscle weakness (shoulder and limb girdle)
  - Dysphagia/dysphonia (esophageal/pharyngeal involvement)
  - Pulmonary disease:
    - Restrictive lung disease from respiratory muscle weakness
    - Interstitial lung disease: in 25% to 65% of patients, can be rapidly progressive and fatal, a leading cause of mortality
  - Synovitis
  - Raynaud’s phenomenon
  - Cardiac disease: rare ECG changes, arrhythmias, cardiomyopathy

- Juvenile DM (JDM):
  - Similar cutaneous features of classic DM in patients younger than 18 years
  - Other clinical features
    - Vasculopathic lesions (SQ nodules, digital ulcers) poorer prognosis
    - Calcinosis cutis: occurs on bony prominences; 40% of children
    - Acquired lipodystrophy (prevalence of 10% to 40%), generalized, partial, or focal, late complication of JDM, associated with more severe, chronic disease and with other disease sequelae such as calcinosis, insulin resistance, diabetes, and hypertriglyceridemia
    - Cardiac: Asymptomatic cardiac conduction delays or right bundle branch block (up to 50% of patients)
  - Thrombospondin-1, a mediator of angiogenesis, is increased in patients with juvenile DM

- DM associated with malignancy
  - Reported rate of malignancy in adults varies widely: 13% to 25%; there is no reported increased risk in JDM patients
  - May precede, coincide with, or follow the diagnosis of DM
  - Risk remains elevated for 3–5 years following diagnosis
  - Presence of malignancy represents a major indicator of poor prognosis in DM
  - Association between a rapid onset of the disease and malignancy
  - Relative risk for ovarian cancer in female patients is 16.7
  - Reported association with the following malignancies: breast (adenocarcinoma most common), gastrointestinal, ovarian, lung

- Drug-induced dermatomyositis: statins, hydroxyurea, penicillamine

- Poor Prognosis associated with: progressive disease, dysphagia, extensive cutaneous lesions on the trunk, cardiac issues, longer duration of symptoms before diagnosis, initiation of therapy after 24 months of muscle weakness, older age, malignancy, progressive disease

- Diagnosis
  - Myositis-specific antibodies (not seen in other CTD patients):
    - Mi-2: nuclear helicase, 5% of PM/DM, 15% to 20% of DM
    - Associated with classic DM, V/shaw sign, cuticular dystrophy
    - Good prognosis
  - Antisynthetase antibodies
    - Antibodies to aminoacyl-tRNA synthetases, cytoplasmic antigens
    - Anti-EJ –: associated with typical skin lesions
    - Anti PL-12 and PL-7 –: prevalence of 25% for both
    - Jo-1 (15% to 20% DM/PM) –: Associated with antisynthetase syndrome:
      - Mechanic’s hands
      - Myositis (may or may not have cutaneous DM)
      - Interstitial lung disease
      - Synovitis
      - Raynaud’s phenomenon
      - Patients often refractory to treatment
  - Annexin XI (56-kDa): most sensitive for juvenile DM
  - Anti-CADM-140: found in 50% of CADM patients
  - Anti-p155kD: malignancy-associated DM
  - Anti-antisignal recognition protein (SRP): associated with severe polymyositis
  - Other antibodies (myositis-associated, not DM-specific):
    - ANA: positive in 60% to 80%, more commonly positive in CADM
    - SS-A/Ro
    - Anti-PM-Scl (seen in overlap of DM/PM and scleroderma)
    - AntiKu (seen in overlap of DM and with scleroderma and/or SLE)

- Laboratory studies
  - Elevation of the following: creatine kinase level (most sensitive for myositis), aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH)
  - Elevated erythrocyte sedimentation rate
  - Muscle studies: electromyelogram (EMG) shows a myopathic pattern, muscle biopsy, MRI
  - Histology: epithelial vacuolar changes with lymphocytic infiltrate at the dermal epidermal junction, identical to findings of CLE
• DIF: C5b-9 deposition at DEJ and perivascularly
• Malignancy workup in all patients with localizing symptoms and patients > 40 years of age at presentation and annually
• Endoscopic studies of the upper and lower gastrointestinal tract should be done according to the patient’s age
• Treatment
  • Systemic corticosteroids for muscle involvement
  • Steroid-sparing agents for maintenance: methotrexate, azathioprine, cyclosporine, mycophenolate mofetil; antimalarials as adjuncts for mild skin disease
  • IV immunoglobulin (IVIG): useful for severe and refractory disease, pulmonary disease
  • Cyclophosphamide: for interstitial lung disease
  • Biologics: rituximab, tumor necrosis factor inhibitors (enterasept, infliximab)
  • Topical tacrolimus: for skin disease

Systemic Sclerosis (SSc)
• Multisystemic connective tissue disease with excessive collagen deposition and vasomotor disturbances
• Associated with HLA-B8, HLA-DR5, HLA-DR3, HLA-DR52, and HLA-DQB2
• Pathophysiology also associated with: genetic, environmental, vascular, and autoimmune factors
• Five forms of systemic sclerosis: diffuse systemic sclerosis (dSSc), limited systemic sclerosis (lSSc), transitory form (dSSc/lSSc), systemic scleroderma sine scleroderma, and malignant scleroderma
• Other factors associated with SSC pathophysiology:
  • Environment-related
  • Criteria for diagnosis of adult SSc: diagnosis when 1 major and 2 minor criterion are present
    – Major features include centrally located skin sclerosis that affects the arms, face, and/or neck
    – Minor features include sclerodactyly, erosions, atrophy of the fingertips, and bilateral lung fibrosis
• Clinical findings
  • Mucocutaneous findings
  • Cutaneous sclerosis: progresses through 3 phases
    – Edematous phase: fingers with edema (“puffy phase”)
    – Indurated or sclerotic phase: thickened tight skin, hair loss and decreased sweating, begins acrally and on face/neck, proximal spread, sclerodactyly: fingertip tapering, loss of fingerpad pulp, pitted scars, digital ulcers (35%) and loss of mobility (Fig. 22-11)
    – Atrophic, or late phase: dermis is firmly adherent to underlying subcutaneous fat
  • Salt-and-pepper dyspigmentation: vitiligo-like depigmentation with perifollicular pigment
  • Skin ulceration: digital tip ulcers (secondary to ischemia); ulcers over the bony prominences (attributable to contractures)
  • Calcium deposits: subcutaneous and/or intracutaneous calcinosis (Fig. 22-12)
  • Nailfold capillary changes: capillary loop dilatation alternating with loop dropout; occurs in 90% of patients
  • Ocular symptoms: dry eyes, blepharitis, retinal hemorrhages (with renal crisis)
  • Oral symptoms: xerostoma, dental decay
• **Raynaud’s phenomenon**
  - Paroxysmal vasospasm of digits in response to cold exposure or emotional stress
  - Endothelial injury results in intimal hyperplasia and fibrosis
  - 95% of SSc patients
  - 3 pathogenic mechanisms—vasoconstriction, ischemia, and reperfusion (white-blue-red appearance of the skin)
  - Typically the first clinical and most common sign of SSc, may precede the disease by 5–10 years
  - Types of Raynaud’s: primary: acral color changes are the only clinical signs without any other symptom and disease; secondary: color changes are associated with clinical symptoms or signs of systemic disease
• **Musculoskeletal**
  - *Muscle weakness*: scleroderma myopathy (proximal muscle weakness) and sclerodermatomyositis (true overlap between scleroderma and polymyositis with severe muscle weakness and elevated CPK and abnormal EMG)
  - *Arthritis*: symmetric polyarthritis and joint stiffness (with or without gross synovitis),
  - *Tendon fibrosis*: may result in myalgia, joint pain, immobility, contractures and fibrinous tenosynovitis with friction rub
• **Gastrointestinal tract** (affects 75% to 90% of patients)
  - *Esophageal dysmotility*
    ▲ 90% of patients, occurs in early disease, secondary to smooth muscle fibrosis
    ▲ may lead to gastroesophageal reflux disease with symptoms of heartburn, dysphagia and resulting in complications of Barrett’s esophagus and esophagitis (may cause esophageal stricture)
  - *Gastric vascular ectasia* may lead to gastroparesis
  - *Small intestinal muscle fibrosis* may lead to functional ileus (pseudoobstruction); bacterial overgrowth may cause malabsorption and diarrhea
  - *Colonic signs and symptoms*: megacolon, constipation and diverticula
• **Pulmonary disease**: 70% of SSc patients; main cause of mortality
  - *Pulmonary interstitial fibrosis*: occurs in early disease, most commonly with diffuse SSc
  - *Pulmonary artery hypertension (PAH)*: 10% to 15% of patients, occurs later in the course of the disease, three types: severe isolated PAH without significant fibrosis (common in lSSc), PAH with fibrosis (common in dSSc), and lastly an indolent PAH
• **Renal**
  - *Scleroderma renal crisis (SRC)*, usually in dSSc (18% of patients): hypertension and oliguric renal failure
• **Cardiac**
  - Myocardial fibrosis (<5% of dSSc), congestive heart failure, myocarditis, pericarditis, ventricular arrhythmias
• **Genitourinary**
  - Erectile dysfunction (12% to 60%)
  - Dyspareunia
• **Clinical features of the two most common forms**
  - **Diffuse cutaneous sclerosis (dSSc):**
    - Associated with topoisomerase I (Scl-70) in 30% – Quick progression of sclerosis of proximal limbs and trunk
    - Associated with pulmonary interstitial fibrosis in 30% to 60%, scleroderma renal crisis
  - **Limited systemic sclerosis (lSSc):**
    - Also known as CREST (calcinosi, Raynaud’s, esophageal dysmotility, sclerodactyly, telangiectasia)
    - Anticentromere antibodies in 40% to 50% – Sclerosis confined to face, neck, and extremities distal to elbows/knees
    - Slowly progressive and indolent
    - Late phase:
      ▲ Calcinosis cutis: calcium apatite crystals found in tissue
      ▲ Matte-like telangiectasias: can also occur with dSSc
      ▲ Pulmonary artery hypertension: leading cause of death in lSSc
• **Juvenile systemic sclerosis:**
  - Children under 16 years of age account for less than 5% of all cases of SSC
  - Fourfold more frequent in girls
  - Raynaud’s phenomenon (RP) is the first sign of the disease in 70% of patients
  - Classification criteria for JSSc: (replaces previous adult classification criteria)
    - Sensitivity of 90%, a specificity of 96%
    - Patient, less than 16 years, with one major and at least two of the 20 minor criteria
      - **Major criterion**: proximal sclerosis/induration of skin
      - **Minor criteria**
        - Skin: sclerodactyly
        - Vascular: Raynaud’s phenomenon, nailfold capillary abnormalities, digital tip ulcers
        - Gastrointestinal: dysphagia, gastro–esophageal reflux
        - Renal: renal crisis, new-onset arterial hypertension
        - Cardiac: arrhythmias, heart failure
        - Respiratory: pulmonary fibrosis (high resolution computed tomography/radiograph), diffusing
lungs for carbon monoxide, pulmonary hypertension

- Musculoskeletal: tendon friction rubs, arthritis, myositis
- Neurologic: neuropathy, carpal tunnel syndrome

**Serology:** antinuclear antibodies, SSc-selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, ant-fibrillin or anti-RNA polymerase I or III)

- **Scleroderma-like disorders:**
  - Localized scleroderma, disorders with mucin deposition: scleromyxedema, Buschke scleroderma, nephrogenic fibrosing dermopathy, disorders with monoclonal gammopathy: scleromyxedema, POEMS syndrome, myeloma with scleroderma-like changes, disorders with eosinophilia: diffuse fasciitis with eosinophilia, eosinophilia-myalgia syndrome, toxic oil syndrome
  - Disorders with defined metabolic/biochemical/endocrine abnormalities: insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), carcinoid syndrome, porphyria, phenylketonuria, nephrogenic fibrosing dermopathy, chronic graft-versus-host disease

- **Chemically induced scleroderma-like disorders:** eosinophilia-myalgia syndrome, toxic oil syndrome, polyvinyl-chloride disease, organic solvents, epoxy resins exposure

- **Drug induced scleroderma-like disorders:** bleomycin, injections of pentazocine, progestin, vitamin B₁₂, vitamin K, cocaine, d-penicillamine, peploymycin, interferon-β₁α, uracil-tegafur, paclitaxel, methysergide, gemcitabine, physical injury (trauma, vibration stress, radiation)

- **Inherited progeroid syndromes (Werner’s syndrome),** heterogeneous group of hereditary disorders with skin thickening (melorheostosis, stiff skin syndrome, porphyria cutanea tarda, phenylketonuria), or tight skin (restrictive dermopathy, scleratrophic Huriez syndrome)

- **Laboratory studies:**
  - **Autoantibodies:**
    - ANA: 15% to 40% of patients patients; 81% to 97% in JSSc, most commonly speckled, nucleolar, centromere
    - Topoisomerase I: (by immunodiffusion), 9% to 20% of adult patients, 20% to 34% in JSSc; associated with diffuse cutaneous involvement, increased mortality rate, due to ventricular failure secondary to pulmonary disease (interstitial fibrosis)
    - Centromere: 20% to 30% of patients, most commonly found with ISSc; associated with a higher risk for calcinosis and ischemic digital loss, lower frequency of interstitial pulmonary fibrosis, increased risk of pulmonary hypertension
    - Fibrillarin (U3-RNP): less than 10% of patients with SSc, associated with diffuse cutaneous disease
    - RNA Polymerases (I-III): specific for SSc, 20% of patients, associated with diffuse cutaneous involvement and SSc-related renal crisis, greater mortality
    - PM-Scl (2% of patients with scleroderma): found in patients with myositis, scleroderma, and the polymyositis-scleroderma overlap syndrome, (myositis, Raynaud phenomenon, arthritis, and interstitial lung disease)
    - Anti-Th/To: 2% to 5% of patients with SSc and are associated with milder skin and systemic involvement, except for more severe pulmonary fibrosis
    - Anti-ku antibodies: scleroderma-myositis overlap syndromes and a wide spectrum of rheumatic diseases
    - Antiphospholipid antibodies (aPL): 20% to 25% of patients, increased frequency of pregnancy losses; anticardiolipin antibodies (aCL): thrombosis and pulmonary hypertension
    - Anti-U1RNP: 8% of patients, less cutaneous and renal involvement and favorable response to corticosteroids
    - Anti-Ro antibodies: < 35% of patients, association of SSc with Sjögren syndrome up to 20%

- **Imaging studies:**
  - Chest radiograph: fibrosis of the lower areas of the lungs
  - Bone radiography: generalized osteopenia
  - Doppler echocardiography: left- and right-sided heart diseases
  - Pulmonary function test
  - Cine esophogram: evaluate for esophageal hypomotility
  - Esophagogastroduodenoscopy: identify erosive esophagitis, superinfection, Barrett’s esophagus, ulceration, and malignant transformation
  - Small bowel series: identifies characteristic hypomotility

- **Histologic findings:**
  - Appendageal atrophy; marked mucopolysaccharide, glycoprotein, and compact collagen (types I and III) deposition in the dermis; subintimal proliferation of small arteries and arterioles

- **Treatment:**
  - Pulmonary: vaccinations (prophylactic influenza and Streptococcus pneumoniae), cyclophosphamide for alveolitis; prostacyclin (epoprostenol and treprostinil), endothelin-1 antagonist (bosentan), and phosphodiesterase type-5 inhibitor (sildenafil) for PAH
MIXED CONNECTIVE TISSUE DISEASE (MCTD)

- Cardiac: nonsteroidal anti-inflammatory drugs or low-dose corticosteroids for pericarditis, high dose corticosteroids for myocarditis. Digitalis and diuretics are also used
- Renal: ACE inhibitors, dialysis, renal transplant
- Raynaud’s, digital ulcers: calcium-channel blockers (nifedipine), topical nitropaste, phosphodiesterase type 5 inhibitor (sildenafil), ACE inhibitors
- Musculoskeletal: NSAIDs
- Skin disease: UVA1 phototherapy, antifibrotic agents (e.g., D-penicillamine, interferon-α and interferon-γ)
- Scleroderma renal crisis: IV captopril
- Gastrointestinal tract involvement: proton pump inhibitors (e.g., omeprazole), H₂ blockers, cisapride, and metoclopramide, endoscopic dilatation, sclerotherapy for ecstatic vessels, broad spectrum antibiotics for bacterial overgrowth
- Other systemic treatments: cyclophosphamide, methotrexate, chlorambucil, 5-fluorouracil, stem cell transplantation

Localized Scleroderma (Morphea)

- Idiopathic fibrosis of the skin and adjacent structures
- Prognosis is good. Progression to systemic sclerosis is rare; lesions tend to regress spontaneously over 3 to 5 years, usually with residual pigmentary and atrophic changes
- Subtypes: plaque, generalized, bullous, linear, and deep
- Etiology
  - Role of autoimmunity in the pathogenesis of morphea
  - Autoimmune conditions associated with morphea: Hashimoto’s thyroiditis, vitiligo, systemic lupus erythematosus, and type 1 diabetes mellitus
  - Cytokines and growth factors released by endothelial and inflammatory cells (TH2 activation) result in fibroblast proliferation and increased deposition of extracellular matrix
  - Factors involved in promoting fibrosis in morphea: transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF), IL-1, IL-4, IL-6, endothelin-1, and tissue inhibitor of metalloproteinase-1.2 T
- Clinical findings
  - Excessive collagen deposition with thickening and induration of the skin and subcutaneous tissue
  - May begin with signs of inflammation, such as erythema and warmth
  - Usually asymptomatic, but may complain of pain or pruritus
  - Surface becomes smooth and shiny, lilac-colored

Types of morphea
- **Plaque-type:**
  - Most common, occurs in more than 50% of cases of morphea
  - Indurated plaques 1 to 30 cm in diameter, may have an associated violaceous border (Fig. 22-13)
  - Lesions progressively become indurated, with a porcelain white or yellow hue and then heal with atrophy, depigmentation, or hyperpigmentation
  - Trunk involved more commonly than extremities
  - Variants: guttate, generalized, keloidal (nodular), atrophoderma of Pasini and Pierini

- Usually progresses over 3–5 years, then regresses, with skin softening and some residual atrophy/hyperpigmentation

**FIGURE 22-13** Plaque morphea. (Courtesy of University of Texas Medical School, Dermatology Resident Teaching Collection.)
- *Generalized morphea*: 13% of patients with morphea; coalescence of individual plaques or the development of multiple lesions in more than 2 anatomical sites; diffuse morphea: progression to involve widespread areas of the body
- *Nodular or keloid morphea*: sclerotic papules and plaques that resemble keloid scars
- *Guttate morphea*: multiple small, usually superficial papules
- *Atrophoderma of Pasini and Pierini*: possibly an end-stage form of plaque-type morphea; dermal/fat atrophy of trunk or proximal extremities with depressed plaques with a blue-brown, gray, or violaceous hue with a sharp cut-off and deep indentation
- *Deep morphea (morphea profunda)*: involves deep dermis, subcutaneous tissue, fascia, muscle, and bone, may calcify
- **Variants:**
  - *Subcutaneous morphea*: mainly subcutaneous involvement with rapid onset of symmetric sclerotic bound-down lesions and ill-defined borders
    - *Morphea profunda*: all skin layers with diffuse, taut, bound-down sclerosis
    - *Eosinophilic fascitis* (or Shulman syndrome): see below
    - *Disabling pansclerotic morphea of children*: poor prognosis, diffuse full-thickness sclerosis of the trunk, face, and extremities, sparing the fingertips and toes, affects the deep subcutaneous tissue, fascia, muscle, and bone
  - *Bullous morphea*: tense subepidermal bullae may occur in plaques of morphea on the extremities, trunk, face, or neck and may be superficial or extend into the dermis
- *Linear morphea*:
  - Accounts for approximately 20% of all cases; comprises up to 65% of cases of juvenile morphea
  - Linear plaques that become confluent and extend longitudinally, can impair mobility of an entire limb, can involve muscle/fascia/tendons, can impair joint mobility
  - *En coup de sabre*: affects frontoparietal scalp; rarely, may extend deeply; ocular complications such as eyelid lesions, exophthalmos, uveitis, episcleritis, xerophthalmia, papilledema, and glaucoma (up to 15% of cases); neurologic involvement with resulting seizures peripheral neuropathy, encephalitis, central nervous system vasculitis, vascular malformations, and/or strokes
- *Progressive facial hemiatrophy* (Parry-Romberg syndrome): variant of linear morphea with progressive hemifacial atrophy; primary lesion occurs in the subcutaneous tissue, muscle, and bone (Fig. 22-14)

**Laboratory studies:**
- **ANA**:
  - Positive in 40% of plaque-type or generalized morphea
  - Positive in 67% of linear morphea
- **Anti-single-stranded DNA**: 50% of morphea patients, especially correlates with linear morphea
- **Antihistone antibodies (AHAs)**: 35% morphea patients
- **Antifibrillarin antibodies**: 30% morphea patients
- **Rheumatoid factor (RF)**: 60% of patients
- **Polyclonal hypergammaglobulinemia**: 50% of patients
- **Complete blood count**: in patients with eosinophilic fasciitis
- **Neurologic and ophthalmologic examinations**: patients with morphea involving the face
- **Histology**: early lesions: dense inflammatory infiltrate composed of lymphocytes, macrophages, plasma cells, late lesions: thickened, hyalinized collagen bundles

**Treatment**
- Topical or intralesional corticosteroids
- Calcipotriene (vitamin D analog)
- UVA-1 phototherapy
- Imiquimod 5% cream

**Generalized morphea**: 13% of patients with morphea; coalescence of individual plaques or the development of multiple lesions in more than 2 anatomical sites; diffuse morphea: progression to involve widespread areas of the body.
Mixed Connective Tissue Disease (MCTD)

- Generalized, linear, and deep morphea: systemic corticosteroids, antimalarial agents, methotrexate, phenytoin, colchicine, and cyclosporine
- Physical therapy for linear morphea

**Eosinophilic Fasciitis (EF, Shulman Syndrome)**

- Disorder characterized by peripheral eosinophilia and fasciitis
- Scleroderma-like induration of the skin, differs from PSS since it usually spares the fingers, hands, and face and does not present with Raynaud’s
- Belongs to the subtype of deep localized scleroderma or deep morphea
- Cause is unknown; however it has been reported in association with vigorous exercise, drugs, borreliosis, arthropod bites, and trauma
- Increased expression of genes for transforming growth factor β (TGF-β) and extracellular matrix proteins in fibroblasts
- Clinical findings:
  - Sudden onset of tender, edematous, and erythematous extremities associated with weakness and muscle pain with limited motility
  - Fascial involvement can lead to contractures (75%) and separation of muscle groups by a line of demarcation (groove sign)
  - Veins may appear depressed (sunken veins)
  - Rippling of the skin and a peau d’orange change often develops
  - Associated with severe cramps, distal sensorimotor neuropathy, mononeuritis multiplex, cognitive symptoms
  - Cardiopulmonary features: pneumonitis, respiratory muscle dysfunction, pulmonary hypertension
- Differential diagnosis
  - Eosinophilia-myalgia syndrome: when EF is accompanied by muscle weakness; however, in eosinophilia-myalgia syndrome there are muscle pains, polyneuropathy or pulmonary disease, and a history of L-tryptophan intake (some cases of EF are reported after L-tryptophan ingestion, suggesting an overlap in the pathogenesis)
- Scleroderma, systemic sclerosis, and mixed connective tissue disorder: typical findings of these diseases include sclerodactyly, Raynaud’s phenomenon, and the presence of antinuclear antibodies not found in EF
- Laboratory signs
  - Peripheral blood eosinophilia (64% of patients)
  - Hypergammaglobulinemia (75% of patients)
  - Erythrocyte sedimentation rate (50% to 70%)
- Histologic findings: inflammation, edema, thickening, and sclerosis of the fascia; presence of lymphocytes, plasma cells, histiocytes, and eosinophils, similar to scleroderma

- Imaging studies: ultrasound and magnetic resonance imaging in order to detect thickened fascia
- Treatment
  - Prednisone, hydroxyzine, ibuprofen, cimetidine, hydroxychloroquine, photochemotherapy and cyclophosphamide
  - Spontaneous remission can occur

**Cryoglobulinemia**

- Cryoglobulins: plasma immunoglobulins or immunoglobulin-containing complexes that precipitate on exposure to cold and redissolve on warming
- Types of cryoglobulins
  - **Type I:** (10% to 15%) monoclonal immunoglobulin, usually IgM or IgG
    - Associated with plasma cell dyscrasias/lymphoproliferative disorders
    - Clinically indistinguishable from those with Waldenström’s macroglobulinemia, multiple myeloma, immunocytoma or chronic lymphocytic leukemia
  - **Type II:** (50% to 60%) monoclonal IgM (rarely IgA or IgG that has rheumatoid factor (RF) activity and bind to polyclonal immunoglobulins (usually IgGs)
  - **Type III:** (25% to 30%) polyclonal IgM that have rheumatoid factor (RF) activity and bind to polyclonal immunoglobulins (usually IgGs)
  - Clinical
    - Typical triad: purpura, weakness, arthralgias
    - Multisystem organ involvement including chronic hepatitis, membrano-proliferative glomerulonephritis, peripheral neuropathy due to leucocytoclastic vasculitis of small and medium-sized vessels
  - Proposed criteria for the classification of mixed cryoglobulinemia:
    - **Major:** serologies: mixed cryoglobulins, low C4; pathology: leukocytoclastic vasculitis
    - **Minor:** serologies: rheumatoid Factor +, HCV +, HBV +; pathology: clonal B cell infiltrates (liver-bone marrow)

  "Definite" mixed cryoglobulinemia syndrome:
Serum mixed cryoglobulins
(± low C4) + purpura + leukocytoclastic vasculitis

Serum mixed cryoglobulins (± low C4) + 2 minor clinical symptoms + 2 minor serological/pathological findings

“Incomplete” or “possible” mixed cryoglobulinemia syndrome:

Mixed cryoglobulins or low C4 + 1 minor clinical symptom + 1 minor serological ± pathological finding

Purpura and/or leukocytoclastic vasculitis + 1 minor clinical symptom + 1 minor serological ± pathological finding

2 minor clinical symptoms + 2 minor serological ± pathological findings

“Essential” or “secondary” mixed cryoglobulinemia syndrome

Absence or presence of well known disorders (infections, immunological, neoplastic)

Clinical findings
- Palpable purpura (55% to 100%): higher in types II and III, intermittent, begin on legs
- Raynaud’s phenomenon: 33% of patients
- Vasculitis: secondary to vascular deposition of circulating immunocomplexes
- Arthralgias and arthritis in the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, knees, and ankles (73%)
- Renal immune-complex disease: 33% of patients, immunofluorescence demonstrates immunoglobulin and C3 deposits in the glomerulus (cryoglobulinemic glomerulonephritis)
- Peripheral sensorimotor polyneuropathy with painful paresthesias, most commonly in types II and III
- Systemic autoimmune disease: connective tissue diseases are seen in patients with types II and III; mainly primary Sjögren’s syndrome and systemic lupus erythematosus
- Liver involvement: high incidence of HCV in MC patients, increased enzymes, hepatomegaly, chronic hepatitis, steatosis, cirrhosis or hepatocellular carcinoma, liver failure leading to death (25%)
- See Table 22-1 for clinical conditions that may be associated with cryoglobulinemia

Laboratory studies
- Serum evaluation: specimen must be obtained in warm tubes (37°C)
- Types I and II precipitate within the first 24 hours
- Type III cryoglobulins may require 7 days
- RF is positive in types II and III

Serum cryoglobulin values usually do not correlate with clinical severity and prognosis of the disease

Complement levels
- Low complement levels are frequently observed in patients with cryoglobulinemia related to autoimmune disorders
- Type II HCV related cryoglobulinemia presents with low levels of C4 and normal C3

Treatment
- Treatment of the underlying disorder
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Immunosuppressives: corticosteroid therapy and/or cyclophosphamide or azathioprine, interferon-α (IFN-α) and ribavirin for HCV-associated disease
- Plasmapheresis with other immunosuppressive treatment: in patients with severe manifestations of MC
- Rituximab: B-cell lymphoproliferative disorders and in autoimmune diseases

Cryofibrinogenemia

Cryofibrinogen:
- Precipitants of protein complexes made up of fibronectin, fibrinogen and fibrin
- Found in the plasma but not in the serum of some individuals
- Reversibly precipitates in cooled plasma at 4°C, and dissolves at 37°C

Classification
- Primary (essential)
- Secondary and associated with
  - Carcinomas, infections, collagen-vascular diseases, thromboembolic diseases, cryoglobulins

Clinical findings
- Often clinically asymptomatic
- Thrombotic vasculopathy characterized by: ischemia, purpura, livedo reticularis, ecchymosis, ulcers, necrosis and gangrene, purpura (77%)
- Histology: fibrin thrombi within superficial dermal vessels

Treatment
- Usually unresponsive to treatment; may respond to fibrinolytic therapy

Seronegative Spondyloarthropathies

- Chronic inflammatory diseases of the joints associated with the HLA-B27 gene
- Characterised by shared rheumatic features including enthesitis, sacroiliitis, peripheral arthritis
- Also with associated extra-articular lesions notably psoriasis, uveitis, and inflammatory bowel disease

Diseases
- Ankylosing spondylitis/juvenile ankylosing spondylitis
## TABLE 22-1 Clinical Conditions That May Be Associated With Cryoglobulinemia

<table>
<thead>
<tr>
<th>Infections</th>
<th>Autoimmune Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral</strong></td>
<td>(Epstein-Barr virus, Cytomegalovirus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, HIV)</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td>(Lyme disease, Syphilis, Lepromatous leprosy, Q fever, Poststreptococcal nephritis, Subacute bacterial endocarditis)</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td>(Coccidioidomycosis)</td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
<td>(Kala-azar Toxoplasmosis, Echinococcosis, Malaria, Schistosomiasis, Trypanosomiasis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic Diseases</th>
<th>Autoimmune Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>Sjögren’s syndrome</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Waldenström’s macroglobulinemia</td>
<td>Autoimmune thyroiditis</td>
</tr>
<tr>
<td>Castleman disease</td>
<td>Temporal arteritis</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>Dermatomyositis-polymyositis</td>
</tr>
<tr>
<td>Thrombocytopenic thrombotic purpura</td>
<td>Henoch-Schönlein disease</td>
</tr>
<tr>
<td>Cold agglutinin disease</td>
<td>Sarcoïdosis</td>
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<tr>
<td></td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Biliary cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Primary antiphospholipid syndrome</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Endomyocardial fibrosis</td>
</tr>
<tr>
<td></td>
<td>Pemphigus vulgaris</td>
</tr>
</tbody>
</table>


- Spondyloarthropathy of inflammatory bowel disease (IBD)
- Psoriatic arthritis
- Reactive arthritis (ReA)/Reiter syndrome (RS)
- Undifferentiated spondylarthropathy
- Ankylosing spondylitis
- Systemic rheumatic disorder of indeterminant etiology, (but with a strong genetic predisposition), and sacroiliac (SI) joint inflammation (sacroilitis)
- HLA-B27: present in 95% of patients
- Reactive arthritis (ReA)
- Previously called Reiter’s syndrome
- Aseptic inflammatory arthritis, triggered by infection at a distant site in genetically susceptible people
Circinate balanitis/vulvitis:
- Painless gyrate white plaques eventually cover the entire surface of the glans penis
- Painless shiny patches of the palate, tongue, and mucosa of the cheeks and lips
- Psoriasiform dermatitis of elbows/knees/scalp
- Pyoderma gangrenosum may also occur

Ocular involvement
- Bilateral conjunctivitis (occurs in 30% of patients); also anterior uveitis

Genitourinary involvement
- Urethritis or cervicitis: typically urethritis precedes conjunctivitis and arthritis
- Dysuria
- Gastrointestinal involvement
- Enteric acquired reactive arthritis usually presents 4 weeks after infection
- Renal involvement:
  - Immunoglobulin A (IgA) nephropathy

Clinical findings
- Acute episode of arthritis resolves spontaneously in 3–12 months
- Reiter’s syndrome (ACR definition):
  - Episode of peripheral arthritis of more than one month’s duration occurring in association with urethritis or cervicitis
  - Musculoskeletal manifestations
    - Arthritis (95% of patients): acute, asymmetric, knees, ankles, feet
    - Spondylitis: low back pain radiating to buttocks or thighs
    - Enthesitis: periarticular inflammation, can lead to “sausage digits”
- Mucocutaneous involvement:
  - Keratoderma blennorrhagica (5% to 10% of patients): pustular psoriasis-like lesions on palms/soles, associated nail dystrophy

Laboratory studies
- Elevated ESR and CRP
- Synovial fluid: leukocytosis; Gram stain/culture negative
- Throat, stool, or urogenital tract cultures
- Full blood count: neutrophilic leukocytosis, thrombocytosis, anemia of chronic disease
- Synovial biopsy: polymorphous infiltrate indistinguishable from other chronic rheumatic diseases
- Electrocardiogram: often normal but may show variable degrees of heart block

Human leukocyte antigen HLA-B27 (class one major histocompatibility complex gene)
- Affects 45% to 90% of patients
- Associated with more severe and prolonged disease, a higher prevalence of back pain, and are more likely to have mucocutaneous disease
- HLA-B27 binds unique peptides of microbial or self origin and presents them to CD8 positive T cells causing specific immune responses
- Usually follows gastrointestinal or genitourinary infections (Table 22-2)
- Sporadic cases of sexually acquired reactive arthritis (SARA) is usually due to infection with Chlamydia trachomatis

Mainly affects patients 20–40 years old
- Male to female ratio: 3:1

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### TABLE 22-2 Conditions to Which Arthritis May Be Reactive

<table>
<thead>
<tr>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infections</td>
<td>Chlamydia pneumoniae</td>
</tr>
<tr>
<td></td>
<td>Chlamydia psittaci</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Genitourinary infections</td>
<td>Chlamydia trachomatis</td>
</tr>
<tr>
<td>Gastrointestinal infections</td>
<td>Campylobacter jejuni</td>
</tr>
<tr>
<td></td>
<td>Salmonella enteritidis</td>
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<tr>
<td></td>
<td>Salmonella typhimurum</td>
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<tr>
<td></td>
<td>Shigella flexneri</td>
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<tr>
<td></td>
<td>Yersinia enterocolitica</td>
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<tr>
<td></td>
<td>Yersinia pseudotuberculosis</td>
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<tr>
<td></td>
<td>Brucella abortus</td>
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<tr>
<td></td>
<td>Clostridia difficile</td>
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<tr>
<td></td>
<td>Cryptosporidium</td>
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<tr>
<td></td>
<td>Entamoeba histolytica</td>
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<tr>
<td></td>
<td>Escherichia coli</td>
</tr>
<tr>
<td></td>
<td>Giardia lamblia</td>
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<tr>
<td></td>
<td>Mycoplasma fermentans</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma genitalium</td>
</tr>
<tr>
<td></td>
<td>Neisseria gonorrhaeae</td>
</tr>
<tr>
<td></td>
<td>Ureaplasma urealyticum</td>
</tr>
</tbody>
</table>
• Treatment
  – Usually self-limited course, with resolution of symptoms by 3 to 12 months; 50% may have recurrent arthritis
  – Empiric treatment for Chlamydia
  – NSAIDs
  – Sulfasalazine, methotrexate, TNF-α-inhibitors

**Psoriatic Arthritis (PsA)**

- Found in 5% to 20% of patients with psoriasis; psoriasis precedes the onset of PsA in 60% to 80% of patients
- Occurs in 5% to 42% of patients with psoriatic skin disease (Ps)
- CASPAR (classification criteria for psoriatic arthritis) criteria for the classification of PsA (Table 22-3)
  - Specificity of 98.7% and sensitivity of 91.4%
- Clinical findings
  - Asymmetric oligoarthritis: 50% of male patients
    – Involvement of hands and feet; DIPs, PIPs, spares MCPs
    – Leads to “sausage digits”
  - Symmetric polyarthritis: most common pattern in women
    – RA-like pattern of hands, feet, ankles
    – Unlike RA, may involve the DIP, RF negative
  - DIP joint: “classic,” but uncommonly exclusively involved
  - Arthritis mutilans: least common variant
    – Severe, rapidly-progressive joint inflammation that results in digital shortening due to “telescoping” of digits and osteolysis (pencil in cup deformity on x-ray)
  - Spondylitis and sacroiliitis: axial arthritis, knees also involved, may have peripheral joint involvement, HLA-B26 positive
  - Psoriatic-onychopachydermoperiostitis (POPP):
    – Psoriatic nail lesions
    – Soft tissue thickening above the terminal phalanx and radiologic involvement of the phalanx with periosteal reaction
- Laboratory studies
  - Elevated ESR and CRP
  - Leukocytosis of synovial fluid
  - Radiologic findings: x-ray—pencil-in-cup deformity, fluffy periosteal bone formation
- Treatment
  - NSAIDs
  - Methotrexate, sulfasalazine, and cyclosporine
  - TNF-α inhibitors: infliximab, etanercept, adalimumab

**Scleredema (Scleredema Adultorum of Buschke, Scleredema Diabeticorum)**

- Benign self-limited cutaneous mucinosis with irreversible glycosylation of collagen that is collagenase resistant
- Pathogenesis: unknown, hypotheses implicating immune mechanisms, direct action of bacterial toxin and effects of adrenal steroids released in response to infection
- 29% cases seen in children
- Type I: infection-association
  – Middle-aged women, preceding febrile illness, streptococcal, (tonsillitis, pharyngitis, and pyoderma), influenza, scarlet fever, measles, and mumps. Sudden-onset hardening of the cervicofacial region, with extension to the upper trunk and proximal extremities
  – Self-limited in several months
- Type II: monoclonal gammopathy-associated
  – Also associated with hyperparathyroidism, multiple myeloma, malignant insulinoma, rheumatoid arthritis, and Sjogren’s syndrome
  – Middle-aged women, no preceding illness
  – Similar course to type I
- Type III: diabetes and obesity associated
  – Middle-aged obese men
  – Slow-onset, persistent, erythema and induration of the posterior neck and back, peau d’orange
- Systemic findings
  – Serositis with possible pleural, pericardial and peritoneal effusions

**TABLE 22-3 The CASPAR Criteria (Classification Criteria for Psoriatic Arthritis)**

Requires the presence of inflammatory articular disease: (joint, spine, or entheseal)
Also presence of 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis (first- or second-degree relative)
2. Typical psoriatic nail dystrophy: onycholysis, pitting, and hyperkeratosis
3. A negative test result for the presence of rheumatoid factor by any method except latex test
4. Either current dactylitis (swelling of an entire digit) or a history of dactylitis
5. Radiographic evidence of juxtaarticular new bone formation
• Dysarthria, dysphagia
• Myositis
• Parotitis
• Ocular abnormalities: trophic corneal disturbances
• Cardiac involvement: Wolff-Parkinson-White syndrome
• Histology: thickened dermis with deposition of mucin between thickened collagen bundles
• Treatment
  • Physical therapy
  • No known effective treatment

**QUIZ**

**Questions**

1. The most specific antinuclear pattern for SLE is:
   A. Rim
   B. Speckled
   C. Homogenous
   D. Nucleolar

2. Systemic lupus erythematosus is associated with:
   A. HLA-DR4
   B. HLA-DR2
   C. HLA-DQ4
   D. HLA-DQ2

3. Which statement is TRUE about acute cutaneous lupus?
   A. ACLE occurs in 80% to 90% of patients with SLE
   B. ACLE tends to spare the nasolabial folds
   C. ACLE flares with systemic disease
   D. Alopecia is common in patients with ACLE
   E. ACLE is the most photosensitive subtype of cutaneous lupus
   F. B, C, and D
   G. B, C, D, and E
   H. All are true

4. Which of the following is NOT an ACR criterion of SLE?
   A. Complement deficiency
   B. Arthritis
   C. IgM anti-phospholipid antibody positivity
   D. Oral ulcers
   E. Positive lupus prep
   F. Hemolytic anemia
   G. A and C are not
   H. A, C, and E are not
   I. All of the above are criteria

5. Which medication would NOT cause the following clinical scenarios?
   A. Hydrochlorothiazide and a patient with SCLE, photosensitivity, arthritis, and a positive ANA in a speckled pattern
   B. Griseofulvin and a patient with SCLE, photosensitivity, and a positive ANA in a speckled pattern
   C. Phenytoin and a patient with a malar rash, photosensitivity, arthritis, pleurisy, and a positive ANA in a nucleolar pattern
   D. Griseofulvin and a patient with a positive ANA in a homogenous pattern, arthritis, oral ulcers, hemolytic anemia, and pleurisy
   E. Hydroxyurea and violaceous erythema over the knuckles, elbows, and knees, and a negative ANA

6. Which of the following is TRUE?
   A. The risk of malignancy in adults with dermatomyositis is 35–40%
   B. Adults with dermatomyositis should have yearly malignancy screening for 2 years following their dermatomyositis diagnosis
   C. The heliotrope eruption is the most common and characteristic cutaneous features of dermatomyositis
   D. A patient with dermatomyositis with violaceous erythema on the elbows has Gottron’s sign
   E. Lipodystrophy, calcinosis cutis, and vasculopathic ulcers may occur in juvenile dermatomyositis
   F. D and E are true
   G. C, D, and E are true

7. Scleroderma-like disorders can be seen in all of the following EXCEPT:
   A. Stiff skin syndrome
   B. Argyria
   C. Crowe-Fukase syndrome
   D. Vitamin K exposure
   E. Isoniazid

8. Which of the following statements about Shulman syndrome is FALSE?
   A. Most cases have now been found to be associated with exposure to adulterated rapeseed oil
   B. Fascial involvement leads to contractures and the “groove sign”
   C. It is characterized by increased expression of genes for TGF-β in fibroblasts
   D. It is usually steroid-responsive
   E. 75% of cases have associated hypergammaglobulinemia
9. Which of the following is NOT associated with the listed type of cryoglobulinemia?
   A. Rheumatoid factor positivity and type I cryoglobulinemia
   B. Peripheral sensory polyneuropathy and type II cryoglobulinemia
   C. Monoclonal IgG and type I cryoglobulinemia
   D. Type I cryoglobulinemia and acrocyanosis
   E. Cryoglobulinemic glomerulonephritis and type II cryoglobulins

10. Which of the following is NOT a feature of reactive arthritis?
    A. Gyrate white plaques on the penis
    B. Shiny patches on the palate
    C. Anterior uveitis
    D. Trachyonychia
    E. IgA nephropathy

Answers

1. A. Although a homogenous pattern is also highly specific for SLE and is the most common pattern in SLE, rim is the most specific. Both are associated with anti-DNA antibodies and antibodies to histone.
2. B. SLE is associated with HLA DR2 and DR3.
3. F. Localized ACLE (malar rash) occurs in only 20% to 60% of patients with SLE, spares the nasolabial folds (unlike dermatomyositis), flares with systemic disease, and is often associated with alopecia (telogen effluvium-like). Although it is quite photosensitive, it is less so than SCLE.
4. A. Complement deficiency is the only item that is not an ACR criterion for SLE.
5. C. Phenytoin can cause drug-induced SLE, but cutaneous manifestations are usually not present, and the ANA pattern is rim or homogenous, corresponding with anti-histone antibodies. Hydrochlorothiazide is a common cause of drug-induced SCLE, and can be associated with mild systemic symptoms and a positive Ro or La antibody. Griseofulvin can cause both drug-induced SLE (associated with anti-histone antibodies and usually without cutaneous involvement) and drug-induced SCLE (associated with anti-Ro/La Abs). Hydroxyurea is associated with cutaneous findings consistent with dermatomyositis, with no associated evidence of muscle weakness, and usually with a negative ANA.
6. F. It is true that patients with violaceous erythema of the elbows have Gottron’s sign and that lipodystrophy, calcinosis cutis and vasculopathic ulcers are possible complications of juvenile DM. The risk of malignancy in adults with DM is in fact 20% to 25%, and the risk remains elevated for at least 3–5 years, so that malignancy surveillance should be done annually for that period of time (perhaps longer). The most common lesion in DM is in fact the Gottron’s papule, not the heliotrope eruption.
7. B. A scleroderma-like disorder is not seen with argyria. Acrogeria, which sounds like argyria, is a premature aging syndrome that can be associated with scleroderma-like changes. Crowe-Fukase syndrome is another name for POEMS syndrome.
8. A. Toxic oil syndrome, which can present similarly to eosinophilic fasciitis, is associated with adulterated rapeseed oil exposure. However, it is a very small subset of patients with the clinical presentation. The other items are true.
9. A. Rheumatoid factor positivity is seen in types II and III cryoglobulinemia. The remaining associations are correct.
10. D. Trachyonychia is not commonly seen in patients with reactive arthritis (previously known as Reiter’s syndrome).

REFERENCES


PORPHYRIAS

Metabolic disorders of heme synthesis; may be hereditary or acquired
- Photosensitivity due to exposure of ultraviolet (UV) radiation in the Soret band (400 to 410 nm)

Classification of Porphyrias: Erythropoietic and Hepatic Forms (Based on the Primary Site of Expression of the Enzymatic Defect)

- Non-acute porphyrias: porphyria cutanea tarda (PCT), erythropoietic porphyria (EPP), congenital erythropoietic porphyria (CEP) and hepatoporpho- poietic porphyria (HEP); most common cutaneous manifestation is photosensitivity
- Acute porphyrias: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP) and ALA dehydratase deficiency porphyria (plumboporphyria)
- Heme biosynthesis:
  - Major sites of heme synthesis are bone marrow (85%) and in the liver
  - Initial reaction takes place in the mitochondrion within the cell
  - Condensation of 1-glycine and 1-succinylCoA by Δ-aminolevulinic acid synthase (ALA synthase): rate-limiting reaction of heme biosynthesis
  - Mitochondrial Δ-aminolevulinic acid (ALA) is transported to the cytosol
  - ALA dehydratase (also called porphobilinogen synthase) dimerizes two molecules of ALA to produce porphobilinogen
  - Uroporphyrinogen I synthase, also called porphobilinogen deaminase or PBG deaminase, causes condensation of four molecules of porphobilinogen to produce intermediate hydroxymethylbilane
  - Hydroxymethylbilane undergoes enzymatic conversion to uroporphyrinogen III by uroporphyrinogen synthase plus a protein known as uroporphyrinogen III cosynthase
  - In the cytosol, the acetate substituents of uroporphyrinogen (normal uroporphyrinogen III or abnormal uroporphyrinogen I) are decarboxylated by uroporphyrinogen decarboxylase
  - The resulting coproporphyrinogen III intermediate is transported to the interior of the mitochondrion, where, after decarboxylation, protoporphyrinogen IX results
  - In the mitochondrion, protoporphyrinogen IX is converted to protoporphyrin IX by protoporphyrinogen IX oxidase
  - Final reaction in heme synthesis takes place in the mitochondrion by ferrochelatase

ERYTHROPOIETIC PORPHYRIAS

Congenital Erythropoietic Porphyria (EP)
GUNTHER DISEASE
- Autosomal recessive with complete absence of UROS gene activity; affects uroporphyrinogen III synthase and the production of uroporphyrinogen III
• Results in massive accumulation and excretion of uroporphyrin I and coproporphyrin I

• Clinical findings
  • Appears soon after birth
  • Cutaneous:
    • Severe photosensitivity with burning, edema, bullae, mutilating scars, loss of brows/lashes, hypertrichosis, hyper/hypopigmentation
    • Ocular: photophobia, kerato conjunctivitis, ectropion, symblepharon, loss of vision
  • Other: gallstones possible, cartilaginous breakdown, red/brown urine, erythrodontia (seen with Wood’s lamp), splenomegaly, hemolytic anemia

• Laboratory findings
  • Urine: uroporphyrin I, coproporphyrin I
  • Stool: coproporphyrin I
  • Blood: plasma-uroporphyrin I, coprophorphyrin I; RBC: uroporphyrin I, coproporphyrin and some protoporphyrin
  • Other diagnostic tests: urine fluoresces reddish pink
  • Treatment: strict photoprotection, splenectomy, blood transfusions, activated charcoal, hydroxyruea

**Erythropoietic Protoporphryia (EPP)**

• Autosomal dominant
  • FECH gene mutation results in partial ferrochelatase deficiency
  • Most common erythropoietic porphyria

• Clinical findings
  • Cutaneous: photosensitivity: painful erythematous, edematous plaques after exposure to UV light that may heal with scarring, skin lichenification, leathery pseudovesicles, nail changes
  • Hepatic: porphyrin gallstones (early age), liver disease (10% of patients): jaundice, cirrhosis

• Laboratory findings
  • Urine: normal
  • Stool: protoporphyrin
  • Blood: RBC/plasma: protoporphyrin
  • Treatment: photoprotection, beta-carotene (synthetic), red blood cell transfusions, cholestyramine, activated charcoal
  • Prognosis: normal life span if liver spared

**CHRONIC HEPATIC PORPHYRIA**

**Porphyria Cutanea Tarda (PCT) (Fig. 23-1)**

• Autosomal dominant
  • Uroporphyrinogen decarboxylase (UROD) deficiency in the liver

• Three types: Type I: decreased hepatic UROD activity, but normal erythrocyte UROD activity (sporadic fashion); Type II: decreased UROD activity in red cells and in the liver (occurs in multiples in a family); Type III decreased hepatic UROD activity and normal erythrocyte activity (occurs in multiples in a family)

• Most common of the porphyrias

• Clinical findings
  • Cutaneous: chronic bullae, vesicles and erosions on sun-exposed skin, bullae and vesicles rupture easily, hypertrichosis, milia, sclerodermoid changes
  • Hepatic: associated with hepatitis C, hepatocellular carcinoma, increased liver iron stores
  • Other: HIV (human immunodeficiency virus) infection, dermatomyositis

• Laboratory findings
  • Urine: uroporphyrin I–III > coproporphyrin; coral-pink fluorescence of urine under Wood’s lamp
  • Stool: isocoproprophyrins, tetracarboxyl porphyrins, protoporphyrin
  • Blood: RBC normal; plasma: increased uroporphyrin
  • Serum iron: increased
  • Liver biopsy: hepatocellular damage with fatty infiltration and hemosiderosis

• Treatment: photoprotection, phlebotomy (until serum transferrin saturation and serum ferritin levels are normalized), antimalarials (hydroxychloroquine
or chloroquine); recombinant erythropoeitin for end stage renal disease patients, avoidance of alcohol, estrogen, iron supplements
  • Interferon for hepatitis C

**Hepatoerythropoietic Porphyria (HEP)**
  • Autosomal dominant
  • Homozygous or compound heterozygous deficiency of uroporphyrinogen decarboxylase (UROD) deficiency
  • Clinical findings
    • Resembles CEP, severe photophotosensitivity with burning, erythema, vesicles, bullae, mutilating scar formation, hypertrichosis, sclerodermoid skin changes
    • Other: hemolytic anemia, splenomegaly, dark urine at birth
  • Laboratory findings
    • Urine: uroporphyrin I–III, isocoproporphyrin
    • Stool: uroporphyrin, coproporphyrin, isocoproporphyrin
    • Blood: RBC: protoporphyrin, plasma: uroporphyrin
  • Treatment: photoprotection, red cell transfusion, hydroxyurea
  • Prognosis: normal lifespan

**Hereditary Coproporphyria (HCP)**
  • Autosomal dominant
  • Coproporphyrinogen oxidase (CPO) deficiency
  • Exacerbated by: barbiturates, endogenous or exogenous steroid hormones
  • Clinical findings
    • Similar to AIP and VP, with gastrointestinal and neurologic attacks
    • Cutaneous: photosensitive bullae (30% of patients), hypertrichosis
    • Other: hemolytic anemia beginning in childhood, increased risk of hepatocellular carcinoma
  • Laboratory findings
    • Urine: coproporphyrin III; ALA, PBG, and uroporphyrin also increased during attacks
    • Stool: coproporphyrin III
    • Blood: normal

**Variegate Porphyria (VP)**
  • Autosomal dominant
  • Protoporphyrinogen oxidase (PPO) deficiency
  • Mixed porphyria: can present with neurological manifestations, cutaneous photosensitivity, or both
  • Most common in South Africans
  • Clinical findings
    • Skin lesions similar to PCT: fragility of skin, vesicles, bullae, erosions, milia, hyperpigmentation, hypertrichosis, and photosensitivity
    • Symptoms similar to AIP: abdominal pain, tachycardia, vomiting, constipation, hypertension, neuropathy, back pain, confusion, bulbar paralysis, psychiatric symptoms, fever, urinary frequency, dysuria, hyponatremia
    • Attacks may be precipitated by alcohol, hormones, and drugs (dapsone, anticonvulsants, barbiturates, sulfonamides, griseofulvin)
  • Laboratory findings
    • Urine: ALA, PBG, uroporphyrin elevated during attacks; coproporphyrin > protoporphyrin (acute and asymptomatic periods: helps distinguish from PCT)
    • Stool: protoporphyrin and coproporphyrin elevated
    • Blood: presence of plasma porphyrin (fluoresces at 626 nm)
    • Biliary porphyrins: increased risk of gallstones in VP, consist mainly of protoporphyrin
  • Treatment: avoid precipitators, photoprotection
  • Treat acute attacks similar to AIP

**ACUTE HEPATIC PORPHYRIAS**

**Acute Intermittent Porphyria (AIP)**
  • Autosomal dominant
  • Mutation of porphobilinogen deaminase (PBGD) gene leading to deficient activity of the enzyme
  • More common in women than in men
  • Attacks may be precipitated by drugs (barbiturates, sulphonamides), hormones, fever, smoking, infections, surgery, stress, or starvation
  • Clinical findings
    • Cutaneous: no skin findings
    • Neurologic: neuropathy, palsy, seizures, coma
    • Psychiatric: confusion
    • Hyponatremia: common during acute attacks, due to inappropriate release of antidiuretic hormone
    • Other: abdominal pain, risk of hepatic carcinoma
  • Laboratory findings
    • Erythrocyte PBG deaminase activity: reduced in type I and type III AIP patients; Type II AIP patients show normal PBGD activity in erythrocytes, but have reduced PBGD activity in non-erythroid cells
    • Urine: latent: aminolevulinic acid (ALA) and porphobilinogen (PBG); acute: ALA, PBG, uroporphyrin, coproporphyrin
    • Stool: normal
    • Blood: normal
  • Treatment: avoid precipitators, IV glucose loading and hematin infusions during attacks; supportive care
  • Prognosis: acute attacks may be life-threatening and leave residual neurologic deficits

**Hepatoerythropoietic Porphyria (HEP)**
  • Autosomal dominant
  • Homozygous or compound heterozygous deficiency of uroporphyrinogen decarboxylase (UROD) deficiency
  • Clinical findings
    • Resembles CEP, severe photophotosensitivity with burning, erythema, vesicles, bullae, mutilating scar formation, hypertrichosis, sclerodermoid skin changes
    • Other: hemolytic anemia, splenomegaly, dark urine at birth
  • Laboratory findings
    • Urine: uroporphyrin I–III, isocoproporphyrin
    • Stool: uroporphyrin, coproporphyrin, isocoproporphyrin
    • Blood: RBC: protoporphyrin, plasma: uroporphyrin
  • Treatment: photoprotection, red cell transfusion, hydroxyurea
  • Prognosis: normal lifespan

**Variegate Porphyria (VP)**
  • Autosomal dominant
  • Protoporphyrinogen oxidase (PPO) deficiency
  • Mixed porphyria: can present with neurological manifestations, cutaneous photosensitivity, or both
  • Most common in South Africans
  • Clinical findings
    • Skin lesions similar to PCT: fragility of skin, vesicles, bullae, erosions, milia, hyperpigmentation, hypertrichosis, and photosensitivity
    • Symptoms similar to AIP: abdominal pain, tachycardia, vomiting, constipation, hypertension, neuropathy, back pain, confusion, bulbar paralysis, psychiatric symptoms, fever, urinary frequency, dysuria, hyponatremia
    • Attacks may be precipitated by alcohol, hormones, and drugs (dapsone, anticonvulsants, barbiturates, sulfonamides, griseofulvin)
  • Laboratory findings
    • Urine: ALA, PBG, uroporphyrin elevated during attacks; coproporphyrin > protoporphyrin (acute and asymptomatic periods: helps distinguish from PCT)
    • Stool: protoporphyrin and coproporphyrin elevated
    • Blood: presence of plasma porphyrin (fluoresces at 626 nm)
    • Biliary porphyrins: increased risk of gallstones in VP, consist mainly of protoporphyrin
  • Treatment: avoid precipitators, photoprotection
  • Treat acute attacks similar to AIP

**Hereditary Coproporphyria (HCP)**
  • Autosomal dominant
  • Coproporphyrinogen oxidase (CPO) deficiency
  • Exacerbated by: barbiturates, endogenous or exogenous steroid hormones
  • Clinical findings
    • Similar to AIP and VP, with gastrointestinal and neurologic attacks
    • Cutaneous: photosensitive bullae (30% of patients), hypertrichosis
    • Other: hemolytic anemia beginning in childhood, increased risk of hepatocellular carcinoma
  • Laboratory findings
    • Urine: coproporphyrin III; ALA, PBG, and uroporphyrin also increased during attacks
    • Stool: coproporphyrin III
    • Blood: normal
Chapter 23  CUTANEOUS MANIFESTATIONS OF METABOLIC DISEASES

- Treatment: avoid precipitators, photoprotection
  - Treat acute attacks as with AIP

**ALA Dehydratase Porphyria (ADP)**
- Autosomal recessive
-ALA dehydratase deficiency
- Due to ALAD mutations
- Clinical findings
  - No skin lesions
  - Symptoms similar to AIP
- Laboratory findings
  - Urine: ALA, coproporphyrin, uroporphyrin
  - Stool: coproporphyrin, protoporphyrin
  - Blood: protoporphyrin
  - Treatment: avoid offending agent: such as alcohol and stress, intravenous infusion of glucose

**SPHINGOLIPIDOSES (LIPID STORAGE DISORDERS)**
- Diseases caused by defects in genes encoding proteins involved in the lysosomal degradation of sphingolipids
- Leads to lysosomal accumulation of the enzyme’s specific sphingolipid substrate
- Diseases are named according to the identity of the storage material
- Mode of inheritance is autosomal recessive except for Fabry’s disease (X-linked recessive)

**Fabry Disease (Angiokeratoma Corporis Diffusum)**
- X-linked recessive, Xq22
- Defective lysosomal α-galactosidase A
- Results in accumulation and deposition of glycosphingolipids (globotriaosylceramide) in plasma and lysosomes of vascular endothelial and smooth muscle cells
- Presents in adolescence
- Clinical findings
  - Ocular: corneal and lenticular opacities
  - Vascular: ischemia, coronary artery disease, cerebrovascular accident (CVA), peripheral neuropathy
  - Cutaneous: angiokeratomas of lower trunk, thighs, oral/ocular mucosa (Fig. 23-2)
  - Renal: failure
  - Genitourinary: maltese crosses in urine: lipid inclusions with characteristic birefringence
  - Other: painful crises, acroparesthesias, hypohidrosis
- Treatment: enzyme replacement therapy arrests progression of disorder, dialysis, symptomatic pain management, phenytoin and carbamazepine for paresthesias

**Gaucher Disease**
- Autosomal recessive
- Decreased glucosylceramide-β-glucocerebrosidase activity with resulting accumulation of glucocerebroside in histiocytes (Gaucher cells)
- Most common form of sphingolipidoses
- Clinical findings
  - Type I (adult): attenuated form; diffuse hyperpigmentation, petechiae, ecchymoses, bone pain, fractures, aseptic necrosis of femoral head hepatosplenomegaly, lymphadenopathy, pinguiculae, pancytopenia
  - Type II (infantile): acute form; CNS involved with hypertonicity, neck rigidity, laryngeal spasm, dysphagia, hepatosplenomegaly, aspiration pneumonia, subset with severe congenital ichthyosis and collodion membrane
  - Type III: (juvenile) subacute form; intermediate variant of types I and II
- Laboratory studies
  - Gaucher cell in the reticuloendothelial system: macrophages are enlarged with cytoplasmic inclusions
  - Elevated glucosylceramide in plasma
  - X-ray: erlenmeyer flask deformity of the distal femur

- Prognosis: death by fifth decade from myocardial infarction, CVA, and renal failure
SPHINGOLIPIDOSES (LIPID STORAGE DISORDERS)

- Treatment
  - **Type I**: imiglucerase (Cerezyme), a recombinant-derived analogue of β-glucocerebrosidase; bone marrow transplant, splenectomy
  - **Type II**: supportive care, antibiotics (enzyme replacement is unable to cross blood-brain barrier); death at 1 to 2 years owing to aspiration
  - **Type III**: bone marrow or stem cell transplants

**Farber (Acid Ceramidase Deficiency, Lipogranulomatosis)**
- Autosomal recessive
- Deficiency of lysosomal acid ceramidase and storage of ceramide in the lysosomes
- Clinical findings
  - **Skeletal**: painful and progressive joint deformations, periarticular swelling
  - **Cutaneous**: subcutaneous nodules (lipogranulomas)
  - **Ocular**: mild macular degeneration
  - **Pulmonary**
  - **Other**: progressive hoarseness, mental retardation
- Treatment: bone marrow transplantation, which improves the peripheral, but not the neurological manifestations

**Mucopolysaccharidoses (MPS) (Lysosomal Storage Diseases)**
- Inherited deficiency of enzymes that are involved in the degradation of glycosaminoglycans (GAGs); also referred to as acid mucopolysaccharides (Table 23-1)
  - Dermatan sulfate, heparan sulfate, keratan sulfate (KS), and chondroitin sulfate are the main GAGs in tissues composed of sulfated sugar and uronic acid residues (except for KS)
- Diseases are autosomal recessive, except for MPS type II (Hunter), which is X-linked recessive

**Hurler Syndrome (MPS-IH, Gargoylism)**
- Autosomal recessive
- Defect in alpha-L-iduronidase, resulting in dermanatan, heparan sulfate accumulation
- Classic form of MPS
- Clinical findings
  - Coarse facies with macrocephaly, hypertelorism, hirsutism, valvular disease, umbilical hernias, upper respiratory infections, corneal opacities, short stature, dysostosis multiplex
  - Scheie MPS-IS: mild form of the MPS-IH, onset at 5 or 6 years, aortic valve disease, joint stiffness, claw hands, deformed feet, genu valgum, deafness, corneal clouding, normal intelligence and life span
  - Scheie and Hurler compound syndromes (MPS-IH/S): clinically intermediate between types IH and IS, healthy at birth; onset of symptoms at 3 to 8 years, corneal clouding, joint stiffness, dysostosis multiplex, and heart disease
- Course: deaths caused by upper airway obstruction and pulmonary complications
**Cutaneous**: ivory papules distributed symmetrically between the angles of the scapulae and posterior axillary lines; marker for the disease, hypertrichosis may result in synophrys

**Ocular**: atypical retinitis pigmentosa

Type B: mild form, clinical features similar to MPS-IS, airway obstruction secondary to accumulation of mucopolysaccharide in the trachea and bronchi, deafness

**Treatment**: symptomatic care; enzyme replacement

---

**TABLE 23-1 Mucopolysaccharidoses (MPS)**

<table>
<thead>
<tr>
<th>Number</th>
<th>Syndrome Name</th>
<th>Enzyme Deficiency</th>
<th>Glycosaminoglycan Stored</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I (severe)</td>
<td>Hurler</td>
<td>α-L-iduronidase</td>
<td>Dermatan sulfate, heparan sulfate</td>
</tr>
<tr>
<td>MPS I (attenuated)</td>
<td>Scheie</td>
<td>α-L-iduronidase</td>
<td>Dermatan sulfate, heparan sulfate</td>
</tr>
<tr>
<td>MPS I (attenuated)</td>
<td>Hurler-Scheie</td>
<td>α-L-iduronidase</td>
<td>Dermatan sulfate, heparan sulfate</td>
</tr>
<tr>
<td>MPS II (severe)</td>
<td>Hunter (severe)</td>
<td>Iduronate sulfatase</td>
<td>Dermatan sulfate, heparan sulfate</td>
</tr>
<tr>
<td>MPS II (attenuated)</td>
<td>Hunter (mild)</td>
<td>Iduronate sulfatase</td>
<td>Dermatan sulfate, heparan sulfate</td>
</tr>
<tr>
<td>MPS III A</td>
<td>Sanfilippo A</td>
<td>Heparan N-sulfatase</td>
<td>Heparan sulfate</td>
</tr>
<tr>
<td>MPS III B</td>
<td>Sanfilippo B</td>
<td>α-N-acetyl-glucosaminidase</td>
<td>Heparan sulfate</td>
</tr>
<tr>
<td>MPS III C</td>
<td>Sanfilippo C</td>
<td>Acetyl CoA: α-glucosaminide acetyltransferase</td>
<td>Heparan sulfate</td>
</tr>
<tr>
<td>MPS III D</td>
<td>Sanfilippo D</td>
<td>N-acetylglucosamine sulfatase</td>
<td>Heparan sulfate</td>
</tr>
<tr>
<td>MPS IV A</td>
<td>Morquio, type A</td>
<td>Galactose-6-sulfatase</td>
<td>Keratan sulfate, chondroitin 6-sulfate</td>
</tr>
<tr>
<td>MPS IV B</td>
<td>Morquio, type B</td>
<td>β-glactosidase</td>
<td>Keratan sulfate</td>
</tr>
<tr>
<td>MPS VI</td>
<td>Maroteaux-Lamy</td>
<td>N-acetylgalactosamine 4-sulfatase (arylsulfatase B)</td>
<td>Dermatan sulfate</td>
</tr>
<tr>
<td>MPS VI</td>
<td>Sly</td>
<td>B-glucuronidase</td>
<td>Dermatan sulfate, heparin sulfate, chondroitin 4-, 6 sulfates</td>
</tr>
<tr>
<td>MPS IX</td>
<td></td>
<td>Hyaluronidase</td>
<td>Hyaluronan</td>
</tr>
</tbody>
</table>

**Hunter Syndrome (MPS II)**

- X-linked recessive
- Defect of iduronate 2-sulfatase
- Accumulation of heparan and dermatan sulfate
- Clinical findings
  - Type A: severe form, clinical features similar to MPS-IH
  - Type B: mild form, clinical features similar to MPS-IS, airway obstruction secondary to accumulation of mucopolysaccharide in the trachea and bronchi, deafness

**Sanfilippo Syndrome (MPS Type III)**

- Heparan-N-sulfatase deficiency
- Accumulation of heparan sulfate
DISORDERS OF AMINO ACID METABOLISM

Alkaptonuria/Ochronosis

- Autosomal recessive, chromosome 3q
- Deficient homogentisic acid oxidase (HGA), intermediate product of phenylalanine and tyrosine breakdown; excessive amounts of HGA are excreted in the urine and turn into a brown pigment on exposure to air causing the urine to appear dark
- Ochronosis is the connective tissue manifestation of alkaptonuria

In the body, polymerized HGA accumulates in connective tissues, such as the skin and cartilage resulting in pigmentation and degeneration
- HGA inhibits enzymes that are needed for the cross-linking of collagen fibers, which can result in degeneration of cartilage resulting in arthralgias
- Exogenous ochronosis: caused by medications such as quinacrine, carbolic acid, hydroquinone, phenol, resorcinol, picric acid, and antimalarials; metabolism of these medications results in an HGA polymer like substance that differs from the polymer found in alkaptonuria

Clinical findings
- Cutaneous: macular blue-gray pigmentation on face, sclera, pinna, nasal ala, papules, milia, and nodules
- Skeletal: narrowing of the joint spaces and disc calcifications, large joint arthropathy
- Cardiac: cardiac valve calcification, stenosis, coronary artery calcification
- Renal: stones
- Other: black cerumen and sweat, dark urine at pH > 7
- Exogenous ochronosis: no joint involvement

Diagnosis:
- Urinary homogentisic acid level
- Darkening of urine with NaOH
- Histology: ochronotic (yellow-brown) pigment in dermis, “yellow bananas,” and within macrophages, homogenization and swelling of collagen bundles
- Magnetic resonance imaging: thickened tendons, asymptomatic tears
- Echocardiogram and CT: coronary artery calcifications and cardiac valve defects
- Ultrasound and x-ray: renal stones

Treatment:
- Arthritis: analgesics, physical therapy
- Supplemental vitamin C
- Nitisinone (inhibits homogentisic acid production)
- Pigment changes persist

Phenylketonuria (PKU)

- Autosomal recessive
- Chromosome arm 12q
- Presents at birth
- Deficiency of phenylalanine hydroxylase, cofactor required for hydroxylation of tyrosine (a precursor of dopamine) and hydroxylation of tryptophan (a precursor of serotonin)

Clinical findings
- Toxic CNS effects
- Mental retardation, seizures, hyperreflexia, microcephaly, brain calcification, cataracts
Treatment: topical therapy, oral retinoids, low-phenylalanine/tyrosine diet can prevent skin and eye manifestations

DEPOSITION DISORDERS

Lipoid Proteinosis (Urbach-Wiethe Disease, Hyalinosis Cutis et Mucosae)

- Autosomal recessive
- Defect in extracellular matrix protein 1 (encoded by the ECM1 gene); ECM1 is known to inhibit bone mineralization, contribute to epidermal differentiation, and stimulate angiogenesis
- Accumulation of eosinophilic material composed of mucopolysaccharides, hyaluronic acid, neutral fat, lipids, and cholesterol
- Clinical findings
  - Cutaneous: patchy areas of alopecia may develop where hyaline deposits are present, early bullae formation on the face and distal extremities that heal with ice-pick scarring, infiltrated nodules on elbows, knees, and hands, skin becomes waxy, thickened, and yellow, beaded papules along the eyelid margins (moniliform blepharosis) (Fig. 23-3)
  - Oral cavity: cobblestone appearance to mucosa due to infiltrative papules on mucous membranes, large “wooden” tongue, parotiditis, dental anomalies
  - Neurologic: psychiatric symptoms due to calcification of the temporal lobes
  - Earliest sign: hoarse cry due to vocal cord infiltration and possible airway compromise

Homocystinuria

- Autosomal recessive
- Cystathionine β-synthetase deficiency, results in defect of methionine metabolism, and accumulation of homocystine
- Competitive inhibitor of tyrosinase
- Presents in early childhood
- Clinical findings
  - Cutaneous: malar flush, livedo reticularis, pale and pink skin: due to tyrosine deficiency, buccal skin shows red macules, hyperhidrosis, xerosis, and acrocyanosis, leg ulcers
  - Ocular: ectopia lentis with downward displacement, glaucoma
  - Vascular: cerebrovascular occlusions, deep venous thrombosis
  - Other: mental retardation, seizures, Marfanoid habitus
- Treatment: low methionine, high-cystine diet, pyridoxine (300 to 600 mg/day), folic acid, betaine, cyanocobalamin
- Course: death in third to fourth decade from vascular events

Richner-Hanhart Syndrome (Tyrosinemia II)

- Autosomal recessive
- Hepatic tyrosine aminotransferase (TAT) deficiency
- Tyrosinemia types I and III do not have skin involvement
- Clinical findings
  - Ocular: herpetiform corneal ulcers, photophobia, corneal clouding with central opacities, neovascularization, blindness
  - Cutaneous: focal or diffuse yellowish palmoplantar keratoderma, lesions associated with hyperhidrosis, bullae, hyperkeratotic plaques on elbows, knees in older patients
  - Other: mental retardation, seizures, self mutilation
- Diagnosis: plasma amino acid and urine organic acid levels of tyrosine are elevated; urinary tyrosine metabolite levels are elevated
- Treatment: low methionine, high-cystine diet, pyridoxine (300 to 600 mg/day), folic acid, betaine, cyanocobalamin
-Course: death in third to fourth decade from vascular events
Diagnosis: CT or x-ray: hippocampal “bean-shaped” calcifications

Histology: deposition of amorphous eosinophilic material at the dermal-epidermal junction, perivascularly and along adnexal epithelia. Hyaline material, PAS (+) and diastase resistant found perpendicularly to the basement membrane. Arranged in “onion skin” layers around blood vessels; cytoplasmic vacuoles in dermal fibroblasts

Treatment: oral dimethylsulfoxide, retinoids may be helpful, CO2 laser for skin lesions, vocal cord lesions and eyelid papules

Course: chronic course

Wilson Disease (Hepatolenticular Degeneration)

Autosomal recessive

Defect of ATP7B gene: copper-transporting adenosine triphosphatase (ATPase) in the liver

Excessive absorption of copper from the small intestine

Decreased excretion of copper by the liver; decreased serum ceruloplasmin and increased copper in the liver

Seen in childhood to adulthood

Diagnostic criteria: seven criteria, including; (1) presence of Kayser-Fleischer (KS) rings; (2) typical neurological symptoms; (3) decreased serum ceruloplasmin concentration; (4) Coombs’ negative hemolytic anemia; (5) elevated urinary copper excretion; (6) high liver copper value in the absence of cholestasis; and (7) mutational findings

Clinical findings
- Copper accumulates in liver, brain, and cornea
- Hepatic: hepatomegaly, cirrhosis
- Ocular: Kayser-Fleischer ring: deposition of copper in Descemet membrane of cornea
- Cutaneous: pretibial hyperpigmentation, blue lunulae, jaundice, varices, spider angiomas, and palmar erythema
- Other: dysarthria, ataxia, dementia

Diagnosis: low serum ceruloplasmin (copper carrier) levels, total serum copper levels are low and serum free-copper levels are elevated

Treatment:
- D-Penicillamine (risk of EPS), copper chelators, liver transplant, decreased copper intake
- Symptoms reverse (except CNS) with early treatment

Amyloidosis

- Insoluble protein (misfolded plasma protein) fibrils accumulate extracellularly
- Up to 24 different proteins have been recognized; all share a common core structure that consists of a cross β core and polypeptide chains (Table 23-2)

Diagnosis
- Typing of systemic amyloidoses with refined immunohistochemical analysis and genetic testing
- Systemic amyloidosis: histologic demonstration of amyloidosis within an organ; in AL amyloidosis fine needle aspiration of abdominal fat can substitute for histological demonstration of amyloidosis
- Histology: eosinophilic, amorphous, fissured masses of amyloid in dermis and subcutaneous tissue, extravasated red blood cells, no lymph, intradermal bullae around blood vessels; amyloid rings (amyloid around individual fat cells)

- Stains:
  - Congo red (brick red, apple-green birefringence)
  - Crystal violet (metachromasia [red])
  - Methyl violet (metachromasia)
  - PAS+ and diastase-resistant
  - Indirect immunofluoresence: differentiates AA/AL
  - Bone marrow: 10% plasma cells (40% of patients)
  - Bence-Jones protein: monoclonal Ig light chain 90% in serum or urine

- Immunoelectrophoresis: monoclonal protein
- Electron microscopy: regular fibrillar structure
- X-ray diffraction: β-pleated sheet structure

Hemochromatosis

Autosomal recessive

Mutations in the HFE gene; chromosome 6

Hereditary hemochromatosis (HH) comprises a group of inherited disorders of iron metabolism that can result in progressive iron overload, morbidity, and mortality

- Increased iron absorption with solid-organ iron deposition
- Presents in fifth decade

Clinical findings
- Cutaneous: diffuse gray hyperpigmentation, sparse hair, koilonychia
- Hepatic: hepatomegaly, cirrhosis, fibrosis, hepatocellular carcinoma
- Cardiac: cardiac failure, arrhythmias
- Other: diabetes, hypogonadism, polyarthritis

Diagnosis: fasting serum transferrin saturation and ferritin levels elevated, serum iron levels increased, liver biopsy (fibrosis, cirrhosis)

Treatment: serial phlebotomy, deferoxamine, supportive care of diabetes, arrhythmias

Course: premature death owing to hepatic failure, hepatocellular carcinoma, heart disease
### Table 23-2 Classification of Amyloidoses

<table>
<thead>
<tr>
<th>Amyloid Protein</th>
<th>Precursor</th>
<th>Systemic (S) or Localized (L)</th>
<th>Syndrome or Involved Tissue</th>
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<td>L</td>
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<td>Lactadherin</td>
<td>L</td>
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<td>L</td>
<td>Cornea; familial</td>
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**Systemic Amyloidosis**
- Fibril protein and related diseases
  - A amyloidosis protein (AA)
    - Formed by N-terminal proteolytic fragments of the acute-phase reactant serum amyloid A (SAA), a polymorphic apolipoprotein of high density lipoproteins (HDL)
    - SAA is an acute-phase protein that increases secondary to chronic inflammatory stimuli (i.e., inflammatory arthritis, leprosy, osteomyelitis, tuberculosis, familial Mediterranean fever, Hodgkin disease, renal cell carcinoma)
  - Clinical findings
    - Cutaneous: no skin findings
    - Renal: proteinuria, nephrotic syndrome and progressive development of renal insufficiency
    - Gastrointestinal: constipation, diarrhea and malabsorption
  - Treatment: colchicine (to prevent AA amyloidosis in familial Mediterranean fever), treat primary inflammatory condition

**AMYLOID LIGHT CHAIN (AL)**
- Primary systemic
- Formed by the N-terminal fragment of a monoclonal immunoglobulin light chain, comprising the variable region and a portion of the constant region, produced by a bone marrow plasma cell clone
- Clinical findings
  - Almost any organ can be involved; multiple organ dysfunction is common
  - Renal: nephrotic syndrome with peripheral edema
  - Cardiac: restrictive cardiomyopathy, arrhythmias
  - Neurological: neuropathies, carpal tunnel (17%)
  - Mucocutaneous: petechiae, soft tissues enlargement, papules, plaques, macroglossia, ecchymoses, pinch purpura (post-traumatic hemorrhage around orbits, umbilicus, axillae, perianal) (Fig. 23-4)
  - Hepatic: hepatosplenomegaly
  - Gastrointestinal: bleeding, weight loss

**HEREDITARY AMYLOIDOSIS**
- Autosomal dominant
- Heterogenous group of diseases associated with mutations in apoliporoteins A1 and A2, fibrinogen A α chain, gelsolin, lysozyme, cystatin C
- Clinical findings depend on the variant protein: deposits primarily in the peripheral nerves, heart, gastrointestinal tract, and vitreous of eyes
- Transthyretin (TTR); familial amyloid polyneuropathy

**DIALYSIS-RELATED AMYLOIDOSIS (DRA)**
- β-2 Microglobulin (Ab2m) protein accumulates in the serum
- Clinical findings: carpal tunnel syndrome, arthropathies, spondyloarthropathies, bone cysts, visceral amyloid deposition (heart, gastrointestinal tract: macroglossia, bowel infarction and perforation; lungs)

**Localized Cutaneous AL Amyloid**
- Local production of fibril precursors derived from N-terminal cleavage fragments of monoclonal immunoglobulin light chains
- Localized to skin
- Deposition of AL protein
- One or several nodules on legs/face (Fig. 23-5)
- Histology: atrophic epidermis, masses of amyloid dermis, subcutaneous fat, appears as “cracks in mud,” lymphocyttoplasmic infiltrate, Russell bodies: round hyaline, eosinophilic bodies inside/outside of plasma cells (with Ig), foreign-body giant cells
- Treatment: surgical excision, CO₂ laser
- Course: may develop systemic amyloidosis
Chapter 23    CUTANEOUS MANIFESTATIONS OF METABOLIC DISEASES

Senile/neuritic plaques: neurofibrillary tangles, vascular lesions
Due to β amyloid = major fibril protein
Amyloid precursor protein (APP)
No skin lesions

XANTHOMAS

- Accumulations of lipid-laden macrophages; arise due to lipoprotein disorders
- Lipoproteins: lipids transported in plasma as complexes with specific apoproteins
- Lipoproteins: may be classified according to their buoyant density:
  - Chylomicrons: triglycerides (TG) that are incorporated into lipoproteins
  - Very low density lipoproteins (VLDLs): hepatic derived triglyceride-rich lipoproteins (contain less TG and more cholesterol compared to chylomicrons)
  - Intermediate-density lipoproteins (IDLs)
  - Low-density lipoproteins (LDLs): mainly contain cholesterol
  - High-density lipoproteins (HDLs): take up free cholesterol from peripheral tissue

Phenotypic Classification of Hyperlipidemias (Table 23-3)

- Familial chylomicronemia syndrome (Frederickson type I hyperlipidemia)
  - Familial lipoprotein lipase deficiency: results in chylomicrons containing triglycerides that accumulate in the serum
  - Clinical findings
    - Cutaneous: eruptive xanthomas located over the buttocks, shoulders and extensor surfaces
    - Also associated with pancreatitis and lipemia retinalis
  - Laboratory: elevated triglycerides
  - Treatment: diet modification
- Apolipoprotein-C2 deficiency
  - Apo-C2 carried on triglyceride-rich lipoproteins and activates LPL (without LPL, chylomicrons are not degraded)
  - Clinical findings: eruptive xanthomata
  - Treatment: diet modification
- Hypercholesterolemia (Frederickson type II hyperlipidemia)
  - Familial homozygous hypercholesterolemia
  - Genetic deficiency of LDL receptors (remove LDL from the circulation)
  - Clinical findings:
    - Cutaneous: tendinous, tuberous, subperiosteal xanthomas, and xanthomatous plaques, as well as xanthelasmas

MACULAR AND LICHEN AMYLOIDOSIS

- Due to altered keratin; amyloid deposits bind to anti-keratin antibodies
- Usually idiopathic or friction related; also associated with connective tissue diseases (i.e., systemic lupus erythematosus)

Macular Amyloidosis

- Affects the upper back and limbs
- May result from constant scratching
- Clinical findings: pruritic brown-gray, reticulated, rippled, macules/patches mainly on upper back, notalgia paresthetica, some postinflammatory hyperpigmentation
- Diagnosis: direct immunofluorescence: IgM, C3, Ig, light chains
  - Histology: amyloid deposits in papillary dermis, globular, colloid deposition in dermis; do not involve blood vessels or adnexal structures
  - Lichen amyloidosis

- Clinical findings: closely set, discrete brown-red papules, pruritic; commonly on the legs
- Diagnosis: histology similar to macular amyloidosis but with irregular acanthosis
- Treatment: topical steroids, intralesional steroids, Dimethyl sulfoxide (DMSO), calcineurin inhibitors, PUVA, dermabrasion, acitretin

SENILE AMYLOIDOSIS

- Associated with Alzheimer disease

Multifactorial hyperlipidemias
- Familial hypertriglyceridemia (Frederickson type IV hyperlipidemia)
  - Liver overproduces VLDL and LDL
  - Xanthomas rare
  - Treatment: low fat diet, fibric acid
- Familial hypertriglyceridemia (Frederickson type V hyperlipidemia)
  - Combined elevations in levels of chylomicrons and VLDL
  - Clinical findings
    - Cutaneous: eruptive xanthomas
  - Other: pancreatitis
  - Treatment: low fat diet, fibric acids, weight reduction

### Types of Cutaneous Xanthomas

- Xanthelasma palpebrarum (Fig. 23-6)
  - Most common of the xanthomas
  - Fifty-five percent of the patients may have hyperlipidemia
  - Clinical: symmetric soft, velvety, yellow, flat, polygonal papules around the eyelids
  - Treatment: trichloroacetic acid, surgical excision, cryotherapy, ablative laser treatment
- Tuberous xanthomas (Fig. 23-7)
Oral cavity of adults as a single papillomatous yellow lesion
Reactive condition with benign behavior
Histology: vacuolated macrophages filled with lipid (foamy macrophages); lipids dissolved and removed from the tissue during histologic processing; multinucleated histiocytes (Touton giant cells)
Treatment: local excision, topical trichloroacetic acid, electrodesiccation, laser therapy
Prognosis: recurrences can occur

DIABETES-ASSOCIATED DISEASES

Acanthosis Nigricans
- Marker of insulin resistance
- Excessive amounts of circulating insulin bind with insulin-like growth factor receptors on keratinocytes and dermal fibroblasts; increased proliferation of keratinocytes and fibroblasts
- Activation of tyrosine kinase receptors expressed on basal cells of the epidermis
- Fibroblast growth factor receptor 3 (FGFR3) mutations
- Exert antiapoptotic and mitogenic effects on keratinocytes

Firm, painless, red-yellow nodules
Can coalesce to form multilobulated tumors
Develop in pressure areas, such as the extensor surfaces of the knees, the elbows, and the buttocks

**Tendinous xanthomas**
- Subcutaneous nodules related to the tendons or the ligaments
- Most common locations are the extensor tendons of the hands, the feet, and the Achilles tendons
- Often related to trauma

**Eruptive xanthomas**
- Crops of small, red-yellow papules on an erythematous base, pruritus is common
- Most commonly arise over the buttocks, the shoulders, and the extensor surfaces of the extremities
- May resolve spontaneously over weeks

**Planar xanthomas**
- Yellow macules, soft papules
- Palmar crease (xanthoma striatum palmare), eyelids (xanthelasma palpebrarum)
- Generalized plane xanthomas: cover large areas of the face, neck, thorax, and flexures
- May be associated with monoclonal gammopathy

**Xanthoma disseminatum**
- Occur in normolipemic patients
- Red-yellow papules and nodules with a predilection for the flexures
- Mucosa of the upper part of the aerodigestive tract is involved
- Usually resolves spontaneously

**Verruciform xanthoma**
- Occurs in normolipemic patients
• Associated conditions:
  - Obesity: most common type; patients have higher fasting plasma insulin levels compared to control subjects
  - Syndromic
    - Insulin resistance
    - Type A syndrome: reduced number or dysfunction of insulin receptors, related to obesity
  - Hyperandrogenemia, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome
  - Polycystic ovaries or signs of virilization (hirsutism, clitoromegaly), high risk of developing diabetes
    - Type B syndrome: due to antibodies directed against the insulin receptor: uncontrolled diabetes mellitus, ovarian hyperandrogenism, or an autoimmune disease (SLE)
  - Examples of other associated syndromes and diseases: Cushing syndrome, connective tissue diseases (lupus erythematosus, scleroderma, dermatomyositis), hypothyroidism
  - Genetic benign
    - Autosomal dominant
    - May develop at birth or during childhood; progresses until puberty, then stabilizes or regresses
  - Drug-induced: nicotinic acid, systemic corticosteroids, oral contraceptives
  - Malignant: most commonly adenocarcinoma of gastrointestinal tract
• Clinical findings
  - Symmetric, hyperpigmented, velvety plaques with accentuation of skin markings (Fig. 23-8)
  - Develop in flexures, such as axillae, groin, and posterior neck
  - Acrochordons (skin tags) often are found
  - Tripe palms
    - Thickening of the palms with accentuation of the ridges and furrows; thought to exist as a form of palmar acanthosis nigricans
    - Associated with acanthosis nigricans (75%)
    - Associated with cancer; pulmonary carcinoma is the most common, followed by lung
• Diagnosis:
  - Laboratory findings: for patients with syndromic AN-glucose tolerance test; total testosterone, dehydroepiandrosterone sulfate (DHEA-S), gonadotropic concentrations, cortisol levels
  - Histology: hyperkeratosis, papillomatosis, and slight irregular acanthosis with minimal or no hyperpigmentation; the dermal papillae project upward as finger-like projections
• Treatment: correct the underlying disease, topical tretinoin, vitamin D3 analogs

Necrobiosis Lipoidica Diabeticorum (NLD) (Fig. 23-9)
• Degenerative disease of collagen in the dermis and subcutaneous fat
• Diabetics account for 14–65% of all cases; it occurs in 0.03% of diabetics
• Clinical findings:

![Figure 23-8 Acanthosis nigricans. (Courtesy of Dr. Asra Ali.)](image)

![Figure 23-9 Necrobiosis lipoidica diabeticorum. (Reproduced with permission from Wolff et al: Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)](image)
• Well-circumscribed, symmetric, oval or irregularly shaped indurated plaques with central atrophy, yellow pigmentation, and telangiectatic vessels on pretibial areas, periphery of lesions have red-brown or violaceous pigmentation
• Koebner phenomenon present; decreased pinprick sensation
• Lesions are typically multiple and bilateral and may ulcerate

Diagnosis
• Histology: neutrophilic vasculitis; granulomas are arranged in a tierlike fashion and are admixed with areas of collagen degeneration, thickening of the blood vessel walls; immune complex vasculitis
• Direct immunofluorescence: immunoglobulin M, immunoglobulin A, C3, and fibrinogen in the blood vessels
• Serum: increased fibronectin, factor VIII-related antigen, α2 macroglobulin
• Treatment: topical and intralesional steroids, antiplatelet aggregation therapy with aspirin and dipyridamole; niacinamide, excision and grafting
• Prognosis: progression of lesion does not correlate with glycemic level, course is indolent, spontaneous remission in less than 20% of patients

Diabetic Dermopathy
• Most common cutaneous finding in diabetes
• Clinical findings:
  • Round to oval atrophic hyperpigmented lesions on the pretibial areas of the lower extremities; sites of trauma
  • Brownish hyperpigmentation hemosiderin deposits
• Histology: edema of the papillary dermis, thickened superficial blood vessels, extravasation of erythrocytes, mild lymphocytic infiltrate
• Course: resolves spontaneously

Bullous Diabeticorum
• Confined to the extremities
• Occurs spontaneously; noninflammatory
• Types
  • Sterile with fluid: heals without scarring; histology shows intraepidermal cleavage without acantholysis
  • Hemorrhagic: heals with scarring, histology shows cleavage below the dermal-epidermal junction, destruction of anchoring fibrils
  • Multiple nonscarring bullae: sun-exposed areas, histology: cleavage at lamina lucida
• Prognosis: runs a benign course

Diabetic Ulcers
• Ischemic ulcers
• Neuropathic ulcers in patients with diminished sensation, especially on areas of pressure sites; presents with a keratotic rim

Acquired Perforating Dermatosis
• Seen in patients with kidney failure associated with diabetes
• Kyrle disease (acquired perforating dermatosis): papules with a keratotic plug due to elimination of collagen and elastin, seen on the extensor surfaces of the lower extremities; histology shows hyperkeratosis surrounding a plug of degenerated material

GLUCAGONOMA SYNDROME
• Caused by glucagon-secreting tumors of the alpha cells of the pancreas, slow growing
• Associated with: hyperglucagonemia, diabetes mellitus, hypoaminoacidemia, cheilosis, normochromic, normocytic anemia, venous thrombosis, neuropsychiatric features
• Mucocutaneous findings: necrolytic migratory erythema (NME), predilection for the perineum, buttocks, groin, lower abdomen, and lower extremities; annular erythematous patches with blisters that erode, atrophic glossitis, cheilosis, dystrophic nails, and buccal mucosal inflammation
• Prognosis: 50% of tumors are metastatic at the time of diagnosis

Carotenemia
• Associated with ingestion of yellow and green vegetables
• Slow conversion of beta-carotene (provitamin A) to vitamin A
• Accelerated by thyroxine and hyperthyroidism
• Conversion occurs in the mucosal cells of the small intestine
• Clinical findings: carotenoderma: yellow/orange color of skin, greatest concentration is in areas with increased sweating (nasolabial folds, forehead); lipophilic: may take months before color of skin returns to normal, sclera and mucous membranes are spared (unlike jaundice)
• Diagnosis: carotene excreted in the stool, skin, and urine

THYROID DERMOPATHY
• Associated with Graves disease (0.5–4%)
• Stimulatory autoantibodies directed at the TSH receptor are the cause of hyperthyroidism
OSTEOMA CUTIS

- Presence of bone within the skin in the absence of a preexisting or associated lesion
- Associated with:
  - Fibrodysplasia ossificans progressive: AD; R206H mutation, endochondral, deep bone formation, early mortality
  - Albright hereditary osteodystrophy: GNAS 1 mutations (adenylate cyclase), complex inheritance
  - Pseudohypoparathyroidism and pseudopseudohypoparathyroidism, short stature, round face, defective teeth, mental retardation, brachydactyly (short fourth metacarpals and metatarsals), tetany in patients with hypocalcemia, osteomas of the soft tissue and skin (intramembranous), miliary osteomas of the face, following acne, neurotic excoriation; milia-like ossification of syringomas in Down syndrome, progressive osseous heteroplasia, intramembranous ossification, asymptomatic papules/nodules; “rice-grain” texture
- Plate-like osteoma cutis: limited form of POH
- Secondary types: cutaneous ossification can also occur by metaplastic reaction to inflammatory, traumatic, and neoplastic processes

Diagnosis
- Laboratory tests: serum calcium and parathyroid hormone (PTH) for hypoparathyroidism and pseudohypoparathyroidism
- Excisional biopsy
- Treatment: excision or laser resurfacing; tretinoin for miliary osteomas

NPHROGENIC SYSTEMIC FIBROSIS

- Idiopathic acquired fibrosing disorder
- Pathogenesis is unknown, most likely multifactorial. Most common factor is the presence of acute or chronic renal insufficiency. Also seen in renal insufficiency patients receiving gadolinium dye for MR-angiography
- Clinical findings
  - Symmetric, indurated plaques with brawny hyperpigmentation; may also present with distinct papules and subcutaneous nodules, extremities more commonly affected than trunk; face usually spared, joint contractures with pain may be present; yellow plaques in sclera; fibrosis of heart, lungs, and skeletal muscle
- Diagnosis
  - Histology: thickened collagen bundles with surrounding clefts, mucin deposition, proliferation of fibroblasts and elastic fibers

Graves disease is characterized by goiter, increased perspiration, heat intolerance, tachycardia, and exophthalmos
- Cutaneous: warm and moist skin, with smooth texture; thin scalp hair, nails are thin, soft and friable with possible onycholysis with an upward curvature (plummer’s nail); hyperpigmentation of the skin (diffuse or local)
- Pretibial myxedema (PTM) (Fig. 23-10): due to deposition of hyaluronic acid in the dermis and subcutis; lateral or anterior aspect of the legs with pink to purple-brown bilateral, firm, nonpitting, asymmetric plaques or nodules, peau d’orange texture. IgG antibodies directed at the thyroid stimulating hormone receptor (TSHR-Ab) are present in 80% of patients, elephantiasic form presents with verruciform plaques
- Diagnosis
  - Histology: hyperkeratosis, mucin (glycosaminoglycans) in the reticular dermis, and a Grenz zone of relatively normal papillary dermis; stains blue with Alcian blue, at a pH of 2.5, and colloidal iron stains; metachromasia with toluidine blue stain
  - Laboratory tests: serum thyroid function tests, thyroid-stimulating immunoglobulins
- Treatment: pretibial myxedema: topical or intral- esional corticosteroids; plasmapheresis; octreotide

**FIGURE 23-10**
HYPOPARATHYROIDISM/
PSEUDOHYPOPARATHYROIDISM

- Hypoparathyroidism can result from surgery, infiltrative disorders, autoimmune conditions, or may be idiopathic
- Pseudohypoparathyroidism is a heritable disorder of target organ unresponsiveness to parathyroid hormone
- Cutaneous findings: xerosis, hyperkeratosis, brittle nails, transverse ridging, coarse and sparse hair, eczematous dermatitis, Albright hereditary osteodystrophy (short neck, brachydactyly, subcutaneous ossifications)

CUSHING SYNDROME

- Results from chronic glucocorticoid excess, caused mainly by pituitary hypersecretion of adrenocorticotrophic hormone (ACTH) or by non-pituitary tumors, adrenal hypersecretion of hyperinsulinism or exogenous administration of corticosteroids
- Clinical findings: progressive central (centripetal) obesity, fat deposition in the cheeks resulting in moon facies
- Cutaneous: atrophic skin, loss of subcutaneous tissue, easy bruising, striae densae (violaceous, >1 cm) commonly seen on upper arms, shoulders, axillae, breasts, hips, buttocks and upper thighs; hyperpigmentation may be generalized, most evident in areas exposed to light; vellus hair on forehead and cheeks; if androgen excess is present then hirsutism, oily facial skin, and acneiform rashes may occur
- Diagnosis: 24-hour urinary free cortisol (UFC), serum ACTH to define the source (low: adrenal, normal to high: pituitary; very high: ectopic)
- Treatment: dependent on the cause. Surgery for pituitary, adrenal, or ectopic tumors with possible radiation or chemotherapy; medications that inhibit steroid synthesis

ADDISON DISEASE

- Most common cause of chronic primary adrenal insufficiency due to autoimmune adrenalitis
- Other etiologies: infection, hemorrhage, neoplasia
- Clinical findings
  - Cutaneous: generalized hyperpigmentation due to increased melanin content in the skin, due to the melanocyte-stimulating activity of high plasma
QUIZ

4. The rate-limiting enzyme in heme biosynthesis is:
   A. Porphobilinogen deaminase
   B. Ferrochelatase
   C. ALA synthase
   D. Uroporphyrinogen decarboxylase
   E. Protoporphyrinogen oxidase

5. A 30-year-old Caucasian man presents with scarring and blisters over his dorsal hands, tachycardia, and occasional constipation. What test would be most useful in confirming a diagnosis of variegate porphyria?
   A. Normal urine
   B. Plasma fluorescence at 626 nm
   C. Uroporphyrinogen/coproporphyrinogen ratio 8:1
   D. Fecal coproporphyrin > protoporphyrin
   E. Urine fluorescence at 626 nm

6. Which of the following diseases is LEAST likely to be diagnosed via 24-hour urine porphyrin collection?
   A. Porphyria cutanea tarda
   B. Erythropoietic protoporphyria
   C. Erythropoietic porphyria
   D. Hereditary coproporphyria
   E. Hepatoerythropoietic porphyria

7. A 30-year-old man presents with recent onset of arthralgias, darkening pigmentation on his face, and darkening of his urine. He most likely has a defect in which enzyme?
   A. Cystathione β synthetase
   B. Tyrosinase
   C. Homogentisic acid oxidase
   D. Ferrochelatase
   E. α-galactosidase

8. A 45-year-old man with hepatitis C and severe anemia develops blisters over the dorsum of his hands and significant elevation of his urine uroporphyrinogen. The BEST treatment for this patient would be:
   A. Phlebotomy twice weekly
   B. Hydroxychloroquine orally twice daily
   C. Hydroxychloroquine orally twice weekly
   D. Stem cell transplant
   E. Topical metronidazole
9. Development of herpetiform corneal ulcers, pal- 
mo-plantar keratoderma, and painful acral lesions 
is most closely related to the metabolism of which 
amin acid? 
A. Tyrosine  
B. Glycine  
C. Arginine  
D. Histidine  
E. Leucine

10. Which of the following is most likely to involve 
deposition of a keratin derived substance on 
the legs? 
A. Nodular amyloid  
B. Macular amyloid  
C. Lichen amyloid  
D. Familial mediterranean fever  
E. Beta-2-microglobulin derived amyloid

**Answers**

1. C. Necrobiosis lipoidica diabeticorum may be 
seen in 0.3% of diabetics, most commonly type 1. 
Clinical presentation generally consists of yel-
low atrophic plaques on both lower extremities. 
Pathology classically demonstrates a granuloma-
tous dermatitis with “layered” appearance.

2. D. Fibrodysplasia ossificans progressive is a genetic 
disorder resulting in deep, endochondral bony 
deposits with early mortality.

3. A. Kyrle disease (acquired perforating dermatosis) 
is most commonly found on the legs of diabetic 
patients requiring dialysis.

4. C. The condensation of glycine and succinyl CoA 
by ALA synthase in the mitochondria is the rate 
limiting step.

5. B. Variegate porphyria and PCT may have simi-
lar cutaneous findings, with variegate porphyria 
more likely to have acute abdominal findings. VP 
patients have a characteristic plasma fluorescence 
at 626 nm and fecal proto > copro. PCT would have 
a uro/copro ratio of 8:1.

6. B. EPP, a deficiency in ferrochelatase, has charac-
teristically normal urine on exam. Stool and blood 
protoporphyrin levels will be abnormal.

7. C. Alkaptonuria, a defect in homgentisic acid ox-
idase, may present in childhood or adulthood. 
Children classically present with black urine (if 
pH > 7); adults tend to have more joint disease 
and skin darkening. Treatment is supplemental 
vitamin C.

8. C. PCT is best treated with serial phlebotomy. In a 
patient with severe anemia, however, phlebotomy 
is contraindicated. Second-line treatment may 
include low dose antimalarials.

9. A. Richner-Hanhart syndrome is an example of a 
tyrosinemia with a defect in hepatic tyrosine ami-
notransferase. Treatment is with a low phenylala-
nine and tyrosine diet.

10. C. Lichen amyloidosus is a deposition of keratin-
derived amyloid most commonly found on the legs. 
Macular amyloid, while also keratin-derived, is 
most commonly found on the upper back. Familial 
Mediterranean fever is related to AA protein. Beta-
2-microglobulin amyloid is a hemodialysis associ-
ated protein that accumulates in end organs.

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BASIC PHARMACOLOGIC PRINCIPLES

- Pharmacokinetics: includes the extent and rate of absorption, distribution, metabolism and excretion (ADME) of medications in the body.
- Pharmacodynamics: defined as the effects of medications on the body (biochemical and physiological)

Concepts of Adverse Effects

- Toxicity: excessive doses or drug levels leading to undesired effects
- Pharmacologic effect: normal drug levels resulting in positive or negative effects
- Adverse effect (side effect): harmful and undesired effect resulting from a medication
- Idiosyncratic reaction (type B reaction): drug reaction which occurs rarely and unpredictably

SYSTEMIC MEDICATIONS

Glucocorticosteroids

- Pharmacology
  - Cortisol binding globulin (CBG, transcortin) binds 90–95% of plasma cortisol; the free fraction is the active form; CBG is increased by pregnancy, estrogen treatment, and hyperthyroidism
  - Short acting: cortisone and hydrocortisone; mineralcorticoid potency > glucocorticoid potency, with cortisone having the lowest glucocorticoid potency
  - Intermediate acting: prednisone, prednisolone, methylprednisolone, and triamcinolone; glucocorticoid potency > mineralcorticoid potency
- Long acting: dexamethasone and betamethasone; glucocorticoid potency only no mineralcorticoid potency
- Mechanism of action
  - Binds to cytosolic receptor, translocates to nucleus, and then binds to glucocorticoid response elements (GRE) on DNA
  - Corticosteroids (CS) reduce the effects of transcription factors that increase the inflammatory response: AP-1 (composed of Jun, Fos or activating transcription factor) and NF-κB (nuclear factor-κB)
  - Decreased synthesis of proinflammatory molecules: cytokines, interleukins, adhesion molecules, growth factors, and proteases
  - CS induced apoptosis in lymphocytes and eosinophils
- Metabolic effects: increased blood glucose secondary to gluconeogenesis
- Glucocorticoid effects: increased appetite
- Mineralocorticoid effects: increased sodium retention due to vasoconstriction; results in hypertension and congestive heart failure in susceptible patients; hypokalemia, increased lipids, Cushingoid change, protein catabolism (except in liver), leading to negative nitrogen balance, increase plasma fatty acids and ketone body formation via increased lipolysis and decreased glucose uptake into fat cells, decrease plasma adrenocorticotropic hormone (ACTH), decrease fibroblasts production of collagen
- Gastrointestinal effects: increased gastric acid and pepsin secretion, peptic ulcer disease, fatty liver changes, esophageal reflux, nausea and vomiting
- Skeletal effects: osteoporosis, osteonecrosis
- Ocular effects: posterior subcapsular cataracts
• **Pulmonary effects**: increase surfactant production in fetal lungs
• **Psychiatric effects**: euphoria, psychoses
• **Cutaneous effects**: telogen effluvium, hirsutism, fat atrophy, acne, increased infection risk, poor wound healing
• **Other effects**: myopathy, pancreatitis, adrenal suppression
• Adverse effects may be reduced by alternate day dosing except for risk of osteoporosis, osteonecrosis, and cataracts
• Interval between doses decreases chance of hypothalamic, pituitary, adrenal (HPA) axis suppression compared to actual dose of steroids
• Pregnancy category C

**Sulfones and Sulfonamides**

• The enzyme dihydropteroate synthase is the target of sulfonamide drugs, which are used extensively in the control of many infections
• Sulfonamides (antimicrobial agents) and sulfones (anti-inflammatory agents) differ in chemical structures and uses

**Dapsone**

• Sulfone derivative
  • **Mechanism of action**
    - Inhibits neutrophil myeloperoxidase and impairs neutrophil chemotaxis, by inhibiting neutrophil adhesion to vascular endothelium integrins
    - Competitive antagonist of dihydropteroate synthetases (causes reduction of folic acid)
  • **Metabolism**: acetylation (by N-acetyltransferase) and hydroxylation occur in the liver
• **Adverse effects**
  - N-hydroxylation of dapsone occurs by P-450 in the liver. The metabolic products are responsible for the hematologic effects of dapsone: methemoglobinemia and hemolytic anemia
  - Dapsone hypersensitivity/mononucleoside-like syndrome: hepatitis, photosensitivity, agranulocytosis (first 3–12 weeks); lupus erythematosus, hypoalbuminemia, fever, hypothyroidism
  - Hemolytic anemia and hemolysis: glucose-6 phosphate dehydrogenase (G6PD) deficient patients are more susceptible
  - Methemoglobinemia: dose-related hemolysis in patients with methemoglobin reductase deficiency; treat with methylene blue (not effective in G6PD deficient patients) or cimetidine
• **Idiosyncratic effects**:
  - **Hematologic**: leukopenia, agranulocytosis (occurs within first 12 weeks)
  - **Hepatic**: hepatitis, cholestatic jaundice, hypoalbuminemia
  - **Neurologic**: peripheral neuropathy (predominantly motor; however, sensory defects can occur), usually reversible; psychosis
  - **Cutaneous**: toxic epidermal necrolysis, morbilliform rash, exfoliative erythroderma
  - **Gastrointestinal**: gastric irritation, anorexia
• **Laboratory studies**
  - **Initial baseline**:
    ▲ Complete blood counts, liver function tests, renal function tests, urinalysis, glucose-6 phosphate dehydrogenase (G6PD) level
  - **Monitor**:
    ▲ Complete blood counts (CBCs), recommended weekly to biweekly for first month of therapy and monthly to bimonthly thereafter for the next 5 months
    ▲ Liver function tests every 3 months
• **Interactions with other medications**
  - **May inhibit anti-inflammatory effects of clofazimine**
  - **Probenecid and folic acid antagonists increase dapsone toxicity**
  - **Trimethoprim/sulfamethoxazole taken with dapsone may increase toxicity of both drugs**
  - **Rifampin, para-amino benzoic acid and activated charcoal may decrease absorption.**
  - **Contraindications**: documented hypersensitivity; known G6PD deficiency or methemoglobin reductase deficiency
• Pregnancy category C

**Sulfasalazine**

• Mechanism of action: unknown; inhibits neutrophil chemotaxis
• **Adverse effects**: gastrointestinal upset, fatigue, headache, drug eruption and photosensitivity; slow acetylators are prone to toxicity, agranulocytosis (within first three months of therapy)
• Pregnancy category B

**Aminoquinolones**

**Hydroxychloroquine/Chloroquine/Quinacrine**

• **Mechanism of action**
  - Inhibits chemotaxis of eosinophils and neutrophils, impairs antigen-antibody complex formation, inhibits release of interleukin 2 (IL-2) from CD4+ T cells, decreases lysosomal size
• **Adverse effects**
  - **Crosses placenta and may cause ocular, CNS, or ototoxicity in fetus; do not use in breast-feeding mothers**
  - **Ocular toxicity**: reversible premaculopathy and irreversible true retinopathy; only
hydroxychloroquine and chloroquine are associated; risk is greatest with chloroquine, corneal deposition (results in halos), blurred vision, photophobia
- **Hemolytic anemia** in patients with G6PD deficiency
- **Mucocutaneous effects:** blue/gray mucocutaneous pigmentation and transverse bands in nailbeds due to hemosiderin and melanin; quinacrine may cause yellow pigmentation; progressive bleaching of hair roots with chloroquine
- **Worsening of psoriasis,** mainly chloroquine
- **Gastrointestinal:** nausea and vomiting
- **Neuromuscular:** headache, psychosis, muscular weakness
- **Eye studies**: Slit lamp and fundoscopic eye exam, visual field test
- **Laboratory tests:**
  - CBC, G6PD, chemistry panel
  - Monitor: eye exam every 6 months, labs (as above) every three months, then every four to six months.
- **Interactions with other medications:**
  - Cimetidine may increase serum levels of chloroquine
  - Digoxin levels may be elevated
  - Magnesium trisilicate may decrease absorption of 4-aminoquinolones
- **Antimalarial contraindications:**
  - **Absolute:** hypersensitivity to the medication
  - **Relative:** pregnancy, lactation, severe blood dyscrasia, significant hepatic dysfunction, significant neurologic disorder, retinal or visual field changes, psoriasis
- **Pregnancy category C**

### Antimetabolic and Cytotoxic Agents

- **Antimetabolites:** mimic natural molecules and are most active while DNA is being synthesized in the S phase
  - Require a target-cell population that is proliferating in order to exert their effect
  - Side effects are most prominent in cells with an innately high proliferative index (e.g., bone marrow)
- **Alkylating agents** interact with preformed DNA molecules
  - Affect proliferating populations of cells and cells that are not actively synthesizing DNA
  - Have a greater propensity for mutagenicity

### Methotrexate

- **Mechanism of action**
  - S phase antimetabolite; competitively and irreversibly inhibits dihydrofolate reductase to block folate metabolism; partially reversibly inhibits thymidylate synthetase downstream to block DNA synthesis
- **Adverse effects:** gastrointestinal distress, renal failure, liver cirrhosis/hepatotoxicity (low risk if cumulative dose is below 1.5 g), abortifacient, pancytopenia (first 4–6 weeks), acute pneumonitis, pulmonary fibrosis, nephrotoxicity, phototoxicity, acral erythema, radiation recall, lymphoma, ulcerative stomatitis
- **Folic acid supplementation** can decrease gastrointestinal side effects
- **Liver biopsy** after cumulative dose of 1.5 g to diagnose methotrexate induced hepatic fibrosis.
- **Drug interactions**
  - Increased methotrexate levels and increased toxicity: salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), probenicid, sulfonamides, dipyridamole, cholramphenicol, phenothiazine, phenytoin, tetracycline
- **Laboratory studies**
  - Monitor: liver function tests, CBC, lipid panel, test for pregnancy, periodic liver biopsy (most suggested after 1.5 g cumulative dose), renal function test, serologic test for hepatitis
- **Leucovorin (folinic acid)** given for acute toxicity
- **Pregnancy category X:** recommended that men are off of methotrexate 3 months and women are off of methotrexate one ovulatory cycle before trying to conceive

### Azathioprine

- **Mechanism of action**
  - 6 thioguanine (active metabolite of azathioprine), a purine analog, inhibits DNA/RNA synthesis and repair; it is immunosuppressive.
- **Three enzymes involved in metabolism after azathioprine is absorbed and converted to 6 Mercaptopurine (6MP):**
  - **Hypoxanthine-guanine phosphoribosyl transferase** (HGPRT): results in 6-thioguanine (active form of 6 MP)
  - **Xanthine oxidase** (XO): 6 MP catalyzed into inactive metabolites
  - **Thiopurine methyl transferase** (TPMT): 6 MP catalyzed to inactive metabolites
- **Adverse effects**
  - Malignancy: lymphoproliferative, squamous cell carcinoma of skin
  - Gastrointestinal distress
  - Hypersensitivity syndrome
  - Myelosuppression/pancytopenia: increased risk in patients with thiopurine methyltransferase deficiency
- **Other effects:** hepatitis, pancreatitis, teratogenicity
• Patients with Lesch-Nyhan syndrome lack HGPRT and are resistant to the cytotoxic effects of the drug
• Drug interactions
  • Allopurinol inhibits xanthine oxidase causing increased toxicity
  • ACE inhibitors and folate antagonists can increase myelosuppression
  • Warfarin levels may decrease
• Laboratory studies:
  • LFTs, CBC, pregnancy, baseline TPMT
• Pregnancy category D

**Mycophenolate Mofetil (MMF) and Mycophenolic Acid (MPA)**

• Mechanism of action
  • MMF is hydrolyzed to MPA (active metabolite) after absorption
  • MPS is an antimetabolite that noncompetitively inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses de novo purine synthesis: conversion of inosine-5-phosphate and xanthine-5-phosphate to guanosine-5-phosphate
  • MMF is cytotoxic for cells that rely predominantly on de novo purine biosynthesis, such as lymphocytes (T and B), and lack the purine salvage pathway
• Adverse effects: gastrointestinal effects (dose-dependent and most common), anal tenderness, dysuria/urinary frequency, leukopenia, lymphoma, increased risk for infection, increased toxicity in patients with renal impairment, caution in active peptic ulcer disease
• Drug interactions
  • MMF can decrease levels of levonorgestrel containing hormonal contraceptives
  • MMF can increase levels of phenytoin, acyclovir, ganciclovir, and theophylline
  • Hydrocodone, oxycodone, tramadol, NSAIDs may increase risk of seizures
  • Do not administer with antacids due to decreased absorption of MMF
  • Cyclosporine can decrease MPA levels
  • Cholestyramine can decrease MMF levels
• Pregnancy category D

**Hydroxyurea**

• Mechanism of action
  • S phase specific; inhibits ribonucleotide reductase, rate limiting step in DNA synthesis
• Adverse effects
  • Hematologic: megaloblastosis (all patients), anemia, pancytopenia
  • Renal: elevated BUN and creatinine
  • Hepatic: elevated transaminases, transient hepatitis
  • Cutaneous: leg ulcers, dermatomyositis-like eruption on dorsae of hands, diffuse hyperpigmentation, vasculitis, urticaria, fixed drug eruption, photosensitivity, atrophy of skin and nails
• Other: flu-like symptoms, radiation recall
• Laboratory studies:
  • CBC, urinalysis (UA), liver function tests (LFTs), serum chemistry
• Interactions
  • Avoid other myelosuppressive agents because of the potential for additive bone marrow toxicity
• Pregnancy category D

**Cyclophosphamide**

• Mechanism of action
  • Alkylating agent derived from nitrogen mustard, cell-cycle-nonspecific cytotoxic drug; suppresses B cells > T cells (CD8 > CD4), forms DNA cross-linkages
• Adverse effects
  • Carcinogenic: transitional cell bladder carcinoma, AML, non-Hodgkin lymphoma, SCC
  • Hematologic: thrombocytopenia, anemia, leukopenia, bone marrow suppression
  • Gastrointestinal distress, dose-related
  • Genitourinary: hemorrhagic cystitis, azoospermia; acrolein, metabolite of cyclophosphamide, causes bladder toxicity and increased risk of bladder carcinoma; treat with mesna (sodium 2-mercaptopethanesulfonate) binds to acrolein to reduce toxicity
  • Endocrine: amenorrhea
  • Mucocutaneous: acral erythema, anagen effluvium, hyperpigmentation, pigmented band on teeth
  • Pulmonary: pneumonitis/pulmonary fibrosis
• Laboratory studies:
  • chemistry panel, CBC, LFTs, UA
• Pregnancy category D

**Chlorambucil**

• Mechanism of action: alkylating agent derived from nitrogen mustard, cell-cycle non-specific, forms DNA cross linkages
• Adverse effects
  • Carcinogenic
  • Hematologic: leukopenia (common, dose-limiting), bone marrow suppression
  • Mucocutaneous: oral ulcers, alopecia
  • Pulmonary: pneumonitis/pulmonary fibrosis
  • Other: azoospermia, amenorrhea, generalized tonic-clonic seizures (especially in children with nephrotic syndrome or adults with seizure history), gastrointestinal effects
SYSTEMIC MEDICATIONS

• Laboratory studies:
  • CBC, LFTs, chemistry panel, UA
• Pregnancy category D

RETINOIDS

• Hormones that possess vitamin A activity (natural and synthetic forms)
• Small molecule delivers retinol to enzymes to form retinoic acid (active form) or retinyl esters (storage form).
• Forms of vitamin A in mammals: retinol (vitamin A alcohol), retinal (vitamin A aldehyde), retinoic acid (vitamin A acid)
• Cytosolic retinol binding protein (CRABP)
• CRABP found in high levels in the epidermis and in certain diseases: psoriasis, Darier’s disease, pyrriasis rubra pilaris, keratosis pilaris
• Retinyl esters: hydrolyzed to retinol, irreversibly metabolized to RA and can be converted to retinol.
• Mechanism of action
  • Function in the regulation of cellular proliferation and differentiation and the modulation of immune function and cytokine function
  • Anti-acne effects: retinoids bind to toll-like receptor 2
  • Anti-inflammatory effects include: decreased release of leukotrienes, inhibits immunoglobulin synthesis from B cells, reduction of lymphocyte proliferation and decreased cytotoxic T-lymphocyte induction
  • Anti-tumor effects: inhibition of selected oncogenes and activation of tumor suppressor genes linked to apoptosis
  • Retinoid effects are mediated by two main families of intracellular receptors:
    - Retinoic acid receptor (RAR; bound and activated by all-trans retinoic acid)
    - Retinoid X receptor (RXR; 9-cis retinoic acid is the proposed ligand)
  • Each family has three receptor subtypes: alpha, beta, and gamma; gamma is the primary receptor subtype in the skin while beta is absent
  • Retinoids are transported to the nucleus by cytosolic retinoic acid binding protein (CRABP), binds to RAR or RXR, and acts as a transcription factor for genes containing retinoic acid response elements
  • Also acts indirectly by antagonizing other transcription factors such as activating protein 1 (AP1) and nuclear factor-interleukin-6 (NF-IL6) (upregulated in a variety of hyperproliferative and inflammatory conditions)
  • Enhances keratinocyte differentiation by increasing filaggrin production, keratohyaline granules, and Odland body secretion of lipids; downregulates keratins 6 and 16
  • Inhibits ornithine decarboxylase

• Three generations of synthetic retinoids:
  • First generation: (monoaromatic): tretinoin, isotretinoin
  • Second generation: (monoaromatic): etretinate and its metabolite, acitretin
  • Third generation: polyaromatic, adapalene, bexarotene, tazarotene

• Side effects
  • Mucocutaneous: cheilitis, dry skin, pruritus, epistaxis, paronychia, periungual pyogenic granulomas, telogen effluvium
  • Ophthalmologic: blepharoconjunctivitis, blurred vision, abnormal night vision
  • Teratogenicity: retinoic acid embryopathy, central nervous system abnormalities (hydrocephalus, microcephaly), external ear abnormalities (anotia, small or absent external auditory canals), cardiovascular abnormalities (septal wall and aortic defects), facial dysmorphia, eye abnormalities (microphthalmia), thymus gland abnormalities, and bone abnormalities; monitor BHCG monthly
  • Skeletal: long bones, decalcification, progressive calcification of ligaments and tendon insertions, cortical hyperostosis, periosteal thickening, premature epiphyseal closure, and possible osteoporosis
  • Myalgias and arthralgias: sometimes associated with high creatinine kinase levels
  • Neurologic: headache, fatigue, lethargy, pseudotumor cerebri
  • Psychologic: anxiety and depression
  • Lipids: increase in plasma lipids (dose-dependent), especially triglycerides; increase in cholesterol levels
  • Gastrointestinal: elevated LFTs, most commonly the transaminases, can occur in approximately 15% of patients; nausea, diarrhea, abdominal pain

ISOTRETINOIN (13-cis-Retinoic Acid)

• Isomer of naturally occurring tretinoin (trans-retinoic acid)
• Decreases sebaceous gland size and sebum production; may inhibit sebaceous gland differentiation and abnormal keratinization
• Absorption increased with food intake
• Dose 1–2 mg/kg range
• Isotretinoin has a terminal half-life in plasma of 10 to 20 hours and is completely cleared from the body within 1 month after the drug is stopped
• Pregnancy category X

ACITRETIN/ETRETINATE

• Second-generation retinoids (aromatic retinoids)
• Acitretin: derived from etretinate, has a terminal half-life in plasma of only 2 days
• Following oral absorption, acitretin undergoes extensive metabolism and interconversion by simple isomerization to its 13-cis form (cis-acitretin)
• Etretinate has a longer half-life than acitretin owing to greater storage of etretinate in adipose tissue; can be formed with concurrent ingestion of acitretin and ethanol
• Oral absorption of acitretin is optimal when given with food
• Acitretin has a terminal half-life of 2 days; however, women who take acitretin must avoid pregnancy for at least 3 years after discontinuing therapy due to conversion to etretinate by alcohol consumption
• Etretinate is stored in body fat deposits; terminal elimination half-life in plasma of about 100 days; detected in serum in trace amounts for as long as 3 years after cessation of therapy
• Pregnancy category X

BEXAROTENE
• Binds to retinoic X receptor, all subtypes; 100-fold stronger than RAR
• Absorption increased by fatty meals
• Monitoring: perform fasting blood lipid determinations before therapy is initiated and weekly until lipid response to the drug is established; obtain and serially monitor baseline CBC, LFTs, and thyroid function tests; advise patients to limit vitamin A supplements and minimize exposure to sunlight and artificial ultraviolet (UV) light
• Bexarotene has a terminal half life of 7 hours; monitor BHCG, LFTs, triglycerides, and TSH monthly (causes central hypothyroidism)
• Pregnancy category X

ANTIHISTAMINES
• Mast cells express high affinity immunoglobulin E receptor (FCERI) that can be cross linked by an antigen, triggering release of histamine and other mediators
• H1 and H2 subclasses of histamine receptors are expressed in human skin; H1 receptors also found in the brain, smooth muscle cells, endothelial cells, adrenal medulla, and heart
• Inverse agonists at tissue receptor sites
• Binding is reversible
• Affect smooth muscle contraction, stimulation of nitric oxide formation, endothelial cell contraction, and increasing vascular permeability
• Central nervous system effects are due to blockade of central muscarinic receptors
• First generation H1 blockers
• Lipophilic; sedating by crossing blood brain barrier
  • Five classes:
    - PIPRIDINE: i.e., cyproheptadine, anti-seratonin effects, pregnancy category B
    - Alkylamine: i.e., chlorpheniramine, pregnancy category C
    - Ethanolamine: i.e., diphenhydramine, also inhibits acetylcholine activity and may cause sedation, urinary retention, may exacerbate angle closure glaucoma. Pregnancy category B
    - Piperazine: i.e., hydroxyzine, may exacerbate porphyria, may cause alterations in T waves on electrocardiography, drowsiness. pregnancy category C
    - Phenothiazine: i.e., promethazine, pregnancy category C
• Second generation H1 blockers
  • Less lipid soluble, therefore, only small amounts cross the blood-brain barrier; also have longer half-lives, allowing for less frequent dosing and less sedation compared to first generation H1 blockers
  • Cetirizine: carboxylic acid metabolite of hydroxyzine; binds H1 receptors in blood vessels, GI tract, respiratory tract; at high doses it may have anticholinergic effects, pregnancy category B
• Others
  • fexofenadine (pregnancy category C)
  • loratadine (pregnancy category B)
  • desloratidine: drug interactions: Erythromycin and ketoconazole increase desloratadine and 3-hydroxydesloratadine plasma concentrations, but no increase in clinically relevant adverse effects, including no increase in QTc, is observed, pregnancy category C
  • levocetirizine: pregnancy category B
• Drug interactions
  • Increased antihistamine levels: macrolide antibiotics, azole antifungals, HIV-1 protease inhibitors, SSRI antidepressants,
  • Increased toxicity: CNS depressants, MAO inhibitors

LEUKOTRIENE INHIBITORS
• Leukotriene receptor antagonists or inhibition of leukotriene production
• Zafirlukast, montelukast: bind CysLT1 receptor
• Zileuton: competitive inhibitor of lipoxygenase— inhibits leukotriene formation (LTB1, LTC1, LTD1, LTE1)
• Adverse effects: possible association with Churg-Strauss vasculitis (zileuton), may increase liver enzymes
• Monitor LFTs
• Pregnancy category B, except for zileuton: category C

ANTIBIOTICS

BETA-LACTAM ANTIBIOTICS
• Include penicillins and cephalosporins
• Active against many gram-positive, gram-negative, and anaerobic organisms
**Penicillins**

- **Mechanism of action**
  - Inhibit bacterial cell wall synthesis; leads to activation of autolytic enzymes that kill the bacteria
  - Active against gram-positive organisms and spirochetes
  - Penicillinase-resistant penicillins include dicloxacillin, nafcillin, and oxacillin
  - Beta-lactamase inhibitor; ampicillin-sulbactam, amoxicillin-clavulanic acid: use in the treatment of bite wounds; active against oral anaerobes, streptococci, anaerobes, and staphylococci
- **Adverse effects:** hemolytic anemia, nephritis, anaphylaxis, TEN (toxic epidermal necrolysis), erythema nodosum, cutis laxa, nail changes
- **Ampicillin** causes a morbilliform eruption when given to patients with infectious mononucleosis and when co-administered with allopurinol
- **Pregnancy category B**

**Cephalosporins**

- **Mechanism of action:** inhibit bacterial cell wall synthesis through inhibition of necessary enzymes known as penicillin binding proteins.
- **Grouped into four generations according to the spectrum of antibacterial activity:**
  - **First generation:** *Streptococci*, methicillin-sensitive *Staphylococcus aureus*, some gram-negative bacilli
  - **Second generation:** increased activity against gram-negative bacilli; all are less active against gram-positive bacteria than first-generation drugs
  - **Third generation:** mostly IV, increased gram negative coverage and less gram positive; gram-negative organisms most often covered by third generation cephalosporins: *Escherichia coli*, *Proteus mirabilis*, *Klebsiella*, indole-positive *Proteus*; also with increased activity (relative to earlier generations) against *Pseudomonas aeruginosa*
  - **Fourth generation:** comparable to third generation but more resistant to some chromosomal beta-lactamases; penetrates well into CSF; good for *P. aeruginosa*
- **Adverse effects:** hypersensitivity, diarrhea, nausea, vomiting, abdominal pain, dizziness, Stevens-Johnson syndrome, toxic epidermal necrolysis, *Clostridium difficile* colitis, nail changes, thrombocytopenia, neutropenia, eosinophilia; cross-reactivity with penicillins: immunologic studies: up to 20% and clinical reports: from 5% to 10%
- **Drug interactions**
  - Probenacid: elevated levels of of B-lactam medications

**Vancomycin**

- **Mechanism of action**
  - Inhibits bacterial cell wall synthesis and causes secondary damage to the cytoplasmic membrane
  - Active against gram-positive organisms
- **Adverse effects:** linear IgA bullous dermatosis, bullous eruptions, red-man syndrome, ototoxicity, nephrotoxicity, thrombophlebitis at injection site; erythema, histamine-like flushing, and anaphylactic reactions may occur when administered with anesthetic agents; when taken concurrently with aminoglycosides, risk of nephrotoxicity; neuromuscular blockade may be enhanced when co-administered with nondepolarizing muscle relaxants
- **Use with caution in patients with renal impairment or with nephrotoxic or ototoxic drugs; facial flushing from histamine release (e.g., red-man syndrome); usually resolves by slowing IV infusion over 2 hours and by giving antihistamines; adjust daily dosing frequency in renal impairment**
- **Pregnancy category C**

**Tetracyclines: Tetracycline, Doxycycline, and Minocycline**

- **Mechanism of action**
  - Bacteriostatic
  - Binds to 30s subunit of bacterial ribosome, interfering with protein synthesis
  - Active against *Mycoplasma pneumoniae*, *Chlamydia*, *Rickettsia*, *Propionibacterium acnes* and *Vibrio* spp., *Borrelia burgdorferi*, *Mycobacterium marinum*
- **Adverse effects:** photosensitivity, gastrointestinal disturbances, esophageal ulceration, enamel dysplasia and delayed bone growth in children (younger than 9 years of age), photo-onycholysis, post-acne cutis, psoriasis exacerbation, vertigo, pseudo-tumor cerebri, dizziness, vertigo, Fanconi’s anemia and uremia in renal disease patients
  - Minocycline: autoimmune hepatitis, systemic lupus erythematosus, blue-grey hyperpigmentation, higher incidence of neurologic side effects
  - Doxycycline and demeclocycline are the most phototoxic
- **Reduce dose in renal impairment; doxycycline is the tetracycline of choice to use in renal failure patients**
- **Drug interactions:** increased levels of warfarin, digoxin, lithium, insulin; increased risk of pseudo-tumor cerebri with Isotretinoin, decreased absorption of tetracycline due to antacids, other cations
(iron, zinc, bishmuth, salts), cimetidine and sodium bicarbonate; possible decreased level of oral contraceptives

- Pregnancy category D

**FLUOROQUINOLONES**

- Ciprofloxacin, ofloxacin, gatifloxacin, levofloxacin, moxifloxacin, sparfl oxacin, grepafloxacin, norfloxac in, enoxacin

- Mechanism of action
  - Bacteriocidal
  - Inhibits bacterial DNA gyrase (bacterial topoisomerase 11)
  - Active against gram-positive organisms (S. aureus, streptococci, except ciprofloxacin and ofloxacin) and gram-negative organisms (mycobacteria, Neisseria gonorrhoeae)

- Adverse effects: photosensitivity, flushing, hyperhidrosis, affects cartilage formation in children (contraindicated younger than age 18), tendonitis and tendon rupture

- Drug interactions: absorption is decreased when administered with calcium, magnesium, or aluminum containing antacids

  - Increased serum levels of theophylline, aminophyl line, warfarin.

- Pregnancy category C

**MACROLIDES: ERYTHROMYCIN, AZITHROMYCIN, CLARITHROMYCIN**

- Mechanism of action
  - Bacteriostatic
  - Bind to 50S bacterial ribosomal subunit to inhibit protein synthesis
  - Active against gram-positive organisms (most streptococci and S. aureus)

- Adverse effects: gastrointestinal distress, eosinophilia, oral mucosal lesions, xerosis; estolate formulation may cause cholestatic hepatitis (caution in liver disease)

- Drug interactions: certain macrolides inhibit hepatic cytochrome P-450 thus decreasing metabolic clearance of certain drugs including phenytoin, theophylline, warfarin, digoxin, cyclosporine, carbamazepine, benzodiazepines, corticosteroids, omeprazole

  - Digoxin: elevated levels due to gut flora changes
  - Fluconazole: may increase clarithromycin levels

- Pregnancy category B for erythromycin and azithromycin; all others category C

**RIFAMPIN**

- Mechanism of action
  - Bactericidal
  - Inhibition of DNA-dependent RNA polymerase

- Activity: broad spectrum; staphylococci, N. meningit is, N. ghtonorrhae, H. influenza, poor gram-negative coverage; active against M. tuberculosis

- Rapid resistance, therefore, use concomitantly with another agent that covers gram positive organisms

- Drug interactions: decreased effect: oral contraceptives, warfarin, steroids, anti-arrhythmics, phenytoin, phenobarbital, theophylline, β blockers, fluoroquinolones, cyclosporine, acetomenophen, dapsone, oral hypoglycemics

- Adverse effects: orange discoloration of urine, hypersensitivity syndrome: flu-like symptoms, GI symptoms, CNS symptoms, bullous pemphigoid like lesions, urticaria, mucositis

**SULFONAMIDES (TRIMETHOPRIM-SULFAMETHOXAZOLE)**

- Mechanism of action
  - Inhibit 50S bacterial ribosomal subunit to inhibit protein synthesis
  - Active against gram-positive organisms (Staphylococcus aureus, streptococci) and anerobes (Propionibacterium acnes), aerobic and anaerobic streptococci (except enterococci)

- Adverse effects: photosensitivity, diarrhea, pseudomembranous colitis (owing to overgrowth of Clostridium difficile), hepatic dysfunction, morbilliform rash, neuromuscular blockade, erythema multiforme, urticaria, anaphylaxis

- Pregnancy category B
in folate deficiency hemolysis may occur in individuals with G6PD deficiency

- Drug Interactions: increased warfarin effects, avoid in patients on methotrexate which also affects folic acid metabolism.
- Pregnancy category C; contraindicated in third trimester due to risk of kernicterus

**Chloramphenicol**

- Mechanism of action
  - Binds to 50S subunit of bacterial ribosomes and inhibits peptidyl transferase
- Used to treat *Salmonella*, *Haemophilus*, and pneumococcal and meningococcal meningitis in penicillin-sensitive patients; treats verruga peruana
- Adverse effects: gray baby syndrome, gastrointestinal disturbances, anemia
- Pregnancy category C

**Aminoglycosides**

- Mechanism of action
  - Gentamicin, tobramycin, and amikacin
  - Bind to 30S subunit of bacterial ribosomes to inhibit protein synthesis
  - Active against aerobic gram-negative organisms
- Adverse effects: ototoxicity, nephrotoxicity, neuromuscular blockade, injection-site necrosis
- Pregnancy category C

**Metronidazole**

- Mechanism of action
  - Forms toxic metabolites in bacteria that inhibit nucleic acid synthesis
  - Active against anaerobes, protozoa
- Adverse effects: glossitis, stomatitis, disulfiram-like reactions with ethanol, mucosal xerosis, vestibular dysfunction
- Pregnancy category B

**Oxazolidinones (Linezolid)**

- Mechanism of action: binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex
- Adverse effects: thrombocytopenia depending on duration of therapy (generally greater than 2 weeks of treatment), nausea, headache, diarrhea, vomiting, pseudomembranous colitis, tongue discoloration
- Activity: bacteriostatic against enterococci and staphylococci including MRSA, vancomycin-resistant enterococci (VRE), and bactericidal against most strains of streptococci
- Drug interactions: can induce the serotonin syndrome when co-administered with selective serotonin reuptake inhibitors

**Parasiticidals**

**Ivermectin**

- Mechanism of action: blocks glutamate-gated chloride ion channels resulting in paralysis of the parasite
- Used to treat onchocerciasis, strongyloidiasis, Norwegian scabies
- Pregnancy category C

**Thiabendazole**

- Mechanism of action: inhibits helminth specific enzyme fumarate reductase
- Used to treat cutaneous larva migrans
- Adverse effects: nausea, vomiting, diarrhea
- Drug interactions: theophylline levels increased
- Pregnancy category C

**Antiviral Agents**

**Acyclovir**

- Mechanism of action: inhibits DNA synthesis by inhibiting viral DNA polymerase; initial phosphorylation of acyclovir to acyclovir monophosphate is catalyzed by virus-induced thymidine kinase
- Activity: human herpes viruses, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and to a lesser extent, cytomegalovirus (CMV) (Cytomegalovirus does not produce thymidine kinase, and so the antiviral activity of acyclovir in cytomegalovirus-induced infections is poor)
- Pharmakokinetics: bioavailability of oral acyclovir is low (15% to 30% of an oral dose is absorbed)
- Adverse effects: nephrotoxicity with IV infusion, seizures
- Resistant herpes simplex virus (HSV) mutants: thymidine kinase negative (*tk–*) or *tk* mutant and hence do not phosphorylate and activate acyclovir; have an altered DNA polymerase that is not as greatly inhibited by the phosphorylated drug
- Pregnancy category B

**Famciclovir**

- Mechanism of action
  - Prodrug of the antiviral agent penciclovir; converted to active form via deacetylation and oxidation
  - Action similar to acyclovir: activated by viral thymidine kinase to inhibit viral DNA polymerase
- Activity: HSV, VZV, CMV
- Pharmakokinetics: bioavailability of penciclovir is 77%
- Adverse effects: nephrotoxicity with IV infusion, seizures
- Pregnancy category B
Valacyclovir
- Mechanism of action
  - Valacyclovir (a prodrug) is the L-valine ester of acyclovir and exerts its action after being transformed into acyclovir during its first pass through the intestine and liver
  - Activated by viral thymidine kinase to inhibit viral DNA polymerase
  - Bioavailability is three to five times greater than acyclovir
  - Activity against HSV, VZV, and CMV
  - Adverse effects: nephrotoxicity with IV infusion, seizures
  - Pregnancy category B

Ganciclovir
- Mechanism of action: nucleoside analogue that competes with deoxyguanosine for incorporation into viral DNA; hydroxymethylated derivative of acyclovir
  - Initially phosphorylated by virus-encoded kinases
  - Ganciclovir triphosphate competitively inhibits herpes virus DNA polymerase and inhibits elongation of the nascent DNA chain
  - HSV and VZV with thymidine kinase deficiency or with viral DNA polymerase mutations may be resistant to ganciclovir
  - Activity: more active than acyclovir against CMV, especially CMV retinitis in immunocompromised patients
  - Adverse effects: mucositis, hepatic dysfunction, seizures, granulocytopenia and thrombocytopenia; may not be totally reversible after cessation
  - Pregnancy category C

Valganciclovir
- Acts as a prodrug for ganciclovir; converted to active drug by intestinal and hepatic esterases
- Adverse effects: similar to parent compound
- Activity: CMV retinitis in patients with AIDS
- Pregnancy category C

Foscarnet
- Mechanism of action: noncompetitively inhibits viral DNA polymerase and HIV-1 reverse transcriptase by binding directly to the enzymes’ pyrophosphate-binding sites
- Does not require phosphorylation for antiviral activity
- Activity: acyclovir-resistant HSV infections in AIDS patients and CMV retinitis in immunocompromised patients
- Adverse effects: nephrotoxicity, electrolyte imbalances, genital and oral ulcerations
- Pregnancy category C

Amantadine and Rimantadine
- Mechanism of action
  - Both inhibit the uncoating of viral RNA within infected host cells, thereby preventing virus replication; effective when administered orally
  - Activity: influenza A and C viruses (but not influenza B), rubella
  - Adverse effects: ataxia, hypertrichosis, livedo reticularis, photosensitivity, peripheral edema, alopecia, anticholinergic reactions, gastrointestinal disturbances; effects less likely with rimantidine
  - Pregnancy category C

Interferons (Interferon-A-2B)
- Mechanism of action
  - Protein product manufactured by recombinant DNA technology
  - Induces differential gene transcription; inhibits viral replication; antiviral and immunomodulatory effects by suppressing cell proliferation; direct antiproliferative effects against malignant cells and modulation of host immune response
  - Adverse effects: flulike symptoms, cardiovascular arrhythmias, eyelash hypertrichosis, spastic diplegia, rhabdomyolysis
  - Pregnancy category C

Ribavirin
- Mechanism of action: inhibits viral RNA polymerase
  - Purine nucleoside analogue that is phosphorylated by host cells
  - Activity: respiratory syncytial virus (RSV), influenza A and B, measles
  - Adverse effects: exanthem
  - Pregnancy category X

Cidofovir
- Mechanism of action: nucleoside analog of deoxycytidine monophosphate
  - Converted by host cell enzymes to cidofovir diphosphate, which competitively inhibits viral DNA polymerase
  - Cidofovir is independent of thymidine kinase activation
  - Adverse effects: renal toxicity (renal tubular damage), granulocytopenia may occur; with topical application, local irritation, pain
  - Pregnancy category C

Zostavax Vaccine
- Live attenuated varicella-zoster virus vaccine
- Indicated for prevention of herpes zoster in patients 60 years or older
- 0.65 mL dose injected subcutaneously in the deltoid
- Pregnancy category C

HHV Vaccine
- Live attenuated vaccine given for prophylaxis of primary varicella
• Administered at 1 year of age
• For ages 12 and under: one dose
• For ages 13 and older: two doses, 1–2 months apart

**Antiretroviral Agents**

**Nucleoside Reverse Transcriptase Inhibitors**

- Zidovudine (AZT, ZDV)
  - Mechanism of action: thymidine analogue; acts as a chain terminator
  - Resistance: due to mutations in the reverse transcriptase gene
  - Adverse effects: myelosuppression; results in anemias and/or neutropenia
  - Pregnancy category C
- Didanosine (ddI)
  - Mechanism: similar to zidovudine
  - Adverse effects: peripheral neuropathy and potentially fatal pancreatitis
  - Pregnancy category B
- Lamivudine (3TC), stavudine (d4T), and zalcitabine (ddC)
  - Mechanism of action: similar to zidovudine
  - Adverse effects: flu-like symptoms, lipodystrophy, acniform eruption, mucosal ulcers, pruritus, melanonychia, hyperpigmentation, eyelash hypertrichosis
  - Pregnancy category C
- Abacavir (ABC)
  - Mechanism of action: similar to zidovudine
  - Adverse effects: alcohol increases levels 41%; hypersensitivity reaction (which can be fatal)
  - Pregnancy category C
- Emtricitabine (FTC)
  - Mechanism of action: similar to zidovudine
  - Adverse effects: minimal toxicity; lactic acidosis with hepatic steatosis (rare)
  - Pregnancy category B

**Nonnucleoside Reverse Transcriptase Inhibitors**

- Nevirapine, delavirdine, efavirenz
  - Bind directly to HIV-1 reverse transcriptase and non-competitively inhibit cDNA synthesis
  - Adverse effects: rash is common (especially with nevirapine), Stevens-Johnson
  - Pregnancy category C

**Protease Inhibitors (PIs)**

- Mechanism of action: inhibit HIV protease activity, blocking Gag and Gag-Pol cleavage required for assembly of progeny virions
  - Saquinavir, indinavir, nelfinavir, amprenavir, fosamprenavir, ritonavir, atazanavir, lopinavir, tipranavir, darunavir
  - Adverse effects: nephrolithiasis (indinavir), abnormal fat deposits such as “buffalo hump” (indinavir), severe diarrhea (nelfinavir), hepatotoxicity associated with concurrent use of other HIV agents and with comorbid hepatitis C, lipodystrophy, osteopenia, insulin resistance, severe lipid abnormalities, sulfatype rashes (darunavir), periungual pyogenic granulomas (indinavir)
- Pregnancy category C

**Nucleotide Analogue: Tenofovir**

- Mechanism of action: inhibits reverse transcriptase
- Adverse effects: peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance; gastrointestinal complaints
- Monitor: changes in serum creatinine and serum phosphorus in patients at risk or with history of renal dysfunction
- Pregnancy category B

**Fusion Inhibitors: Enfuvirtide**

- Mechanism of action: binds to proteins on viral envelope and inhibits conformational change needed for fusion between viral envelope and CD4 cells
- Pregnancy category B

**Antifungal Agents**

**Allylamines**

- Mechanism of action: inhibits first step of ergosterol synthesis by blocking the activity of squalene epoxidase; fungistatic
  - Examples: butenafine, naftifine, terbinafine
- Adverse effects: hepatocellular injury, delayed gastric emptying, dysgeusia (metallic taste), reversible agranulocytosis, lupus erythematosus; terbinafine can cause gastrointestinal disturbance and nausea
- Pregnancy category B

**Azoles**

- Class members
  - Imidazoles: azole ring contains two nitrogen atoms
    - Examples: ketoconazole, clotrimazole, miconazole
  - Triazoles: azole ring contains three nitrogen atoms
    - Examples: fluconazole, itraconazole, voriconazole, posaconazole
- Mechanism of action: blocks ergosterol synthesis by binding to and inhibiting the fungal CYP-450 dependent enzyme lanosterol 14-α-demethylase (converts lanosterol to ergosterol); fungistatic
- Voriconazole and posaconazole are being used for invasive fungal infections, i.e., aspergillus, fusarium
- Adverse effects:
  - Hepatitis (greatest risk with ketoconazole); congestive heart failure and hypertriglyceridemia (itraconazole)
• Ketoconazole: endocrine effects (gynecomastia, infertility, menstrual irregularities)
• Miconazole: thrombophlebitis after IV administration
• Voriconazole: visual disturbances in 30% of patients; altered/enhanced visual perception, blurred vision, color vision change, and or photophobia—effects clear after discontinuation of medication
• Drug interactions
  • Itraconazole and ketoconazole inhibits CYP 3A4
  • Fluconazole inhibits CYP 2C9; can increase INR when given with warfarin
• Pregnancy category C

**Immunosuppressive Agents**

**Cyclosporine**

- Mechanism of action
  • Binds to an immunophilin called cyclophilin A (CyPA) and inhibits calcineurin
  • Calcineurin regulates the transcription factor NFAT (nuclear factor of activated T cells) by dephosphorylating the cytoplasmic component (NFATc); NFATc translocates into the nucleus, where it binds NFATn
  • NFATn regulates cytokine-encoding genes, including interleukin 2 (IL-2) and interferon-γ (IFN-γ)
- Adverse effects: hypertension, hyperkalemia, hyperuricemia, hypomagnesemia, hyperlipidemia, renal toxicity, hypertrichosis, gingival hyperplasia, neurotoxicity (headache, tremor, paresthesias), lymphoma (especially in transplant patients), increased incidence of skin cancer, osteoporosis
- Monitor: chemistry panel, magnesium, lipid panel, blood pressure, lymph nodes; serum creatinine in long-term cyclosporin A therapy is a poor predictor of altered renal function (check creatinine clearance); contraindicated with PUVA
- Drug interactions: any medication that induces, inhibits, or competes for CYP 3A4 (see Table 24-1); cyclosporine can increase risk of rhabdomyolysis when used with statins
• Pregnancy category C

**Polyenes**

- Amphotericin B
  • Mechanism of action: binds to ergosterol and forms amphotericin B–associated membrane pores, altering the fungal membrane’s permeability and causing leakage of intracellular Na⁺, K⁺, and H⁺ ions, leading to cell death
  • Adverse effects:
    • Amphotericin B binds cholesterol (mammalian cell membranes) to a far lesser extent than ergosterol
    • Hepatitis, infusion reactions, anemia, fever, flushing/generalized erythema, nephrotoxicity, hypotension
  • Resistance: develops when binding of the drug to ergosterol is impaired or when ergosterol concentration in the membrane is decreased
• Pregnancy category B

**Glucan Synthesis Inhibitors/Echinocandins**

- Caspofungin
  • IV administration
  • Mechanism of action: inhibits glucan synthesis (essential polysaccharide of the fungal cell wall)
  • Activity: primarily Candida, Aspergillus
• Pregnancy category C

**Griseofulvin**

- Mechanism of action: interferes with microtubule function, causing metaphase arrest
  • Produced by Penicillium griseofulvum
  • Activity: fungistatic for dermatophytes
  • Adverse effects: gastrointestinal disturbance, headaches, hypersensitivity, photosensitivity, paresthesias, hepatotoxicity, amenorrhea, exacerbation of acute intermittent porphyria (contraindicated in patients with porphyria)
  • Drug interactions: griseofulvin decreases warfarin, and oral contraceptive concentrations
• Pregnancy category C

**Immunobiologicals**

**Etanercept**

- Fully human receptor fusion protein comprised of a dimer of the p-75 external domain of tumor necrosis factor-α (TNF-α) receptor linked to the Fc portion of human IgG1
  • Mechanism of action competitively binds to soluble and membrane-bound TNF-α and binds to TNF-β
  • Dose: 25mg or 50mg subcutaneous injection once or twice weekly
  • Baseline CBC, CMP, LFT, and PPD recommended for all TNF-α inhibitors; some also advocate baseline ANA and chest x-ray
  • Adverse effects: injection site reaction, reactivation of latent tuberculosis, multiple sclerosis and CNS demyelinating disorders, positive antinuclear antibody ANA (11%), exacerbation of or new-onset congestive heart failure (CHF) (caution use in patients with CHF)
  • Relative contraindications: family history of demyelinating disease or multiple sclerosis
  • Absolute contraindications: infections and known hypersensitivity
  • Avoid live vaccines
• Pregnancy category C

**Ketoconazole:** endocrine effects (gynecomastia, infertility, menstrual irregularities)
- **Miconazole:** thrombophlebitis after IV administration
- **Voriconazole:** visual disturbances in 30% of patients; altered/enhanced visual perception, blurred vision, color vision change, and or photophobia—effects clear after discontinuation of medication
- **Drug interactions:**
  - Itraconazole and ketoconazole inhibits CYP 3A4
  - Fluconazole inhibits CYP 2C9; can increase INR when given with warfarin
- **Pregnancy category C**
**TABLE 24-1** Examples of CYP3A4 Subfamily Substrates, Inducers, and Inhibitors*

<table>
<thead>
<tr>
<th>CYP3A4 Substrates</th>
<th>CYP3A4 Inducers</th>
<th>CYP3A4 Inhibitors</th>
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<tbody>
<tr>
<td>Alprazolam</td>
<td>Carbamazepine</td>
<td>Cimetidine</td>
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<tr>
<td>Atorvastatin</td>
<td>Cortisol</td>
<td>Clarithromycin</td>
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<tr>
<td>Buspirone</td>
<td>Dexamethasone</td>
<td>Diltiazem</td>
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<tr>
<td>Busulfan</td>
<td>Griseofulvin</td>
<td>Erythromycin</td>
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<tr>
<td>Cyclosporine</td>
<td>Nevirapine</td>
<td>Felninavir</td>
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<tr>
<td>Digoxin</td>
<td>Omeprazole</td>
<td>Fluconazole (high dose)</td>
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<td>Didanosine</td>
<td>Pantoprazole</td>
<td>Fluoxetine</td>
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<td>Docetaxel</td>
<td>Phenobarbital</td>
<td>Fluvoxamine</td>
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<td>Dofetilide</td>
<td>Phenylbutazone</td>
<td>Gestodene</td>
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<td>Erythromycin</td>
<td>Phenytoin</td>
<td>Grapefruit</td>
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<td>Felodipine</td>
<td>Prednisone</td>
<td>Indinavir</td>
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<td>Fluconazole (antifungal)</td>
<td>Primdone</td>
<td>Itraconazole</td>
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<td>Glyburide</td>
<td>Rifabutin</td>
<td>Ketoconazole</td>
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<tr>
<td>Indinavir</td>
<td>Rifampicin</td>
<td>Miconazole</td>
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<tr>
<td>Itraconazole (antifungal)</td>
<td>Rifampin</td>
<td>Mibefradil</td>
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<td>Ketoconazole (antifungal)</td>
<td>Troglitazone</td>
<td>Nefazodone</td>
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<td>Loratadine (antihistamine)</td>
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<td>Nifedipine</td>
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<td>Lovastatin (statins)</td>
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<td>Omeprazole</td>
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<td>Metformin</td>
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<td>Propranolol</td>
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<td>Miconazole (antifungal)</td>
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<td>Ritonavir</td>
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<td>Midazolam</td>
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<td>Saquinavir</td>
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<td>Nifedipine</td>
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<td>Sildenafil</td>
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<td>Pimozide</td>
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<td>Simvastatin (statins)</td>
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<td>Prednisonal</td>
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<td>Warfarin</td>
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*This is not a complete list, and readers should refer to the manufacturer’s individual package insert for current information.


**INFliximAB**

- Mouse-human chimeric IgG1 monoclonal antibody specific for TNF-α (human antibody constant regions and murine antibody variable region)
- Mechanism of action: binds to TNF-α only and inhibits its binding to soluble and transmembrane TNF-α receptors
- IV infusion 3–10 mg/kg, 4- to 8-week intervals
- Adverse effects: infusion reactions, risk of serious infections, reactivation of tuberculosis, positive ANA, serum sickness, hepatotoxicity, rare pancytopenia, malignancy risk, CNS demyelinating disorders, exacerbation of or new-onset CHF
- Anti-drug antibodies to the chimeric portion can form and reduce efficacy
• CHF and family history of demyelinating disease or multiple sclerosis are relative contraindications; infections and known hypersensitivity are absolute; avoid live vaccines
• Pregnancy category B

**ADALIMUMAB**
• Fully human IgG1 monoclonal antibody to TNF-α only
• Mechanism of action: blocks TNF-α interaction with the p55 and p75 transmembrane TNF receptor
• Dose: subcutaneous injection 40 mg every other week
• Adverse effects: injection site reactions, increased rate of infection in clinical trials, positive ANA, demyelinating disorders, malignancy, exacerbation of or new-onset CHF
• Contraindications same as etanercept; avoid live vaccines
• Pregnancy category B

**EFALIZUMAB**
• Humanized IgG1 monoclonal antibody against human CD11a subunit of leukocyte function antigen-1 (LFA-1)
• Mechanism of action: blocks the interaction of LFA-1 on T cells with intercellular adhesion molecule 1 (ICAM-1) on antigen presenting cells
• Subcutaneous injection weekly; weight based with conditioning dose
• Adverse effects: thrombocytopenia, psoriasis-like eruption during administration and rebound of psoriasis after discontinuation, hypersensitivity reaction, anti-drug antibodies, rare LFT elevation
• Monitor platelet counts monthly (discontinue if platelets <100,000); no live or acellular vaccines
• Pregnancy category C
• No longer available due to possible risk of progressive multifocal leukoencephalopathy (PML)

**AFLACEPT**
• Fully human dimeric fusion protein of LFA-3 linked to the Fc portion of human IgG1
• Mechanism of action: blocks the interaction of LFA-3 on antigen presenting cells with CD2 on T cells (mostly memory CD45RO+ cells)
• Also links CD2 with CD16 (Fcγ III receptor) on natural killer cells triggering apoptosis of selected memory T cells expressing high levels of CD2 on the surface
• Intramuscular injection given weekly for 12 weeks, followed by 12-week observation period
• Adverse effects: lymphopenia with low CD4 (greatest at 6–8 weeks), malignancies (most commonly skin cancer), infections, hypersensitivity reactions, injection-site reactions, increased LFTs, anti-drug antibodies
• Monitoring: CD4+ T-lymphocyte counts should be monitored weekly during the 12-week dosing period; dose should be held if CD4+ T-lymphocyte counts fall below 250 cells/μl; medication should be discontinued if counts remain below 250 cells/μl for 1 month
• Pregnancy category B

**USTEKINUMAB**
• Fully human monoclonal antibody targeting p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23)
• 45 mg or 90 mg subcutaneous injection at weeks 0, 4, and then every 12 weeks.
• Approved for the treatment of moderate to severe psoriasis

**DENILEUKIN DIFTITOX**
• Mechanism of action
• Diphteria toxin and the receptor-binding domain of human IL-2 are fused
• Drug binds to the IL-2 receptor [cluster of differentiation 25 (CD25)]
• Internalized by receptor-mediated endocytosis and inhibits protein synthesis by translocation of the active portion of diphtheria toxin into the cytosol
• 50% of patients with mycosis fungoides or Sézary syndrome have malignant cells that express CD25; patient’s malignant cells should be tested for CD25 expression to see if this medication would be helpful
• Adverse effects: hypersensitivity/vascular leak syndrome: if two or more of the following three symptoms are present: hypotension, edema, and hypoalbuminemia; common during the first 2 weeks of infusion and may persist or worsen after completing treatment; hypoalbuminemia: occurs after 1 to 2 weeks (serum albumin levels should be at least 3.0 g/d); infectious complications; hypersensitivity
• Pregnancy category C

**THALIDOMIDE**
• Mechanism of action: TNF-α and IL-12 suppressor, antiangiogenic; downregulates adhesion molecules
• Drug of choice for erythema nodosum leprosum
• Adverse effects: sedation, constipation, peripheral (sensory) neuropathy, teratogenicity, leukopenia, bradycardia, rash and fever (mainly in HIV patients), severe birth defects; malformations of extremities, microphthahmia, neural tube defects, cardiac and renal malformations, esophageal fistulas, duodenal atresia, vaginal obstruction
• Monitoring: baseline and monthly neurologic examinations; CBC
• Serum pregnancy testing 24 hours prior to starting medication, then every week for the first month, then monthly thereafter; contraception, testing, and drug therapy compliance survey by patient
• Drug interactions: additive sedative effects: alcohol, barbiturates, chlorpromazine, reserpine

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• Adverse effects: sedation, constipation, peripheral (sensory) neuropathy, teratogenicity, leukopenia, bradycardia, rash and fever (mainly in HIV patients), severe birth defects; malformations of extremities, microphthahmia, neural tube defects, cardiac and renal malformations, esophageal fistulas, duodenal atresia, vaginal obstruction
• Monitoring: baseline and monthly neurologic examinations; CBC
• Serum pregnancy testing 24 hours prior to starting medication, then every week for the first month, then monthly thereafter; contraception, testing, and drug therapy compliance survey by patient
• Drug interactions: additive sedative effects: alcohol, barbiturates, chlorpromazine, reserpine

**USTEKINUMAB**
• Fully human monoclonal antibody targeting p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23)
• 45 mg or 90 mg subcutaneous injection at weeks 0, 4, and then every 12 weeks.
• Approved for the treatment of moderate to severe psoriasis

**DENILEUKIN DIFTITOX**
• Mechanism of action
• Diphteria toxin and the receptor-binding domain of human IL-2 are fused
• Drug binds to the IL-2 receptor [cluster of differentiation 25 (CD25)]
• Internalized by receptor-mediated endocytosis and inhibits protein synthesis by translocation of the active portion of diphtheria toxin into the cytosol
• 50% of patients with mycosis fungoides or Sézary syndrome have malignant cells that express CD25; patient’s malignant cells should be tested for CD25 expression to see if this medication would be helpful
• Adverse effects: hypersensitivity/vascular leak syndrome: if two or more of the following three symptoms are present: hypotension, edema, and hypoalbuminemia; common during the first 2 weeks of infusion and may persist or worsen after completing treatment; hypoalbuminemia: occurs after 1 to 2 weeks (serum albumin levels should be at least 3.0 g/d); infectious complications; hypersensitivity
• Pregnancy category C

**THALIDOMIDE**
• Mechanism of action: TNF-α and IL-12 suppressor, antiangiogenic; downregulates adhesion molecules
• Drug of choice for erythema nodosum leprosum
• Adverse effects: sedation, constipation, peripheral (sensory) neuropathy, teratogenicity, leukopenia, bradycardia, rash and fever (mainly in HIV patients), severe birth defects; malformations of extremities, microphthahmia, neural tube defects, cardiac and renal malformations, esophageal fistulas, duodenal atresia, vaginal obstruction
• Monitoring: baseline and monthly neurologic examinations; CBC
• Serum pregnancy testing 24 hours prior to starting medication, then every week for the first month, then monthly thereafter; contraception, testing, and drug therapy compliance survey by patient
• Drug interactions: additive sedative effects: alcohol, barbiturates, chlorpromazine, reserpine
• Antagonized by thalidomide: acetylcholine, histamine, prostaglandins, serotonin
• Pregnancy category X

**Antimycobacterial Agents**

**ISONIAZID**
- Mechanism of action: disrupts mycobacterial cell walls, inhibits mycolic acid synthesis
- Bacteriostatic at most concentrations
- Elimination through acetylation
- Fast and slow acetylation of patient affects elimination half-life: fast = 70 minutes, slow = 180 minutes
- Adverse effects: neuropathic, hepatotoxic, hemolysis in G6PD deficiency, lupus erythematosus, aceneform eruption, onycholysis, pellagra-like eruption, photosensitivity, pyridoxin (B<sub>6</sub>) deficiency with high doses
- Pyridoxine supplementation can decrease risk of peripheral neuritis
- Pregnancy category C

**RIFAMPIN**
- Mechanism of action
- Macrocyclic antibiotic derived from *Streptomyces mediterranei*
- Mechanism of action: bactericidal; inhibits DNA-dependent RNA polymerase, interfering with bacterial RNA synthesis
- Activity: *Mycobacterium tuberculosis*, many gram-negative organisms, many chlamydiae
- Adverse effects: orange-red discoloration of skin, urine, tears; glossodynia; increased risk of deep venous thrombosis; anti-drug antibodies; IgE mediated anaphylaxis
- Monitoring: CBC and LFT at baseline and during therapy; interruption of therapy and high-dose intermittent therapy associated with thrombocytopenia (reversible if therapy is discontinued as soon as purpura occurs)
- Rifabutin: semisynthetic rifampin that is more effective in treating atypical mycobacteria
- Drug interactions: potent inducer of multiple CYP enzymes
- Pregnancy category C

**CLOFAZIMINE**
- Red, fat-soluble, crystalline dye
- Mechanism of action: inhibits mycobacterial growth by binding preferentially to mycobacterial DNA
- Adverse effects: skin discoloration; secretions discolored: red urine; ichthyosis; severe abdominal symptoms, splenic infarction (rare), bowel obstruction, and gastrointestinal bleeding; crystalline deposits of clofazimine in tissues, including intestinal mucosa, spleen, liver, and mesenteric lymph nodes
- Pregnancy category C

**ETHAMBUTOL**
- Mechanism of action: inhibits metabolite synthesis in susceptible bacteria, resulting in impaired cellular metabolism and cell death
- Bacteriostatic
- Useful for organisms resistant to streptomycin and isoniazid (no cross-resistance)
- Adverse effects: dose-dependent visual disturbances, neurotoxicity, hyperhidrosis, gout
- Pregnancy category C

**PYRAZINAMIDE (PZA)**
- Mechanism of action: unknown
- Bacteriostatic or bactericidal against *M. tuberculosis* depending on concentration of drug attained at site of infection
- Adverse effects: photosensitivity, myalgias, hyperuricemia, gastrointestinal irritation, red-brown change in skin color, alopecia, flushing, hepatic injury (most common and serious side effect); gout can be precipitated by inhibition of excretion of urate
- Pregnancy category C

**STREPTOMYCIN**
- Mechanism of action: bactericidal antibiotic; interferes with normal protein synthesis
- Added as a fourth drug for *M. tuberculosis* treatment
- Given by injection
- Adverse effects: renal tubular damage, vestibular damage, and ototoxicity; caution with myasthenia gravis, hypocalcemia, and conditions that depress neuromuscular transmission
- Pregnancy category D

**Miscellaneous**

**PENICILLAMINE**
- Mechanism of action
- Metal chelator used to treat arsenic poisoning; historical usage for scleroderma
- Adverse mucocutaneous effects: elastosis perforans serpiginosa, bullous diseases (pemphigus, pemphigoid), drug induced lupus, pseudoxanthoma elasticum, and lichen planus
- Pregnancy category D

**COLCHICINE**
- Mechanism of action: binds to tubulin dimers in metaphase; antimitotic
SPIRONOLACTONE
- Mechanism of action: aldosterone antagonist, weak antiandrogen activity by blocking androgen receptor and by inhibiting androgen biosynthesis; may be converted by progesterone 17-hydroxylase to active metabolites that decrease testosterone and dihydrotestosterone (DHT) production.
- Clinical use: dermatologic uses are off label and include acne vulgaris, androgenetic alopecia, hirsutism, hidradenitis suppurativa
- Adverse effects: menstrual irregularities, hyperkalemia, hyponatremia, potential teratogenicity as an antiandrogen (feminization of a male fetus)
- Monitor: serum androgens (testosterone, dehydroepiandrosterone (DHEAS) if abnormal at baseline, periodic serum potassium
- Contraindications: renal insufficiency, anuria, hyperkalemia, pregnancy, abnormal uterine bleeding, family or personal history of estrogen dependent malignancy
- Drug interactions: increased potential of hyperkalemia: angiotensin-converting enzyme inhibitors, thiazide diuretics, potassium supplements
- Pregnancy category D

POTASSIUM IODIDE
- Mechanism of action: unknown; may inhibit granuloma formation and suppress delayed type hypersensitivity reactions by releasing heparin from mast cells
- Used to treat sporotrichosis, erythema nodosum, subacute nodular migratory panniculitis
- Adverse effects: hypothyroidism from Wolff-Chaikoff effect (excess iodide blocks organic iodide binding in thyroid hormone synthesis); iododerma, acneiform, and vascular eruptions; flare-up of dermatitis herpetiformis
- Pregnancy category D

AURANOFIN
- Mechanism of action: gold is taken up by macrophages, which in turn inhibit phagocytosis and lysosomal membrane stabilization
- Alters immunoglobulins, decreasing prostaglandin synthesis and lysosomal enzyme activity
- Monitor: discontinue therapy if platelet counts fall to less than 100,000/mm³, white blood cell count to less than 4000/mm³, granulocytes to less than 1500/mm³
- Pregnancy category C

INTRAVENOUS IMMUNOGLOBULINS (IVIG)
- Immunoglobulins are extracted from pooled plasma requiring between 10,000 and 20,000 donors
- Mechanism of action: blockade of Fc receptors, prevents complement mediated effects, reduces circulating pathogens and antibodies, alters cytokine/cytokine antagonist ratios
- Adverse effects: increases in creatinine and blood urea nitrogen, infusion reaction (within one hour) headache, flushing, chills, myalgia, wheezing, tachycardia, low back pain, nausea, and/or hypotension.
- Monitor: LFT’s, renal function tests, immunoglobulin levels (in order to exclude IgA deficiency), rheumatoid factor and cryoglobulin levels, screen for HIV and hepatitis
- Contraindications: documented hypersensitivity; IgA deficiency; anti-IgE/IgG antibodies
- Pregnancy category C

PHOTOTHERAPY
- Ultraviolet B (UV-B): 290–320 nm
- Narrow band UV-B (311 nm)
- Goeckerman regimen: coal tar followed by UV-B exposure
- Ingram method: anthralin application following a tar bath and UV-B treatment
- Psoralen and ultraviolet A (wavelengths 320–400 nm) photochemotherapy (PUVA)
- Mechanism of action:
  - Uses the photosensitizing drug methoxsalen (8-methoxypsoralens) in combination with ultraviolet A (UV-A) irradiation
  - Interferes with DNA synthesis by inhibiting mitosis and binding covalently to pyrimidine bases in DNA when photoactivated by UV-A
  - Decreases cellular proliferation, and also induces apoptosis of cutaneous lymphocytes leading to a localized immunosuppression
- Adverse effects of PUVA therapy: nausea, pruritus, and burning; known to be carcinogenic, with risk being dose-dependent; minimize exposure to outdoor or bright indoor light for 24 hours after each dose due to photosensitivity; PUVA lentigines
- Contraindications: diseases associated with photosensitivity
- Pregnancy category C
TOPICAL TREATMENTS

Vehicles in Dermatologic Therapy
Combination of various chemicals to enhance the usability of the treatment

- Common vehicle ingredients:
  - Emollients: used to retard transepidermal loss, occlude the active molecule, increase flexibility of the skin. (i.e., glycerin, petrolatum, mineral oil, stearic acid, propylene glycol stearate)
  - Emulsifying agents: help create oil-in-water preparations: cream and lotions. (i.e., lanolin, sodium lauryl sulfate)
  - Solvents: help to create a less viscous product (i.e., alcohol, propylene glycol)
  - Humectants: used in all oil-in-water preparations to maintain the required water content (i.e., glycerin, propylene glycol)
- Types of vehicles:
  - Cream: a semisolid emulsion of oil in water; contains a preservative to prevent overgrowth of microorganisms; stabilized by an aqueous emulsifier
  - Gel: a semisolid, transparent, nongreasy emulsion (cellulose cut with alcohol or acetone)
  - Lotion: liquid vehicle, aqueous or alcohol-based, that may contain a salt in solution
  - Ointment: a semisolid grease/oil, sometimes also containing powder, but little or no water; the active ingredient is suspended; usually no preservative needed
  - Paste: an ointment with a high proportion of powder that gives a stiff consistency
- Other vehicles:
  - Foam
  - Hydrogel: (alcohol and surfactant free)

Acne Preparations

Benzoyl Peroxide
- Mechanism of action: broad spectrum bactericidal agent with oxidizing activity
- Activity against: P. acnes, S. capitis, S. epidermidis, S. hominis, P. avidum, P. granulosum and Pityrosporum ovale
- Antibacterial effect greater than comedolytic effects
- Adverse effects: skin irritation and drying; contact allergy (1%)

Azelaic Acid
- Dicarboxylic acid
- Mechanism of action
  - Reduces production of keratin and inhibits growth of Propionibacterium acnes, antityrosinase activity
- Adverse effects: may produce hypopigmentation, skin irritation
- Pregnancy category B

Salicylic Acid
- Keratolytic
- Adverse effects: erythema and peeling.
- Systemic toxicity (occurs when blood concentrations exceed 35 mg/dl) nausea, vomiting, confusion, dizziness, delirium, psychosis, stupor, coma, death, respiratory alkalosis, metabolic acidosis, hypoglycemia, tinnitus, hyperventilation

Sulfur
- Comedolytic, keratolytic, mild antibacterial dose 5–10%
- Adverse effects: odor, application site reaction
- Lotion 5% sulfur, 22% alcohol
- Combination: sulfur–sodium sulfacetamide
- Lotion 50 mg sulfur, 100 mg sulfacetamide

Retinoids
- Mechanism of action: see systemic section for details
- Tretinoin (all-trans retinoic acid)
  - Binds with approximately equal affinity to all three RARs and also can be converted to forms that activate the RXRs
  - Adverse effects: tenderness, erythema, and burning; also increased risk of sunburn
  - Pregnancy category C
- Adapalene
  - Retinoid properties from a synthetic naphtholic acid derivative
  - Equal selectivity for the nuclear RAR-β/γ receptors (RAR-γ predominant receptor in epidermis) and weakly for RAR-α
  - Pregnancy category C
- Tazarotene
  - Prodrug is hydrolyzed rapidly in tissues to the active metabolite tazarotenic acid
  - Binds to RAR-β > RAR-γ > RAR-α receptors, no RXR
  - Pregnancy category X
- Alitretinoin (9-cis-retinoic acid): binds to and activates both RXRs and RARs, all subtypes; used for Kaposi’s sarcoma

Alpha-Hydroxy Acids (See Chapter 14)

Topical Antibiotics
See above for mechanisms of other antibiotics.

Mupirocin
- Produced by fermentation of Pseudomonas fluorescens
- Mechanism of action: inhibits bacterial isoleucyl-tRNA synthetase and blocks bacterial RNA synthesis
- Pregnancy category B

Retapamulin
- Belongs to the pleuromutilin class
• Mechanism of action: inhibits the initiation of protein synthesis at the level of bacterial 50S ribosome; bacteriostatic
• Pregnancy category B

**Silver Sulfadiazine**
• Mechanism of action: inhibiting DNA replication and modification of the cell membrane adverse effects—early luekopenia (in post burn patients)

**Dapsone**
• Sulfone derivative with anti-inflammatory properties
  • Mechanism of action: see systemic section above
  • 5% gel applied twice daily
  • Indicated for acne
  • Adverse events: oiliness, peeling, dryness, erythema at the application site, no cross reactivity with sulfonamides (antimicrobial agents)
• Pregnancy category C

**Bleaching Agents**

**Hydroquinone**
• Inhibits tyrosinase (causes oxidation of tyrosine to 3, 4-dihydroxyphenylamine)
• Prepared 2%, 3%, and 4% concentrations
• Adverse events: exogenous ochronosis
• Pregnancy category C

**Kojic Acid**
• Mechanism of action: inhibits tyrosinase
• Adverse effects: contact sensitivity

**Mequiol**
• Mechanism of action: exact action unknown; it is a substrate for tyrosinase, and thus, a competitive inhibitor of the formation of melanin precursors
• Pregnancy category X when used with tretinoin

**Topical Anesthetics (See Chapters 13 and 14)**
• Topical Immunosuppressives

**Tacrolimus and Pimecrolimus**
• Macrolide derived from *Streptomyces tsukubaensis*
• Mechanism of action
  • Binds to FK-506 binding protein (receptor within cytoplasm) and the drug-protein complex inhibits calcineurin (a calcium-dependent phosphatase enzyme)
  • Without the phosphatase activity of calcineurin, nuclear factor of activated T-cells (NF-AT) cannot translocate to the nucleus and activate transcription of proinflammatory cytokines
    - IL-2, IL-3, IL-4, IL-5, IL-10, GM-CSF, and TNF-α
• Reduction in the activity of T-lymphocytes in the immune system
• Adverse effects: minimally absorbed into the blood; application site stinging
• Pregnancy category C

**Topical Antivirals**

**Imiquimod 5% Cream**
• Imidazoquinoline amine
• Mechanism of action
  • Induction of cytokines after binding to a transmembrane receptor: Toll-like receptor 7 (an innate immunity response)
  • Stimulation of the cellular arm of acquired immunity through induction of IFN-α, IFN-γ, and IL-12; T memory cells are created after activation from dendritic cells
• Adverse effects: local skin irritation
• Pregnancy category C

**Acyclovir, Penciclovir**
• Mechanism of action and side effects: See oral section

**Podophyllin**
• Extract from May apple plant
• Mechanism of action: binds to protein tubulin and arrests cells in metaphase; antimitotic
• Pregnancy category X

**Antifungals**

**Zinc Pyrithione**
• Mechanism of action: inhibitor of membrane transport in fungi
• Adverse effects: allergic contact dermatitis
• Azoles, allylamines, polyenes: see oral section

**Selenium Sulfide**
• Mechanism of action: increase fungal shedding by decreasing comeocyte production; sporocidal
• Adverse effects: skin irritation, hair loss

**Ciclopirox**
• Mechanism of action: chelation of polyvalent metal cations (e.g., Fe³⁺ and Al³⁺); inhibits metal-dependent enzymes, responsible for the degradation of peroxides within microbial cells
• Adverse effects: contact dermatitis and pruritus
• Pregnancy category B

**Androgenetic Alopecia Treatment**

**Minoxidil**
• Mechanism of action
• relaxes arteriolar smooth muscle, causing vasodilation; mechanism for hair growth not known
- Adverse effects: may exacerbate angina pectoris; caution in pulmonary hypertension, congestive heart failure, coronary artery disease, and significant renal failure
- Pregnancy category C

**Finasteride**
- Mechanism of action: inhibits conversion of testosterone to dihydrotestosterone by inhibiting competitive inhibition of type II 5α-reductase
- Adverse effects: decreased libido or erectile dysfunction (2%)
- Pregnancy category X

**Treatment of Hirsutism**

**Efllornithine HCL 13.9% Cream**
- Mechanism of action: inhibits enzyme ornithine decarboxylase (ODC)
- Metabolic activity in the hair follicle decreases, and hairs grow in more slowly
- Adverse effect: mild skin irritation
- Pregnancy category C

**Sunscreens**
- Chemical Blockers
- Aromatic compounds conjugated with a carbonyl group

**Ultraviolet B Filters**
- Aminobenzoic acid and derivatives
  - Padimate O (most potent UV-B absorber)
  - para-Aminobenzoic acid (PABA): high incidence of hypersensitivity
- Cross-sensitivity with PABA: artificial sweeteners (e.g., saccharin, sodium cyclamate); ester-type anesthetics, Azo dyes (e.g., aniline, paraphenylenediamine), sulfonamide antibiotics, sulfonamide-based oral hypoglycemics, or thiazide diuretics
- Cinnamates
  - Octyl methoxycinnamate (second most potent UV-B absorber compared with padimate O)
- Cross sensitivity to cinnamino derivatives: balsam of Peru, balsam of Tolu, Cassia, cinnamic acid, cinnamic alcohol, cinnamic aldehyde, cinnamon oil, coca leaves
- Salicylates
  - Octyl salicylate: used to augment the UV-B protection in a sunscreen, 280–320 nm
  - Weak UV-B absorbers
- Octocrylene
  - May be used in combination with other UV absorbers, 250–360 nm
  - Phenylbenzimidazole sulfonic acid, selective UV-B filter

**Ultraviolet A Filters**
- Benzophenones oxybenzone, absorbs well through UV-A II (benzophenone-3) wavelengths, benzophenones are primarily UV-B absorbers, 270–350 nm
- Anthranilates: menthyl anthranilate, absorbs mainly in the near UV-A portion, 260–380 nm
- Dibenzoylmethanes
  - Avobenzone (Parsol 1789), 320–400 nm
  - Dioxybenzone, 250–390 nm
  - Mexoryl

**Physical Blockers**
- Titanium dioxide, 290–700 nm
- Zinc oxide, 290–700 nm

**Parasiticidals**

**Malathion**
- Mechanism of action: irreversible cholinesterase inhibitor hydrolyzed (and therefore detoxified) rapidly by mammals, but not by insects
- Binds to hair and may provide some residual protection after therapy
- Adverse effects: alcohol may irritate excoriated skin; the lotion is flammable; take care to avoid mucosal surfaces, eyes; do not apply to lashes
- Pregnancy category B

**Permethrin**
- Mechanism of action: synthetic pyrethrin
- Neurotoxin that causes paralysis and death in ectoparasites
- Adverse effects: lack of safety data on children younger than 2 months as well as pregnant and breastfeeding women
- Pregnancy category B

**Lindane 1% (Gamma-Benzene Hexachloride)**
- Mechanism of action: neurotoxin that causes seizures and death in parasitic arthropods
- Adverse effects: do not use in infants, small children, patients with a history of seizure, or lactating or pregnant women

**Precipitated Sulfur 6%**
- Topical formulation can be used to treat scabies in pregnant women and young infants

**Crotonitom**
- 10% cream or lotion
- Indicated for scabies
- Mechanism: unknown
- Pregnancy category C

**Topical Corticosteroids**
- Mechanism of action: see systemic section for details
- Efficacy of an individual topical corticosteroid is related to its potency (the intensity of a TCS’s clinical effect)
- Pharmacokinetics: clinical potency of a TCS preparation depends on three factors: structure, vehicle, and
type of skin to which it is applied. The addition of functional groups (e.g., hydroxy, hydrocarbon, ester, fluoro, chloro, acetonide, ketone)

- Hydroxyl group changes: affects lipophilicity, solubility, percutaneous absorption, glucocorticoid receptor (GCR)-binding activity.
- Halogenation: augments glucocorticoid and mineralocorticoid activity.
- Fluorination or chlorination: enhances potency
- Class 1: superpotent
- Classes 2 and 3: high
- Classes 4 and 5: intermediate
- Class 6: low
- Class 7: least potent
- Adverse effects: local: acne, tachyphylaxis, skin atrophy (striae, telangiectasia and purpura), glaucoma/cataracts, delayed wound healing, allergic dermatitis, tachyphylaxis, systemic: may suppress hypothalamic-pituitary-adrenal (HPA) axis (rare)
- Risk factors for adverse effects: young age, liver disease, renal disease, amount of topical steroid applied, potency of topical steroid, use of occlusion, location of topical application (face, neck, axilla, groin, upper inner thighs)

**Topical Corticosteroid Allergic Contact Dermatitis Cross-Reaction Groups**

- **Group A**: hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, prednisone
- **Group B**: triamcinolone acetonide, triamcinolone alcohol, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, halcinonide
- **Group C**: betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone
- **Group D**: hydrocortisone-17-valerate, hydrocortisone-17-butyrate, aclometasone dipropionate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone acetate.
- Screening agents for patch testing: tixocortol pivalate, hydrocortisone-17-butyrate, budesonide.

**Topical Chemotherapy Agents**

**Nitrogen Mustard**

- Mechanism of action: cytotoxic to cancer cells via DNA alkylation
- Adverse effects: delayed hypersensitivity (35% to 60%), can be overcome with use of topical steroids or desensitization and less common with use of ointment; associated with an increased risk of nonmelanoma skin cancers
- Pregnancy category D

**5-Flurouracil**

- Mechanism of action: inhibits thymidylate synthetase, leading to inhibition of DNA synthesis and cell death
- Adverse effects: local pain, pruritus, hyperpigmentation, irritation, inflammation and burning at the site of application, allergic contact dermatitis, scarring, soreness, tenderness, suppuration, scaling and swelling
- Pregnancy category D

**Other**

**Castellani Paint**

- Compound solution of resorcinol (8 g), acetone (4 ml), magenta (0.4 g), phenol (4.0 g), boric acid (0.8 g), industrial methylated spirit 90% (8.5 ml), and water (100 ml)
- Fungicidal and bactericidal
- Adverse effects: magenta can stain clothing and skin; may be toxic in children because of phenol content; may cause irritation
- Pregnancy category C

**Photodynamic Therapy (PDT)**

- Mechanism of action:
  - Topical application of aminolevulinic acid (ALA) on skin leads to the accumulation of the endogenous photosensitizer protoporphyrin IX (PpIX) in epidermal cells
  - Conversion of ALA to PpIX occurs in skin cells by enzymes in the heme biosynthetic pathway
  - Rapidly proliferating skin cells convert more ALA to PpIX than do less rapidly proliferating normal epidermal cells
  - Subsequent illumination of the lesion with noncoherent blue light (417 nm) 3 to 6 hours after ALA application causes ALA to be enzymatically converted into the active endogenous photosensitizer PpIX
  - Methyl 5-aminolevulinate also can be used instead of ALA with red light (630nm); other light sources are between 400–800nm (visible spectrum) and include pulsed dye laser and intense pulsed light
- Apoptotic cell death and vascular injury for PDT-mediated tissue ablation
- Adverse effects: burning pain, stinging, or itching restricted to the illuminated area; erythema and mild edema of the treated area; generalized cutaneous photosensitivity, photophobia, and/or ocular discomfort, residual hyperpigmentation and hypopigmentation
- Pregnancy category C

**Calcipotriene (Calcipotriol)**

- Mechanism of action:
  - Synthetic analog of calcitriol. Vitamin D has been shown to inhibit the proliferation of keratinocytes
DRUG SIDE EFFECTS

in culture and to modulate epidermal differentiation; vitamin D inhibits production of IL-2 and IL-6 by T cells, blocks transcription of interferon (IFN)-gamma and granulocyte-macrophage colony-stimulating factor (GM-CSF), messenger ribonucleic acid (mRNA) and inhibits cytotoxic and natural killer T cell activity.

• Adverse effects: hypercalcemia: use should not exceed 100 g per week
• Pregnancy category C

ANTHRALIN

• Mechanism of action
  • Naturally occurring saturated dicarboxylic acid–possessing antibacterial, comedolytic, and anti-inflammatory activities
  • Stimulates monocytes proinflammatory activity and induces extracellular generation of free radicals
  • Inhibits cell growth and restores cell differentiation
  • Prolonged contact method uses 0.5%–1.0% preparations applied for several hours; short contact method uses higher concentrations of anthralin (0.5%–1.0%) but usually applied for only 1 hour or less
• Adverse effects: irritating to normal skin
• Applications in excessive amounts may stain clothing; long-term corticosteroid treatment withdrawal may cause complications of rebound phenomenon
• Pregnancy category C

Antiperspirants

ALUMINUM SALTS

• Mechanism of action: reversibly inhibits eccrine gland secretion by an unknown mechanism.
• Aluminum chloride 10% to 30% in distilled water or 60% alcohol
• Adverse effects: irritant dermatitis
• Pregnancy category C

Botulinum Toxin

• See Chap. 14.

PREGNANCY CATEGORIES

• All drugs are classified into the following categories
  • A. Controlled studies show no risk
    • Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to fetus
  • B. No evidence of risk in humans
    • Either animal findings show risk but human findings do not, or if no adequate human studies have been done, animal findings are negative
  • C. Risk cannot be ruled out
• Human studies are lacking, and the animal studies are either positive for fetal risk or lacking. However, potential benefits may justify the potential risk
• D. Positive evidence for risk
  • Investigational or postmarketing data show risk to fetus. Nevertheless, potential benefits may outweigh the potential risk
• X. Contraindicated in pregnancy
  • Studies in animals or humans or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient

DRUG SIDE EFFECTS

• Acanthosis nigricans: NODES: nicotinic acid/niacin, oral contraceptives, dilantin, estrogens, steroids
• Acne (pimples): phenytoin, Isoniazid, iodides, moisturizers, phenobarbitol, lithium, ethionamide, steroids
• Acral erythema: Ara-C, bleomycin, doxorubicin, etoposide, 5-FU, hydroxyurea, mercaptopurine, methotrexate
• Acral sclerosis: bleomycin
• Acute generalized exanthematous pustulosis: penicillin, macrolide antibiotics, alopecia, chemotherapy agents, anticoagulants, hormones, anticonvulsants, amantidine, captopril, cholesterol-lowering drugs, isotretinoin, ketoconazole, propranolol, cimetidine
• Blue-gray hyperpigmentation: desipramine, amiodarone, antimalarials/anticonvulsants, minocycline, imipramine, thorazine
• Bullous eruptions: lasix, penicillamine, thiols (captopril), penicillin, sulfonamides. PUVA
• Cutis laxa: penicillin
• Dental abnormalities: tetracycline (gray, discolored teeth)
• Dermatomyositis: hydroxyurea, penicillamine
• Elastosis perforans serpiginosa: penicillamine
• Erythema nodosum: OCP, antibiotics (sulfonamides, tetracycline, penicillin), 13-cis retinoic acid, gold, opiates, halogens
• Eyelash growth: interferon, lumigan
• Fixed drug eruptions: NSAIDs (pigmented), sulfonamides (pigmented), pseudoephedrine (nonpigmented), phenothaleine laxatives, OCP, tetracycline, aspirin, barbiturates, carbamazepine
• Gingival hyperplasia: calcium channel blockers, cyclosporine, dilantin
• Gray baby syndrome: chloramphenicol
• Hypertrichosis: cyclosporine (but not Prograf), diazoxide, danazol, minoxidil, spironolactone, psoralen
• **Ichthyosis**: nicotinic acid
• **Leg ulcers**: hydroxyurea
• **Lichenoid eruptions**: lasix, penicillamine, gold, thiazides, chlorpropamide, antimalarials, methyldopa, phenylthiazides, beta blockers
• **Linear IgA**: vancomycin
• **Lipodystrophy**: crixivan (“crix belly”)
• **Livedo reticularis**: quinidine (photodistributed), amantadine
• **SCLE**: D-penicillamine, HCTZ, lamisil, sulfonureas, griseofulvin, naproxen, diltiazem, procaainamide, PUVA, minocycline
• **Systemic lupus erythematosus (D-CHIPS)**: dilantin, chlorpropamide, hydralazine, isoniazid, procaainamide, sprouts (alfalfa sprouts/L-canaavanine)
• **Melanonychia striata**: AZT (zidovudine), neutrophilic ecrine hidradenitis, Ara-C, bleomycin
• **Optic neuritis**: ethambutol
• **Pellagra-like eruption**: isoniazid, azathioprine, 5-FU
• **Pemphigus vulgaris**: penicillamine, thiols (captopril)
• **Penile ulcers**: foscarinet
• **Photoallergic drug reaction**: griseofulvin, NSAIDs, phenothiazines, quinidine, sulfonamide, sulfa drugs. thiazide diuretics. *para*-amino benzoic acid. *para*-phenylene diamine
• **Photo-onycholysis**: tetracycline, 8-MOP
• **Photo-toxic drug reaction**: amiodarone, nalidixic acid, NSAIDS, phenothiazines (chlorpromazine), tetracyclines
• **Pityriasis rosea-like eruptions**: barbiturates/bismuth, omeprazole, beta blockers, captopril, clonidine, griseofulvin, isoretinoin, metronidazole, penicillin
• **Porphyria cutanea tarda**: griseofulvin, rifampin, antimalarials/alcohol, busulfan/benzenes, hormones, iron, phenols, sulfonylurea
• **Pseudolymphoma**: anticonvulsants (dilantin, phenobarbitol), antihypertensives (beta blockers, ACE inhibitors, calcium channel blockers), tricyclic antidepressants, allopurinol
• **Pseudomembranous colitis**: clindamycin
• **Pseudoporphyrina**: tetracycline, isoretinoin, naproxen, nalidixic acid, piroxicam, lasix, sulfonamides, hemodialysis for chronic renal failure
• **Pseudotumor cerebri**: isoretinoin, tetracycline, steroids
• **Pseudoxanthoma elasticum**: penicillamine
• **Psoriasis**: GCSF, INH, NSAIDs, steroids, lithium, ACE inhibitors/antimalarials, beta blockers, penicillamine, OCP
• **Pulmonary fibrosis**: methotrexate, interferon-α, gold, azathioprine, cyclophosphamide, cytotoxan, bleomycin
• **Raynaud’s**: bleomycin, vincristine
• **Red-orange body fluids (tears/urine)**: rifampin

- **Sweet’s syndrome**: filgrastim, OCP, minocycline, all trans retinoic acid, TMP-SMZ, celecoxib
- **Toxic epidermal necrolysis**: sulfonamides, penicillin, allopurinol, NSAIDs, anticonvulsants (phenytoin, phenobarbitol, carbamazepime), pentamidine
- **Urticaria**: aspirin, NSAIDs, antibiotics (penicillin, sulfonamides, rifampin, vancomycin), opiates, barbiturates, contrast dye, ACE inhibitors (captopril)
- **Vasculitis**: ampicillin, sulfonamides, thiazides, furosemide, NSAIDs, cimetidine, ACE inhibitors
- **Vestibular toxicity**: aminoglycosides

### QUIZ

#### Questions

1. Match the following medication with the enzyme it inhibits.
   A. Methotrexate i. Dihydropteroate synthetase
   B. Dapsone ii. Dihydrofolate reductase
   C. Sulfonamides
   D. Trimethoprim

2. The following adverse effects of corticosteroids are not reduced by alternate day dosing EXCEPT:
   A. Osteoporosis
   B. Osteonecrosis
   C. Adrenal crisis
   D. Cataracts

3. The following medications can cause increased myelosuppression when given with azathioprine EXCEPT:
   A. Folate antagonists
   B. Beta blockers
   C. ACE inhibitors
   D. Allopurinol

4. Which of the following cytotoxic agents can cause reproductive side effects including azoospermia and amenorrhea?
   A. Cyclophosphamide
   B. Chlorambucil
   C. Mycophenolate mofetil
   D. A and B only

5. Match the topical retinoid to its appropriate nuclear receptors.
   A. Tretinoin i. RAR-β and RAR-γ equally
   B. Alitretinoin weakly to RAR-α
   C. Adapalene ii. All subtypes of RXR equally
   D. Tazarotene iii. All subtypes of RAR and RXR
   E. Bexarotene iv. RAR-β > RAR-γ > RAR-α
   v. All subtypes of RAR equally
6. Match the following antibiotic to its appropriate side effect.
   A. Minocycline
   B. Erythromycin estolate
   C. Linezolid
   D. Vancomycin
   E. Cefaclor

   i. Thrombocytopenia
   ii. Linear IgA bullous dermatosis
   iii. Serum sickness like reaction
   iv. Osteoma cutis
   v. Cholestatic jaundice

7. All of the following metabolic abnormalities can be caused by cyclosporine EXCEPT:
   A. Hyperkalemia
   B. Hyperuricemia
   C. Hypermagnesemia
   D. Hyperlipidemia

8. Match the appropriate class of antifungal with its mechanism of action.
   A. Allylamines
   B. Azoles
   C. Echinocandins
   D. Griseofulvin
   E. Polyenes

   i. Interferes with microtubule formation
   ii. Inhibits glcan synthesis
   iii. Inhibits lanosterol
   iv. Binds to ergosterol and forms membrane pores
   v. Inhibits squalene

9. All of the following immunobiologicals are pregnancy category B EXCEPT:
   A. Efalizumab
   B. Adalimumab
   C. Etanercept
   D. Infliximab

10. In an average adult, approximately how many grams of ointment does the whole body require in a single dose?
    A. 5–10 g
    B. 20–30 g
    C. 60–70 g
    D. 100–110 g

Answers
1. A. ii; B. i; C. i; D. ii; Folate is converted to dihydrofolate by dihydropteroate synthetase, which is blocked by dapsone and sulfonamides. Dihydrofolate is then converted to tetrahydrofolate by dihydrofolate reductase, which is blocked by methotrexate and trimethoprim. Note that methotrexate competitively and irreversibly inhibits dihydrofolate reductase. Furthermore, tetrahydrofolate is used as a cofactor and acted on by thymidylate synthetase for DNA synthesis. Methotrexate also causes partial, reversible inhibition of thymidylate synthetase.

2. C. The risk of cataracts, osteoporosis, and possibly osteonecrosis are not reduced by alternate day dosing of corticosteroids. However, the risk of adrenal crisis can be reduced by alternate dosing.

3. B. ACE inhibitors, folate antagonists such as methotrexate, and xanthine oxidase inhibitors such as allopurinol can increase the risk of myelosuppression when given with azathioprine. Beta blockers are not associated with this risk.

4. D. Both cyclophosphamide and chlorambucil can cause azoospermia and amenorrhea. It can occur after prolonged therapy and may be irreversible with cyclophosphamide. Mycophenolate mofetil is not associated with reproductive side effects and most commonly causes dose dependent gastrointestinal side effects.

5. A. v; B. iii; C. i; D. iv; E. ii. Tretinoin binds to all subtypes of RAR equally. Alitretinoin binds to all subtypes of RAR and RXR, although with slightly more affinity to RAR. Adapalene binds to RAR-ß and RAR-γ equally; weakly to RAR-α. Tazarotene binds to RAR-ß > RAR-γ > RAR-α. Bexarotene binds to all subtypes of RXR equally. Note that RAR-γ is the predominant nuclear receptor in the epidermis.

6. A. iv; B. v; C. i; D. ii; E. iii. Minocycline can cause osteoma cutis. The estolate form of erythromycin can cause cholestatic jaundice. Linezolid can cause reversible thrombocytopenia. Vancomycin can cause linear IgA disease. Cefaclor can cause serum sickness like reaction.

7. C. Cyclosporine can cause hypomagnesemia. Besides metabolic abnormalities, cyclosporine can also cause hypertension in approximately one quarter of patients and blood pressure should be checked on every visit.

8. A. v; B. iii; C. ii; D. i; E. iv. In the fungal cell membrane synthesis pathway, squalene is converted to lanosterol by squalene epoxidase, which is blocked by allylamines. Lanosterol is converted to 14-α demethyl lanosterol by cytochrome p-450 dependent 14-α demethylase. This enzyme is blocked by the azoles. The end product, ergosterol, cannot be synthesized. The echinocandins (capsofungin) inhibits glucan synthesis, an essential polysaccharide of the fungal cell wall. The polyenes (amphotericin) binds to ergosterol and forms membrane pores altering permeability to ions. Griseofulvin interferes with microtubule formation and causes metaphase arrest.
9. A. Efalizumab is pregnancy category C. Adalimumab, etanercept, infliximab, and alefacept are all pregnancy category B.
10. B. The whole body of an average adult requires 20–30 g of ointment per single dose. Face or neck requires 1 g. Each side of trunk requires 3 g. Each arm requires 1½ g. Each hand requires ½ g. Each leg requires 3 g. Each foot requires 1 g.

REFERENCES


ANATOMIC REVIEW OF ARTERIES AND VEINS AND LYMPHATICS

Arteries of the Head and Neck
(Fig. 25-1, Table 25-1)

- Blood supply to the head and neck
  - The internal carotid artery (ICA)
  - External carotid artery (ECA) and their branches
- Intimate anastomoses between ICA and ECA in the region of the upper central face (nose, glabella, periorbital, and forehead)
- These connections are important clinically in that:
  - Infections in this area may extend intracranially via ICA
  - Steroid injections in the periorbital skin may embolize to the retinal artery and cause blindness
- Named arteries give rise to unnamed branches and perforators that nourish overlying muscles, fascia, subcutaneous fat, and skin
  - Septocutaneous arteries: travel through septa to skin
  - Musculocutaneous arteries: perforate muscles to skin
  - Subdermal plexus arteries: at the junction of the subcutaneous fat and the deep reticular dermis
    - Arise from septocutaneous and musculocutaneous arteries
    - Main blood supply to the skin
    - Undermine at least below midfat to preserve the subdermal plexus as immediate subdermal undermining may compromise the subdermal plexus

Venous System of the Lower Extremities
(Fig. 25-2, Table 25-2)

- Consists of the superficial (above muscular fascia) and deep (below muscular fascia) venous system
- The superficial and deep systems are connected via perforator veins
- Flow is unidirectional
  - Superficial veins drain into the deep veins via the perforators
  - Deep veins merge to form the common femoral vein
  - Venous valves permit only one-way flow (upward), when competent
  - Greatest density in the calf and progressively fewer valves in the thigh
- Calf muscles act as a muscular pump to drain venous blood
  - Venous blood is moved only during muscle contraction
  - Lying still or standing still does not drain the venous system

Lymphatics

LYMPH GLANDS OF THE HEAD AND NECK
- See Figure 25-3

LYMPH GLANDS OF THE UPPER EXTREMITY
- Divided into two sets: superficial and deep
  - Superficial lymph glands: few and of small size
  - Deep lymph glands: chiefly grouped in the axilla

LYMPHATICS OF THE LOWER EXTREMITY
- Anterior tibial gland: small and inconstant
- Popliteal glands: small in size and some six or seven in number; imbedded in the fat
- Inguinal glands: situated at the upper part of the femoral triangle

ANATOMIC REVIEW OF MUSCLES

See Tables 25-3 and 25-4.
ANATOMIC REVIEW OF NERVES

Nerve Blocks: General Considerations

- Aspirate before injecting
  - Use a 30-gauge needle with a 60-degree beveled point
  - If pain/dysesthesia is elicited during insertion or injection, withdraw the needle slightly to avoid injuring the nerve itself
  - Do not inject the nerve directly; goal is to bathe the perineural space with local anesthetic
  - Wait at least 10 to 20 minutes for effective anesthesia
  - Most importantly: know your anatomy

Innervation of the Head and Neck (Tables 25-5, 25-6, and 25-7; Figs. 25-5 and 25-6)

- Facial nerve (CN VII)
  - Emerges from cranium through the stylomastoid foramen and runs in the deep body of the parotid in the lateral cheek/jaw
  - Sensory (minor role): sensation to the external auditory meatus along with auriculotemporal and vagus nerves
  - Motor (major function): five branches that innervate the muscles of facial expression:
    - Temporal
    - Zygomatic
    - Buccal
### TABLE 25-1 Branches of the Carotid Artery

<table>
<thead>
<tr>
<th>Internal Carotid Artery Branches</th>
<th>External Carotid Artery Branches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplies structures inside the skull, except for central facial arteries that nourish the periorbital skin, forehead, glabella, and nose:</td>
<td></td>
</tr>
<tr>
<td>• Supraorbital</td>
<td></td>
</tr>
<tr>
<td>• Supratrochlear</td>
<td></td>
</tr>
<tr>
<td>• Infratrochlear</td>
<td></td>
</tr>
<tr>
<td>• Dorsal nasal</td>
<td></td>
</tr>
<tr>
<td>• External nasal arteries</td>
<td></td>
</tr>
<tr>
<td>• Superficial temporal</td>
<td></td>
</tr>
<tr>
<td>• Maxillary</td>
<td></td>
</tr>
<tr>
<td>– Anterior tympanic</td>
<td></td>
</tr>
<tr>
<td>– Middle meningeal</td>
<td></td>
</tr>
<tr>
<td>– Inferior alveolar</td>
<td></td>
</tr>
<tr>
<td>– Accessory meningeal</td>
<td></td>
</tr>
<tr>
<td>– Masseteric</td>
<td></td>
</tr>
<tr>
<td>– Ptterygoid</td>
<td></td>
</tr>
<tr>
<td>– Deep temporal</td>
<td></td>
</tr>
<tr>
<td>– Buccal</td>
<td></td>
</tr>
<tr>
<td>– Sphenopalatine</td>
<td></td>
</tr>
<tr>
<td>– Descending palatine</td>
<td></td>
</tr>
<tr>
<td>– Infraorbital</td>
<td></td>
</tr>
<tr>
<td>– Posterior superior alveolar</td>
<td></td>
</tr>
<tr>
<td>– Middle superior alveolar</td>
<td></td>
</tr>
<tr>
<td>– Pharyngeal</td>
<td></td>
</tr>
<tr>
<td>– Anterior superior alveolar</td>
<td></td>
</tr>
<tr>
<td>– Artery of the ptterygoid canal</td>
<td></td>
</tr>
<tr>
<td>• Posterior auricular</td>
<td></td>
</tr>
<tr>
<td>• Occipital</td>
<td></td>
</tr>
<tr>
<td>• Facial</td>
<td></td>
</tr>
<tr>
<td>• Lingual</td>
<td></td>
</tr>
<tr>
<td>• Ascending pharyngeal</td>
<td></td>
</tr>
<tr>
<td>• Superior thyroid</td>
<td></td>
</tr>
</tbody>
</table>

These three nerves line up vertically at the midpupillary line, which is 2.5 cm from the facial midline (Fig. 25-6).

Intraoral approach to infraorbital and mental nerve is preferred to reduce patient discomfort, which is greater with transcutaneous injections.

**Supraorbital nerve block**
- Supraorbital and supratrochlear nerves innervate the frontal part of scalp and forehead.

**TABLE 25-2  Leg Veins**

<table>
<thead>
<tr>
<th>Location</th>
<th>Superficial Leg Veins</th>
<th>Deep Leg Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Veins lie above the deep muscular fascia and drain into the deep venous system</td>
<td>Veins lie below the deep muscular fascia</td>
</tr>
<tr>
<td></td>
<td>There are three major networks in the superficial venous system</td>
<td>Tibial veins: anterior and posterior (aTV, pTV)</td>
</tr>
<tr>
<td></td>
<td>Great saphenous vein (GSV)</td>
<td>• Drain into popliteal vein</td>
</tr>
<tr>
<td></td>
<td>• Originates from the dorsal arch veins of the foot, runs anterior to medial malleolus, up medial calf, knee, and inner thigh, and empties into the common femoral vein via the saphenofemoral junction (SFJ)</td>
<td>Popliteal vein (PV)</td>
</tr>
<tr>
<td></td>
<td>• The longest superficial vein of the lower leg</td>
<td>• Drains into superficial femoral vein</td>
</tr>
<tr>
<td></td>
<td>• Most common cause of superficial venous insufficiency</td>
<td>Femoral vein (FV)</td>
</tr>
<tr>
<td></td>
<td>Small saphenous vein (SSV)</td>
<td>• This is a deep vein despite its name</td>
</tr>
<tr>
<td></td>
<td>• Runs behind the lateral malleolus, up the posterior calf, and empties into the popliteal vein (where it empties may vary with individuals) within or near the popliteal fossa</td>
<td>Deep femoral vein (DFV)</td>
</tr>
<tr>
<td></td>
<td>• Drains skin and superficial fascia of the lateral and posterior side of the foot and leg</td>
<td>• At the groin/upper thigh, this is the site of drainage for multiple veins:</td>
</tr>
<tr>
<td></td>
<td>Lateral venous system (LVS)</td>
<td>– GSV</td>
</tr>
<tr>
<td></td>
<td>• Lateral venous system: series of veins on the lateral thigh that drain this area</td>
<td>– Circumflex-iliac</td>
</tr>
<tr>
<td></td>
<td>• Anterolateral thigh vein: drains the lateral and anterior thigh; empties into the GSV; lateral segment is part of the lateral venous system</td>
<td>– External pudendal</td>
</tr>
<tr>
<td></td>
<td>• Venous thromboses in a superficial vein do not have to be treated with anticoagulation unless the thrombus is progressive or near the junction with a deep vein (proximal thrombus)</td>
<td>– Epigastric</td>
</tr>
</tbody>
</table>

- Marginal mandibular
- Cervical
- **Trigeminal nerve (CN V) (Table 25-6)**
- **Cervical plexus (Table 25-7)**
  - Facial nerve blocks
  - The most common facial nerve blocks target supraorbital (V1), infraorbital (V2), and mental (V3) nerves which exit into the face through foramina of the same names
  - These three nerves line up vertically at the midpupillary line, which is 2.5 cm from the facial midline (Fig. 25-6)
  - Intraoral approach to infraorbital and mental nerve is preferred to reduce patient discomfort, which is greater with transcutaneous injections
  - **Supraorbital nerve block**
    - Supraorbital and supratrochlear nerves innervate the frontal part of scalp and forehead
then inject 1 to 2 mL and massage the site to spread the anesthetic near the nerve
• If no resistance is felt after inserting the needle 1 cm, then you are likely below the orbital rim or in the foramen itself. Withdraw the needle, and then insert it again, but redirect it to be above the rim
• To extend the block medially or laterally, a bleb of anesthesia may be injected along the superior orbital rim medially and laterally from the supraorbital starting point
• Infraorbital nerve block
  • Infraorbital nerve innervates the lower eyelid, medial aspect of the cheek, upper lip, and lateral portion of the nose
  • Intraoral (mucosal) approach is preferred
  • Use a 1-inch 30-gauge needle, and when possible, apply viscous lidocaine or EMLA cream to the gingival sulcus above the upper canines for 5 minutes prior to injection
  • Position yourself on the opposite side of the nerve to be blocked, and have the patient slightly turn his or her head toward you. For example, to block the right infraorbital nerve, stand at the patient’s left side. This permits better access to the medially oriented foramen and causes less flexion of the injecting wrist
  • Place the third or fourth finger of the noninjecting hand over the infraorbital foramen (1 cm below the palpable infraorbital margin), and peel back the ipsilateral upper lip with the index finger and thumb of the same hand (use a gauze to lift up the lip to avoid slipping)
  • Inject a bleb of anesthesia at the gingival-labial sulcus above the apex of the canine fossa. Insert and aim the needle toward the foramen, or just

![Figure 25-3](image.png)

**FIGURE 25-3** Lymph nodes of the head and neck.

- Supraorbital foramen/notch may or may not be palpable. Use the midpupillary line as a guide to the supraorbital nerve
- With patient in slight reverse Trendelenburg, stand behind the patient’s head. This position will afford better access to the superior orbital rim and prevent the patient from seeing the needle approach
- Raise a cutaneous wheal of anesthesia over the superior orbital rim in the midpupillary line. Insert the needle down to the rim until resistance is felt. Aspirate to ensure no blood return, and

---

**TABLE 25-3 Embryology**

<table>
<thead>
<tr>
<th>Group</th>
<th>Muscles</th>
<th>Derived From</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscles of mastication</td>
<td>Temporalis, masseter, medial pterygoid, lateral pterygoid</td>
<td>First branchial arch mesoderm</td>
<td>Trigeminal nerve (CN V)</td>
</tr>
<tr>
<td>Muscles of facial expression</td>
<td>See Fig. 25-4 and Table 25-4</td>
<td>Second branchial arch mesoderm</td>
<td>Facial nerve (CN VII)</td>
</tr>
<tr>
<td>Lower face muscles</td>
<td>Risorius, platysma, depressor anguli oris</td>
<td>Embryonic platysma</td>
<td>Tend to not have bony insertions or origins</td>
</tr>
<tr>
<td>Middle and upper face muscles</td>
<td>Muscles of the forehead, scalp, periorbital, upper mouth</td>
<td>Embryonic sphincter colli profundus muscle</td>
<td>May have bony insertions</td>
</tr>
</tbody>
</table>
## TABLE 25-4 Muscles of Facial Expression With Innervations (Fig. 25-4)

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Action</th>
<th>Rhytids</th>
<th>Branch of Facial Nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper Face Muscles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Occipitalis</td>
<td>Moves scalp posteriorly</td>
<td></td>
<td>Postauricular</td>
</tr>
<tr>
<td>- Frontalis</td>
<td>Raises eyebrows</td>
<td>Horizontal forehead lines</td>
<td>Temporal</td>
</tr>
<tr>
<td></td>
<td>Wrinkles forehead</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Periorbital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Corrugator supercolli</td>
<td>Pulls eyebrows medially</td>
<td>Glabellar lines</td>
<td>Temporal</td>
</tr>
<tr>
<td>- Orbicularis oculi</td>
<td>Closes and squeezes eyelids shut</td>
<td>Crow’s feet</td>
<td>Temporal Zygomatic</td>
</tr>
<tr>
<td><strong>Nose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Procerus</td>
<td>Pulls skin over glabella inferiorly</td>
<td></td>
<td>Temporal Zygomatic</td>
</tr>
<tr>
<td></td>
<td>Wrinkles nose upwards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Zygomaticus major and minor</td>
<td>Elevates corner of mouth</td>
<td></td>
<td>Zygomatic Buccal</td>
</tr>
<tr>
<td>- Nasalis</td>
<td>Dilates nares</td>
<td>Bunny lines</td>
<td>Buccal</td>
</tr>
<tr>
<td>- Depressor septi nasi</td>
<td>Pulls columella inferiorly</td>
<td></td>
<td>Buccal</td>
</tr>
<tr>
<td><strong>Mouth-Lip Elevators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Levator labii superioris</td>
<td>Elevates upper lip</td>
<td></td>
<td>Buccal</td>
</tr>
<tr>
<td>- Levator labii superioris alaeque nasi</td>
<td>Lifts upper lip</td>
<td></td>
<td>Buccal</td>
</tr>
<tr>
<td></td>
<td>Dilates nares</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Levator anguli oris</td>
<td>Elevates corner of mouth</td>
<td></td>
<td>Buccal</td>
</tr>
<tr>
<td>- Risorius</td>
<td>Pulls corner of mouth laterally</td>
<td></td>
<td>Buccal</td>
</tr>
<tr>
<td><strong>Mouth-Lip Depressors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Buccinator</td>
<td>Flattens cheek</td>
<td></td>
<td>Buccal</td>
</tr>
<tr>
<td></td>
<td>Whistle, blow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Depressor anguli oris</td>
<td>Depresses corner of mouth</td>
<td></td>
<td>Buccal Marginal mandibular</td>
</tr>
<tr>
<td></td>
<td>(Marionette lines)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Depressor labii inferioris</td>
<td>Depresses lower lip</td>
<td></td>
<td>Marginal mandibular</td>
</tr>
<tr>
<td>- Mentalis</td>
<td>Protrudes lower lip</td>
<td>Mental crease</td>
<td>Marginal mandibular</td>
</tr>
<tr>
<td>- Orbicularis oris</td>
<td>Closes mouth</td>
<td>Vertical lip lines</td>
<td>Buccal Marginal mandibular</td>
</tr>
<tr>
<td></td>
<td>Purses lips</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pucker</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protrudes lip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Platysma</td>
<td>Pulls corner of mouth inferiorly</td>
<td>Horizontal neck lines</td>
<td>Cervical</td>
</tr>
<tr>
<td></td>
<td>Webs, tenses neck</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Below the overlying finger. Stop when resistance or bone is felt.
- Aspirate and confirm that no blood returns, and then inject 2 to 3 mL of local anesthetic. If you are in the proper location, then the finger overlying the infraorbital foramen should feel a bleb of anesthesia.
- Mental nerve block (Fig. 25-7)
  - Mental nerve innervates the lower lip and chin
  - Intraoral (mucosal) approach is preferred

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Innervates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandibular branch of trigeminal (CN V3)</td>
<td>Muscles of mastication</td>
</tr>
<tr>
<td>Facial nerve (CN 7)</td>
<td>Muscles of facial expression</td>
</tr>
<tr>
<td>Oculomotor (CN 3)</td>
<td>Levator palpebrae superioris (LPS)</td>
</tr>
<tr>
<td>Sympathetic innervation</td>
<td>Superior palpebral muscle of Müller (involuntary elevates upper eyelid in flight or fight situations)</td>
</tr>
</tbody>
</table>

### TABLE 25-5  Motor Nerves to the Face

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Innervates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandibular branch of trigeminal (CN V3)</td>
<td>Muscles of mastication</td>
</tr>
<tr>
<td>Facial nerve (CN 7)</td>
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</tr>
<tr>
<td>Oculomotor (CN 3)</td>
<td>Levator palpebrae superioris (LPS)</td>
</tr>
<tr>
<td>Sympathetic innervation</td>
<td>Superior palpebral muscle of Müller (involuntary elevates upper eyelid in flight or fight situations)</td>
</tr>
</tbody>
</table>

### TABLE 25-6  Three Branches of the Trigeminal Nerve (CN V) (Provide Sensation to the Head) (Fig. 25-5)

<table>
<thead>
<tr>
<th>CNV Branch</th>
<th>Ophthalmic Nerve (V1 Sensory)</th>
<th>Maxillary Nerve (V2 Sensory)</th>
<th>Mandibular Nerve (V3 Sensory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Travels through superior orbital fissure (SOF) and passes through orbit Divides into three branches</td>
<td>Leaves the skull through the foramen rotundum Divides into four branches</td>
<td>Exits the cranium through the foramen ovale. Divides into five branches</td>
</tr>
<tr>
<td>Branches</td>
<td>Frontal nerve • Supraorbital nerve • Supratrochlear nerve Nasociliary nerve • Infratrochlear nerve • External nasal branch of anterior ethmoid Lacrimal nerve</td>
<td>Zygomaticotemporal Zygomaticofacial Infraorbital Nasopalatine • superior alveolar and palatine nerves (sensation to upper teeth, gingival, palate, nasal mucosa)</td>
<td>Buccal nerve Lingual nerve Mental nerve Inferior alveolar nerve Auriculotemporal nerve</td>
</tr>
<tr>
<td>Innervates</td>
<td>Forehead Scalp</td>
<td>Side of the nose Lower eyelid Upper lip</td>
<td>Mucous membranes of the mouth and cheek Anterior two-thirds of the tongue Lower teeth Skin of the lower jaw Side of the head and scalp Meninges of the anterior and middle cranial fossae</td>
</tr>
</tbody>
</table>
• Use a 1-inch, 30-gauge needle, and when possible, apply viscous lidocaine or EMLA cream to the gingival-labial sulcus below the second bicuspid for 5 minutes prior to injection.

• Stand behind the patient’s head with the patient body in reverse Trendelenburg. Mark the mental foramen position in the midpupillary line (rarely, the foramen may be palpable (the foramen is approximately midway between the oral commissure and the mandibular rim in the midpupillary line), and place the third or fourth finger of the noninjecting hand over this site. Peel the ipsilateral lower lip outward with the index finger and thumb of the same hand.

• Inject and raise a bleb of local anesthetic at the gingival-labial sulcus below the second bicuspid.
TABLE 25-7  Cervical Plexus (Three Nerves) Supplies Sensation to the Neck
(See Fig. 25-6)

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Innervation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesser occipital</td>
<td>Sensation to posterior neck, scalp, occiput, and upper posterior ear</td>
</tr>
<tr>
<td>Greater auricular</td>
<td>Sensation to earlobe and posterior auricle</td>
</tr>
<tr>
<td>Transverse cervical</td>
<td>Sensation to anterior neck</td>
</tr>
</tbody>
</table>

All exit in proximity at the posterior border of the sternocleidomastoid muscle in a region called Erb’s point (discussed in the section “Surgical Anatomy: Danger Zone”).

FIGURE 25-5  Facial subunits and sensory innervations: (pink) ophthalmic (V1), (green) maxillary (V2), (lavender/blue) mandibular (V3).
Chapter 25    SURGERY AND ANATOMY

Radial nerve –
Ulnar nerve –
Median nerve –

Hand blocks

- Median nerve block (Fig. 25-10)
  - Median nerve innervates the skin of the palmar side of the thumb, the index and middle finger, half the ring finger, and the nail bed of these fingers. The lateral part of the palm is supplied by the palmar cutaneous branch of the median nerve
  - Nerve enters the hand between the flexor carpi radialis (radial side) and palmaris longus (ulnar side) tendons beneath the flexor retinaculum
  - Both tendons are identified by asking the patient to oppose the thumb and the fifth digit.
Needle is angled at 45 degrees and enters between the tendons at the level of the proximal wrist crease.

- Inject 2 to 5 mL local anesthetic.
- If the patient has congenital absence of the palmaris longus muscle, the injection can be made on the medial aspect (toward the ulna) of the flexor carpi radialis tendon.
- As the needle passes through the flexor retinaculum, a loss of resistance is felt, marking the point at which the injection should be made.
- If paresthesias are elicited, the needle should be withdrawn slightly (i.e., approximately 2 mm) to avoid nerve damage or intraneural injection.

Digital nerve block (Fig. 25-11)

- On the dorsal surface of the fingers, the digital nerves are branches of the radial and ulnar nerves.
- On the ventral or palmar surface of the fingers, the digital nerves are branches of the median and ulnar nerves.
- The digital nerves that supply the toes are branches of the peroneal nerve on the dorsal surface, whereas the tibial nerve innervates the ventral or plantar surface of the toes.
- Avoid circumferential injections, which may lead to digital ischemia.
- Limit injection volumes to 3 mL total.
- Epinephrine may be used cautiously in digital blocks (see epinephrine discussion in section on local anesthesia below).
### TABLE 25-8 Innervation of the Hand and Fingers (Fig. 25-10)

<table>
<thead>
<tr>
<th></th>
<th>Radial</th>
<th>Ulnar</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sensory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsum of hand</td>
<td>Skin of dorsum of thumb and 2½ digits as far as the distal interphalangeal joint</td>
<td>Ulnar 1½ digits and adjacent part of dorsum of hand</td>
<td>Median nerve: sensory to skin of ulnar 1½ digits</td>
</tr>
<tr>
<td>Palm of hand</td>
<td></td>
<td>Ulnar nerve: sensory to skin of ulnar 1½ digits</td>
<td>Median nerve: sensory to skin of the palmar aspect of thumb and 2½ digits, including the skin on the dorsal aspect of the distal phalanges</td>
</tr>
<tr>
<td>Fingers</td>
<td>Dorsal digital nerves</td>
<td>Dorsal digital nerves</td>
<td>Ventral digital nerves</td>
</tr>
</tbody>
</table>

- Block should be as far back as possible from the surgical site
- Two nerves run on each side of the fingers and toes
- These may be blocked with injections on each side of the digit
- Needle is inserted perpendicular to the digit, midway between the palmar and dorsal surfaces of the digit, 1 to 2 cm distal to the web space
- Once resistance or bone is felt, aspirate to ensure no blood return, then inject 0.5 mL
- Withdraw the needle slightly, and redirect the needle to the dorsal surface, and inject 0.5 mL
- Repeat 0.5 mL for the palmar surface
- The side, palmar, and dorsal injections all may be done through one insertion point at the side of the finger by redirecting the needle
- Anesthetic is administered along the side of the digit as the needle is withdrawn
- Epinephrine may be used with caution (see epinephrine discussion above and in section local anesthesia below)
- **Sensory nerves of the leg and ankle**
  - Leg and ankle innervated by branches of the femoral nerve (Table 25-9):
    - Saphenous
    - Posterior tibial
    - Sural
    - Deep peroneal
    - Superficial peroneal
  - Sensory innervation to the dorsum of the foot (three nerves) (Fig. 25-13):
    - Dorsum, medial: saphenous nerve
    - Dorsum, lateral: superficial peroneal nerve
    - Between first and second toes: deep peroneal nerve
  - **Sensory innervation of sole of the foot (two nerves) (Fig. 25-13)**
    - Plantar surface (majority of): posterior tibial nerve
FIGURE 25-10 Technique for median nerve block of hand: to accentuate the landmarks, have the patient oppose the thumb to touch the small finger while slightly flexing the wrist (A), then inject at the wrist crease between the flexor carpi radialis and Palmaris longus (*) (B), or if the Palmaris longus is absent, inject on the ulnar side of the flexor carpi radialis (*) C.

FIGURE 25-11 Digital block technique: The needle is inserted perpendicular to the digit, midway between the palmar and dorsal surfaces of the digit and 1-2 cm distal to the web space (*).

FIGURE 25-12 Web space block technique: the needle is inserted from the dorsal aspect of the web space (*) and advanced until the tip tents the palmar skin; the anesthetic is administered along the side of the digit as the needle is withdrawn.
### TABLE 25-9 Femoral Nerve Branches

<table>
<thead>
<tr>
<th>Branch</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Saphenous nerve | Largest cutaneous branch of femoral nerve  
Enters foot anterior to medial malleolus  
Provides sensory innervation to the medial aspect of the ankle and the  
medial-dorsal foot up to the first metatarsal bone |
| Sciatic nerve   | Consists of the tibial nerve and common peroneal nerves                                                                                   |

#### Tibial Nerve Divides Into → Posterior Tibial Nerve + Sural Nerve

<table>
<thead>
<tr>
<th>Branch</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Posterior tibial nerve | Enters foot posterior to tibial artery at medial malleolus  
Gives rise to two nerves that supply most of the sensation to the sole of the foot  
Lateral plantar nerve: lateral sole of foot  
Medial plantar nerve: medial sole of foot |
| Sural nerve     | Formed by branches of the common peroneal and tibial nerves  
Enters the foot posterior to lateral malleolus  
Sensation to lateral and posterior lower third of inferior leg  
Sensory to small portion of lateral margin of foot and lateral side of fifth toe |

#### Common Peroneal Nerve Divides Into → Deep Peroneal Nerve + Superficial Peroneal Nerve

<table>
<thead>
<tr>
<th>Branch</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Deep peroneal nerve | Underneath flexor retinaculum anteriorly  
Branch of the common peroneal nerve  
At level of the lateral malleolus, it is bounded medially by the tendon of  
the extensor hallucis longus and laterally by the anterior tibial artery  
Skin sensation between first and second toes |
| Superficial peroneal nerve | Above retinaculum  
Skin sensation of lateral dorsum of foot and toes except for the first interdigital  
space (deep peroneal nerve) and lateral aspect of the foot (sural nerve) |

#### FIGURE 25-13 Innervation of the foot:

- Lateral foot and fifth toe: sural nerve
- Nerve blocks for the foot
  - Dorsum of the foot nerve blocks: anterior ankle block
  - Superficial peroneal nerve block
    - Insert needle immediately above and anterior to the lateral malleolus
    - Inject 5 mL anesthetic subcutaneously between the anterior border of the tibia and the superior aspect of the lateral malleolus
  - Deep peroneal nerve block
    - Patient supine and the ankle in slight plantar flexion
    - Needle is inserted at the upper level of the malleoli between the tendons of the tibialis anterior and extensor hallucis longus

DP = deep peroneal nerve, PT = posterior tibial nerve, AT = anterior tibial nerve, SU = sural nerve, SA = saphenous nerve.
– Tendons can be accentuated by dorsiflexing the ankle and the great toe against resistance
– If the anterior tibial artery can be palpated, the needle should be inserted just lateral to the artery
– Needle is advanced deep to the tendons just above the periosteum, and 5 mL of 1% lidocaine is injected after aspiration

• Saphenous nerve block
  – Insert needle immediately above and anterior to the medial malleolus
  – Inject 3 to 4 mL anesthetic into the subcutaneous tissue around the great saphenous vein

• Sole of the foot nerve blocks: posterior ankle block
  – Sural nerve
    – Patient is positioned prone with the foot in slight dorsiflexion
    – Needle is inserted lateral to the Achilles tendon and 1 to 2 cm above the level of the distal tip of the lateral malleolus
    – Needle is redirected in a fan-shaped pattern from side to side as anesthetic is infiltrated
  – Posterior tibial nerve
    – Patient is positioned prone with the foot in slight dorsiflexion. Feel for the posterior tibial artery pulsation (the nerve is just behind the artery)
    – Needle is inserted midway between the medial malleolus anteriorly and the Achilles tendon posteriorly. Raise a wheal at this site, and advance the needle toward the posterior tibial artery
    – Tibial nerve lies under the dense flexor retinaculum; advance the needle until a slight give is felt as the needle penetrates the retinaculum
    – Aspirate and confirm no blood return, and inject 5 mL of 1% lidocaine. Another 5 mL is injected as the needle is withdrawn

SURGICAL ANATOMY: DANGER ZONES

• The greatest danger is injury to a major motor nerve, especially at its proximal trunk, because permanent paralysis or weakness may result, causing facial asymmetry and atrophy
• All motor nerves and major vessels lie below the superficial musculoaponeurotic system (SMAS) plane and muscle
  – Staying above the SMAS (when defined) or muscle (when the SMAS is ill-defined) is always safe to avoid motor nerve injury
  – The SMAS-muscle plane, however, is thin or difficult to identify in three areas, which then are the three danger zones in the head and neck for motor nerve injury (Table 25-10)

• Facial layers (from most superficial to deepest) (Tables 25-11 and 25-12)
  – Epidermis (most superficial)
  – Dermis
  – Subcutaneous fat
  – SMAS
  – Muscle
  – Deep fat (variable)
  – Periosteum
  – Bone (deepest)
  – Other branches of the facial nerve: zygomatic, buccal
    – Rarely injured because they are well protected by a well-defined layer of SMAS and muscle
    – Injury to these nerves usually does not cause permanent injury because they have multiple rami and cross-innervate muscles
  – Nerves medial to a line connecting the lateral canthus to the oral commissure are usually well arborized, and permanent injury is rare medial to this line
• Undermining
  – Done to separate vertical and lateral fibrous/fascial attachments that restrict tissue mobility
  – Increases tissue mobility, decreases wound edge tension, and facilitates wound closure, thereby enhancing postoperative cosmesis
  – Undermining should always be above SMAS and muscle with few exceptions:
    – Forehead: below the frontalis muscle, between the two superior temporal lines laterally
    – Nose: below the nasalis muscle
  – Disadvantages:
    – Too deep: may injure vital structures (i.e., motor nerves or deep arteries)
    – Too superficial: may compromise tissue viability by thinning the vascular pedicle excessively

ANATOMIC REVIEW OF HEAD AND NECK

• Superficial musculoaponeurotic System (SMAS) (Fig. 25-15)
  – A fascial envelope that encircles the muscles of facial expression in a broad plane across the face via fibrous septa that extends and inserts into the dermis above
  – It also serves as a protective anatomic plane: all major motor and sensory nerve trunks and named vessels are deep (below) to the SMAS
<table>
<thead>
<tr>
<th>Nerve</th>
<th>Danger Zone</th>
<th>Innervates</th>
<th>Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNVII Temporal branch (Motor)</td>
<td>Temporal fossa&lt;br&gt;Superior border: superior temporal line (line palpable from the frontal-temporal hairline to the lateral eyebrow)&lt;br&gt;Inferior border: zygomatic arch&lt;br&gt;Medial border: lateral orbital rim&lt;br&gt;Posterior border: superficial temporal artery and temporal hairline&lt;br&gt;Most vulnerable as it exits the superior parotid and crosses the zygomatic arch&lt;br&gt;Next most vulnerable location: as it travels across the temporal fossa (temple) toward the lateral forehead.&lt;br&gt;Nerve is protected medial to the superior temporal line because it now lies underneath the frontalis muscle</td>
<td>Frontalis</td>
<td>Drooping of affected eyebrow&lt;br&gt;Flattening of the ipsilateral forehead</td>
</tr>
<tr>
<td>CNVII Marginal mandibular branch (Motor)</td>
<td>Nerve is relatively superficial as it enters the face where the anterior border of the masseter muscle and mandibular rim intersect (the facial artery also enters the face here)&lt;br&gt;At this region, the marginal mandibular is superficial to the facial artery.&lt;br&gt;The platysma above protects both the artery and the nerve.&lt;br&gt;Nerve becomes even more superficial as it travels obliquely up toward the corner of the mouth.&lt;br&gt;As long as one stays above the lip depressor muscles, however, the nerve will not be injured&lt;br&gt;There is great variation, however, in where the nerve lies relative to the mandibular rim.</td>
<td>Lip depressors</td>
<td>Asymmetry of corners of mouth</td>
</tr>
<tr>
<td>CNXI Spinal accessory nerve (Motor)</td>
<td>Posterior cervical triangle at Erb’s point (see Fig. 25-14): intersection of the following lines&lt;br&gt;Draw a horizontal line connecting the mastoid to the mandibular angle&lt;br&gt;At the midpoint of this line, a vertical line then is drawn inferiorly to intersect with the posterior border of the sternocleidomastoid muscle (SCM).&lt;br&gt;The nerve is located within a 2- to 4-cm radius of this point.&lt;br&gt;Several other nerves are at risk in this anatomic location:&lt;br&gt;• spinal accessory (motor)&lt;br&gt;• greater auricular (sensory)&lt;br&gt;• transverse cervical (sensory)</td>
<td>Trapezius muscle</td>
<td>Shoulder drooping&lt;br&gt;Restricted shoulder elevation and abduction</td>
</tr>
</tbody>
</table>
With few exceptions, all motor nerves innervate their respective muscles on the muscle’s underside. Therefore, staying above the SMAS and muscle will prevent motor nerve injury. Peripheral sensory nerves and vessels may perforate the SMAS and travel above it in a superficial plane, but the proximal roots are still sub-SMAS. The SMAS in the scalp and upper face and the SMAS of the lower face fuse at the zygoma.

Anatomic extensions of the SMAS include:
- Superficial fascia of the face and superficial temporalis fascia (also known as the temporal-parietal fascia)
- Superficial fascia of the parotid
- Platysma in the neck. (NOTE: Superficial fascia of the neck, however, is not SMAS. It is deep to the SMAS/platysma and represents the superficial leaflet of the deep cervical fascia)
- Galea on the scalp and its forehead extension (below the frontalis muscle)
- The SMAS may be plicated and imbricated (done in face lift surgery) to draw the facial skin tight, as well as, help to decrease wound tension during reconstruction
- Cosmetic units and subunits of the face
- Figs. 25-16, 25-17, and 25-18 illustrate anatomy of the eyelid, nose, and ear, respectively

**ELECTROSURGERY (TABLES 25-12 AND 25-13)**

- Refers to the use of electric current in surgery to produce tissue destruction

---

**TABLE 25-11 SMAS Architecture**

<table>
<thead>
<tr>
<th>SMAS Layer</th>
<th>Type 1: Distinct SMAS Layer</th>
<th>Type 2: Wispy or Membranous SMAS Layer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Meshwork of fibrous septa envelops lobules of fat cells</td>
<td>Meshwork of intermingled collagen and elastic fibers and muscle fibers</td>
</tr>
<tr>
<td>Region</td>
<td>Forehead, temple (zone 1 in Fig. 25-15) Zygomatic, infraorbital region, and lateral part of the nasolabial fold (zone 2 in Fig. 25-15)</td>
<td>Upper, lower lips (zone 3 in Fig. 25-15) Medial part of the nasolabial fold (zone 2 in Fig. 25-15)</td>
</tr>
</tbody>
</table>

**TABLE 25-12 Five Zones of SMAS**

<table>
<thead>
<tr>
<th>Zones of SMAS</th>
<th>Characteristics</th>
<th>Region</th>
<th>SMAS Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fronto-occipital</td>
<td>Galea together with frontalis and occipitais muscles</td>
<td>Forehead</td>
<td>Type 1: distinct</td>
</tr>
<tr>
<td>Suprazygomatic</td>
<td>Musculoaponeurotic excursion covering the temporal aponeurosis, including the suprazygomatic periauricular muscles</td>
<td>Temporal and parotid</td>
<td>Type 1: distinct</td>
</tr>
<tr>
<td>Infrazygomatic</td>
<td>Musculoaponeurotic excursion covering the cheek</td>
<td>Cheek</td>
<td>Type 1: distinct</td>
</tr>
<tr>
<td>Perioral</td>
<td>Musculoaponeurotic excursion covering the paranasal and perioral area</td>
<td>Nose, perioral, upper and lower lips</td>
<td>Type 2: Wispy or membranous</td>
</tr>
<tr>
<td>Platysmal</td>
<td>Plastysma and its superficial fascia</td>
<td>Neck</td>
<td>Type 1: distinct</td>
</tr>
</tbody>
</table>
• Complete electrical circuit: needs three basic system components, along with the patient: a power unit, an active electrode, and a dispersive or return electrode
• Active electrode: i.e., handpiece
• Dispersive, return electrode: i.e., grounding pad
• Resistance = impedance: degree to which an object opposes electric current, measured in ohms
• Voltage: force pushing current through the resistance, measured in volts
• Direct current (DC): electric current that flows in one direction (i.e., electrolysis and electrocautery)
• Alternating current (AC): electrons that alternate or regularly reverse direction
• Frequency: measure of the number of occurrences of a repeating event per unit time, measured in hertz
• Hertz: number of cycles of electric current flow (one direction and back) per second
• Radiofrequency (RF): an electric current occurring at high frequencies, usually >400,000 cycles per second (Hz)
• Electrode: a physical device; close to or in contact with the patient, through which electrosurgical energy is received or transmitted
• AC electrical waveforms: may be damped or undamped to produce tissue effects of coagulation, cutting, or fulguration (desiccation)
  – Damped: Waves produced are initially intense and strong and then diminish rapidly. The more rapidly the sine waves return to baseline, the more damped is the current. Damped current coagulates tissue, adding to hemostasis, but causes collateral tissue damage (i.e., electrofulguration, electrodessication, electrocoagulation, AKA coagulation)
  – Undamped: Waves produced are pure sine waves. Undamped current cuts tissue without hemostatic effect (i.e., electrosection, AKA cutting)
  – Blended current: combined characteristics of cutting and coagulation waveforms that result in cutting with moderate hemostasis
• Monoterminal: delivery of current using only one treatment electrode, without a dispersive electrode (i.e., electrofulguration, electrodessication with hyfrecator)
• Biterminal: delivery of current via two electrodes, one treatment electrode and one dispersive electrode (usually at a distance from the treatment end) (i.e., electrocoagulation, electrosection). May be unipolar or bipolar
• Unipolar: one treatment electrode and one dispersive electrode (usually a grounding pad at distant site)
• **Bipolar**: a forceps-like device contains both the treatment and the dispersive electrodes (dispersive pad is not required). Passage of current is restricted between these two tines, which results in substantially less tissue damage than in monopolar devices. Safest for patients with automatic implantable cardiac defibrillators (AICDs) or pacemakers

• **Electrical surgery unit (ESU)**: generates the radiofrequency current in commercial electrosurgery machines

• **Ground-referenced ESU**: the current is referenced to a ground (i.e., the electric circuit is completed through a grounded object). If there is any interruption or high impedance in the normal return path, the current will seek an alternate path, possibly causing alternate-site burns

• **Radiofrequency (RF)–isolated units**: most monopolar ESUs are now this type. The isolation transformer inside the unit isolates the therapeutic current from the ground, and therefore the therapeutic current is only returned to the ESU and is not connected to the earth ground. This arrangement eliminates the flow of energy if there is no completed pathway to the ESU

• **Complications of electrosurgery**
  - **ESU burn**: occurs when the heat produced, over time, is not dissipated safely by the size or conductivity of the patient return electrode (i.e., poor grounding pad contact). Burn = heat × time/area
  - **Interference with an implanted pacemaker**
  - **Precautions in patients with an automatic implantable pacemaker and cardioverter/defibrillators (AICDs)**
    - The risk of electrosurgery-induced arrhythmia is greater with an AICD than with a pacemaker
Chapter 25 SURGERY AND ANATOMY

**FIGURE 25-16** Eyelid anatomy.

- A. Upper lid
- B. Lateral canthus
- C. Lower lid
- D. Infraorbital crease
- E. Nasojugal fold
- F. Medial canthus
- G. Superior palpebral sulcus
- H. Eyebrow

**FIGURE 25-17** Nasal anatomy.

- A. Root
- B. Lateral side wall
- C. Dorsum
- D. Tip
- E. Ala nasi
- F. Soft triangle
- G. Columella

**FIGURE 25-18** Ear anatomy.

- A. Triangular fossa
- B. Scaphoid fossa
- Concha:
  - C. Cymba
  - D. Cavum
- E. External auditory meatus
- F. Helix
- G. Antihelix
- H. Superior helix
- I. Crura of antihelix
- J. Crus of helix
- K. Tragus
- L. Antitragus
- M. Lobule
TABLE 25-13 Electrosurgery

<table>
<thead>
<tr>
<th>Current</th>
<th>Electrosurgery</th>
<th>Mechanism of Action</th>
<th>Waveform</th>
<th>Spark Gap Outlet</th>
<th>Voltage</th>
<th>Amperage = Current/Damage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC</td>
<td>Electrolysis</td>
<td>• Galvanic electrolysis works by causing salt and water in the skin around the probe to be chemically altered to produce a small amount of sodium hydroxide, or lye. If enough is produced, it can damage the cells that cause hair growth.</td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td>Positive electrode = anode Negative electrode = cathode The chemical reaction is expressed like this: NaCl (salt) + H₂O (water) + direct current = NaOH (sodium hydroxide) + Cl (chlorine) + H (hydrogen)</td>
</tr>
<tr>
<td>DC</td>
<td>Electrocautery (heat)</td>
<td>• Heats electrodes • Rate at which heat is produced determines whether a waveform vaporizes tissue or creates a coagulum.</td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td>High • High heat: vaporization • Low heat: coagulum</td>
</tr>
<tr>
<td>AC</td>
<td>Electrodesic (coagulation of tissue)</td>
<td>• Damped waveform • Treatment electrode is in direct contact with tissue • No spark is generated</td>
<td>Intermittent</td>
<td>Markedly damped</td>
<td>High</td>
<td>Low/moderate</td>
<td>Monoterminal</td>
</tr>
<tr>
<td>AC</td>
<td>Electrofulguration (coagulation of tissue)*</td>
<td>• AKA noncontact surface coagulation • Damped waveform</td>
<td>Intermittent</td>
<td>Markedly damped</td>
<td>High</td>
<td>Low/moderate</td>
<td>Monoterminal</td>
</tr>
</tbody>
</table>

*Intermittent short bursts of high voltage produce superficial coagulation and tissue char • Treatment electrode is not in contact with tissue
<table>
<thead>
<tr>
<th>Current</th>
<th>Electrosurgery</th>
<th>Mechanism of Action</th>
<th>Waveform</th>
<th>Spark Gap Outlet</th>
<th>Voltage</th>
<th>Amperage = Current/Damage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>Electrocoagulation (coagulation)†</td>
<td>• Electric current “sparks” from the electrode tip across the air gap onto the tissue. The electrode is close enough for sparks to bridge the air gap</td>
<td>Intermittent</td>
<td>Moderately damped</td>
<td>Moderate</td>
<td>Moderate/high</td>
<td>• Biterminal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Unipolar or bipolar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Excellent for hemostasis of small blood vessel diameter (&lt; 2 mm) (&gt; 2 mm may need suture ligation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Some degree of collateral tissue damage with electrocoagulation</td>
</tr>
</tbody>
</table>
| AC      | Electrosection (cut) | • Undamped waveform concentrates energy in a small area for quick, clean cutting
• Causes extreme heating and vaporizing of intracellular fluid that bursts cells | Continuous | Undamped | Low | High/high (vaporized) | • Biterminal
• Bipolar |

* Electrofulguration and electrodessication are identical in electrical properties, except that the former is noncontact, and the latter has contact with the treated tissue. Owing to direct tissue contact, charring depth may be slightly deeper in electrodessication than in electrofulguration

† Both electrodessication and electrofulguration cause superficial coagulation and have hemostatic effects. However, they are technically not electrocoagulation. Average power of coagulation current is less than that of a cutting current
- Electrosurgery current may mimic the electrical activity of the heart and stimulate the cardiac pacemaker/defibrillator, potentially causing an unnecessary shock (AICD) or an alteration of pacemaker function
- Options for patients with pacemakers or AICDs
  - Electrocautery: safe; no electric current passes into the patient
  - Bipolar (biterminal) electrocoagulation: relatively safe in patients with pacemakers and AICDs because the current is restricted between the two forcep tips
  - Unipolar electrocoagulation (biterminal): may be used cautiously in patients with pacemakers and AICDs in the following circumstances
    ▲ Bursts of current are short (5 seconds or less)
    ▲ Lowest effective setting is used
    ▲ The dispersive pad/electrode is placed far away from the cardiac device such that the device is not in the path of the current flow
    ▲ The electrosurgery is not directly over the cardiac device
  - Magnet device: placed over a cardiac pacemaker to inhibit it during the procedure. Pacemaker then must be interrogated postoperatively to ensure function
  - AICD deactivation: requires rhythm monitoring and resuscitation abilities during the procedure

**CRYOSURGERY (CRYOTHERAPY)**
- Defined as the application of extreme cold to destroy abnormal or diseased tissue
- Mechanism of action can be divided into three phases: (1) heat transfer, (2) cell injury, and (3) inflammation (Tables 25-14 and 25-15)
- Cryosurgery is used to treat a number of diseases and disorders
  - **Benign lesions:** verruca, xanthelasma, seborrheic keratoses, milia, venous lake, hemangiomas, keloids, lentigines or other epidermal hyperpigmentation, granuloma annulare, prurigo nodularis, myxoid cysts, condyloma
  - **Malignant lesions:** actinic keratosis, basal and squamous cell carcinomas, lentigo maligna, Kaposi's sarcoma

**WOUND HEALING (TABLES 25-16 TO 25-19)**
- Wound healing is the restoration of tissue continuity after injury
- Original tissue is replaced with nonspecific connective tissue, which forms a functionally inferior scar
- 48 hours: re-epithelialization (sealing of wound)
- 7 days: peak collagen formation
- 3 weeks: 20% of full wound tensile strength
- 4 months: 60% of full wound tensile strength (never exceeds 80% of full)
- 6 to 12 months: mature scar forms
- Macrophages are the most important cells for wound healing, releasing:
  - Transforming growth factors (TGFs)
  - Cytokines
  - Interleukin-1 (IL-1)
  - Tumor necrosis factor (TNF)
  - Platelet-derived growth factor (PDGF)
- Neutropenic or lymphopenic patients do not have impaired wound healing, whereas macrophage-deficient (quantity or function) patients heal poorly

**ANTISEPTICS**
- Infection control
  - Minor procedures (i.e., biopsies): cleanse with isopropyl alcohol and use nonsterile gloves
  - More invasive procedures (i.e., excisions with layered closure, flaps, grafts): prepare skin with povidone-iodine or chlorhexidine scrub, followed by placement of sterile towels or drapes around the field
  - Preoperative shaving of hair has been associated with an increase in wound infections. Hairs may be trimmed but not shaved
- Antiseptic (Table 25-20)
  - Agent that kills or inhibits the growth of microorganisms on the external surfaces of the body
  - Unlike antibiotics that act selectively on a specific target, antiseptics have multiple targets and a broader spectrum of activity, which include bacteria, fungi, viruses, and protozoa

**ANTIBIOTICS**
- Antibiotics and surgical procedures
  - Risk of wound infection after skin surgery is small (1–2%)
  - Routine prophylactic antibiotics are usually indicated for
    - Patient populations: immunosuppressed, debilitated patients, and those with reduced blood flow to the surgical site (i.e., peripheral vascular disease, diabetes mellitus) (Tables 25-21 and 25-22)
### TABLE 25-14 Cyrosurgery Mechanism of Action

<table>
<thead>
<tr>
<th>Event</th>
<th>Heat Transfer</th>
<th>Cell Freeze</th>
<th>Cell Injury</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Cryogen (heat sink) is applied to the skin</td>
<td>• Formation of ice crystals (-5 to -10°C)</td>
<td>• Occurs during cellular thaw</td>
<td>• Inflammation is the response to cell death and helps in local cell destruction</td>
</tr>
<tr>
<td></td>
<td>• Heat is transferred from the skin to the cryogen</td>
<td>• Intracellular ice crystals: form with fast freeze; more destructive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cryogen evaporates as boiling point is reached</td>
<td>• Extracellular ice crystals: form with slow freeze; less tissue damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment</td>
<td>• Rate of heat transfer depends on the temperature difference between the skin and cryogen</td>
<td>• Greatest destruction seen with rapid freeze, slow thaw</td>
<td>• Cell sensitivity to cryogen damage</td>
<td>• Observed as erythema and edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Significant vascular stasis occurs during thaw, contributing to cellular death</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May cause basement membrane separation and vesicle (blister) formation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−4 to −7°C</td>
<td>Melanocytes (most delicate; reason for hypopigmentation with cryotherapy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−20 to −30°C</td>
<td>Keratinocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−30 to −35°C</td>
<td>Dermal fibroblasts (most resistant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−50°C</td>
<td>Malignant tumors (core tissue temperature for optimal destruction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−20 to −25°C</td>
<td>Benign lesions</td>
</tr>
</tbody>
</table>

### TABLE 25-15 Commonly Used Cryogens and Their Temperatures

<table>
<thead>
<tr>
<th>Cryogen</th>
<th>Boiling Point STP (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon dioxide (solid)</td>
<td>~78.5 (~109.3°F)</td>
</tr>
<tr>
<td>Nitrous oxide (liquid)</td>
<td>~89.5 (~129.1°F)</td>
</tr>
<tr>
<td>Liquid nitrogen</td>
<td>~195.8 (~320.4°F)</td>
</tr>
</tbody>
</table>

### TABLE 25-16 Categories of Wound Healing

<table>
<thead>
<tr>
<th>Category</th>
<th>First Intention</th>
<th>Secondary Intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound</td>
<td>Seen in clean, well-perfused, incised surgical wounds and casual wounds inflicted by sharp-edged objects where there is minimum destruction of tissue</td>
<td>When the wound is large, when there has been significant loss or destruction of tissue such that the edges cannot be apposed</td>
</tr>
<tr>
<td>Healing</td>
<td>Primary subtype: edges of the wound are closely apposed shortly after injury, and healing occurs without complication\nDelayed primary subtype: If the wound edges are not reapproximated immediately, delayed primary wound healing transpires</td>
<td>See Table 25-17: Phases of Wound Healing Process</td>
</tr>
</tbody>
</table>

### TABLE 25-17 Phases of Wound Healing Process

<table>
<thead>
<tr>
<th>Phase</th>
<th>Hemostasis</th>
<th>Inflammation</th>
<th>Granulation Re-epithelialization</th>
<th>Remodeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>• Immediate</td>
<td>• First 6 to 8 hours</td>
<td>• Days 5 to 7; can last up to 4 weeks in the clean and uncontaminated wound</td>
<td>• Begins after third week; can last for years</td>
</tr>
<tr>
<td>Comment</td>
<td>• Vasoconstriction\n• Coagulation with fibrin clot</td>
<td>• Monocytes also exude from the vessels and become macrophages once in tissue\n• Neutrophils flood the wound via TGF-β</td>
<td>• Fibroblasts have migrated into the wound, producing glycosaminoglycans (GAGs) and fibronectin\n• Formation of new vasculature (endothelial bud formation)\n• Reepithelization via migration of cells from the periphery of the wound and adnexal structures</td>
<td>• Dynamic continuation of collagen synthesis and degradation\n• Highly vascular granulation tissue undergoes a process of devascularization as it matures into less vascular scar tissue</td>
</tr>
</tbody>
</table>
TABLE 25-18 Growth Factors in Wound Repair

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGF, TGF-β</td>
<td>Epidermal growth factor, Transforming growth factor β, Reepithelialization</td>
</tr>
<tr>
<td>KGF</td>
<td>Keratinocyte growth factor, Reepithelialization</td>
</tr>
<tr>
<td>HBEGF</td>
<td>Heparin-binding epidermal growth factor, Reepithelialization, fibroblast proliferation</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelet-derived growth factor, Fibroblast chemotaxis, proliferation, and contraction</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like growth factor, Fibroblast proliferation, extracellular matrix production</td>
</tr>
<tr>
<td>aFGF-1, bFGF-2</td>
<td>Aciddid fibroblast growth factor, Basic fibroblast growth factor, Fibroblast proliferation, angiogenesis</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor, Angiogenesis</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Transforming growth factor β, Fibroblast chemotaxis and contraction, extracellular matrix production, protease inhibitor production</td>
</tr>
</tbody>
</table>

TABLE 25-19 Macrophage Effects

<table>
<thead>
<tr>
<th>Activity</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phagocytosis and killing of microorganisms</td>
<td>Wound decontamination</td>
</tr>
<tr>
<td>Phagocytosis of tissue debris</td>
<td>Wound debridement</td>
</tr>
<tr>
<td>Growth factor release</td>
<td>Formation of new tissue</td>
</tr>
</tbody>
</table>

Anatomic sites at greater risk for infection: ears, perineum, legs, and feet
- If antibiotics are given, they must be in the bloodstream at time of surgery in order to be effective (i.e., 90 minutes before incision, but may depend on antibiotic half-life)
- Open wounds almost never become infected, whereas closed wounds with hematomas or a large amount of necrotic tissue are at increased risk for infection
- Prophylactic antiherpesvirus medications for susceptible patients undergoing lip surgery, including laser procedures

Regimens for procedures on infected skin, skin structure or musculoskeletal tissue
- Staphylococci and (beta)-hemolytic streptococci are likely to cause infective endocarditis
- Patients with the conditions listed in Table 25-21 below who undergo a surgical procedure that involves infected skin, skin structure, or musculoskeletal tissue, should receive prophylactic antibiotics

WOUND CLOSURE
- The wound closure algorithm (Fig. 25-19) is not all inclusive
<table>
<thead>
<tr>
<th></th>
<th>Alcohol</th>
<th>Chlorhexidine Gluconate</th>
<th>Iodine Iodophores</th>
<th>Hexachlorophene</th>
<th>Triclosan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of action</strong></td>
<td>Denaturation of proteins, DNA, RNA, lipids, etc.</td>
<td>Disruption of the microbial cell membrane with precipitation of cell contents</td>
<td>Iodine precipitates microorganism proteins by forming salts via direct halogenation (oxidation-substitution) Results from the combination of molecular iodine and polyvinylpyrrolidone</td>
<td>Disruption of the microbial cell membrane Chlorinated bisphenol antiseptic</td>
<td>Disruption of the microbial cell membrane Derived from phenol</td>
</tr>
<tr>
<td><strong>Gram-positive bacteria</strong></td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Gram-negative bacteria</strong></td>
<td>Excellent</td>
<td>Good</td>
<td>Good</td>
<td>Fair/Poor</td>
<td>Good (can use for <em>Pseudomonas</em>)</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis</strong></td>
<td>Good</td>
<td>Fair</td>
<td>Good</td>
<td>Fair</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Virus</strong></td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Fair</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>Very rapid</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Slow to intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Residual activity</strong></td>
<td>None</td>
<td>Excellent</td>
<td>Minimal</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td><strong>Toxicity/side effects</strong></td>
<td>Volatile</td>
<td>Ototoxicity Keratitis</td>
<td>Absorbed through the skin; possible toxicity and irritation</td>
<td>Absorbed through intact skin Neurotoxic, especially in neonates</td>
<td>Under investigation</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Avoid open flame</td>
<td>Avoid contact with eyes, external auditory meatus</td>
<td>Molecular iodine can be very toxic for tissues; therefore, iodine is combined with a carrier, decreasing iodine availability</td>
<td>Avoid use on neonates, pregnant women</td>
<td>Avoid contact with eyes</td>
</tr>
</tbody>
</table>
TABLE 25-21  Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis of Which Prophylaxis With Dental Procedures Is Reasonable

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prophylaxis Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatic cardiac valve or prosthetic material used for cardiac valve repair</td>
<td>Yes</td>
</tr>
<tr>
<td>Previous infective endocarditis</td>
<td>Yes</td>
</tr>
<tr>
<td>Congestive heart disease (CHD)*</td>
<td>Yes</td>
</tr>
<tr>
<td>• Unrepaired cyanotic CHD, including palliative shunts and conduits</td>
<td>Yes</td>
</tr>
<tr>
<td>• Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†</td>
<td>Yes</td>
</tr>
<tr>
<td>• Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiac transplantation recipients who develop cardiac valvulopathy</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

TABLE 25-22  Prophylactic Antibiotics Regimens

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Dose</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin</td>
<td>2 g</td>
<td>50 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Unable to take oral medication</td>
<td>Ampicillin</td>
<td>2 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefazolin or ceftriaxone</td>
<td>1 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
<td></td>
</tr>
<tr>
<td>Allergic to penicillins or ampicillin – oral</td>
<td>Cephalexin*</td>
<td>2 g</td>
<td>50 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>600 mg</td>
<td>20 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azithromycin or clarithromycin</td>
<td>500 mg</td>
<td>15 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Allergic to penicillins or ampicillin and unable to take oral medication</td>
<td>Cefazolin or ceftriaxone clindamycin</td>
<td>1 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg IM or IV</td>
<td>20 mg/kg IM or IV</td>
<td></td>
</tr>
</tbody>
</table>

IM, intramuscular; IV, intravenous.
*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage. Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

• The type of repair of a wound greatly depends on the defect location (i.e., a 1-cm defect on the nose demands greater consideration and complexity than the same sized wound on the cheek).
• Wound defect sizes: Small (< 1 cm), medium (1-3 cm), large (> 3 cm)
• Location of a wound is critical
• Defects > 3 mm in depth will likely heal with a contour depression (unless in concave area), especially if overlying convex surfaces or sebaceous skin
• Small, superficial defects in concave areas are ideal for second intention healing. Avoid second intention if bare bone, tendon, or neurovascular structures are exposed
Large defects will also heal well if superficial. However, anticipate significant wound contraction and its impact, if any, on free margins or function.

- **Full thickness skin graft (FTSG):** consists of the epidermis and the whole thickness of the dermis, may be applied to any defect that is well vascularized
  - Superficial defects with FTSG will maintain contour
  - If deep defects are repaired with FTSG, contour depressions may result unless delayed (partial granulation to fill the depth) skin grafting is performed
- **Split thickness skin graft (STSG):** consists of the epidermis and part of the dermis, have less metabolic demand and survive better in poorly vascularized defects. However, significant graft contraction (with potential effect on free margins) is assured compared to FTSG
- **Composite grafts:** consists of epidermal keratinocytes seeded on a fibroblast-containing collagen matrix, work best for small deep wounds at free margins. Due to their bulk and high metabolic demand, composite grafts survive poorly if sized > 1.5 cm
- **Combination closures:** may involve flap + flap, flap + graft, or flap + 2nd intention; should be considered in wounds involving multiple subunits

**FLAPS (TABLE 25-23 AND FIGS. 25-20 TO 25-32)**

- Transfer of tissue (donor site) with its vascular supply into a wound defect (recipient site) for closure
### TABLE 25-23 Flap Types and Characteristics

<table>
<thead>
<tr>
<th>Flap Design</th>
<th>Advancement Flap</th>
<th>Rotation Flap</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral designs</td>
<td>1. Burow’s wedge advancement (Fig. 25-21)</td>
<td>Rotation (Fig. 25-25)</td>
</tr>
<tr>
<td>2. Crescentic advancement (can be unilateral or bilateral (Fig. 25-22)</td>
<td>1. Cervicofacial rotation (Fig. 25-26)</td>
<td></td>
</tr>
<tr>
<td>3. V to Y or Island pedicle (kite) (Fig. 25-23)</td>
<td>2. Dorsal nasal rotation (Rieger, hatchet) (Fig. 25-13)</td>
<td></td>
</tr>
<tr>
<td>Bilateral designs</td>
<td>3. O to Z bilateral rotation (Fig. 25-27)</td>
<td></td>
</tr>
<tr>
<td>1. H-plasty</td>
<td>4. Innervated myocutaneous lip and cheek (Karapandzic)</td>
<td></td>
</tr>
<tr>
<td>2. A to T bilateral advancement (Fig.25-24)</td>
<td>5. O to T bilateral rotation</td>
<td></td>
</tr>
<tr>
<td>Interpolation subtype</td>
<td>6. Comet flap</td>
<td></td>
</tr>
<tr>
<td>1. Retroauricular staged flap (This is a staged flap that has a linear movement. However, it may also be classified as a transposition design since it crosses over intervening island of normal skin to reach the defect.)</td>
<td>Transposition subtype</td>
<td></td>
</tr>
<tr>
<td><strong>Movement</strong></td>
<td>Linear</td>
<td>Pivotal (movement is in an arc)</td>
</tr>
<tr>
<td><strong>Vascular supply</strong></td>
<td>Random pattern</td>
<td>Random pattern or Axial (paramedian forehead flap, lip-switch flap)</td>
</tr>
<tr>
<td><strong>Flap:Defect ratio</strong></td>
<td>2-4:1</td>
<td>2-4:1 (flap:defect ratio may be greater with axial flap)</td>
</tr>
<tr>
<td><strong>Tension</strong></td>
<td>Tension is reduced and redistributed but is not redirected.</td>
<td>Tension is reduced, redistributed, and redirected.</td>
</tr>
<tr>
<td><strong>Mobility</strong></td>
<td>Recruits some adjacent tissue laxity laterally</td>
<td>Optimizes recruitment of lax donor tissue lateral and distant from the defect.</td>
</tr>
<tr>
<td><strong>Restraint</strong></td>
<td>Lateral restraint</td>
<td>Pivotal restraint (Fig. 25-32) Arises from inherent tissue stiffness at the flap’s pivot point and prevents the flap’s tip from reaching distal margin of the operative defect. Secondary movement expected at the primary defect.</td>
</tr>
</tbody>
</table>

- Tissue may be directly connected to the defect or nearby but not contiguous
- Usually performed when a primary straight-line closure is not possible (owing to excess tension or potential anatomic/functional distortion)
- A secondary defect is always created
- May be categorized by the following characteristics
  - Location with respect to the surgical defect (i.e., local, regional, or distant)
  - Movement (i.e., advancement, rotation) {NOTE: In reality, flaps may have more than one movement}
FLAPS

Definition of terms: general

- **Tension vector**: the direction of pull or stress on a wound during its closure
- **Primary defect**: the wound that requires closure
- **Secondary defect**: the wound that results from closure of the primary defect
- **Primary movement**: the motion (advancement, rotation, or transposition) and tension vectors required for closure of the primary defect. Rotation and transposition flaps have in common a pivoting or arclike motion, whereas advancement flaps have a sliding motion in straight lines
- **Secondary movement**: the motion and tension vectors required to close the secondary defect
- **Burrow's triangle (dog-ear, standing cutaneous cone)**: redundant skin that is removed as wounds are closed
- **Primary Burrow's triangle**: The dog-ear directly connected to the primary defect that is removed during closure
- **Secondary Burrow's triangle**: the dog-ear directly connected to the secondary defect that is removed during closure
- **Subunit**: a surface area demarcated by either natural or arbitrary lines that has unique textural, cosmetic, or functional characteristics (i.e., upper lip has four subunits: bilateral upper cutaneous lip, philtrum, and mucosal lip). In general, repairs within a subunit or incisions placed at junctions of subunits yield the best cosmetic results
- **Local flap**: adjacent and contiguous
- **Regional flap**: nearby but not directly adjacent
- **Advancement flap**: a random-pattern flap where the primary flap movement is linear and provides the least mobility among the different flap types
- **Rotation flap**: a random- or axial-pattern flap where the donor tissue pivots in a curved or arclike motion
- **Transposition flap**: a subset of either a rotation or advancement flap where the donor tissue is nearby but not directly adjacent to defect. The flap, therefore, must move across and over an intervening segment of normal skin to close the defect
- **Interpolation flap**: a subset of transposition flap that is usually indicated for larger defects and typically requires at least two separate stages of surgery (usually separated by 3 weeks between stages) (i.e., melolabial interpolation flap, paramedian forehead flap)
- **Island pedicle flap (IPF)**: a random-pattern flap where the flap is completely separated from the surrounding skin (literally an island) and subcutis except for an underlying subcutaneous pedicle. Classically, IPFs are considered advancement flaps but practically/both advancement and rotation


- Vascular supply (i.e., random pattern, axial, or microvascular)
- Stage (i.e., single or multi-stage)
- Configuration (i.e., note, rhomboid, bilobed, banner, etc.)
- Eponym (i.e., Abbé, Rieger, Mustarde, etc.)
  - No single classification accounts for every design or definition variation
  - Eponyms should generally be avoided
  - Most flaps in cutaneous surgery are local (adjacent and contiguous skin) and regional (nearby but not directly adjacent)
  - Within this context, the most useful classification scheme is based on movement and vascular supply
FIGURE 25-21 Burow's wedge advancement flap.

FIGURE 25-22 Crescentic advancement flap.
movements are involved, including even transposition movements. V to Y advancement is a type of IPF
- Backcut: a relaxing incision on the far end of a rotation curve to release lateral flap restraints and facilitate movement
- Z-plasty: distinct form of transposition often used for scar revision for scar length and changing scar orientation (Table 25-24)
  - Change (redirection) of tension vectors of the original wound/scar
  - Lengthening and breaking up of a scar into multiple zigzag lines. The extent of scar lengthening depends on the degree of transposition of the Z-plasty
- Pedicle: the vascular supply to a flap (blood vessels are contiguous with the flap)
- Random-pattern flap: flap that is nourished by unnamed vessels from underlying arterial perforators. Random flaps rely on a rich vascular plexus of subcutaneous tissue that directly connects with the flap
- Axial-pattern flap: flap that has a named vessel for its pedicle
  - Paramedian forehead flap (supratrochlear artery) (Fig. 25-20)
  - Cheek interpolation flap (angular artery)
- Abbé (tip-switch) flap: inferior or superior labial arteries

**GRAFTS (TABLES 25-25 AND 25-26)**

- Autologous skin grafts
- Skin that is detached completely from its blood
supply, removed from its donor site, and transplanted to a recipient site for wound closure in the same individual

- All grafts contract to some degree, but contraction is greatest with split-thickness skin grafts
- Graft survival depends on the establishment of new vasculature between the wound recipient site and the donor graft

LOCAL ANESTHESIA (TABLES 25-27 TO 25-29)

- **Mechanism of action**
  - Anesthetics block membrane Na+/K+ channels, thus preventing effective depolarization and nerve transmission
  - Unmyelinated C-type nerve fibers (slow conduction) conduct temperature and pain (blocked more easily)
  - Myelinated A-type fibers (fast conduction) carry pressure and motor fibers
- **Side effects**
  - Vasovagal reaction with hypotension and bradycardia (most frequent)
    - Place patient in Trendelenburg position to increase cerebral perfusion; supportive care; atropine for severe reactions
    - Bruising and edema, especially in periorbital area
    - Transient motor nerve paralysis
    - Prolonged paresthesia (nerve injury can occur in nerve blocks if needle traumatizes nerve)
  - Allergy to anesthetic
    - True allergy is rare (more common with esters than amides)
    - Allergic reactions are usually IgE-mediated type I reactions with urticaria, angioedema, or anaphylaxis with hypotension and tachycardia
    - Cocaine (ester group) is vasoconstricting; all other anesthetics are vasodilating
    - Longer-lasting anesthetics (> 2 hour duration) are more protein bound (bupivacaine, etidocaine)
  - **Lidocaine 1% with 1:100,000 epinephrine**
    - Most common local anesthetic for skin surgery
    - Very acidic (low pH)
    - Addition of NaHCO₃ to lidocaine with epinephrine neutralizes solution, reducing burning on injection and facilitating anesthetic diffusion
    - **Lidocaine toxicity**
      - Maximum dose of lidocaine: 5 mg/kg of 1% lidocaine plain; 7 mg/kg of 1% lidocaine with 1:100,000 epinephrine
      - Systemic lidocaine toxicity: starts with circumoral numbness and tingling; can progress to seizures and cardiovascular collapse with severe overdosage; toxic effects are exacerbated by acidosis and hypoxia
  - **Prilocaine toxicity**
    - Metabolizes to ortho-toluidine, an oxidizing agent capable of converting hemoglobin to methemoglobin, potentially causing methemoglobinemia

**FIGURE 25-26** Cervicofacial rotation flap.
• Patients at risk of methemoglobinemia include
  - Patients < 1 year old
  - Patients with G-6-PD deficiency
  - Methemoglobinemia-inducing agents: dapsone, nitroglycerin, nitrofurantoin, antimalarials, sulfonamides, phenobarbital, phenytoin, nitroprusside, acetaminophen
  - See EMLA below

• Bupivacaine toxicity
  - Risk of cardiac toxicity, with ventricular arrhythmias and cardiovascular collapse
Epinephrine
- Epinephrine prolongs duration of anesthesia by 100% to 150% and decreases the anesthetic’s systemic toxicity by slowing absorption
- Epinephrine is hemostatic in a dilution of up to 1:1,000,000
- Epinephrine is used in digital anesthesia (fingers/toes)
  - Safe to use in digital blocks and local anesthesia as long as these guidelines are followed
  - Epinephrine dilution of 1:200,000 or greater
  - Volumes injected are minimal (digital block should not exceed 3 mL—1.5 mL max per side)
  - Circumferential injection (ring block) is avoided
  - Patients with vascular compromise are avoided (smokers, diabetes, peripheral vascular disease, Raynaud’s phenomenon)
- Contraindications
  - Absolute: uncontrolled hyperthyroidism and pheochromocytoma
  - Relative contraindications: hypertension, blood pressure instability, severe cardiovascular disease, pregnancy, and narrow-angle glaucoma, beta blockers, phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants
  - Epinephrine may be used by diluting it to 1:500,000; use sparingly
- Side effects
  - Self-limited palpitations, anxiety, fear, diaphoresis, headache, tremor, weakness, and tachycardia
  - Serious side effects: arrhythmias, ventricular tachycardia, ventricular fibrillation, cardiac arrest, and cerebral hemorrhage
- Topical anesthetics
  - Conjunctiva anesthetized with: proparacaine or tetracaine eyedrops
  - Superficial mucous membrane anesthesia: Surfacaine, Topicale, Dyclone, Anbesol, viscous lidocaine, and lidocaine jelly
  - Intranasal mucosa: 4% to 10% cocaine solution is effective, and hemostatic
  - EMLA (eutectic mixture of local anesthetics) cream contains 2.5% lidocaine and 2.5% prilocaine; applied under occlusion 1 to 2 hours preoperatively depending on location
Should be applied to intact skin only and in patients older than 1 year of age.

Application to denuded skin or to large surface areas may result in substantial prilocaine absorption and risk of systemic methemoglobinemia.

30% to 40% lidocaine in acid-mantle cream may also be applied under occlusion 1 to 2 hours before a procedure.

- ELA-Max (4% lidocaine) liposomal delivery; thus no occlusion necessary; no chance of methemoglobinemia as with EMLA. Available over the counter; comes in 5- and 30-g tubes.

- Iontophoresis of lidocaine also can achieve superficial skin anesthesia.

- Tumescent anesthesia (TA)
  - TA is the use of dilute lidocaine (i.e., 0.05% to 0.1%) and epinephrine (i.e., 1:1,000,000) for local anesthesia.
Large volumes of TA may be infiltrated subcutaneously to achieve complete anesthesia and effective hemostasis.

- TA pharmacology applies only to dilute lidocaine and epinephrine; it cannot be extrapolated to other anesthetics (i.e., bupivacaine cannot be substituted for lidocaine).
- Originally developed for liposuction.
- Other uses: face lift surgery, reconstruction, ambulatory phlebectomy, ablative laser resurfacing, hair transplantation, endovenous radiofrequency ablation.

- Advantages of TA
  - Increases maximum safe dose of lidocaine to 55 mg/kg.
  - Dilute epinephrine achieves pronounced vasoconstriction of subdermal vessels, thereby limiting systemic absorption while achieving excellent hemostasis.

- Disadvantages of TA
  - Requires equipment and understanding of tumescent pharmacology.
  - Swelling of subcutaneous space is typical but may be prolonged in the lower extremities.

- Alternatives to esters and amides for local anesthesia:
  - Diphenhydramine hydrochloride (Benadryl) 12.5 mg/mL.
  - Normal saline injected intradermally (transient brief anesthesia).
  - Cryoanesthesia with ice or cryogen (i.e., fluoroethyl or frigiderm) for superficial procedures (i.e., dermabrasion).

**SUTURE REVIEW (TABLES 25-30 AND 25-31)**

- Suture characteristics (Fig. 25-33)
  - **Tensile strength**: measure of a material or tissue’s ability to resist deformation and breakage.
  - **Knot strength**: force required for a knot to slip.
  - **Configuration**
    - Monofilament (less risk of infection)
    - Braided multifilament (easier to handle and tie).
  - **Elasticity**: degree suture stretches and returns to original length.
  - **Memory or suture stiffness**: inherent capability of suture to return to or maintain its original gross shape.
  - **Plasticity**: measure of the ability to deform without breaking and to maintain a new form after relief of the deforming force.
  - **Pliability**: ease of handling of suture material; ability to adjust knot tension and to secure knots (related to suture material, filament type, and diameter).

**FIGURE 25-33** Suturing techniques for epidermal approximation (A) Simple running. (B) Simple running locked. (C) Vertical mattress (left), horizontal mattress (middle), and simple interrupted (right).
### TABLE 25-24 Z-Plasties and Scar-Lengthening Properties

<table>
<thead>
<tr>
<th>Degree of Transposition</th>
<th>Extent of Scar Lengthening (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30°</td>
<td>25</td>
</tr>
<tr>
<td>45°</td>
<td>50</td>
</tr>
<tr>
<td>60°</td>
<td>75</td>
</tr>
</tbody>
</table>

### TABLE 25-25 Graft Take

<table>
<thead>
<tr>
<th>Phase</th>
<th>Timing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma imbibition</td>
<td>First 48 hours</td>
<td>Imbibition means to take in or absorb fluid, causing swelling. Ischemic and edematous phase of graft because no blood flow established. Grafts survive the first 1 to 2 days by absorbing wound exudate and passive diffusion of nutrients. Fibrin also forms between the recipient bed and graft, promoting graft adhesion and reducing infection.</td>
</tr>
<tr>
<td>Inosculation</td>
<td>Days 2 to 3</td>
<td>Initial establishment of vessels between the recipient bed and graft. New vessels form from the recipient bed and migrate to anastamose with vasculature from the graft. Fibrin mesh established during imbibition facilitates vessel migration.</td>
</tr>
<tr>
<td>Capillary ingrowth, revascularization</td>
<td>Days 4 to 7</td>
<td>Additional vascular anastamoses occur between wound base and graft. Blood flow evident by days 5 to 7.</td>
</tr>
<tr>
<td>Keratinocyte activation</td>
<td>Day 4 to week 4</td>
<td>Epidermal activation and proliferation, greater in split-thickness skin grafts. Lymphatic flow reestablished.</td>
</tr>
<tr>
<td>Sensory innervation</td>
<td>Begins after 2 to 3 months</td>
<td>Starts at edge of graft and moves centrally.</td>
</tr>
</tbody>
</table>
### TABLE 25-26 Types of Autologous Skin Grafts

<table>
<thead>
<tr>
<th></th>
<th>Full-Thickness Skin Graft (FTSG)</th>
<th>Split-Thickness Skin Graft (STSG)</th>
<th>Composite Grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Entire epidermis and a dermis harvested. Dermis may be of varying thickness depending on donor site.</td>
<td>Epidermis and only partial-thickness dermis&lt;br&gt;Thin (0.005 to 0.012 in)&lt;br&gt;Intermediate (0.012 to 0.018 in)&lt;br&gt;Thick (0.018 to 0.030 in)</td>
<td>Contains two different tissue layers (i.e. skin and cartilage)</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Minimal contraction during healing phase. Potential for good match with recipient site if donor site properly selected. Donor site is usually sutured or closed</td>
<td>Much thinner, requires less metabolic support, and survives better than FTSGs. Able to cover large wounds, line cavities, resurface mucosal deficits, exposed bone, close donor sites of flaps, and resurface muscle flaps.</td>
<td>Provides scaffolding (cartilage) as well as soft tissue covering (skin).</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Donor site morbidity. FTSGs require more metabolic support (thicker) and do not survive as well as STSGs</td>
<td>Requires more equipment. Significant graft contraction. Cosmetically poor compared to FTSGs Discomfort and appearance of donor site (donor site heals by second intention; a rectangular discolored patch is typical postoperative appearance)</td>
<td>Most metabolically demanding of all graft types. Most composite grafts over 1 cm do not survive completely</td>
</tr>
<tr>
<td><strong>Donor sites</strong></td>
<td>Selected based on matching qualities for thickness, texture, pigmentation, actinic damage, and morbidity of donor harvesting (i.e., upper eyelid, nasolabial fold, pre- and postauricular regions, conchal bowl, and the supraclavicular fossa)</td>
<td>Harvested from any surface of the body (i.e., thigh, buttock, abdomen, scalp)</td>
<td>Donor site is usually crux of the helix to include skin and cartilage</td>
</tr>
</tbody>
</table>
### TABLE 25-27 Two Main Groups of Local Anesthetics: Esters and Amides—Groups Differentiated by Their Intermediate Chain

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Amide</th>
<th>Ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolized</td>
<td>• N-dealkylated and hydrolyzed by microsomal liver enzymes cytochrome P450 3A4</td>
<td>• Hydrolyzed by tissue pseudocholinesterases • Excreted by kidney</td>
</tr>
<tr>
<td>Caution</td>
<td>• Lidocaine is class B in pregnancy; avoid complex procedures in the first trimester; small volumes of lidocaine without epinephrine may be used for essential procedures • Possible drug interaction with medications that are metabolized via liver cytochrome P450 enzymes • End-stage liver disease (altered drug metabolism)</td>
<td>• Pseudocholinesterase deficiency • Severe renal compromise • Allergy to PABA compounds (esters cross-react with PABA): sulfonamides, sulfonylureas, thiazides, and paraphenylene diamine</td>
</tr>
<tr>
<td>Comment</td>
<td>• Amide anesthetics have 2 “i”s in the name</td>
<td>• Ester anesthetics only have 1 “i”</td>
</tr>
</tbody>
</table>

### TABLE 25-28 Local Anesthetics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Primary Use</th>
<th>Relative Potency</th>
<th>Onset</th>
<th>Duration* Plain</th>
<th>Maximum Dose† Plain</th>
<th>Maximum Dose with Epinephrine†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Marcaine</td>
<td>Infiltration</td>
<td>8</td>
<td>2–10 min</td>
<td>30–10 h</td>
<td>175mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>Dibucaine</td>
<td>Nupercaine</td>
<td>Topical</td>
<td>6</td>
<td>Rapid</td>
<td>Short</td>
<td>300 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>Duranest</td>
<td>Infiltration</td>
<td>2</td>
<td>Rapid</td>
<td>3–10 h</td>
<td>300 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Xylocaine</td>
<td>Topical/Infiltration</td>
<td>2</td>
<td>3–5 min</td>
<td>1–2 h</td>
<td>300 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>Carbocaine</td>
<td>Infiltration</td>
<td>2</td>
<td>3–20 min</td>
<td>Rapid</td>
<td>400 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Citanest</td>
<td>Infiltration</td>
<td>2</td>
<td>Rapid</td>
<td>2–4 h</td>
<td>400 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Prilocaine/ lidocaine</td>
<td>EMLA</td>
<td>Topical</td>
<td>2</td>
<td>30–120 min</td>
<td>Short</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Esters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzocaine</td>
<td>Anbersol, etc.</td>
<td>Topical</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>Nesacaine</td>
<td>Infiltration</td>
<td>1</td>
<td>Rapid</td>
<td>0.5–2 h</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td>1</td>
<td>1–3 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaaine</td>
<td>Novocaine</td>
<td>Infiltration</td>
<td>Rapid</td>
<td>1–1.5 h</td>
<td>500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proparacaine</td>
<td>Ophthalm</td>
<td>Topical</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Pontocaine</td>
<td>Infiltration</td>
<td>Slow</td>
<td>2–3 h</td>
<td>20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Cetacaine</td>
<td>Topical</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Clinically, duration of anesthesia may be less than stated above, especially for head and neck; addition of epinephrine prolongs anesthesia by factor of two.
† Maximum doses are for a 70-kg person.
### TABLE 25-29 Lidocaine Toxicity

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Signs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Early (1–5 μg/ml) Tinnitus, circumoral pallor, metallic taste in mouth, lightheadedness, talkativeness, nausea, emesis, diplopia</td>
<td>Recognition, observation, hold lidocaine</td>
</tr>
<tr>
<td></td>
<td>Middle (8–12 μg/ml) Nystagmus, slurred speech, hallucinations, muscle twitching, facial, hand tremors, seizures</td>
<td>Diazepam, airway maintenance</td>
</tr>
<tr>
<td></td>
<td>Late (20–25 μg/ml) Apnea, coma</td>
<td>Respiratory support</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Myocardial depression, bradycardia, atrioventricular blockade, ventricular arrhythmias, vasodilation, hypotension</td>
<td>Oxygen, vasopressors, cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>Allergy</td>
<td>Pruritus, urticaria, angioedema, nausea, wheezing, anaphylaxis</td>
<td>Antihistamines; epinephrine 0.3 ml 1:1000 SQ, oxygen, airway</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Pallor, diaphoresis, hyperventilation, lightheadedness, nausea, syncope</td>
<td>Trendelenburg position, cool compresses, observation</td>
</tr>
</tbody>
</table>

### TABLE 25-30 Suture Materials

<table>
<thead>
<tr>
<th>Material (Trade Name)</th>
<th>Type</th>
<th>Memory</th>
<th>Tissue Reactivity</th>
<th>Tensile Strength Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonabsorbable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotton</td>
<td>Twisted</td>
<td>Low</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td>Nylon (Ethilon, Demalon)</td>
<td>Twisted</td>
<td>Low</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td>Nylon (Nurolon, Surgilon)</td>
<td>Twisted</td>
<td>Low</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td>Polybutester (Novafil)</td>
<td>Braided</td>
<td>Low</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td>Polyester, uncoated (Mersilene)</td>
<td>Braided</td>
<td>Low</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td>Polyester, coated (EthiGoodd)</td>
<td>Braided</td>
<td>Low</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td>Polypropylene (Prolene, Surgilene)</td>
<td>Monofilament/twisted</td>
<td>Very low</td>
<td>Very low</td>
<td>—</td>
</tr>
<tr>
<td>Polypropylene (Prolene, Surgilene)</td>
<td>Braided/twisted</td>
<td>Very low</td>
<td>Very low</td>
<td>—</td>
</tr>
<tr>
<td>Polypropylene (Prolene, Surgilene)</td>
<td>Monofilament</td>
<td>Very high</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td>Silk</td>
<td>Braided</td>
<td>Low</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>Braided</td>
<td>Low</td>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td><strong>Absorbable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gut, fast absorbing/mild</td>
<td>Twisted</td>
<td>Very high</td>
<td>High</td>
<td>2 days</td>
</tr>
<tr>
<td>chromic</td>
<td>Twisted</td>
<td>Very high</td>
<td>High</td>
<td>4 days</td>
</tr>
<tr>
<td>Gut, chromic</td>
<td>Twisted</td>
<td>Very high</td>
<td>High</td>
<td>1 week</td>
</tr>
<tr>
<td>Polyglycolic acid (Dexon)</td>
<td>Braided</td>
<td>Very low</td>
<td>Low</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Poliglecaprone 25 (Monocryl)</td>
<td>Braided</td>
<td>Very low</td>
<td>Low</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Polyglyconate (Maxon)</td>
<td>Monofilament</td>
<td>Very low</td>
<td>Low</td>
<td>1 week</td>
</tr>
<tr>
<td>Polydextanone (PDS)</td>
<td>Monofilament</td>
<td>Very low</td>
<td>Low</td>
<td>1 month</td>
</tr>
</tbody>
</table>

### TABLE 25-31 Epidermal Suture Applications

<table>
<thead>
<tr>
<th>Suture Technique</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Simple running            | Fast epidermal closure  
|                           | May not approximate skin as precisely as simple interrupted  
|                           | May unravel if one segment is severed                                                                                                    |
| Simple interrupted        | Time-consuming  
|                           | Best for correcting minor differences in overlapping edge  
|                           | Most accurate for skin approximation                                                                                                     |
| Vertical mattress         | Suture line perpendicular to wound edge  
|                           | Time-consuming  
|                           | Best suture for additional wound edge eversion  
|                           | May strangulate wound edge if tied too tightly                                                                                             |
| Horizontal mattress       | Suture line parallel to wound edge  
|                           | Time-consuming  
|                           | Moderate wound edge eversion  
|                           | Helpful in hemostasis for nonspecific wound edge oozing                                                                                   |
| Running subcuticular      | Entire suture is buried in the superficial dermis except for an entry and exit point on either ends of the wound edge  
|                           | Time-consuming  
|                           | Beneficial for closure that requires epidermal support greater than 1 week; running subcuticular suture may be left in place greater than 1 week and removed later without railroad tracks on skin |

*Note:* All epidermal sutures will leave cross-marks of railroad-track lines on skin if not removed within 1 week.

#### Questions

1. Where do the internal carotid and external carotid arteries *not* anastamose?
   - A. Perinasal
   - B. Glabella
   - C. Mentum
   - D. Periorbital

2. Put the following items in order from least to most sensitive to cryogen exposure:
   1. Melanocytes
   2. Keratinocytes
   3. Fibroblasts
   - A. 1, 2, 3
   - B. 1, 3, 2
   - C. 2, 1, 3
   - D. 2, 3, 1
   - E. 3, 2, 1
   - F. 3, 1, 2
3. Matching:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Wound Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Neutropenic</td>
<td>A. Not impaired</td>
</tr>
<tr>
<td>2. Lymphopenic</td>
<td>B. Impaired</td>
</tr>
<tr>
<td>3. Macrophage deficient</td>
<td></td>
</tr>
</tbody>
</table>

4. Matching:

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sterilization</td>
<td>A. Destruction of ALL infectious agents from an environment. This includes algae, bacteria, fungi, protozoa, viruses dormant endospores and poorly characterised agents such as viroids and the agents that are associated with spongiform encephalopathies</td>
</tr>
<tr>
<td>2. Disinfection</td>
<td>B. Refers to the removal of some microbes from an environment that may cause disease</td>
</tr>
<tr>
<td>3. Antisepsis</td>
<td>C. Less harsh in their action than are disinfectants</td>
</tr>
</tbody>
</table>

5. Matching:

<table>
<thead>
<tr>
<th>Antibiotic prophylaxis</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Keflex</td>
<td>A. Cutaneous defect</td>
</tr>
<tr>
<td>2. Amoxicillin</td>
<td>B. Mucosal defect</td>
</tr>
<tr>
<td>3. Clindamycin</td>
<td>C. Cutaneous defect, penicillin allergic</td>
</tr>
<tr>
<td>4. Azithromycin</td>
<td>D. Mucosal defect, penicillin allergic</td>
</tr>
</tbody>
</table>

6. How much will a scar lengthen with a 60-degree Z-plasty transposition?

- A. 10%
- B. 25%
- C. 50%
- D. 55%
- E. 75%

7. Which of the following in not a risk factor for a patient developing methemoglobinemia while using topical EMLA?

- A. Patient < 1 year old
- B. Patient with G-6-PD deficiency
- C. Patient with sickle cell anemia
- D. Patient taking dapsone
- E. Patient taking phenobarbital

8. When does inosculation occur after skin graft placement?

- A. First 48 hours
- B. Days 2 to 3
- C. Days 4 to 7
- D. Day 4 to week 4
- E. After 2 to 3 months

9. How is procaine metabolized?

- A. Pseudocholinesterase
- B. Microsomal liver enzymes
- C. Monoamine oxidase
- D. Peroxidase
- E. Glutathione s-transferase

10. Which nonabsorbable suture has more tissue reactivity?

- A. Polypropylene
- B. Silk
- C. Polyglactin 910
- D. Gut

11. Which absorbable suture has less tissue reactivity?

- A. Polypropylene
- B. Silk
- C. Polyglactin 910
- D. Gut

**Answers**

1. C. Mentum. Blood supply to the head and neck is via the internal carotid artery (ICA) and external carotid artery (ECA) and their branches. Intimate anastamoses between ICA and ECA occur in the region of the upper central face (nose, glabella, periorbital, and forehead). These connections are important clinically in that: (1) infections in this area may extend intracranially via ICA; (2) steroid injections in the periorbital skin may embolize to the retinal artery and cause blindness.

2. E. 3, 2, 1 (fibroblast, keratinocyte, melanocyte). Different cells and tissues demonstrate a range of temperature sensitivity. Melanocytes are more sensitive than keratinocytes, and with cold injury, dyspigmentation should be discussed as an adverse outcome when treating dark skinned individuals.
Fibroblasts and other stromal structures are less sensitive to cold, which may contribute to the lack of scarring after superficial cold injury and/or cryosurgery.

3. 1, A; 2, B; 3, C. The inflammatory response is an important component after wounding of the skin. Macrophages are the most important cells for wound healing, releasing numerous growth factors and cytokines. Neutropenic or lymphopenic patients do not have impaired wound healing, whereas macrophage-deficient (quantity or function) patients heal poorly.

5. 1, A; 2, B; 3, C.D; 4, C.D. Although the risk of wound infection after skin surgery is small (1–2%), routine prophylactic antibiotics are usually indicated for: 1) certain patient populations: immunosuppressed, debilitated patients, and those with reduced blood flow to the surgical site (i.e., peripheral vascular disease, diabetes mellitus); 2) anatomic sites at greater risk for infection: ears, perineum, legs, and feet. Prophylactic antibiotic regimen depends on the endogenous flora of the operative site, as well as, patient specific issues (i.e., penicillin allergic).

6. E. 75%. The Z-plasty is a form of transposition flap that is often used for scar revision for scar length and changing scar orientation. It alters the change (redirection) of tension vectors of the original wound/scar, in addition to lengthening and breaking up of a scar into multiple zigzag lines. The extent of scar lengthening depends on the degree of transposition of the Z-plasty.

7. C. Sickle cell anemia. EMLA (eutectic mixture of local anesthetics) cream contains 2.5% lidocaine and 2.5% prilocaine. Prilocaine is metabolized to ortho-toluidine, an oxidizing agent capable of converting hemoglobin to methemoglobin, potentially causing methemoglobinemia. Patients at risk of methemoglobinemia include: patients <1 year old, patients with G-6-PD deficiency, and patients taking methemoglobinemia-inducing agents (dapsone, nitroglycerin, nitrofurantoin, antimalarials, sulfonamides, phenobarbital, phenytoin, nitroprusside, acetaminophen).

8. B. Day 2 to 3. A skin graft is any skin that is detached completely from its blood supply, removed from its donor site, and transplanted to a recipient site for wound closure in the same individual. Graft survival depends on the establishment of new vascular between the wound recipient site and the donor graft through the following phases: imbition, inosculation, capillary ingrowth and neovascularization, keratinocyte activation, and finally, sensory innervation.

9. A. Pseudocholinesterase. Several major enzymes and pathways are involved in drug metabolism. Amide anesthetics are N-dealkylated and hydrolyzed by microsomal liver enzymes cytochrome P450 3A4. Ester anesthetics are hydrolyzed by tissue pseudocholinesterases and excreted by kidney. Procaine is an ester anesthetic.

10. B. Silk. Suture characteristics include: tensile strength, knot strength, configuration, elasticity, memory or suture stiffness, plasticity, and pliability. Suture reactivity is another characteristic defined as the amount of inflammatory response that is elicited, which is dependent on the material from which it is made. Synthetic sutures are made from synthetic collagen derived from polymers and are broken down by hydrolysis as opposed to enzymatic degradation in natural sutures, causing less tissue reaction. In contrast, natural sutures are made from natural materials such as collagen derived from the gastrointestinal track of animals, woven cotton, raw silk, linen, or steel. Of the answer choices listed, polypropylene and silk are non-absorbable suture made from synthetic and natural materials, respectively.

11. C. Poliglactin. Suture characteristics include: tensile strength, knot strength, configuration, elasticity, memory or suture stiffness, plasticity, and pliability. Suture reactivity is another characteristic defined as the amount of inflammatory response that is elicited, which is dependent on the material from which it is made. Synthetic sutures are made from synthetic collagen derived from polymers and are broken down by hydrolysis as opposed to enzymatic degradation in natural sutures, causing less tissue reaction. In contrast, natural sutures are made from natural materials such as collagen derived from the gastrointestinal track of animals, woven cotton, raw silk, linen, or steel. Of the answer choices listed, polyglactin 910 and gut suture are absorbable suture made from synthetic and natural materials, respectively.

REFERENCES


SKIN AGING

- Intrinsic: natural aging, genetic process
- Extrinsic: exogenous causes; ultraviolet radiation, smoking
- Photoaging: skin is changed or damaged as a result of exposure to ultraviolet radiation in sunlight and other sources
  - Long-term effects include
    - Wrinkles
    - Discoloration
    - Telangiectasia
    - Susceptibility to cancer
    - Solar elastosis (heliosis): term applied to the chronic inflammatory changes and degradation of elastin and collagen

PHOTOAGING

- Glogau photoaging classification
  - Qualitative visual grading system (Table 26-1)
- Fitzpatrick skin types: classification of a patient’s cutaneous reaction to ultraviolet skin exposure. The lower the skin type number, the greater the susceptibility to photoaging. (Table 26-2)
- Molecular mechanism of photoaging
  - UV light activates activator protein 1 (AP-1)
  - AP-1 upregulates extracellular matrix (ECM)–degrading metalloproteinases (MP)
- Molecules related to aging
  - Extracellular signal-regulated kinase (ERK): photoaging
  - c-Jun NH2-terminal kinase (JNK): natural aging
  - UV light: generates hydroxyl radicals, damages DNA
    - Blocks transforming growth factor β (TGF-β) receptor II gene; prevents procollagen promoter with a reduction of collagen formation
- Telomeres and aging skin
  - Telomeres: tandem repeats of the DNA base sequence (TTAGGGG) (T-thymine, G = guanine, A = adenosine), at the end of mammalian chromosomes, telomere extension occurs by the action of telomerase (Fig. 26-1)
  - DNA polymerase does not copy the final bases on each chromosome, resulting in telomere shortening after each round of cell division
  - When the telomeres become too short, the cell will no longer divide
  - 3′ telomeric overhang (T-oligos): 3′-guanine-rich single-stranded overhang that is concealed in a protective loop
  - Most important: telomeric repeat binding factor 2 (TRF2)
  - Exposed during DNA damage or progressive telomere shortening
  - T-oligos: taken up into the nucleus and recognized by a sensor; initiates DNA damage signaling

ELECTROMAGNETIC RADIATION

Light Properties

- A quanta of light energy is a photon
- Photons display duality: both particle-like and wave-like behavior
- Electromagnetic radiation (EMR): form of energy, moves through space as a wave and comprised of photons, organized along an electromagnetic spectrum (Table 26-3 and Fig. 26-2)
TABLE 26-1  Glogau Photoaging Classification

<table>
<thead>
<tr>
<th>Glogau Photoaging Scale</th>
<th>I (Mild)</th>
<th>II (Moderate)</th>
<th>III (Advanced)</th>
<th>IV (Severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of photoaging</td>
<td>Early</td>
<td>Early to</td>
<td>Advanced</td>
<td>Severe</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20s-30s</td>
<td>moderate</td>
<td>50s or greater</td>
<td>60s or</td>
</tr>
<tr>
<td>Rhytids</td>
<td>None</td>
<td>Slight lines</td>
<td>Static</td>
<td>Numerous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>near the</td>
<td>(present at</td>
<td>rhytids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eyes and</td>
<td>rest)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous appearance</td>
<td>Minimal</td>
<td>No visible</td>
<td>Noticeable</td>
<td>Yellow or</td>
</tr>
<tr>
<td>and lesions</td>
<td>to no</td>
<td>keratoses</td>
<td>discolorations</td>
<td>gray color</td>
</tr>
<tr>
<td></td>
<td>discoloration</td>
<td>(skin</td>
<td>to skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>overgrowths)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


TABLE 26-2  Fitzpatrick Skin Types

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Very white or freckled</td>
<td>White</td>
<td>White to olive</td>
<td>Brown</td>
<td>Dark brown</td>
<td>Black</td>
</tr>
<tr>
<td>appearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burns?</td>
<td>Always burns</td>
<td>Usually burns</td>
<td>Sometimes burns</td>
<td>Rarely burns</td>
<td>Very rarely</td>
<td>Never burns</td>
</tr>
<tr>
<td>Tans?</td>
<td>Never tans</td>
<td>Some ability to tan</td>
<td>Easily tans</td>
<td>Always tans</td>
<td>Always tans</td>
<td>Always tans</td>
</tr>
</tbody>
</table>

- Photon energy is proportional to wave frequency and inversely related to wavelength.
- Ultraviolet (UV) light is part of the electromagnetic spectrum. UVA and UVB light has physiologic effects on the skin; UVC is filtered by the ozone layer (Table 26-4).

**LASER Properties**
- LASER (Light amplified by stimulated emission of radiation)
- LASER is a form of electromagnetic radiation
  - Characteristics of lasers (Table 26-5)
    - Monochromaticity: single, discrete wavelength. Active medium determines the emission wavelength, which is restricted to a very narrow band
      - Coherency: monochromatic light in phase. Highly directional
      - Collimation: light in parallel fashion to achieve its propagation across long distances without light divergence (constant diameter beam)
      - Intensity: amplification process allows the emission of high-energy level laser

**Chromophores**
- Skin components that absorb the laser light
  - Endogenous: water, melanin, protein, and hemoglobin
**FIGURE 26-1** Telomere extension by telomerase.

**TABLE 26-3** Electromagnetic Spectrum

<table>
<thead>
<tr>
<th>Electromagnetic Spectrum</th>
<th>Wavelengths</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radio waves</td>
<td>&gt; 30 cm</td>
<td>Combines electric and magnetic fields</td>
</tr>
<tr>
<td>Microwaves</td>
<td>1 mm–30 cm</td>
<td>Used for radar and cooking (heats water)</td>
</tr>
<tr>
<td>Infrared</td>
<td>700 nm–1 mm</td>
<td>Invisible; usually delivers heat</td>
</tr>
<tr>
<td>Visible light</td>
<td>400–700 nm</td>
<td>Passes through atmosphere</td>
</tr>
<tr>
<td>Ultraviolet</td>
<td>10 nm–350 nm</td>
<td>Majority filtered by ozone layer</td>
</tr>
<tr>
<td>X-rays</td>
<td>0.01 nm–10 nm</td>
<td>Ionization of the inner electrons of an atom</td>
</tr>
<tr>
<td>Gamma rays</td>
<td>&lt; 0.01 nm</td>
<td>From nuclear decay at atom’s center</td>
</tr>
</tbody>
</table>
### FIGURE 26-2  Electro-magnetic spectrum.

<table>
<thead>
<tr>
<th>Wavelength (meters)</th>
<th>10^{-14}</th>
<th>10^{-12}</th>
<th>10^{-10}</th>
<th>10^{-8}</th>
<th>10^{-6}</th>
<th>10^{-4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible Light</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wavelength (nanometers)</td>
<td>400</td>
<td>500</td>
<td>600</td>
<td>700</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 26-4  Ultraviolet Light Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ultraviolet C Light (UV-C)</th>
<th>Ultraviolet B Light (UV-B)</th>
<th>Ultraviolet A Light (UV-A)</th>
</tr>
</thead>
</table>
| Wavelengths | • 100 to 290 nm | • 290 to 320 nm | • UV-A I: 340 to 400 nm  
• UV-A II: 320 to 340 nm |
| Characteristics | • Most dangerous type of UV light  
• Cannot penetrate Earth’s ozone layer | • Photons 1000 times more energetic than UV-A  
• Absorbed by the epidermis, approximately 10% penetrating to deeper layers of the skin  
• Causes acute sunburn, skin cancer | • 10-fold greater abundance in terrestrial sunlight compared to UV-B  
• Approximately 50% of UV-A radiation penetrates the epidermis and reaches the papillary dermis  
• Causes delayed tanning |

### TABLE 26-5  LASER Characteristics

<table>
<thead>
<tr>
<th>LASER Characteristic</th>
<th>Symbol</th>
<th>Unit of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wavelength</td>
<td>λ</td>
<td>Nanometer (nm)</td>
</tr>
</tbody>
</table>
| Spot size | d (diameter)  
s (square) | Centimeter (cm) |
| Pulse duration | T (exposure time) | Seconds (sec) |
| Power output | P (power)  
Energy delivery per unit time | Watts (W) = Joules/sec (J/sec) |
| Fluence | Φ | Joules/cm² (J/cm²) |
| Irradiance (not to be confused with intensity) | Power delivered per unit area | W/cm² |
• Exogenous: tattoo ink
• Lasers effects on tissue components (chromophores) depend on absorption spectra (Fig. 26-3)

**Skin Optics**
- Reflection: waves encounter a surface or other boundary that does not absorb the energy of the radiation and bounces the waves away from the surface
- Absorption: energy is deposited in a chromophore
- Scattering: energy is redirected elsewhere in the skin, dermal light scattering varies inversely with wavelength
- Tyndall effect: short (blue) wavelengths are scattered more than long (red) wavelengths
- Transmission: direction of photon path is unchanged

**Depth of Penetration**
- Depends on absorption and scattering
- Depth of penetration increases with wavelength
  - Amount of scattering of laser energy is inversely proportional to the wavelength of incident light

**Laser-Tissue Interactions**
- Photothermal reaction: various effects on the skin occur directly from heat (Table 26-6)
- Photochemical reaction: reaction of an endogenous or exogenous photosensitizer with UV or visible light
- Photomechanical reaction: rapid absorption of a laser pulse resulting in a rapid temperature change along with sudden tissue vaporization, shock wave, or pressure wave formation
- Selective photothermolysis
  - Controlled destruction of a targeted lesion without significant thermal damage to surrounding normal tissue
- Thermal damage can be induced in tissue targets that absorb photons well at the emitted wavelength
- Pulse duration or exposure time should be shorter than the cooling time or thermal relaxation time (defined as the time required for the targeted site to cool to one-half its peak temperature immediately after laser irradiation) of the target

**Laser Media (Fig. 26-4)**
- Laser beam wavelength is determined by the lasing medium (Tables 26-7 and 26-8)
  - Solid-state lasers
    - Lasing material distributed in a solid matrix
    - Ruby or neodymium:yttrium-aluminum garnet (Nd:Yag) lasers
  - Gas lasers
    - Primary output of visible red light
    - Helium and helium-neon (HeNe)
  - Excimer lasers
    - Name is derived from the terms excited and dimers
    - Use reactive gases, chlorine and fluorine, mixed with inert gases such as argon, krypton, xenon
    - When electrically stimulated, a pseudo-molecule (dimer) is produced
    - When lased, the dimer produces light in the ultraviolet range
  - Dye lasers: use complex organic dyes
  - Semiconductor lasers (diode lasers)
- Laser treatment for tattoo, pigment, and vascular lesions are describe in Tables 26-9–26-11
- The differences between ablative, nonablative, and fractional skin resurfacing are described in Tables 26-12 and 26-13

**Non-Laser Light Sources**
- Intense pulsed light (IPL)
  - Noncoherent light within 500 to 1200 nm

---

**TABLE 26-6 Thermal Effects on Skin Cells**

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Thermal Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of 5 to 10°C</td>
<td>Cell injury and inflammation</td>
</tr>
<tr>
<td>Above 60°C</td>
<td>Denaturation of protein</td>
</tr>
<tr>
<td>Above 70°C</td>
<td>Denaturation of DNA</td>
</tr>
<tr>
<td>Over 100°C</td>
<td>Vaporization of water</td>
</tr>
</tbody>
</table>
  (Boiling point of water = 100°C)
TABLE 26-7  Laser Beam Types

<table>
<thead>
<tr>
<th>Continuous-Wave (CW) Lasers</th>
<th>Quasi-Continuous-Mode (QSW)</th>
<th>Pulsed Lasers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Continuous beam of light</td>
<td>Select pulse duration based on target size. Long pulse (millisecond): 0.5 to 400 ms allows for targeting of most hair and blood vessels (i.e., visible to near infrared lasers)</td>
</tr>
</tbody>
</table>

(Continued)
Continuous-Wave (CW) Lasers

- Little or no variation in power output over time (stable average beam power)
- Long exposure times with low peak power

Quasi-Continuous-Mode (QSW)

- Produce individual pulses of light
- Energy within the pulse is not constant but rather builds, peaks, and tapers off within a very short time
- Peak power outputs of pulsed lasers are often up to 100 times the maximum output of CW lasers

Pulsed Lasers

- Short pulse (microsecond): modified to produce very short pulses with high peak power in a repetitive fashion; developed to reduce the amount of thermal damage that occurs adjacent to a vaporized area or a laser incision; when applied to CO₂ laser, allows for much safer skin resurfacing (i.e., CO₂)
- Q-switched (QS) (nanosecond): allows buildup of extremely high energy in the laser cavity before discharge in very short single pulses. (Q stands for the quality factor of the laser cavity and represents the rate of discharge of energy of quality-switched lasers.) (i.e., alexandrite, ruby, QS-Nd:YAG)

Complications

- Can result in non-selective tissue injury (scar) as heat spreads from chromophore
- Lower the risk of thermal injury to surrounding non-targeted structures

Examples

- CO₂, Argon
- Argon-pumped tunable dye Potassium-titanyl-phosphate (KTP)
- Copper vapor Krypton

**TABLE 26-8 Types of Lasers and Light Sources**

<table>
<thead>
<tr>
<th>Laser</th>
<th>Wavelength (nm)</th>
<th>Color</th>
<th>Chromophore</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excimer</td>
<td>308</td>
<td>Ultraviolet</td>
<td>Protein</td>
<td>QCW</td>
</tr>
<tr>
<td>Narrow-band blue light</td>
<td>407–420</td>
<td>Violet/blue</td>
<td>Endogenous porphyrins</td>
<td>CW</td>
</tr>
<tr>
<td>Argon</td>
<td>488/514</td>
<td>Blue</td>
<td>Vascular and pigmented lesions</td>
<td>CW</td>
</tr>
<tr>
<td>Pulsed dye (PDL)</td>
<td>510</td>
<td>Yellow</td>
<td>Pigmented lesions, vascular lesions</td>
<td>Pulsed</td>
</tr>
<tr>
<td>Copper vapor</td>
<td>511/578</td>
<td>Yellow/green</td>
<td>Pigmented lesions, vascular lesions</td>
<td>CW</td>
</tr>
<tr>
<td>Krypton</td>
<td>530/568</td>
<td>Yellow/green</td>
<td>Pigmented lesions, vascular lesions</td>
<td>CW</td>
</tr>
<tr>
<td>Potassium-titanyl-phosphate (KTP), Nd:YAG, frequency-doubled</td>
<td>532</td>
<td>Green</td>
<td>Pigmented lesions, red tattoos</td>
<td>QS</td>
</tr>
<tr>
<td>Argon-pumped tunable dye</td>
<td>577/585</td>
<td>Yellow</td>
<td>Vascular lesions</td>
<td>CW</td>
</tr>
<tr>
<td>Pulsed dye laser (PDL)</td>
<td>585–595</td>
<td>Yellow</td>
<td>Vascular lesions, hypertrophic/ keloid scars, striae, verrucae, nonablative dermal remodeling</td>
<td>Pulsed</td>
</tr>
</tbody>
</table>
### Table 26-8 (Continued)

<table>
<thead>
<tr>
<th>Laser</th>
<th>Wavelength (nm)</th>
<th>Color</th>
<th>Chromophore</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruby, normal mode</td>
<td>694</td>
<td>Red</td>
<td>Hair removal</td>
<td>Pulsed</td>
</tr>
<tr>
<td>QS ruby</td>
<td>694</td>
<td>Red</td>
<td>Pigmented lesions, blue/black/ green/tattoos</td>
<td>QS</td>
</tr>
<tr>
<td>Alexandrite, normal mode</td>
<td>755</td>
<td>Red</td>
<td>Hair removal, leg veins</td>
<td>Pulsed</td>
</tr>
<tr>
<td>QS alexandrite</td>
<td>755</td>
<td>Red</td>
<td>Pigmented lesions, blue/black/ green tattoos</td>
<td>QS</td>
</tr>
<tr>
<td>Diode</td>
<td>800–810</td>
<td>Red</td>
<td>Hair removal, leg veins</td>
<td>Pulsed</td>
</tr>
<tr>
<td>Qs Nd:YAG</td>
<td>1064</td>
<td>Infrared</td>
<td>Pigmented lesions, blue/black tattoos</td>
<td>QS</td>
</tr>
<tr>
<td>Normal mode</td>
<td>1064</td>
<td>Infrared</td>
<td>Hair removal, leg veins, nonablative dermal remodeling</td>
<td>Pulsed</td>
</tr>
<tr>
<td>Nd:YAG</td>
<td>1320</td>
<td>Infrared</td>
<td>Water: nonablative dermal remodeling</td>
<td>Pulsed</td>
</tr>
<tr>
<td>Diode</td>
<td>1450</td>
<td>Infrared</td>
<td>Water: nonablative dermal remodeling</td>
<td>Pulsed</td>
</tr>
<tr>
<td>Erbium</td>
<td>2940</td>
<td>Infrared</td>
<td>Water</td>
<td>CW</td>
</tr>
<tr>
<td>CO₂</td>
<td>10,600</td>
<td>Infrared</td>
<td>Water (vaporization and coagulation): actinic cheilitis, verrucae, rhinophyma Ablative skin resurfacing, epidermal/dermal lesions</td>
<td>CW, Pulsed</td>
</tr>
</tbody>
</table>

**Note:** CW, continuous-wave; Nd, neodymium; QCW, Quasi continuous wave; QS, quality-switched; YAG, yttrium-aluminum-garnet.

### Table 26-9 Laser Treatment of Tattoo Pigment (Chromophore Is Tattoo Ink)

<table>
<thead>
<tr>
<th>Laser Type</th>
<th>Wavelength</th>
<th>Tattoo Pigment Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmented PDL</td>
<td>510 nm</td>
<td>Orange, yellow, purple</td>
</tr>
<tr>
<td>QS Nd:YAG, frequency-doubled</td>
<td>532 nm</td>
<td>Red, orange, yellow</td>
</tr>
<tr>
<td>QS ruby</td>
<td>694 nm</td>
<td>Blue, blue-black Occasionally green and brown</td>
</tr>
<tr>
<td>QS alexandrite</td>
<td>755 nm</td>
<td>Blue, black, and green</td>
</tr>
<tr>
<td>QS Nd:YAG</td>
<td>1064 nm</td>
<td>Blue-black</td>
</tr>
</tbody>
</table>

### Table 26-10 Lasers Used for Vascular Lesions (Chromophore Is Hemoglobin)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Port-wine stain</td>
<td>PDL, IPL</td>
</tr>
<tr>
<td>Hemangiomas</td>
<td>PDL</td>
</tr>
<tr>
<td>Telangiectasias</td>
<td>Green-light lasers (532 nm)</td>
</tr>
<tr>
<td>Pyogenic granuloma</td>
<td>PDL</td>
</tr>
<tr>
<td>Angiofibromas</td>
<td>Carbon dioxide laser, combined continuous-wave/pulsed</td>
</tr>
</tbody>
</table>

### TABLE 26-11 Laser Treatment of Pigmented Lesions (Chromophore Is Melanin)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentigines</td>
<td>QS ruby</td>
</tr>
<tr>
<td></td>
<td>QS alexandrite</td>
</tr>
<tr>
<td></td>
<td>QS Nd:YAG (532 nm)</td>
</tr>
<tr>
<td></td>
<td>IPL</td>
</tr>
<tr>
<td>Nevus of Ota</td>
<td>QS ruby</td>
</tr>
<tr>
<td></td>
<td>QS alexandrite</td>
</tr>
<tr>
<td></td>
<td>QS Nd:YAG (1064 nm)</td>
</tr>
<tr>
<td>Congenital melanocytic nevi</td>
<td>Normal ruby</td>
</tr>
<tr>
<td></td>
<td>QS ruby</td>
</tr>
<tr>
<td></td>
<td>QS Nd:YAG (532 nm)</td>
</tr>
<tr>
<td>Café-au-lait macules</td>
<td>QS ruby</td>
</tr>
<tr>
<td></td>
<td>QS Nd:YAG (532 nm)</td>
</tr>
<tr>
<td></td>
<td>Copper vapor</td>
</tr>
<tr>
<td>Nevus spilus</td>
<td>Normal ruby</td>
</tr>
<tr>
<td></td>
<td>Normal alexandrite</td>
</tr>
<tr>
<td></td>
<td>QS ruby</td>
</tr>
<tr>
<td></td>
<td>QS Nd:YAG (532 nm)</td>
</tr>
</tbody>
</table>

### TABLE 26-12 Laser and Other Devices for Nonablative Remodeling

<table>
<thead>
<tr>
<th>Indication</th>
<th>Laser</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrinkles or acne scars</td>
<td>Pulsed-dye laser</td>
<td>Chromophore is hemoglobin</td>
</tr>
<tr>
<td></td>
<td>Nd:YAG (1064, 1320 nm)</td>
<td>Chromophore is water</td>
</tr>
<tr>
<td></td>
<td>Diode (1450 nm)</td>
<td>Chromophore is water</td>
</tr>
<tr>
<td>Nonsurgical lift</td>
<td>Radiofrequency</td>
<td>Heat from electrical resistance</td>
</tr>
</tbody>
</table>

### TABLE 26-13 Comparative Summary of Ablative and Nonablative Skin Resurfacing and Fractional Photothermolysis

<table>
<thead>
<tr>
<th></th>
<th>Ablative Skin Resurfacing</th>
<th>Nonablative Skin Resurfacing</th>
<th>Fractional Photothermolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromophore</td>
<td>Water</td>
<td>Hemoglobin, melanin</td>
<td>Water</td>
</tr>
<tr>
<td>Mode of application</td>
<td>Stamping approach; bulk heating</td>
<td>Stamping approach: bulk heating</td>
<td>Uniform beam; fractional heating; tissue sparing</td>
</tr>
<tr>
<td>Mode of thermal damage</td>
<td>Epidermal vaporization and coagulation of underlying dermis</td>
<td>Thermal damage, mainly dermal</td>
<td>Columns of thermal damage in epidermis and dermis</td>
</tr>
<tr>
<td>Laser and light sources</td>
<td>CO₂ laser (10,600 nm)</td>
<td>PDL (585–595 nm)</td>
<td>Erbium-doped fiber laser (1,550 nm)</td>
</tr>
<tr>
<td></td>
<td>Erbium: YAG laser (2,940 nm)</td>
<td>IPL (515–1,200 nm)</td>
<td>CO₂ laser (10,600 nm)</td>
</tr>
<tr>
<td></td>
<td>Q-switched Nd:YAG laser (1,064 nm)</td>
<td>Q-switched Nd:YAG laser (1,064 nm)</td>
<td>Erbium laser (2,940 nm)</td>
</tr>
<tr>
<td></td>
<td>Long-pulsed Nd:YAG laser (1,320 nm)</td>
<td>Long-pulsed Nd:YAG laser (1,320 nm)</td>
<td>Nd: YAG Laser (1,440 nm)</td>
</tr>
<tr>
<td></td>
<td>Diode laser (1,450 nm)</td>
<td>Erbium: Glass laser (1,540 nm)</td>
<td>Radiofrequency device</td>
</tr>
<tr>
<td></td>
<td>Erbium: Glass laser (1,540 nm)</td>
<td>Erbium: Glass laser (1,540 nm)</td>
<td></td>
</tr>
<tr>
<td>Recovery time</td>
<td>Up to 6 months</td>
<td>Up to 1 month</td>
<td>1–2 weeks</td>
</tr>
<tr>
<td>Efficacy (%)</td>
<td>60–90%</td>
<td>10–80%</td>
<td>70–80%</td>
</tr>
</tbody>
</table>

(Continued)
### Table 26-13 (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Ablative Skin Resurfacing</th>
<th>Nonablative Skin Resurfacing</th>
<th>Fractional Photothermolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Hyperpigmentation, Hypopigmentation, Erythema, Pruritus, Dryness, Acne, Milia, Scarring, Infection</td>
<td>Hyperpigmentation, Hypopigmentation, Erythema, Scarring</td>
<td>Erythema, Pruritus, Dryness, Acne</td>
</tr>
</tbody>
</table>

- Filtered xenon flashlamps are used to eliminate shorter wavelengths
- Single-, double-, or triple-pulse sequences; pulse durations of 2 to 25 ms and delays between pulses ranging from 10 to 500 ms
- Light-emitting diodes (LEDs)
  - Narrow-band light source (i.e., not a single wavelength)
  - Emit noncoherent light; restricted range of ±20 nm; pulse signal to stimulate mitochondria in fibroblasts

### Laser Safety
- Fire prevention with CO₂ lasers
  - Saline-soaked drapes or cloths should be used intraoperatively
  - Exposed hair-bearing areas should be kept moist; alcohol-based skin preparations should be strictly avoided
- Eye protection: permanent visual loss can result
- Aerosolized particles: smoke evacuator with clean filters and tubing

### Topical Anesthetic Compounds
- Can be applied under occlusion for 30 to 90 minutes before laser treatment
  - **EMLA cream 5%**: lidocaine 2.5% and prilocaine 2.5%
  - **LMX**: 4% or 5% lidocaine
  - **S-caine peel**: lidocaine and tetracaine
    - Applied to the skin as a cream 30 minutes before treatment
    - Dries to a thin, flexible film that can be peeled away easily
  - For ablative laser skin resurfacing procedures: consider combination anesthesia (i.e., topical, tumescent, nerve blocks, sedation)

### Possible Laser Side Effects
- General: dyspigmentation (most common), erythema, pain, scar, incomplete removal of target
- Laser tattoo or pigmented lesion removal: purpura, eschar
- Laser treatment of vessels: purpura, vesiculation
- Laser hair removal: perifollicular edema, vesiculation
- Ablative laser skin resurfacing
  - Short term: edema, exudation, infection (Herpes simplex virus, Candida, or bacterial)
  - Medium term: acne/milia, pruritus, hyperpigmentation, dermatitis
  - Permanent: hypopigmentation, scar, ectropion
- Nonablative resurfacing: vesiculation

### Skin Cooling
- Decreases risk of vesiculation and pigmented changes (most common) by protecting epidermis
- Methods of cooling
  - Inert: ice, cold gel, water-cooled glass or sapphire treatment tips
  - Active: forced air cooling, cryogen spray

### Skin Resurfacing Chemical Peels
- Depth of peels and peeling agents are listed in Tables 26-14 and 26-15

### Table 26-14 Depth of Peel

<table>
<thead>
<tr>
<th>Depth of Peel</th>
<th>Wound Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superficial</strong></td>
<td>Necrosis of all or part of the epidermis</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td>Necrosis extends to part or all of the papillary dermis</td>
</tr>
<tr>
<td><strong>Deep</strong></td>
<td>Wounding extends into the mid-reticular dermis</td>
</tr>
</tbody>
</table>
## TABLE 26-15 Peeling Agents

<table>
<thead>
<tr>
<th>Chemical Agent</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-hydroxy acid (AHA)</td>
<td>Glycolic, lactic, citric, and malic acids&lt;br&gt;Dependent on the contact time with the skin&lt;br&gt;Carboxylic acids normally found in many foods&lt;br&gt;Thins the stratum corneum, although the epidermis thickens&lt;br&gt;May increase photosensitivity</td>
</tr>
<tr>
<td>Glycolic acid</td>
<td>Derived from sugar cane&lt;br&gt;Concentrations range from 20% to 70%&lt;br&gt;Decreases corneocyte cohesion by promoting exfoliation of the outer layers of the stratum corneum&lt;br&gt;Neutralize with sodium bicarbonate&lt;br&gt;Dispersal of melanin pigmentation and a return to a more normal rete pattern</td>
</tr>
<tr>
<td>Lactic acid (LA)</td>
<td>Derived from sour milk&lt;br&gt;Acts as a humectant (causes the skin to hold onto water), keratolytic</td>
</tr>
<tr>
<td>Beta-hydroxy acid (BHA)</td>
<td>Derived from willow bark, wintergreen leaves, or sweet birch&lt;br&gt;Concentrations of 20% or 30% (OTC preparations contain only 2%)&lt;br&gt;Exhibits anti-inflammatory capabilities, producing less irritation&lt;br&gt;Lipophilic&lt;br&gt;Penetrates the follicular sebaceous material (anticomedogenic effect)&lt;br&gt;Does not need to be neutralized, and the frost is visible&lt;br&gt;No need to time the peel: after 2 minutes, there is very little absorption of the active agent&lt;br&gt;Contraindicated in pregnancy, breast-feeding, and aspirin allergies&lt;br&gt;Adverse effect: salicylism (nausea, disorientation, and tinnitus)</td>
</tr>
<tr>
<td>Jessner's solution</td>
<td>14% salicylic acid, 14% lactic acid, 14% resorcinol in alcohol&lt;br&gt;Keratolytic effects</td>
</tr>
<tr>
<td>Carbon dioxide (CO₂)</td>
<td>Boiling point: 78°C&lt;br&gt;Physical peeling method&lt;br&gt;Solid block of CO₂ ice dipped in an acetone-alcohol mixture&lt;br&gt;Applied to the skin for 5 to 15 seconds</td>
</tr>
<tr>
<td>Resorcinol</td>
<td>1,3-Dihydroxybenzene&lt;br&gt;Concentrations of 20% to 50%</td>
</tr>
<tr>
<td>Trichloroacetic acid</td>
<td>Can be used for superficial, medium, and less often deep peels&lt;br&gt;No need to neutralize&lt;br&gt;No systemic toxicity&lt;br&gt;Causes coagulation of proteins in the skin (results in frost)</td>
</tr>
<tr>
<td>Baker Gordon phenol</td>
<td>Phenol 88%, 2 mL distilled water, 8 drops Septisol, and 3 drops croton oil&lt;br&gt;Septisol (triclosan) causes deeper penetration of phenol and a deeper peel&lt;br&gt;Croton oil (especially the toxic fraction solubilized in phenol) causes a deeper peel&lt;br&gt;Exfoliation to middle reticular dermis&lt;br&gt;New zone of collagen forms&lt;br&gt;Occluded method uses zinc oxide tape or other artificial barrier product to prevent evaporation of the phenol from the skin, thus enabling the solution to penetrate deeper&lt;br&gt;&lt;i&gt;Litton’s formula&lt;/i&gt;: replaces Septisol (triclosan) with glycerin&lt;br&gt;&lt;i&gt;Beeson McCollough formula&lt;/i&gt;: uses aggressive defatting and heavier application of Baker Gordon solution</td>
</tr>
</tbody>
</table>
Indications
- Actinic keratoses
- Superficial scarring
- Hyperpigmentation and melasma
- Mild wrinkles
- Acne

Chemical peel strengths
- Depend on the amount of free acid present
  - Free acid availability (pKa)
  - pKa = pH at which half is in acid form
  - Lower pKa = more free acid available
- Affected by
  - Percentage of acid
  - Type of vehicle used
  - Buffering
  - pKa of acid preparation
  - Contact time

Defatting
- Acetone, rubbing alcohol, or Septisol (triclosan)
- Essential for penetration as most agents are not lipid soluble

Frost
- Whitish tint of skin due to keratin agglutination
- Dependent on pre-existing degree of photo damage, choice of applicator, adequacy of defatting
- Level of peel can be correlated with the intensity of the frost (Table 26-16)

Complications of chemical peels
- Arrhythmias (need electrocardiogram and pulse oximeter monitoring with phenol peels)
- Pigmentary change
- Scarring
- Infection
- Prolonged erythema
- Acne
- Milia

### Microdermabrasion and Dermabrasion

The differences between microdermabrasion and dermabrasion are listed in Table 26-17.

| TABLE 26-16  Correlation of Frost to Depth of Penetration |
|----------------|----------------|----------------|----------------|
| Level          | 0              | 1              | 2              |
| Clinical appearance | No frost          | Irregular light frost | Uniform white frost with pink showing through |
| Depth of penetration | Stratum corneum | Superficial epidermis | Full thickness epidermis |

### Table 26-17 Microdermabrasion Versus Dermabrasion

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Microdermabrasion</th>
<th>Dermabrasion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Produces a superficial ablation, primarily in the epidermis</td>
<td>Manual abrasion, wound healing by second intention allows re-epithelialization to occur from the underlying adnexal structures Depth of procedure: operator-dependent process and depends on coarseness of the dermabrading tip (fraise), number of brush strokes, pressure exerted on the electric handpiece, and tissue contact time</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>Superficial skin conditions Early photoaging, fine lines, and superficial scarring Effective microdermabrasion usually requires a series of 5–12 treatments</td>
<td>Lesions or defects of epidermis, papillary dermis, and upper reticular dermis Tattoos, rhinophyma, acne scarring, actinic keratoses, solar elastosis, and discoloration of photoaging 6–8 weeks following incision or injury (except when certain surgical procedures that involve extensive undermining, such as face lifts or brow lifts, to allow reestablishment of the underlying vascular bed. Wait at least 6 months)</td>
</tr>
<tr>
<td><strong>Instruments</strong></td>
<td>Components common to all systems Pump: generates a high-pressure stream of aluminum oxide or salt crystals Connecting tube and handpiece: delivers the crystals to the skin Vacuum: removes the crystals and exfoliated skin Crystals are discarded after use Eye protection from stray crystals</td>
<td>Abrasive wire or diamond wheel Rotational speeds of 12,000 to 15,000 rpm High-speed rotary motors are used to drive an ablading end piece</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Active herpes infection Malignant skin tumors Evolving dermatoses Certain keratoses</td>
<td>History of hypertrophic scarring Isotretinoin within 6 to 12 months Active herpetic infection Malignant skin tumors Evolving dermatoses Certain keratoses</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Rare; only mild postinflammatory hyperpigmentation Ocular complications (ie. corneal abrasion) – use eye protection Low risk, rapid recovery</td>
<td>Milia formation and a flare-up of acne Transient postoperative hyperpigmentation Postoperative viral infections Hypertrophic scarring</td>
</tr>
</tbody>
</table>

**TABLE 26-18** Commercially Available BTX

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox (Allergan, Inc., Irvine, CA)</th>
<th>Dysport (Ipsen, Slough, U.K.)</th>
<th>Myobloc (Elan Pharmaceuticals, Sandiego, CA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype</td>
<td>• BTX type A</td>
<td>• BTX type A (abobotulinum toxin A)</td>
<td>• BTX type B</td>
</tr>
</tbody>
</table>
| FDA (Food and Drug Administration) | • FDA approved in 1989 for treatment of strabismus and blepharospasm  
• FDA approved in 2000 for treatment of cervical dystonia  
• FDA approved in 2002 for treatment of glabellar rhytides, and hyperhidrosis  
• Currently available in the United States | • FDA approved in 2009 for treatment of glabellar lines and cervical dystonia | • FDA approved in 2000 for treatment of cervical dystonia.  
• Off-label treatment for facial wrinkles and hyperhidrosis. Currently available in United states  
• Available in Europe under the name Neurobloc |
| Packaging | • Comes in a vial containing 100 units | • Comes in a vial containing 500 units | • Available in vials containing 2500, 5000, and 10,000 units |
| Storage | • Must be stored frozen and then refrigerated when reconstituted | • Can be stored at room temperature | • Does not require constitution and is ready to use at pH 5.6  
• Can be diluted to desired concentration |
• Lasts approximately 3 to 5 months
• Muscle function returns as new neuromuscular junctions form (axonal sprouting)

• Antibodies to Botox
  • Antibody may develop to the binding site on the heavy chain of the BTX molecule
  • Prevents BTX binding to its receptor and thereby cripples the actions of the BTX
  • Increased risk of antibody formation at doses of more than 300 units at a time
  • Myobloc binding domain distinct from Botox (i.e., antibodies that neutralize BTX A would not neutralize BTX B, and vice versa)

• Uses for Botox on the face and neck
  • Numerous injection sites and concentrations published in literature
  • Glabellar rhytides are the only FDA-approved use of Botox for wrinkles
  • Injections under the guidance of electromyography (EMG) monitoring can be performed

• Glabellar furrows
  • Muscles involved (Fig. 26-6)
    – Procerus: brow depressor
    – Corrugator: brow depressor
    – Orbicularis oculi (medial fibers)

• Complications
  • Eyelid ptosis may develop when BTX affects the levator palpebrae superioris muscle, which normally elevates the eyelid


FIGURE 26-7 Iodine starch test for evaluation of hyperhidrosis. A. An iodine solution is applied to the affected area. B. Potato starch is then sprinkled over the area. C. The starch turns black in reaction to sweat, clearly delineating affected areas.
SOFT-TISSUE AUGMENTATION

- Injectable fillers are generally considered soft tissue augmentation materials
- Temporary injectable fillers are the most commonly used soft tissue augmentation products
- Used for wrinkles, scars, and augmentation of the lips and other tissues (Tables 26-19–26-22)

SCLEROTHERAPY

- When performing sclerotherapy, skin should be taut to facilitate cannulating the vessel
- Stretching the skin in opposite directions perpendicular to the vessel
- Compression should be applied to the injected site immediately post injection (Table 26-23)

ACNE SCAR TREATMENT

- Acne scarring classification and treatment options are described in Table 26-24
<table>
<thead>
<tr>
<th>Filler</th>
<th>Type</th>
<th>FDA approved Indications</th>
<th>Treatment Techniques</th>
<th>Duration</th>
<th>Complication and Potential Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat transfer</td>
<td>Autologous filler</td>
<td>N/A</td>
<td>Inject into subcutaneous fat layer and/or muscle. Overcorrection is necessary</td>
<td>N/A</td>
<td>Prolonged edema, bruising, under-/overcorrection, migration, clumping, irregularities, fat necrosis, and infection</td>
</tr>
<tr>
<td>Fat autograft muscle injection (FAMI)</td>
<td>Autologous filler</td>
<td>N/A</td>
<td>Require nerve block if treated on face. Inject into muscle and immediate surrounding planes</td>
<td>Permanent or long lasting</td>
<td>Rare, including swelling, bruising, infection, scarring, and dyspigmentation</td>
</tr>
<tr>
<td>Autologen cultured human fibroblasts</td>
<td>Autologous filler</td>
<td>Stimulates cutaneous collagen formation</td>
<td>Overcorrect by at least 20–30%. Nerve blocks, local or topical anesthesia are needed. Require a minimum of three injections over several weeks. Skin testing not required.</td>
<td>3–6 months</td>
<td>No risk for disease transmission or allergic reaction</td>
</tr>
<tr>
<td>AlloDerm</td>
<td>Cadaver-derived implant</td>
<td>Lip augmentation</td>
<td>Make tiny incision at both corners of lips. Pass instrument from one incision to the other to make a tunnel. Pass implant along the tunnel</td>
<td>From 6–12 months to several years</td>
<td>Overcorrection</td>
</tr>
<tr>
<td>Cymetra (acellular allogeneic dermis)</td>
<td>Cadaver-derived implant</td>
<td>Rhytides, nasolabial folds, and lips</td>
<td>Inject at midreticular level. Double allergy testing is recommended</td>
<td>3–6 months</td>
<td>Bruising, redness, swelling, and wrinkling of skin</td>
</tr>
<tr>
<td>Human cadaver tissue (injectable, microparticulate acellular allogenic dermis)</td>
<td>Cadaver-derived implant</td>
<td>N/A</td>
<td>N/A</td>
<td>Lasts longer than bovine collagen</td>
<td>N/A</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Filler</th>
<th>Type</th>
<th>FDA approved Indications</th>
<th>Treatment Techniques</th>
<th>Duration</th>
<th>Complication and Potential Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human cadaver tissue (fascian lyophilized human particulate fascia lata)</td>
<td>Cadaver-derived implant</td>
<td>Stimulation of cutaneous collagen formation</td>
<td>N/A</td>
<td>3–6 months</td>
<td>Edema, erythema, and ecchymosis, inflammatory hyperpigmentation.</td>
</tr>
<tr>
<td>Zyderm (bovine dermal collagen dispersed in phosphate-buffered physiological saline containing 3% lidocaine)</td>
<td>Temporary filler</td>
<td>Facial rhytides, scars, and lip augmentation</td>
<td>Inject intradermally Infiltrate into superficial papillary dermis Require second skin test on contralateral arm Overcorrection is mandatory</td>
<td>3–6 months</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Zyplast (bovine collagen cross-linked with glutaraldehyde and suspended in saline and 3 mg/ml lidocaine)</td>
<td>Temporary filler</td>
<td>Facial rhytides, scars, and lip augmentation</td>
<td>Place into midreticular or deep reticular dermis at dermal subcutaneous interface Require second skin test on contralateral arm Overcorrection is mandatory</td>
<td>3–6 months</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>CosmoDerm (human-based collagen insolated from human fibroblast cell cultures)</td>
<td>Temporary filler</td>
<td>Rhytides and scars (superficial skin defects)</td>
<td>Require pretreating with topical anesthetic cream Allergy test is not required</td>
<td>3–6 months</td>
<td>Mild swelling, erythema, bruising, and rarely, palpable lumps</td>
</tr>
<tr>
<td>CosmoPlast (human-based collagen cross-linked with glutaraldehyde)</td>
<td>Temporary filler</td>
<td>Rhytides and scars (reserved for deeper lines)</td>
<td>Require pretreating with topical anesthetic cream Allergy test is not required</td>
<td>3–6 months</td>
<td>Mild swelling, erythema, bruising, and rarely, palpable lumps</td>
</tr>
<tr>
<td>Restylane (hyaluronic acid derived from bacterial biofermentation process)</td>
<td>Temporary filler</td>
<td>Perlane 20 mg/mL; nasolabial folds and lips (fullness and pouting)</td>
<td>Should not be overcorrected Linear threading Serial puncture Fanning Cross-hatching</td>
<td>3–6 months</td>
<td>Redness, swelling, localized granulomatous reactions, bacterial infection, acneiform and cystic reaction, hypersensitivity</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Filler</th>
<th>Type</th>
<th>FDA approved Indications</th>
<th>Treatment Techniques</th>
<th>Duration</th>
<th>Complication and Potential Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Restylane 20 mg/mL: rhytides at glabellar, oral commissures and lip fullness, pouting, and vermilion border</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restylane fine line 20 mg/mL: thin superficial lines, worry lines, periorbital and perioral lines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvederm (viscoelastic, nonanimal hyaluronic acid gel)</td>
<td>Temporary filler</td>
<td>18 mg/g: superficial dermis, fine lines and rhytides</td>
<td>Correct placement in deep dermal and/or deep dermal subcutaneous plane</td>
<td>3–6 months</td>
<td>Redness, swelling, localized granulomatous reactions, bacterial infection, acneiform and cystic reaction, hypersensitivity</td>
</tr>
<tr>
<td>Hylaform (viscoelastic hyaluronic acid gel from rooster combs)</td>
<td>Temporary filler</td>
<td>Cosmetic use</td>
<td>Correct placement in deep dermal and/or deep dermal subcutaneous plane</td>
<td>2–3 months</td>
<td>Delayed inflammatory skin reactions</td>
</tr>
<tr>
<td>Sculptra (new-fill poly-L-lactic acid)</td>
<td>Temporary filler</td>
<td>Absorbable suture material and treatment of HIV-associated lipoatrophy</td>
<td>Correct placement in deep dermal and/or deep dermal subcutaneous plane</td>
<td>12–18 weeks</td>
<td>Infection, allergic reaction, and inflammatory granulomas</td>
</tr>
<tr>
<td>Filler</td>
<td>Type</td>
<td>FDA approved Indications</td>
<td>Treatment Techniques</td>
<td>Duration</td>
<td>Complication and Potential Adverse Reactions</td>
</tr>
<tr>
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</tr>
<tr>
<td>Radiesse (radiance synthetic calcium hydroxyapatite microspheres suspended in polysaccharide gel)</td>
<td>Semi-permanent filler</td>
<td>Vocal cord augmentation and urinary incontinence</td>
<td>Inject into subdermis Intradermal placement can result in swelling, pain, persistent erythema, and visible or palpable granules. Slight over-correction is recommended Repeat injections 1-3 months after initial treatment Skin testing is mandatory</td>
<td>9–12 months</td>
<td>Pruritus or hypertrophic scarring, allergic reaction, granulomas (can be treated with corticosteroid injections)</td>
</tr>
<tr>
<td>Artecoll/Artefill (polymethylmethacrylate microspheres in denatured bovine collagen)</td>
<td>Permanent filler</td>
<td>Pending for correction of facial rhytides, scars, and lip augmentation</td>
<td>Inject into the junction of dermis and subcutaneous space using tunneling technique Use small needle Overcorrection is not recommended Repeat treatment every 6 weeks until adequate augmentation Allergy test is required</td>
<td>Long lasting</td>
<td>Inflammation, induration, discoloration, ulceration, migration, and formation of granulomas</td>
</tr>
<tr>
<td>Silskin, AdatoSil 5000, Silikon 1000, Silicone oil</td>
<td>Permanent filler</td>
<td>Ocular medical purpose (not approved for cosmetic use)</td>
<td>Microdroplets of silicone oil are dispersed within dermal tissues, and fibrosis around these droplets localizes the material and provide “bulk” No allergy testing is required</td>
<td>Long lasting</td>
<td>Risks of infection, generally due to granuloma formation as the silicone becomes encapsulated as a foreign body in a chronic inflammatory reaction</td>
</tr>
<tr>
<td>Filler</td>
<td>Type</td>
<td>FDA approved Indications</td>
<td>Treatment Techniques</td>
<td>Duration</td>
<td>Complication and Potential Adverse Reactions</td>
</tr>
<tr>
<td>--------------------------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>UltraSoft, SoftForm (expanded polytetra-fluoroethylene)</td>
<td>Implant</td>
<td>Subdermal soft tissue augmentation SoftForm: lip border, smile lines, nasolabial fold, and frown lines UltraSoft: cheek and temple</td>
<td>Under local anesthesia Insert subdermally via 14- to 160-gauge angiocatheter</td>
<td>Long lasting</td>
<td>Higher rate of infection than permanent injectable microimplants</td>
</tr>
<tr>
<td>Gore-Tex (dual-porosity expanded polytetra-fluoroethylene)</td>
<td>Implant</td>
<td>Vascular grafts, implant material, and soft tissue repair</td>
<td>Under local anesthesia Insert subdermally via 14- to 160-gauge angiocatheter</td>
<td>Long lasting</td>
<td>Transient bruising and swelling to infection of implant site, formation of fistula, and implant extrusion</td>
</tr>
<tr>
<td>Advanta facial implant (dual-porosity expanded)</td>
<td>Implant</td>
<td>Fill deep wrinkles or folds or to enhance, augment, or repair soft tissues of facial areas, such as lips</td>
<td>Require local anesthesia</td>
<td>Long lasting</td>
<td>Low incidence of complications</td>
</tr>
</tbody>
</table>
### TABLE 26-20 Filler Contraindications

<table>
<thead>
<tr>
<th>Common Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insotretinoin for 6 months prior or following treatment because it may increase chance of keloid-like scarring</td>
</tr>
<tr>
<td>Collagen/scarring/connective tissue disorders</td>
</tr>
<tr>
<td>Lupus for patients seeking bovine or porcine collagen. Other products may cause flare-ups as well</td>
</tr>
<tr>
<td>Active diseases may affect outcome or increase risks</td>
</tr>
<tr>
<td>Diabetes may affect outcome or increase risks</td>
</tr>
<tr>
<td>Coagulation problems</td>
</tr>
<tr>
<td>Excessive oral plaque or dental abscesses</td>
</tr>
<tr>
<td>Herpes labialis</td>
</tr>
<tr>
<td>Pregnant or lactating women</td>
</tr>
<tr>
<td>Psychological conditions</td>
</tr>
</tbody>
</table>

### TABLE 26-21 Specific Product Contraindications

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Precautions/Contraindications</th>
</tr>
</thead>
</table>
| Zyderm/Zyplast (bovine dermal collagen)                          | Adverse reaction to allergy test  
|                                                                 | Presence of severe allergies manifested by history of anaphylaxis or multiple severe allergies  
|                                                                 | Lidocaine hypersensitivity  
|                                                                 | History of allergies to any bovine collagen product  
|                                                                 | Contraindicated for use in the glabellar region                                                                                                             |
| Cymetra (injectable microparticulate acellular allogenic dermis) | Autoimmune connective tissue disease  
|                                                                 | Infected or nonvascular surgical sites  
|                                                                 | Patients sensitized to specific antibiotics used in the manufacture of this preparation  
|                                                                 | Periocular line correction or glabellar contouring                                                                                                           |
| CosmoPlast/CosmoDerm (human-based collagen cross-linked with glutaraldehyde) | Severe allergies manifested by history of anaphylaxis  
|                                                                 | Lidocaine hypersensitivity  
|                                                                 | Contraindicated for use in glabellar region, breast augmentation, and implantation into bone, tendon, ligament, or muscle |
| Juvederm (viscoelastic, nonanimal hyaluronic acid)                | Autoimmune disease  
|                                                                 | Pregnancy  
|                                                                 | Lactation  
|                                                                 | Allergies to hyaluronic acid  
<p>|                                                                 | Direct sunlight or intense heat on treatment area for several days post injection                                                                                           |
| Hylaform (hyaluronic acid)                                       | Poultry allergy                                                                                                                                                                                                                 |</p>
<table>
<thead>
<tr>
<th>Injection Techniques</th>
<th>Fillers</th>
<th>Defects</th>
<th>Placement Level</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kneading</td>
<td>Collagen</td>
<td>Superficial defects</td>
<td>Papillary dermis</td>
<td>Shallow injection with needle inserted almost parallel to the skin. The bevel of needle should be controlled with regard to its angle in relation to the skin surface. A small bleb and blanching of the skin is seen with correct placement. Gentle massage after injection to ensure the even distribution.</td>
</tr>
<tr>
<td>Piercing</td>
<td>Collagen</td>
<td>Moderate sized defects</td>
<td>Mid dermis</td>
<td>Piercing the skin with needle at an angle of 30 to 45 degree. A bleb will not be produced but blanching may be seen.</td>
</tr>
<tr>
<td></td>
<td>Hyarulonic acid</td>
<td>Deep defects</td>
<td>Deep dermis/dermosubcutaneous junction/subcutaneous fat</td>
<td>May need multiple injections. The needle should enter the skin at 45 to 90 degree angle.</td>
</tr>
<tr>
<td>Threading or tunneling</td>
<td>Hyarulonic acid / poly-l-lactic acid/calcium hydroxyapatite</td>
<td>Defects in a skin fold</td>
<td>Deep dermis/dermosubcutaneous junction/subcutaneous fat</td>
<td>Single injection. The needle pierces the skin once and is advanced parallel to the overlying defect. The fillers can be delivered as the needle is inserted or withdrawn.</td>
</tr>
<tr>
<td>Serial puncture</td>
<td>Hyarulonic acid / poly-l-lactic acid/calcium hydroxyapatite</td>
<td>Defects in a skin fold</td>
<td>Deep dermis/dermosubcutaneous junction/subcutaneous fat</td>
<td>Multiple injections. The skin is held taut as the product is delivered in multiple small boluses over the entire length of the defect.</td>
</tr>
<tr>
<td>Fanning</td>
<td>Hyarulonic acid / poly-l-lactic acid/calcium hydroxyapatite/autologous fat</td>
<td>Wide defects such as scars and areas of atrophy</td>
<td>Deep dermis/dermosubcutaneous junction/subcutaneous fat</td>
<td>The needle insertion site remains the same with multiple threading injections extended across the defect in a “fan” shape.</td>
</tr>
<tr>
<td>Agents</td>
<td>FDA Approval</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Vein Diameter (mm)</td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>------------</td>
<td>---------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Osmotic Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertonic saline (18%)</td>
<td>Approved abortificient</td>
<td>Lack of allergenicity</td>
<td>Damage to cellular tissues, produce ulcerations, necrosis, hyper-pigmentation, pain, muscle cramping</td>
<td>0.4–0.5</td>
</tr>
<tr>
<td>Hypertonic glucose/saline (Sclerodex)</td>
<td>Not approved</td>
<td>Minimized pain, less muscle cramping</td>
<td>Superficial necrosis, allergic reaction, hyper-pigmentation, mild pain</td>
<td>0.4–0.5 0.6–2</td>
</tr>
<tr>
<td><strong>Chemical irritants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromated glycerine (Scleromo)</td>
<td>Not approved</td>
<td>Rare post-treatment hyper-pigmentation, necrosis, and bruising, even if injected extra-vascularly</td>
<td>Weak agent, therefore requires more treatment sessions, high viscosity, pain</td>
<td>&lt;0.4</td>
</tr>
<tr>
<td>Polyiodinated iodine (Variglobin, Sclerodine)</td>
<td>Not approved</td>
<td>Direct destruction of the endothelium</td>
<td>Necrosis, pain</td>
<td>0.4–0.5 0.6–2 0.6–2</td>
</tr>
<tr>
<td><strong>Detergent sclerosing solutions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium morrhuate</td>
<td>Approved</td>
<td>N/A</td>
<td>Extremely caustic, necrosis, allergic reaction, anaphylaxis, pain</td>
<td>0.4–0.5 0.6–2 3–5</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Agents</th>
<th>FDA Approval</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Vein Diameter (mm)</th>
<th>Recommended Concentrations</th>
<th>Recommended Maximum Quantity Injected per Treatment Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanolamine oleate (Ethamolin)</td>
<td>Not approved</td>
<td>Decreased risk of allergic reaction</td>
<td>Allergic reaction, pain</td>
<td>0.4–0.5 0.6–2</td>
<td>2% 5%</td>
<td>&lt;12 mL</td>
</tr>
<tr>
<td>Sodium tetradecyl sulfate</td>
<td>Approved</td>
<td>N/A</td>
<td>Epidermal necrosis, allergic reaction, hyper-pigmentation, pain</td>
<td>0.4–0.5 0.6–2 3–5 &gt;5</td>
<td>0.1% 0.25% 0.5–1% 2–3%</td>
<td>4 mL of a 3% solution by British manufacturers, and 10 ml of a 3% solution by U.S. and Canadian manufacturers</td>
</tr>
<tr>
<td>Polidocanol (Aethoxy-sklerol)</td>
<td>Pending</td>
<td>Will not produce ulcerations, necrosis and allergic reaction are very rare, less hyper-pigmentation and painless</td>
<td>Rare necrosis and allergic reaction</td>
<td>0.4–0.5 0.6–2 3–5 &gt;5</td>
<td>0.25–0.5% 0.75% 1–2% 3–5%</td>
<td>10 mL of a 6% solution</td>
</tr>
<tr>
<td>Grade</td>
<td>Level of disease</td>
<td>Examples of scars</td>
<td>Characteristics</td>
<td>Treatment options</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Macular</td>
<td>Erythematous, hyper- or hypopigmented flat marks</td>
<td>Erythematous, hyper- or hypopigmented flat marks visible to patient or observer at any distance</td>
<td>Time, optimized home skin care, light strength peels, microdermabrasion, vascular or pigmented lasers, or intense pulsed light (IPL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Mild rolling, small soft papular</td>
<td>Mild atrophy or hypertrophy that may not be obvious at social distances of 50 cm or greater and may be covered adequately by makeup or the normal shadow of shaved beard hair in men or normal body hair (if extrafacial)</td>
<td>Nonablative lasers, blood transfer, skin needling or rolling, microdermabrasion, dermal fillers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>More significant rolling, shallow boxcar, mild to moderate hypertrophic or popular scars</td>
<td>Moderate atrophic or hypertrophic scarring that is obvious at social distances of 50 cm or greater and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair (if extrafacial), but is still able to be flattened by manual stretching of the skin (if atrophic)</td>
<td>Ablative lasers, dermabrasion, medical skin rolling, fractionated resurfacing, dermal fillers, subcision and blood transfer (if local), intralesional corticosteroids or fluorouracil and/or vascular laser (if hypertrophic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Punched out atrophic (deep boxcar), ice pick, bridges and tunnels, marked atrophy, dystrophic significant hypertrophy or keloid</td>
<td>Severe atrophic or hypertrophic scarring that is obvious at social distances greater than 50 cm and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair (if extrafacial) and is not able to be flattened by manual stretching of the skin</td>
<td>Punch techniques (float, excision grafting), focal trichloroacetic acid (CROSS technique) with or without resurfacing techniques (including fractionated resurfacing), fat transfer, occasionally rhytidectomy (if grossly atrophic), intralesional corticosteroids or fluorouracil and/or vascular laser (if hypertrophic)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Questions

1. What shortens with age?
   A. Ribosome
   B. Nucleolus
   C. Endoplasmic reticulum
   D. Telomere
   E. Golgi

2. Which of the following is the shortest visible wavelength?
   A. X-ray
   B. Infrared
   C. Gamma rays
   D. Radio waves

3. Which wavelength is within UV-A II?
   A. 360 nm
   B. 330 nm
   C. 380 nm
   D. 311 nm
   E. 300 nm

4. What is the unit of measurement for irradiance?
   A. Joules/second
   B. Watts
   C. Watts/cm²
   D. Joules/cm²
   E. Nanometer

5. Uniform white frost with pink showing through correlates with what depth of injury after a trichloroacetic acid peel?
   A. Stratum corneum
   B. Superficial epidermis
   C. Full thickness epidermis
   D. Papillary dermis
   E. Reticular dermis

6. What neurotransmitter is blocked by botulinum toxin?
   A. Epinephrine
   B. dopamine
   C. Norepinephrine
   D. Gamma aminobutyric acid
   E. Acetylcholine

7. What does Botox cleave?
   A. Synaptosomal-associated protein
   B. Vesicle-associated protein
   C. Syntaxin
   D. Cholinergic receptor
   E. Acetylcholine

8. Which of the following is NOT a contraindication for use of Botox cosmetic?
   A. History of a neuromuscular disease (Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or myasthenia gravis)
   B. Age younger than 18 years
   C. Known history of sensitivity to Botox
   D. Known sensitivity to human albumin
   E. Pregnancy, lactation

9. Which filler is contraindicated in a patient with poultry allergy?
   A. Zyderm
   B. Zplasty
   C. Hylaform
   D. Restylane
   E. Evolence

10. Which sclerosing agent is FDA approved for use in sclerotherapy?
    A. Hypertonic saline
    B. Hypertonic glucose
    C. Sodium morrhuate
    D. Polyiodinated iodine
    E. Polidocanol

Answers

1. D. Telomere. Telomeres are tandem repeats of the DNA base sequence (TTAGGGG) (T-thymine, G = guanine, A = adenosine), at the end of mammalian chromosomes. Telomere extension occurs by the action of telomerase; however, the DNA polymerase does not copy the final bases on each chromosome, resulting in telomere shortening after each round of cell division (i.e., aging). When the telomeres become too short, the cell will no longer divide.

2. D. Gamma rays. Electromagnetic spectrum organizes radiation by energy. Photon energy is inversely proportional to wavelength (i.e., the shorter the wavelength, the higher the energy). From shortest to longest wavelength: gamma rays, x-ray, ultraviolet, visible, infrared, microwave, radio wave.

3. B. 330 nm. Ultraviolet radiation is divided into UV-A I (400 to 340 nm), UV-A II (340 to 320 nm), UVB (320 to 290 nm). UV-A, a longer wavelength, causes delayed tanning and reaches deeper into the papillary dermis. UV-B causes acute sunburn and is predominantly absorbed by the epidermis.

4. C. Watt/cm². Irradiance is measured in watts/cm². Other laser characteristics include: wavelength (nanometer), spot size (millimeter), pulse duration (seconds), fluence (joules/cm²), power (joules/second).
5. C. Full thickness epidermis. After defatting the skin, chemical peeling agents are applied to the skin. Skin keratin begins to agglutinate. Depth of peel can be correlated with the intensity of the frost: no frost (stratum corneum), irregular light frost (superficial epidermis), and uniform white frost with pink showing through (full thickness epidermis).

6. E. Acetylcholine. Neurotransmitters are chemicals used to signal between a neuron and another cell. They are present in the presynaptic element, bind to post-synaptic receptors, and must be in sufficient quantity to affect the post-synaptic cell. Botulinum toxin blocks neurotransmitter release at peripheral cholinergic nerve terminals. Epinephrine, dopamine, noradrenaline, gamma aminobutyric acid, melatonin, serotonin and glutamic acid are other neurotransmitters.

7. A. Synaptosomal-associated protein. Seven botulinum toxin serotypes (A–G) bind to different sites on the motor nerve terminal and within the motor neuron. Botox is botulinum toxin type A, and Myobloc is botulinum toxin type B. Synaptosomal-associated protein (SNAP-25) is cleaved by serotypes A and E. Vesicle-associated membrane protein (VAMP, Synaptobrevin) is cleaved by serotypes B, D, F, and G. Syntaxin 1 is cleaved by serotype C1. Cleavage of these proteins prevents exocytosis of acetylcholine into the synapse between the motor neuron and the skeletal muscle cell.

8. B. Age under 18 years. Contraindications for use of Botox include: history of a neuromuscular disease (Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or myasthenia gravis); known history of sensitivity to Botox or human albumin; aminoglycoside use which can interfere with neuromuscular transmission; pregnancy; lactation; and age younger than 12 years of age.

9. C. Hylaform. Fillers are derived from various sources and should be avoided if patients are allergic to components within each filler. For instance, Zyderm and Zyplast are derived from bovine dermal collagen, Restylane is derived from non-animal hyaluronic acid gel, Evolence from porcine collagen, and Hylaform from rooster combs.

10. C. Sodium morrhuate. Only sodium morrhuate and sodium tetradecyl sulfate are FDA approved for use in sclerotherapy. All others are not approved. Hypertonic saline is FDA approved as an abortificacient.

REFERENCES

THE IMMUNE RESPONSE (FIG. 27-1)

- The human body can respond to antigen via innate and/or adaptive immunity
- Innate immunity (nonspecific, nonclonal, no anamnestic characteristics)
  - Characteristics
    - Immediate first line defense against pathogens composed of three major components
      ▲ Nonspecific physical and chemical barriers
      ▲ Recruitment and activation of leukocytes
      ▲ Release and/or activation of extracellular humoral mediators (i.e., cytokines, complement)
    - Exists prior to exposure to a given microbe or antigen (requires no previous exposure) and is rapidly available on pathogen encounter (minutes)
  - Key components
    - Physical and chemical barriers to pathogen invasion:
      ▲ Skin, mucous membranes, cilia, and secretions (mucous and sweat) cover body surfaces and prevent microorganisms and other potentially injurious agents from entering the tissues beneath
      ▲ Mucous traps, dissolves, and sweeps away foreign substances
      ▲ Sweat contains lactic acid and other substances that maintain the surface of the epidermis at an acidic pH, thereby decreasing colonization by bacteria and other organisms
      ▲ Chemical barrier antimicrobial substances include enzymes that can directly injure or kill microbial pathogens

Complement
- Alternate pathway of complement can be spontaneously activated by microbial surfaces in the absence of specific antibodies

Antimicrobial Peptides
- Produced by keratinocytes; include cathelicidins and B-defensins
  - Defensins (alpha or beta) and cathelicidins have multiple receptor-mediated effects on the immune cells
  - Defensins are secreted by resident epithelial cells or by transient leukocytes that coat and destabilize the cell membrane of pathogens
  - β-Defensins interact with chemokine receptor 6 (CCR6) which results in attraction of dendritic cells and memory T cells
  - Defensins may facilitate microbial antigen delivery to dendritic cells
  - Cathelicidins are secreted by neutrophils, keratinocytes, epithelial cells, mast cells, and monocytes-macrophages

Pattern Recognition Receptors (PRR)
- Phagocytic cell PRRs recognize highly conserved pathogen amino acid sequences and result in a variety of signals
  - Examples of PRRs:
    - Toll-like receptors (TLRs): mediate innate immune response in host defenses; expressed in peripheral blood leukocytes (monocytes, B cells, T cells, granulocytes, and dendritic cells. Modulate inflammatory responses via cytokine release. Activation of TLRs can lead to tissue injury (e.g., TLR2 activation by Propionibacterium acnes induces inflammatory responses in acne which result in tissue injury)
Innate transmembrane receptors that recognize different types of pathogen-associated molecular patterns (PAMPs), which are molecular patterns unique to pathogens. Ligands include lipopolysaccharide, peptidoglycan, and CpG DNA. Humans have at least 10 different TLRs. TLRs identify the nature of the pathogen and result in NF-κB activation, which results in appropriate cytokine and chemokine expression, along with increased expression of additional immune system receptors. Triggering receptors expressed on myeloid cells (TREM): amplify innate immune responses.

**CELLS OF THE INNATE IMMUNE SYSTEM**

- **Phagocytes**
  - Integral to the innate immune response and are composed of macrophages and polymorphonuclear cells; activity is sometimes regulated by TLR’s and complement receptors.
  - Phagocytes can also be activated by cells of the adaptive immune system: CD4+ cells can activate macrophages to produce TNF-alpha, IL-1, IL-12, interferon-gamma and nitric oxide.
  - Phagocytic cells (macrophage, neutrophils) recognize pathogens via cell-surface pattern recognition receptors (PRRs).
  - Macrophage mannose receptor: only on macrophages, recognizes certain sugar molecules found on bacteria and some viruses (HIV), direct phagocytic receptor (transmembrane bound).
  - Scavenger receptors: recognize anionic polymers and also acylated low-density lipoproteins, involved in the removal of old red blood cells and pathogens.

- **Natural killer (NK) cells**
  - Large granular lymphocytes: ~2% of the circulating lymphocytes. Kill pathogens within infected cells through perforin/granzyme- or Fas/FasL-dependent mechanisms or indirectly through cytokine secretion activated by IFN-γ, IFN-β, and macrophage-derived cytokines (TNF-α, IL-12).
  - Reside in blood, spleen, lung, liver, GI tract, and uterine deciduas.
  - Main function is to provide cytotoxic activity toward virally infected cells and neoplastic cells—both antibody-independent and -dependent pathways exist.
  - Respond early to microbial assault and interact with other cells of the innate immune system; able to nonspecifically kill target cells without prior sensitization.
  - While they express neither a T-cell receptor nor a B-cell receptor, NK cells demonstrate specificity in their ability to recognize targets.
  - NK cells recognize killer inhibitory receptors on MHC class I molecules which results in a negative signal to the NK cell. The NK cell recognizes the cell as self and does not kill the cell.
  - Express distinct surface molecules:
    - CD16 is a receptor for the Fc portion of Ig (used in antibody-dependent cellular cytotoxicity).
    - CD56 is a neural adhesion molecule that can bind to CD56 on other cells.
  - Activated by IL-2, IL-7, IL-12, and IL-18.
    - NK cells express the beta chain of the IL-2 receptor; therefore, resting NK cells can respond directly to IL-2.
    - Capable of producing cytokines following activation, such as IFN-γ and TNF-α, which can affect the proliferation and differentiation of other cell types.
  - Mechanisms of cytotoxicity:
    - NK cells lyse targets through calcium-dependent release of preformed granules that contain perforin and granulysin.
    - Perforin, like complement, intercalates into the target cell membrane, forming pores.
    - Granulysin is a cationic protein that can induce apoptosis by initiating DNA fragmentation; may potentiate the activity of perforin in the lysis of target cells.

**FIGURE 27-1 The immune response.** (Reprinted with permission from Wolff, K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)
Receptor-induced apoptosis

- Activated NK cells will induce apoptosis or lysis of target cells expressing certain receptors such as FAS and TRAIL ligands death receptor-4 and death receptor-5
- NK cells are also capable of killing specifically when they are provided with an antibody [antibody-dependent cellular cytotoxicity (ADCC)]; ADCC occurs via binding of the antibody to the Fcγ receptor (CD16) located on the NK cell, leading to apoptosis of the target cell
- NK cell killing activity can be regulated by interaction with MHC-I on the target cell via called the killer cell inhibitory receptor (KIR)
- Dendritic cells are stimulated to move from the periphery to the lymph node by TNF-α, where they mature from phagocytes into nonphagocytic efficient antigen-presenting cells

Eosinophils

- Develop and mature from CD34+ hematopoietic progenitor cells and are released into the circulation as mature cells
- Bilobed nucleus
- IL-5 (released by T_{h}2 cells) increases the production of mast cells in the bone marrow
- Possess chemokine receptors that, when bound, activate, degranulate, and coordinate chemotaxis
- Membrane bound core containing secondary granules which contain basic proteins
- Four basic proteins: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), eosinophil derived neurotoxin (EDN)
- Primary granules: lack a core and have variable sizes; contain Charcot-Leyden crystal protein (galectin-10)
- Cyclooxygenase and 5- and 15-lipoxygenase which are required to synthesize prostaglandins and leukotrienes
- Activation of eosinophils: various mediators activate eosinophils: cytokines (TNF alpha, GM-CSF, IL-3 and IL-5), complement components (C3a and C5a), lipid mediators (LTC4 and PAF), chemokines and IgA and IgG Fc receptors. CC chemokine subfamily (CCL5, CCL7, CCL11, CCL14 and CCL240) bind to the chemokine receptor CCR3
- Eosinophil activating cytokines IL-3, IL-5 and GM-CSF enhance cell survival, eosinophil maturation, chemotactic responses, and leukotriene production

Types of eosinophil activation: expression of P selectin on endothelial surface, induction by non specific activators such as IL-1 and TNF alpha, induction by IL-4 and IL-13
- After cytokine and chemokine activation, the high affinity IgE receptors (FceRI) are expressed along with an increase in complement receptors
- Degranulation releases major basic protein, which causes degranulation of mast cells and basophils

Basophils

- Growth factors include IL3, IL-5, and GM-CSF
- TGF-β IL3 suppress eosinophil differentiation and promote basophil differentiation
- Eotaxins attract and degranulate (release histamine and IL-4)
- Pathogens coated with fragments of the complement protein C3 bind strongly to B cells

Keratinocytes

- Can activate an immune and/or inflammatory response through secretion of cytokines, arachadonic acid metabolites, complement components, and antimicrobial peptides
- Following appropriate stimuli the following cytokine response may occur:
  - Initiation of inflammation: IL-1, TNF-alpha, IL-6
  - Modulation of langerhan cells: IL-1, GM-CSF, TNF-alpha, IL-10, IL-15
  - T cell activation: IL-15, IL-18
  - T cell inhibition: IL-10, TGF-beta
  - Th1 response: IL-12, IL-18, Th2 response: thymic stromal lymphopoietin or Th17: IL-23
- Bridging innate immunity to adaptive immunity
  - Macrophages and dendritic cells present antigens to T cells
  - Interaction of PAMPs and TLRs on the surface of dendritic cells triggers secretion of innate immune cytokines (INF-α, INF-β, IL-12, TNF-α) and chemokines, which may affect both T and B cells

ADAPTIVE IMMUNITY

- An antigen-specific immune response resulting in the activation of humoral and cell-mediated immunity, mediated by specific antibodies
- T-lymphocytes and B-lymphocytes differentiate from a common lymphoid stem cell in the bone marrow
- B-lymphocytes (B cells): antibody-producing cells
  - Represent 5% to 10% of the lymphocytes found in the blood
  - Express cell membrane immunoglobulin (Ig): majority expresses both IgM and IgD
A small minority of B cells expresses surface IgG or IgA.

Possess a variety of receptors on their surface (complement receptors, class I and II MHC molecule receptors).

Analogous to T cells, B cells have specific antigen receptors, which are immunoglobulins (Ig).

On activation and cross-linking of surface Ig by specific antigen, B cells undergo proliferation and differentiation to produce plasma cells.

Plasma cells are nondividing, specialized cells whose only function is to secrete Ig.

Immunoglobulins (Igs) (Fig. 27-2)

- Exquisite specificity for antigen is achieved by a mechanism of genetic recombination that is unique to Ig and T-cell receptor genes.
- The antigen-binding site consists of a highly variable sequence created by the juxtaposition of two constituent polypeptides: heavy (H) chain and one of two alternative light (L) chains, κ or λ.

- These polypeptides can be divided into two segments: antigen-binding amino-terminal variable domain and one or more carboxy-terminal constant (nonvariable) domains that are generally responsible for biologic functions and activities of the molecules.

- Ig antigen receptor

  ▲ A virtually limitless array of specific-antigen receptors is possible.

  ▲ The great variability is accomplished by recombination of genomic segments that encode the variable portions of Ig.

  ▲ The products of these rearranged genes provide the B cell with its own unique receptor.

  ▲ The mature receptor consists of the products of two or three such rearranged segments:

    ▲ V (variable) and J (joining) for IgL (light) chains

    ▲ V, D (diversity), and J for IgH (heavy) chains.

  ▲ DNA rearrangement

    ▲ Controlled by recombinases.

    ▲ Sequential and carefully regulated process.

    ▲ Leads to translation of one receptor of unique specificity for any given B-lymphocyte.

    ▲ Unique specificity is achieved through a process termed allelic exclusion (only one member of a pair of allelic genes potentially contributing to an Ig is rearranged at a time).

  ▲ Somatic hypermutation

    ▲ A feature of the V-region construction that is unique to B cells.

    ▲ As antigen is introduced into the system, and mature B cells remain genetically responsive to the antigenic environment.

    ▲ As a result, a few B cells increase their affinity for the antigen.

    ▲ Higher-affinity B cells are preferentially activated at exposure to the antigen.

    ▲ As a result, the average affinity of antibodies produced during the course of an immune response increases (termed affinity maturation).

**Figure 27-2** Immunoglobulin (Ig) molecule.
(Reprinted with permission from Wolff, K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill, 2008.)
ADAPTIVE IMMUNITY

T cell subpopulations are based on surface expression of CD4 and CD8, as well as by their function in the immune response.

- Helper T cells (TH cells): express CD4 surface molecules and recognize antigen bound to class II major histocompatibility complex (MHC) molecules.
- Play a central role in the initiation and regulation of immune responses through the secretion of cytokines and activation of macrophages.
- Important effectors of cell-mediated immunity.
- Essential contributors to the generation of chronic inflammatory responses.
- Cytotoxic activity either through the elaboration of cytotoxic cytokines (i.e., lymphotoxin, tumor necrosis factor α) or directly through interaction with antigen bound to MHC class II molecules.
- Function depends on the cytokine profile produced, which characterizes them as TH type 1 (TH1) or TH type 2 (TH2).

Naïve CD4+ cells differentiate into immature effector T cells (TH0). Depending on activation signals and the cytokine milieu in the microenvironment, TH0 can differentiate into several different classes of cells: (1) TH1, (2) TH2, (3) Th17, (4) regulatory T cells, (5) natural killer T cells (see section above).

1. TH1 cells produce primarily IFN-γ, IL-2, and tumor necrosis factor α (TNF-α); important in cell-mediated immunity to intracellular pathogens (i.e., tubercle bacillus).

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**TABLE 27-1 Classes of Immunoglobulin**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heavy chain</strong></td>
<td>γ</td>
<td>α</td>
<td>μ</td>
<td>δ</td>
<td>ε</td>
</tr>
<tr>
<td><strong>Light chain</strong></td>
<td>κ, λ</td>
<td>κ, λ</td>
<td>κ, λ</td>
<td>κ, λ</td>
<td>κ, λ</td>
</tr>
<tr>
<td><strong>J chain</strong></td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>150,000</td>
<td>160,000–400,000</td>
<td>900,000</td>
<td>180,000</td>
<td>190,000</td>
</tr>
<tr>
<td><strong>Serum half-life (days)</strong></td>
<td>23</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Serum concentration</strong></td>
<td>1200</td>
<td>140–400</td>
<td>20–50</td>
<td>4</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Complement fixation</strong></td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Placental transfer</strong></td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

CD8+ cells have also been described. The mechanism of suppression is via production of IL-10 and TGF-β. CD28–/CD8+ regulatory T cells. The mechanism of suppression is thought to be via direct cell contact and also via induction of regulatory receptors on other cells.

Thought to involve the production of nonspecific inhibitory cytokines.

Cytotoxic T cells (Tc cells): cytotoxic effectors

- CD8+ cells have also been described. Mechanism of suppression is via production of IL-10 and TGF-β.
- CD28–/CD8+ regulatory T cells. Mechanism of suppression is thought to be via direct cell contact and also via induction of regulatory receptors on other cells.
- Thought to involve the production of nonspecific inhibitory cytokines.

- **Cytoxic T cells** (Tc cells): cytotoxic effectors
- Cytotoxic CD8+ T cells can further differentiate into Tc1 or Tc2 cells.
  - Express CD8 surface molecules and recognize antigen bound to class I MHC molecules.
  - Capable of direct killing of target cells expressing an appropriate viral peptide bound to a self-MHC class I molecule.
  - Highly specific process that requires direct apposition of Tc cell and target cell membrane.
  - Following killing, Tc cell is capable of detaching from target and seeking another target cell.
  - Destruction of target cells requires the insertion of perforins from the Tc cell into the target cell membrane that results in fragmentation of target cell nuclear DNA (apoptotic).

**Cell-Mediated and Humoral Immune Response**

- Antibodies, dissolved in blood, lymph, and other body fluids, bind the antigen and trigger a response to the antigen (i.e., release cytokines).
ADAPTIVE IMMUNITY

**T-cell response**
- Viruses and intracellular parasite antigens are processed into peptides within antigen-presenting cells (APCs) and are bound to the heavy chain of an MHC class I and presented to a CD8+ (cytotoxic) T cell
- If a specific antigen encounters its specific T-cell receptor, IL-2 is released, and T-cell activation, along with expansion of the antigen-specific cytotoxic T-cell (Tc) line, follows
- If an antigen-specific Tc cell encounters a cell expressing its specific antigen, the activation signal that ensues results in exocytosis of granymes (granules containing enzymes), perforins, cytolysins, lymphotoxins, and serine esterases, which kill the APC

**Extracellular antigens**
- Taken up by APCs by pinocytosis and then processed into peptides
- Peptides are presented in the context of an MHC class II molecule to a CD4+ T cell
- After activation, CD4 and CD8 cells may differentiate toward T_{H1} or T_{H2} cytokine profiles depending on cytokine milieu
  - **T_{H1} cell activation**
    - Goal: macrophage activation and increased cell-mediated immunity
    - T_{H1} cytokine profile: IL-2, IFN-γ, TNF-α, and IL-12
      - IL-2: T- and B-cell activation
      - IFN-γ: activator of macrophages and NK cells
      - TNF-α: activates macrophages and stimulates the acute-phase response along with IL-1
      - IL-12 activates CD8+ (Tc) cell proliferation
      - Antigen binding to receptors results in release lytic agents (perforins, cytolysins, lymphotoxins)
  - **T_{H2} cell activation**
    - Goal: B-cell activation
    - IL-2 production by T_{H1} cells induces the CD4+ T_{H2} cells to transform, differentiate, and divide
    - T_{H2} cytokine profile: IL-4, IL-5, IL-10, and IL-13
      - IL-4: promotes the synthesis of antibodies by stimulating B-cell differentiation
      - Downregulates IFN-γ; therefore, can suppress cell-mediated immunity
      - Can cause production of IgE
      - IL-5: helps with B-cell differentiation
      - Facilitates IgA synthesis
      - Stimulates growth of eosinophils
      - IL-4, IL-10, and IL-13 can inhibit T_{H1} cell release of IFN-γ and IL-2; thus capable of suppressing cell-mediated immunity

**B-cell response**
- Like T cells, B cells contain membrane bound IgM antibody specific for the antigen epitope
- Primary immune response: initial encounter
  - Antigen bound to the APC receptor along with cytokines IL-2 and IL-4 (stimuli for T cells) triggers the antigen-specific B cell to differentiate and divide
  - IgM is secreted initially, and subsequent gene arrangements result in a switch to IgG, IgA, and IgE
  - B memory cells of all classes are generated and migrate to various lymphoid tissues, where they have extended survival
  - Plasma cell: B cell that secretes antibodies
- Secondary immune response: subsequent exposure to the same antigen
  - Activation of antigen-specific B cell results in more efficient antibody synthesis and faster isotype switching from IgM to IgG
  - A greater amount of IgG with higher affinity for the antigen during subsequent encounters
  - Predominance of IgA secretion in mucosal tissues

**Myeloid Progenitor Cell**
- Dendritic cells express costimulatory molecules and cytokines in response to pathogen antigens
- Proteoglycans first recognized by PRRs
- Then costimulatory molecules and cytokines are upregulated via toll-like receptor-2

**Langerhans Cells and Other Dendritic Cells**
- Bone marrow derived leukocytes that can migrate and present antigen
- **Langerhans cells** (LC) are found in all stratified squamous epithelia
- The following molecules are expressed by LCs:
  - Langerin (CD 207): calcium dependent lectin; helps identify LC cells, CD1a, MHC class II antigens: HLA-DR, HLA-DP, HLA-DQ; and CD 39
  - Birbeck granules: pentilaminar cytoplasmic structures that appear as a tennis racket shape with electron microscopy
- LC are activated under inflammatory conditions. LC express chemokine receptors CCR2 and CCR6 (their ligands are secreted by endothelial cells and keratinocytes)
Dendritic leukocytes (DDC) are found in the dermis
- Express the following molecules: CD1b and CD1c and factor XIIIa, MHC class II molecules DEC205/CD205
- DDCs enter the skin secondary to CCR2-dependent cell migration; other dendritic cells also migrate to the skin (plasmacytoid DCs and inflammatory dendritic epidermal cells)
- Dendritic cells: stimulate antigen specific responses in naïve, resting T cells. (T cells are not able to recognize soluble protein antigen)
- CD1 dependent antigen presentation: CD1 family expressed by LCs and DDCs
- Antigens presented to T cells bound to MCH class II molecules are recognized by CD4 cells, while antigens bound to MCH class I are recognized by CD8+ cells
- Second signals: MHC-peptide complexes provide the first signal to T cells, but this first signal is insufficient for the full activation of naïve T cells, co-stimulatory molecules deliver second signals which are induced by surface receptors triggered by ligands secreted by other somatic cells or by microbial products
- Examples of co-stimulatory molecules and their ligands:
  - ICAM-1 binds to LFA-1 and LFA-3 (ligand of T cell expressed CD2), CD24/CD24L, CD40/CD40L, CD70/CD70L, receptor activator of nuclear factor KB (RANK)/RANKL

Secondary cytokines: induced after stimulation by IL-1 and/or TNF family molecules Th17: IL-17
- Jak/STAT pathway: common cell surface to nucleus pathway used by the majority of cytokines. Jaks (Janus family kinases) are upregulated after stimulation of cytokine receptors (such as IFN gamma), Jak kinases phosphorylate STATs (signal transducers and activators of transcription) through Src homology 2 (SH2) domains; STATs translocate to the nucleus and stimulate transcription of specific genes (Fig. 27-3)
- The IL-1 family share a common signaling domain with the TLRs: Toll/L-1 receptor (TlR) domain. When activated by TlR domain-containing proteins (i.e., MyD88), TlR will activate IL-1R-associated kinase (IRAK) and ultimately activation of nuclear factor KB (NF-KB), IL-1 accessory protein (RAcP) and tumor necrosis factor receptor-associated factor (TRAF)
- Tumor necrosis factor alpha can trigger apoptosis and/or nuclear factor KB activation
- Medications that target cytokines include receptor fusion proteins (etanercept), monoclonal antibodies (infliximab and adalimumab), and receptor antagonists that neutralize or inhibit various cytokines

Chemokines
- Class of cytokines that express both chemoattractant and cytokinetic properties
  - Leukocytes can respond to a panel of different chemokines
  - Neutrophils are recruited first, while monocytes and immature dendritic cells are recruited later
  - Structures contain a four-cysteine motif with a disulfide bond between cysteines 1,3 and 2,4 along with an N-terminus critical for receptor recognition and activation
  - Four subfamilies, based on the position of the first two of four conserved cysteines (α, β, γ, and κ)
  - Multiple cell types can produce the same chemokine, and a cell can produce many different chemokines in response to a single stimulus
  - Chemokine receptors
    - Members of the large family of G protein–coupled receptors possessing seven transmembrane-spanning domains
    - One receptor is capable of binding to various chemokines
    - Binding of the ligand to the chemokine receptor induces conformational changes in the receptor and leads to activation of G proteins
<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Major Sources</th>
<th>Responsive Cells</th>
<th>Features of Interest</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1α</td>
<td>Epithelial cells</td>
<td>Infiltrating leukocytes</td>
<td>Activate from stored in keratinocytes</td>
<td>IL-1Ra used to treat rheumatoid arthritis</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Myeloid cells</td>
<td>Infiltrating leukocytes</td>
<td>Caspase 1 cleavage required for activation</td>
<td>IL-1Ra used to treat rheumatoid arthritis</td>
</tr>
<tr>
<td>IL-2</td>
<td>Activated T cells</td>
<td>Activated T cells, Treg cells</td>
<td>Autocrine factor for activated T cells</td>
<td>IL-2 fusion toxin targets CTCL</td>
</tr>
<tr>
<td>IL-4</td>
<td>Activated Th2 cells, NKT cells</td>
<td>Lymphocytes, endothelial cells, keratinocytes</td>
<td>Causes B-cell class switching and Th2 differentiation</td>
<td></td>
</tr>
<tr>
<td>IL-5</td>
<td>Activated Th2 cells, mast cells</td>
<td>B cells, eosinophils</td>
<td>Regulates eosinophil response to parasites</td>
<td>Anti-IL-5 depletes eosinophils</td>
</tr>
<tr>
<td>IL-6</td>
<td>Activated myeloid cells, fibroblasts, endothelial cells</td>
<td>B cells, myeloid cells, hepatocytes</td>
<td>Triggers acute-phase response, promotes immunoglobulin synthesis</td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>T cells, NK cells</td>
<td>Myeloid and lymphoid cells</td>
<td>Inhibits innate and acquired immune response</td>
<td></td>
</tr>
<tr>
<td>IL-12</td>
<td>Activated APCs</td>
<td>Th1 cells</td>
<td>Promotes Th1 differentiation, shares p40 subunit with IL-23</td>
<td>Anti-p40 inhibits Crohn disease and psoriasis</td>
</tr>
<tr>
<td>IL-13</td>
<td>Activated Th2 cells</td>
<td>Monocytes, keratinocytes, endothelial cells</td>
<td>Mediates tissue response to parasites</td>
<td></td>
</tr>
<tr>
<td>IL-17</td>
<td>Activated Th17 cells</td>
<td>Multiple cell types</td>
<td>Mediates autoimmune diseases</td>
<td>Potential drug target in autoimmune disease</td>
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<td>IL-23</td>
<td>Activated dendritic cells</td>
<td>Memory T cells, Th17 cells</td>
<td>Directs Th17 differentiation, mediates autoimmune disease</td>
<td>Anti-p40 inhibits Crohn disease and psoriasis</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Activated myeloid, lymphoid, and epithelial cells</td>
<td>Infiltrating leukocytes</td>
<td>Mediated inflammation</td>
<td>Anti-TNF-α effective in psoriasis</td>
</tr>
<tr>
<td>IFN-α and IFN-β</td>
<td>Plasmacytoid dendritic cells</td>
<td>Most cell types</td>
<td>Major part of antiviral response</td>
<td>Elicited by topical imiquimod</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Activated Th1 cells, CD8 T cells, NK cells, dendritic cells</td>
<td>Macrophages, dendritic cells, naive T cells</td>
<td>Macrophage activation, specific isotype switching</td>
<td>IFN-γ used to treat chronic granulomatous disease</td>
</tr>
</tbody>
</table>

APC = antigen-presenting cell; CTCL = cutaneous T-cell lymphoma; IFN = interferon; IL = interleukin; NK = natural killer; NKT = natural killer T cell; Th = T helper; TMF = tumor necrosis factor; Treg = T regulatory.
• The G protein causes exchange of GDP for GTP and begins a chain of events resulting in intracellular signaling responses

• Biologic effects of chemokines
  • Influences leukocyte trafficking at all stages of maturation
  • Regulates cells trafficking within primary and secondary lymphoid organs (i.e., from bone marrow to the spleen, lymph node, or thymus)
  • Controls the type of inflammatory infiltrate at a site of inflammation
  • Regulates the expression and activity of adhesion molecules on the leukocyte surface to increase the adhesion of leukocytes to activated endothelium
  • Recruitment and activation of neutrophils and mononuclear cells to sites of inflammation
  • Regulates proliferation of subsets of mature stem cells and immature progenitor cells

• Secretion of chemokines
  • Released by endothelial cells, leukocytes, and tissue cells at the sites of inflammation
  • Locally retained on cell surface proteoglycans, establishing a chemokin activity gradient that begins at the endothelium surface and increases as the cell approaches the focus of inflammation
  • Thought to be upregulated in inflammatory foci and certain inflammatory diseases (i.e., glomerulonephritis, rheumatoid arthritis, ulcerative colitis, and Crohn disease)

EICOSANOIDs

• Large, complex family of immunomodulatory and vasoactive compounds derived from arachidonic acid (AA) generated by mast cells, basophils, eosinophils, and mononuclear leukocytes

• General
  • Peroxidation of AA by phospholipases generates prostaglandins (via the cyclooxygenase [COX] pathway) or thromboxanes and leukotrienes (via the lipoxygenase [LO] pathway)
    – Play a key role in inflammatory and anaphylactic responses
  • Arachidonic acid
    • Polyunsaturated fatty acid with 20 carbon atoms and four double bonds
    • Resides in cell membrane lipids
    • Derived from dietary sources or synthesized by desaturation and elongation of linoleic acid

• Cyclooxygenase (COX) pathway
  • Key enzyme in the pathway, cyclooxygenase (COX), has two different isoforms
    – COX-1: constitutively expressed in cells and associated with cellular homeostasis
    – COX-2: requires specific induction, upregulated in inflammatory conditions, and associated with synthesis of proinflammatory prostaglandins
  • COX-1 and COX-2 are inhibited by nonsteroidal anti-inflammatory drugs

• Derivatives of the cyclooxygenase pathway
  – Prostaglandins (PGs)
    ▲ PGD2
      △ Released by activated mast cells
      △ Generated very rapidly after IgE-dependent activation
      △ Enhances venular permeability
      △ Promotes leukocyte adherence to vascular endothelial cells
      △ Coronary and pulmonary vasoconstrictor
      △ Peripheral vasodilator
      △ Potent inhibitor of platelet aggregation
      △ Chemokinetic for neutrophils and in conjunction with LTD4 can induce the accumulation of neutrophils in the skin
      △ Important hypotensive effects, particularly in mastocytosis, suggesting that it is probably an important contributor to the anaphylactic response
      △ Metabolite of PGD2 is elevated in patients with systemic mastocytosis
  ▲ PGE2
    △ Proinflammatory effects
    △ Released in response to infection with ameba (specifically Entamoeba histolytica) and parasites
    △ Released by endothelial cells following trauma, leading to tissue inflammation
    △ Plays an important role in the secondary immunosuppression following surgical stress
    △ Synthesized by the synovial lining in rheumatoid arthritis
  ▲ PGJ2 and PGE2
    △ Potent vasodilators
    △ Enhance capillary permeability and edema formation

• Derivatives of lipoxygenase (LO) pathway
  – Thromboxanes/thromboxane A2
- Promotes platelet aggregation, bronchoconstriction, and vasoconstriction
- Contributes to the pulmonary hypertension and acute tubular necrosis that occurs in shock
- Predominately found in platelets and monocytes
- **Leukotrienes**
  - Mediate wheal and flare reactions, edema formation, and bronchial constriction
  - Combined with histamine can result in hypotension
  - One of the major inflammatory mediators involved in asthma pathogenesis
  - Enhances airway hyperresponsiveness and smooth muscle hypertrophy
  - Causes mucus hypersecretion and mucosal edema
  - Induces influx of eosinophils into the airway tissue key players in anaphylactic reactions and IgE-mediated syndromes
  - Mediators of the vascular sequelae of anaphylaxis as well as of shock states resulting from sepsis or tissue injury
- LTB4
- Predominantly formed and released by neutrophils
- Neutrophil chemoattractant
- LTC4
- Derived from activated mast cells, basophils, and eosinophils
- Potent vasodilator

- Classical pathway
  - Activated primarily by antibody-antigen complexes
  - Also activated by oligosaccharides, porins from gram-negative bacteria, ligand-bound C-reactive protein
  - The starting point of the classical pathway is C1
  - Steps of classical pathway (Fig. 27-4)
    - Aggregation of IgG or IgM activates C1
    - C1 is a calcium-dependent complex of three subunits: C1q, C1r, and C1s
    - Activated C1 then cleaves C4 to C4a and C4b
    - C4a is a weak anaphylatoxin
    - C4b binds C2 in the presence of Mg²⁺
    - C1 cleaves the attached C2 into C2a and C2b
    - C2b is released, cleaved by plasmin, and has kinin-like activity
    - C2a stays bound to C4 to form C4b2a—the classical pathway C3 convertase that generates C3
- **Alternative pathway**
  - Activation usually occurs independent of antibody
  - May be activated by bacterial surfaces, virusinfected cells, certain viruses, abnormal erythrocytes, and lymphoblastoid cell lines
  - The starting point of the alternative pathway is C3b
  - Steps of the alternative pathway (Fig. 27-5)
    - Starts with internal hydrolysis of C3 on interaction with water to form C3 (H₂O)
    - C3 (H₂O) then binds factor B and magnesium
    - Factor D then cleaves the bound factor B into Ba and Bb
    - Ba is released
    - Bb stays bound to C3(H₂O) to form C3 (H₂O), which is the initial C3 convertase of the alternative pathway that cleaves C3
    - C3 is cleaved to C3a and C3b
    - C3a is released and becomes a potent anaphylatoxin
    - C3b binds factor B in the presence of magnesium, and factor B is cleaved by factor D into Bb and Ba
    - Ba is released
    - Bb stays bound to form C3bBb, the C3 convertase of the alternative pathway
- **Lectin pathway**
  - C4 activation can be achieved without antibody and C1 participation
  - Pathway is initiated by three proteins: a mannan-binding lectin (MBL) [mannan-binding
The two convertases assist in the cleavage of C3 to C3a (an anaphylatoxin) and C3b. C3b binds to the next protein, C5. C5 is also cleaved by the C3 convertases into C5a and C5b. C5a is released and becomes the most potent anaphylatoxin. C5b becomes the point of assembly for MAC (membrane attack complex). C5b associates with target cell membrane and C6. C5b6 then associates with the assembly of C7, C8, and C9.

- The two convertases assist in the cleavage of C3 to C3a (an anaphylatoxin) and C3b.
- C3b binds to the next protein, C5.
- C5 is also cleaved by the C3 convertases into C5a and C5b.
- C5a is released and becomes the most potent anaphylatoxin.
- C5b becomes the point of assembly for MAC (membrane attack complex).
- C5b associates with target cell membrane and C6.
- C5b6 then associates with the assembly of C7, C8, and C9.
- C5b6789 is the MAC that forms transmembrane channels (holes) in the cell membrane that allow an influx of water and ions to cause cell swelling and lysis

- Points of regulation
  - Classical pathway
    - C1 is inhibited by C1 inhibitor (C1 INH)
    - C1 esterase inhibitor (C1 INH) deficiency causes angioedema
    - Factor I inhibits formation of C3 convertase
    - C4-binding protein inhibits formation of C3 convertase
    - Decay accelerating factor (DAF) inhibits formation of C3 convertase
  - Alternative pathway
    - Factor H inhibits formation of C3 convertase
    - Factor P (properdin) protects C3 convertase
  - Anaphylatoxins
    - C3a, C5a, C4a
    - Cause release of histamine from mast cells, degranulation of basophils, increase in vascular permeability
    - Anaphylatoxins are regulated by a carboxipeptidase present in plasma

- Neutrophils
  - Derived from a pluripotent hematopoietic stem cell
  - Myeloblasts develop into neutrophils, the stages are under the influence of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF)
  - Cytoplasmic granules include lysozyme, myeloperoxidase, defensins

**FIGURE 27-5 Alternate pathway of complement activation. (Reprinted with permission from Wolff, K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)**
Cytoplasmic granule content, size, and susceptibility to pharmacologic treatments vary with location of the cells

- All mast cells contain tryptase, histamine, proteoglycans (heparin and chondroitin sulfate E)
- Types of mast cells
  - TC mast cells (MCTC): contain tryptase and chymase, located in submucosal tissue
  - T mast cells (MCT): contain tryptase and lack chymase; increased in allergic and parasitic diseases, decreased in gastrointestinal mucosa in patients with human immunodeficiency virus
  - Chymase only mast cells: located in skin, lymph nodes, intestinal submucosa

- Mast cell activation and mediators: see Table 27-3
- Pre-formed secretory mediators are released in response to aggregation of the high-affinity IgE receptor
- Histamine and tryptase are released after activation of mast cells
- Histamine receptors: H1 on epithelial cells, vascular and perivascular cells; H2 on epithelial cells of the gastrointestinal tract, H3 are found in the brain and gastrointestinal tract and may be associated with headache; H4 expressed on bone marrow cells, eosinophils and mast cells

Examples of Immune-Mediated Dermatologic Diseases

Hypersensitivity Reactions: Resulting From Humoral Immunity or Cell-Mediated Immunity

- **Type I reactions**: anaphylaxis reactions (IgE-mediated)
  - Immediate hypersensitivity reactions: symptoms begin within 30 minutes of the exposure
  - Clinical classification of Type I reactions:
    - **Local**: allergic rhinitis, allergic asthma, atopic (familial predisposed) dermatitis
    - **Systemic/anaphylaxis**: hypersensitive response in genetically susceptible individuals to small amounts of antigen to which they have been sensititized previously
  - Generalized vasodilation and increased vascular permeability can lead to hypotension, shock, and ultimately death
  - Early signs and symptoms include angioedema, urticaria, dyspnea, vomiting, and abdominal cramping
  - Common triggers are foods (peanuts, eggs, shellfish), drugs (aspirin, radiocontrast media, penicillin and other beta-lactam antibiotics), Hymenoptera venom, and pollens

- **Secondary granules** include lactoferrin, collagenase, gelatinase, vitamin B12 binding protein, and complement receptor 3
- Granules fuse with incoming phagocytic vacuoles that contain ingested bacteria
- IL-8 is a potent chemoattractant and neutrophil activator, other chemoattractants include: N-formylmethionyl-leucyl-phenylalanine, complement facor 5a, leukotriene B4, and platelet activating factor (PAF)
- Neutrophils adhere to sites along endothelium after recognizing sites of activation (e.g., chemokine expression) and traverse the endothelium to enter the tissue and fight infection
- Neutrophils produce cytokines that stimulate and attract other phagocytes and lymphocytes
- Mechanisms of killing may be oxygen dependent or independent
- Mast cell
  - Arise from CD34+, KIT+ pluripotent progenitor stem cell
  - Primary cell in immunoglobulin E-mediated inflammatory reactions
Mechanism
- Sensitization to a particular antigen occurs after an initial exposure by injection, ingestion, inhalation, or insect sting
- IgE antibody is produced, which then binds to its receptor on the surface of mast cells and basophils
- After reintroduction of antigen to the sensitized host, the antigen binds to several cell-bound IgE antibody molecules, resulting in cross-link and signal transduction
- Mast cells degranulate and release histamine, leukotriene, serotonin, and bradykinin, resulting in vasodilation, increased vascular permeability, contraction of smooth muscle in bronchi, and increased secretions
- Primary mediators include TNF-α, IL-1, IL-6, prostaglandins, leukotrienes, and histamine

### TABLE 27-3 Selected Mast Cell Mediators

<table>
<thead>
<tr>
<th>Mediators</th>
<th>Biologic Effects</th>
<th>Possible Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-formed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>Vasodilation, increased vascular permeability, gastric hypersecretion, bronchoconstriction</td>
<td>Hypotension, flushing, urticaria, abdominal pain; (peptic, colic) diarrhea, malabsorption</td>
</tr>
<tr>
<td>Heparin</td>
<td>Anticoagulant, inhibition of platelet aggregation</td>
<td>Prolonged bleeding time</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Endothelial cell activation, fibrinogen cleavage, mitogenic for smooth muscles cells</td>
<td>Osteoporosis/osteopenia, disruption of cascade systems (clotting, etc.)</td>
</tr>
<tr>
<td>Chymase</td>
<td>Converts angiotensin I to II, lipoprotein degradation</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Newly Synthesized</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Increase vascular permeability, bronchoconstriction, vasoconstriction</td>
<td>Brochospasm, hypotension</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Vasodilation, bronchoconstriction</td>
<td>Flushing, urticaria</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stem cell factor</td>
<td>Growth and survival of mast cells, chemotaxis of KIT+ cells</td>
<td>Mast cell hyperplasia, focal aggregates</td>
</tr>
<tr>
<td>Tumor necrosis factor-α</td>
<td>Activation of vascular endothelial cells, cachexia, fatigue</td>
<td>Weight loss, fatigue</td>
</tr>
<tr>
<td>Transforming growth factor-β</td>
<td>Enhanced production of connective tissue components</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>IL-5</td>
<td>Eosinophil growth factor</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>IL-6</td>
<td>Growth and survival of mast cells</td>
<td>Fever, bone pain, osteoporosis/osteopenia</td>
</tr>
<tr>
<td>IL-16</td>
<td>Lymphocyte accumulation</td>
<td>Focal aggregates</td>
</tr>
</tbody>
</table>

Hypertension IL = interleukin.
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- **Type II reactions**: cell surface antigen-antibody cytoxicity reactions (antibody-mediated)
  - Antibody is directed against an antigen that may be intrinsic (innately part of the host tissues) or extrinsic (absorbed onto host tissue surfaces during exposure)
  - IgG and IgM antibodies bound to these antigens form in situ complexes that activate the classical pathway of complement and generate mediators of acute inflammation at the site
  - Antibody-dependent cell-mediated cytotoxicity (ADCC): NK cells destroy antibody-coated target cells via perforins and serine proteases, which results in pore formation and cell lysis
  - In some cases, formation of the antigen-antibody complexes does not lead to activation of the complement system but still can lead to cell injury
  - Examples of cytotoxic reactions: transfusion reactions, reactions to certain drugs (penicillin, quinidine, methylprednisolone), and autoimmune hemolytic anemia or thrombocytopenia

- **Type III reactions**: antigen-antibody complex reactions
  - Circulating antibodies bind to antigen and form complexes that, in the presence of excess antigen, escape phagocytosis and deposit on the surface of blood vessels or tissues
  - Antigen-antibody complexes activate complement and release C5a that acts as a potent neutrophil chemotactic factor and anaphylatoxin; clotting factors are also activated
  - Neutrophils are attracted to the area of complex deposition and release lysosomal enzymes, causing tissue destruction
  - Examples of antigen-antibody complex reactions
    - **Arthus reaction**: local type III reaction usually seen when antigen is injected into the skin
      - An IgG antibody directed against the antigen forms immune complexes that bind Fc receptors on leukocytes and mast cells
      - The immune complexes also activate complement and release of chemotactic factors (C3a, C5a), leading to neutrophil infiltration and activation
    - **Serum sickness**: allergic vasculitis characterized by joint pain, fever, pruritic rash, and lymphadenopathy that leads to a complement-mediated systemic immune complex reaction
      - Occurs by the injection of foreign serum or its products into the blood
      - Antibody-antigen complexes activate the complement cascade and also trigger ligation of the FcγRIII mast cell receptor, resulting in histamine release

- **Type IV reactions**: delayed-type hypersensitivity (DTH) reactions
  - Consequence of cell-mediated immunity (antigen-specific T cells): appears in 24 to 48 hours
  - Three clinical examples of Type IV reactions:
    - **Delayed-type hypersensitivity**: antigen introduced by sting (venom) or iatrogenically (PPD)
    - **Contact hypersensitivity**: antigen in the form of haptens from a topical exposure (i.e., Rhus dermatitis, nickel)
    - **Gluten-sensitive enteropathy**: antigen introduced parenterally

**Vitiligo**

- Clinical: depigmented patches of skin in various distributions on the body
- Etiology: loss of melanocytes from the epidermis
- Considered by most to be an autoimmune phenomenon
  - Both melanocyte autoantibodies and T cells are involved in the pathogenesis
  - CD4+/CD8+ ratio is reversed, with predominant CD8+ T cells suggesting a role of CD8+ mediated cytotoxicity to melanocytes in disease etiology
  - Associated with other autoimmune diseases as well as organ-specific autoantibodies: diabetes mellitus, pernicious anemia, systemic lupus erythematosus, thyroid disease (Graves’ disease)
- Treatment: steroids, immune modulators: calcinuerin inhibitors, phototherapy, punch grafts

**Psoriasis**

- Clinical: a systemic inflammatory disorder that manifests as sharply dermarcated red plaques with silvery-white scales on the extensor surfaces and scalp
- Types
  - **Plaque psoriasis**: raised lesions most common on the extensor surfaces of the knees, elbows, scalp, and trunk (Fig. 27-7)
  - **Guttate psoriasis**: droplike lesions; may follow streptococcal pharyngitis
  - **Inverse psoriasis**: flexural surfaces, intertrigenous areas
  - **Pustular psoriasis**: diffuse erythema with pustular eruption can occur with fever
  - **Nail psoriasis**: nail pitting, oil spots, and onycholysis
  - **Scalp psoriasis**: erythema and silvery scale
  - **Erythrodermic psoriasis**: widespread inflammation and exfoliation; exacerbation of unstable plaque psoriasis

- Associated medications include sulfonamides, penicillin, cephalosporins, phenytoin, thiourea, lamotrigine and streptokinase
**EXAMPLES OF IMMUNE-MEDIATED DERMATOLOGIC DISEASES**

- **Inflammatory progressive arthritis**: approximately 10% to 30% of patients; asymmetric oligoarticular occurs in as many as 70% of patients with psoriatic arthritis

- **Pathogenesis**
  - T cells and macrophages can be detected in newly forming lesions
  - Activated memory T-lymphocytes release proinflammatory cytokines, which results in proliferation of keratinocytes and leukocyte recruitment
  - CD4+ and CD8+ T cells are both present in the dermal and epidermal infiltrate, respectively
  - T_{H1} cytokines (IL-2, INF-γ, IL-6, IL-12, and TNF-α) are produced by the T cells, keratinocytes, and antigen-presenting cells
  - IL-23 is overproduced by dendritic cells and possibly keratinocytes in psoriatic lesions

- **Treatment**: targets T cells or their cytokines
  - Ultraviolet A (UV-A) light; etanercept, efalizumab, psoralen plus UV-A light (PUVA); UV-B light; Goeckerman regimen (coal tar followed by UV-B exposure); Ingram method, (anthralin cream is applied to the skin after a tar bath and UV-B treatment); oral retinoids; methotrexate; cyclosporine; alefacept; infliximab; etanercept, adalimumab, ustekinumab; topical steroids; topical calcipotriene; coal tar; topical tazarotene; laser treatment; and combinations of the preceding treatments; patients should avoid oral steroids owing to rebound effect

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**FIGURE 27-7** Psoriasis.
Alopecia Areata (AA)
- Clinical: an autoimmune nonscarring alopecia; usually localized; however, more severe forms may affect the entire scalp (alopecia totalis) or body (alopecia universalis)
- Pathogenesis
  - Associated with certain HLA alleles (HLA-DR4, -DR6, -B12, -B18, -B13, and -B27)
  - CLA+ CD4 and CD8 T-lymphocytes are thought to be involved in the pathogenesis
  - Associated autoimmune diseases: diabetes mellitus, systemic lupus erythematosus, Graves, and vitiligo

Sarcoid
- Clinical: a multisystemic disorder, unknown etiology, clinical manifestations include cutaneous lesions (25% of patients); are categorized as specific or nonspecific based on the histologic presence or absence of noncaseating epithelioid granulomas, respectively; systemic involvement is seen in 70% of cutaneously involved patients
- The skin disease does not correlate with prognosis or extent of visceral involvement (except in erythema nodosum which is a self-limiting condition)
- Nonspecific lesions seen in sarcoidosis (biopsy does not show granulomas):
  - Erythema nodosum (EN): most common nonspecific lesion; tender, erythematous nodules most commonly on legs; associated with a better prognosis
  - May be self-limited and asymptomatic; better prognosis
- Specific lesions (biopsy shows granulomatous inflammation)
  - Lupus pernio (Fig. 27-8): violaceous patches and plaques most commonly on the nose; more common in women and associated with pulmonary involvement; resolution with scarring is possible; marker for insidious disease; progresses over many months. The cheeks, ears, digits, and toes may be similarly affected. Complications include ulceration and involvement of underlying bone structures
  - Papules/plaques/nodules
  - Head and neck more common for papules
  - Legs: plaques; angiolupoid sarcoid (plaques with telangectasias); marker for pulmonary fibrosis
  - Subcutaneous nodules (Darier-Roussy): firm, painless subcutaneous nodules that represent sarcoidosis; this subset is highly associated with systemic disease
  - Scar sarcoidosis (i.e., vaccination site, tattoos)
- Unique variants: ulcerative (legs), ichthyosiform lesions, scarring/nonscarring alopecia
- Syndromes
  - Lofgren’s syndrome: hilar adenopathy, EN, fever, migrating polyarthitis, and acute iritis
  - Heerfordts-Waldenstrom syndrome (uveoparotid fever): parotid gland enlargement, fever, cranial nerve palsy, anterior uveitis
- Systemic disease manifestations
  - Pulmonary
    - Interstitial lung disease may be subclinical
    - Symptoms: dyspnea, dry cough
    - Fifty percent clear spontaneously
  - Lymphadenopathy: hilar, cervical, axillary, inguinal
  - Ophthalmic: anterior uveitis
  - Cardiac: ECG rhythm disorders owing to conduction abnormalities
  - Gastrointestinal: hematemesis, 10% with granulomas
  - Neurologic: facial palsy
  - Renal: overproduction of 1-25 dihydroxy vitamin D, increased Ca²⁺
  - Muscle: biopsy; granulomas, no symptoms
  - Bone: If hands involved, check for bone cysts; joint pain in 25% to 40%
- Diagnosis
  - Histology
    - Naked (absent to sparse inflammation at periphery), noncaseating granulomas, Schaumann bodies (round, laminated, calcified

FIGURE 27-8 Lupus pernio. (Courtesy of Dr. Asra Ali.)
Although self-limited in duration, angioedema involvement of the upper respiratory tract may be life-threatening owing to laryngeal obstruction.

- Recurrent episodes of urticaria and/or angioedema of <6 weeks’ duration are considered acute; >6 weeks’ duration are designated as chronic.

- Pathology: dermal edema characterizes urticaria; edema of both the dermis and subcutaneous tissue characterizes angioedema; collagen bundles are widely separated, venules are often dilated, perivenular infiltrate may include lymphocytes, eosinophils, and neutrophils.

- Classification based on etiology

  - IgE dependent: due to specific antigen sensitivity (pollens, foods, drugs, fungi, molds, Hymenoptera venom, helminthes)
    - Mechanism
      - A sensitized individual possesses IgE antibodies against a specific antigen
      - IgE antibodies are attached to the surfaces of mast cells
      - When rechallenged with the same antigen, the result is release of biologically active products from the mast cells, the most important being histamine

- Physical urticaria: numerous types

  - Dermographism: linear wheals following minor pressure or scratching of the skin
  - Solar urticaria: characteristically occurs within minutes of sun exposure and often is a sign of erythropoietic protoporphyria
  - Cold urticaria: precipitated by exposure to the cold, and, therefore, exposed areas usually are affected
    - In some cases, the disease is associated with abnormal circulating proteins, more commonly cryoglobulins and less commonly cryofibrinogens and cold agglutinins
    - Additional systemic symptoms include wheezing and syncope, thus explaining the need for these patients to avoid swimming in cold water

- Cholinergic urticaria: precipitated by heat, exercise, or emotion; characterized by small wheals with relatively large flares; occasionally associated with wheezing

- Complement-mediated

  - Hereditary/acquired angioedema
    - Caused by C1 inhibitor (C1 IN—H) deficiency: hereditary angioedema (HAE)—low levels of the plasma protein C1 inhibitor (C1 INH)
    - Acquired angioedema (AAE) caused by consumption of C1 INH
    - C1 INH inhibits klikerin and factor Xia; therefore, kinin forming pathway is augmented when C1 INH is missing
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The pathway is then shifted to the production of other metabolites, including leukotrienes. Leukotriene release ultimately results in release of vasoactive substances (histamine) that alter vascular permeability and produce dermal edema (urticaria).

• **Idiopathic**
  - **Chronic idiopathic urticaria**
    ▲ Autoantibodies to the high-infinity IgE receptor or to IgE itself have been identified in these patients
    ▲ Autoantibodies possess histamine-releasing activity
    ▲ Wheals and itching daily for at least 6 weeks
    ▲ Hashimoto thyroiditis and Grave disease are associated with CIU
    ▲ Laboratory: thyroid function, antithyroid peroxidase, and thyroglobulin antibody titers

**Urticarial Vasculitis (Immune Complex–Mediated)**

- Sometimes a reflection of an underlying systemic illness such as lupus erythematosus, Sjögren syndrome, hereditary complement deficiency, serum sickness, or infections such as hepatitis B or C infection
- Individual erythematous wheals last longer than 24 hours and usually develop central petechiae that can be observed even after the urticarial phase has resolved
- On biopsy, there is a leukocytoclastic vasculitis of the small blood vessels
- Treatment
  ▲ Any suspected medication should be discontinued
  ▲ Avoidance of precipitating factors may be helpful for some of the physical urticarias, such as solar and cold urticaria
  ▲ Symptomatic therapy usually includes H1 antihistamines given on a regular rather than an intermittent, as-needed basis
  ▲ The tricyclic antidepressant doxepin (Sinequan) is also effective and has been shown to have both H1 and H2 antihistamine activity

**Hereditary angioedema (HAE):** type 1 (85%), autosomal dominant; suppressed C1 INH levels due to abnormal secretion or intracellular degradation; type 2 (15%), autosomal dominant, leads to synthesis of dysfunctional C1 INH, therefore, levels may be normal or elevated

▲ HAE: normal C1q, depressed C4 levels
▲ Occurs without accompanying urticaria
▲ Trauma often precipitates attacks
▲ Results in massive local swelling and occasionally fatal laryngeal edema
▲ **Aquired angioedema:** may be associated with B-cell lymphoma or connective tissue disease with consumption of C1 INH; may also be associated with autoimmune disorders with circulating IgG antibody to C1 INH
▲ Aquired angioedema has depressed C1q levels and depressed C4 levels
▲ Bradykinin is the mediator of the swelling in both hereditary and acquired angioedema
▲ Angiotensin-converting enzyme inhibitors can cause angioedema: swelling also caused by increased bradykinin (due to a decreased degradation)

- **Serum sickness**
  ▲ Due to deposition of immune complexes in blood vessel walls
  ▲ Leads to fixation of complement and inflammation
  ▲ Clinical: fever, urticaria, lymphadenopathy, myalgia, arthritis
  ▲ Treatment: symptoms are self limited, last 4–5 days
- Reaction to blood product administration
  ▲ Urticaria/angioedema may result from immune complex formation and complement activation that leads to direct vascular smooth muscle changes and indirectly via anaphylatoxins to mast cell mediator release
- **Infections**
  ▲ Acute urticaria may be associated with upper respiratory tract infections due to viruses; hepatitis B virus has also been associated with urticaria
- **Abnormalities of arachidonic acid Metabolism**
  ▲ Urticaria/angioedema may occur in reponse to aspirin

- **Nonimmunologic**
  - **Direct mast cell–releasing agents:** opiates, antibiotics, curare, D-tubocurarine, radiocontrast media
  - **Agents that alter arachidonic acid metabolism:** aspirin and other NSAIDs, azo dyes, benzoates
  ▲ Blocks the production of prostaglandins from arachidonic acid

▲ Graft-Versus-Host Disease (GVHD)
- Occurs when immunologically competent cells are introduced into an immunoinceptent host
- Most commonly seen in hematopoietic cell transplantation (HCT), both allogeneic (between two individuals) and autologous (from the same individual)
- Solid-organ transplants, blood transfusions, and maternal-fetal transfusions also have been reported to cause GVHD
• The skin often is the earliest organ affected
• GVHD remains a primary cause of morbidity and mortality after HCT
• Classifications: arbitrarily defined based on days from transplant
  • Acute GVHD
    − Occurs within the first 100 days of a transplant
    − Consists of a triad of dermatitis, enteritis, and hepatitis
    − Usually begins as scattered erythematous macules and papules that may evolve into a generalized erythroderma or bullous eruption
    − Mediated by T_{H1} cells
    − Graded in five steps (0–IV)
      ▲ Grade 0: no clinical evidence of disease
      ▲ Grade I: rash on less than 50% of skin and no gut or liver involvement
      ▲ Grade II: rash covering more than 50% of skin, bilirubin 2 to 3 mg/dL, diarrhea 10 to 15 mL/kg per day, or persistent nausea
      ▲ Grade III or IV: generalized erythroderma with bullous formation, bilirubin greater than 3 mg/dL, or diarrhea more than 16 mL/kg per day
  • Chronic GVHD
    − Develops after 100 days
    − Consists of an autoimmune syndrome directed toward multiple organs
    − May occur as a late phase of acute GVHD or as a distinct entity
    − The skin is the primary organ involved and may be characterized as localized or generalized with lichen planus–like or sclerodermoid lesions commonly encountered
    − Mediated by T_{H2} cells
• Pathophysiology
  • Three components are required for the development of GVHD
    − The graft must contain immunologically competent cells
    − The host must appear foreign to the graft
    − The host must be incapable of reacting sufficiently against the graft
  • Disease is caused by recognition of epithelial target tissues as foreign by the immunocompetent cells and subsequent induction of an inflammatory response and eventual apoptotic death of the target tissue (regardless of whether the immunoreactive T cells are derived from a nonidentical donor or from the recipient)
  • While T cells may orchestrate the initial inflammatory response, many cell types (e.g., CD4+, CD8+ T-cell subsets, natural killer cells) are found at sites of epithelial injury
• Histology
  • Acute: epidermal basal vacuolization, followed by epidermal basal cell apoptotic death with lymphoid infiltration; satellite cell necrosis (direct apposition of a lymphocyte to a necrotic keratinocyte)
  • Chronic: basal cell degeneration and necrosis, epidermal atrophy, and dermal fibrosis; lichenoid changes with mononuclear infiltrates, epithelial cell necrosis
• Treatment
  • Immunosuppression is the mainstay of therapy: limiting the graft-versus-host tissue response while maintaining the graft-versus-tumor effect is crucial
  • T-cell depletion with Campath 1H or thymoglobulin during transplant is useful
  • Prophylaxis with cyclosporine, mycophenolate mofetil, and tacrolimus is common; however, exacerbations of GVHD frequently require prednisone
  • Newer biologicals (CTLA-4-Ig, infliximab, etanercept, and anti-CD25 agents such as daclizumab) appear interesting and may prove useful
  • Immune modulation with photopheresis or phototherapy also has been helpful

**Atopic Eczema (Atopic Dermatitis)**

• Clinical: pruritic poorly demarcated, erythematous scaly patches, small vesicles, excoriations, crusting, lichenification and impetiginization that have a predilection for the skin flexures (neck, antecubital fossa, and popliteal fossa) in children and extensors in adults; chronic scratching and rubbing can lead to hyperpigmentation and lichenification; periorbital fold (Denny Morgan sign) may be present
• Pathogenesis
  • Believed to be multifactorial
  • Allergens (house dust mites, pollen, animal dander), outdoor pollution, climate, diet, and prenatal or early-life factors such as infections
  • Patients appear to have a genetic predisposition that can then be exacerbated by these numerous factors
  • Atopic skin has decreased human b-defensin 3 predisposing patients to frequent skin infections
• Histology: edema within the epidermis (spongiosis) and infiltration with lymphocytes and macrophages in the superficial dermis
• Diagnosis
  • Made by the typical morphology and distribution of the lesions
  • Family and personal history of atopy (asthma, allergic rhinitis, or atopic dermatitis) also can help with the diagnosis
• Prognosis
  • There is currently no cure; however, various interventions exist to control symptoms
Can be expected to clear in 60% to 70% of children by their early teens, although relapses may occur

Treatment
- Includes emollients, oral antihistamines, topical corticosteroid ointments, topical tacrolimus, topical pimecrolimus
- More severe cases sometimes use UV-B phototherapy or PUVA
- Occasionally, a short course of systemic steroids is necessary to bring the disease under control
- Steroid wet wraps and baths are helpful in treating acute atopic dermatitis
- Avoidance of environmental factors that enhance itching is important
- Moisturizers reduce dry skin and itching
- Topical and/or oral antibiotics, bleach baths for bacterial superinfection

**Nummular Eczema (Nummular Dermatitis)**
- Occurs most frequently in patients who are in their fifties and sixties
- In temperate climates, this condition is seen most frequently in the winter
- More frequently encountered in patients of Asian descent
- The etiology is unclear, although xerosis plays a significant role in the pathogenesis
- Clinical
  - Pruritic, coin-shaped, erythematous patches that exhibit scale (hyperkeratosis) and occasionally pin-head sized vesicles on the legs, arms, and legs (in decreasing order of frequency)
  - Lesions may become excoriated and lichenified
- Treatment
  - Liberal use of emollients, avoidance of long hot showers, topical use of corticosteroids or immune modulators, and oral antihistamines
  - Severe cases may require UV-B phototherapy, PUVA, or oral corticosteroids

**Seborrheic Dermatitis**
- A common problem affecting 3% to 5% of the healthy population
- Waxing and waning course that parallels the increased sebaceous gland activity occurring in infancy and after puberty
- Clinical: erythematous patches and plaques with indistinct margins and yellowish, greasy-appearing scales affecting sebaceous hairy regions of the body (scalp, eyebrows, nasolabial creases, ears, chest, intertriginous areas, axilla, groin, buttocks and inframammary folds); variable amount of pruritus
- Refractory or more widespread disease may be associated with underlying HIV infection (approximately one-third of patients with AIDS and AIDS-related complex) or neurologic disorder (i.e., Parkinson’s disease)
- Pathogenesis
  - Thought to be an inflammatory reaction to the resident skin yeast, *Pityrosporum ovale*
  - *P. ovale* is a lipophilic yeast that is normally found on the seborrheic regions of the skin
- Diagnosis: usually made on clinical grounds alone
- Treatment
  - Antiseborrheic shampoos containing zinc pyrithione, selenium sulfide, or ketoconazole are the mainstay of treatment
  - Topical steroids
  - Topical antifungals

**Other Systemic Inflammatory Diseases**
- Familial Mediterranean fever:
  - Autosomal recessive
  - MEFV gene; chromosome 16, mutation in the gene *pyrin* (*Marenostrin*)
  - Clinical findings: self-limited attacks of fever accompanied by peritonitis, pleurisy, and arthritis, erysipelas-like eruption on lower legs, urticaria, Henoch-Schönlein purpura
  - Treatment: colchicines, anti-TNF
- Muckle-Wells
  - Autosomal dominant
  - CIAS1, encoding cryopyrin
  - Clinical findings: urticaria, fever, paresthesias, limb pain, deafness, renal, abdominal pain, polyarthralgia, conjunctivitis, systemic amyloidosis (25%)
  - Treatment: IL-1 receptor antagonist

**QUIZ**

**Questions**
1. A positive reaction resulting in skin induration to a tuberculin test is a:
   A. Histamine-releasing immediate hypersensitivity reaction
   B. Antibody and antigen (purified protein derivative) complex reaction
   C. Antibody formation to the purified protein derivative
   D. Plasma cell antibody response to purified protein derivative
   E. T-cell response to purified protein derivative
2. A vesicular eruption on the lips following a sunburn is most likely caused by production of which cytokine?
A. IL-2
B. IL-4
C. IL-6
D. IL-10
E. IL-12

3. Low natural protection from developing skin ulcers following infection with *Leishmania braziliensis* are seen in patients with elevated production of what cytokine?
A. IL-12
B. IFN-gamma
C. IL-10
D. TNF-alpha
E. IL-13

4. Interferon-gamma____________.
A. Is a potent activator of macrophages
B. Promotes differentiation of lymphocytes
C. Leads to increased expression of MHC class I and II molecules
D. Activates leukocytes and endothelial cells
E. All of the above

5. Cytokines involved in decreased expression of human beta defensin-3 (HBD-3) and subsequent increased susceptibility to *Staphylococcus aureus* infections in atopic patients include all of the following EXCEPT:
A. IL-4
B. IL-10
C. IL-12
D. IL-13
E. None of the above

6. Pick the correct pairing of enzyme and end-product involved in arachidonic acid metabolism
A. Cyclooxygenase – thromboxanes, lipooxygenase – leukotrienes
B. Cyclooxygenase – prostaglandins, lipooxygenase – leukotrienes
C. Cyclooxygenase – leukotrienes, lipooxygenase – prostaglandins
D. Cyclooxygenase – leukotrienes, lipooxygenase – thromboxanes
E. None of the above

7. Which cytokine is an important activator of eosinophils?
A. IL-2
B. IL-3
C. IL-4
D. IL-5
E. IL-6

8. Which of the following statements regarding regulatory T cells is false?
A. Key cytokines are TGF-beta and TNF-alpha
B. They can be subsets of both CD4+ or CD8+ T cells
C. A mechanism of suppression is by secretion of IL-10
D. Cell-to-cell contact is a mechanism of suppressive activity
E. None of the above

9. The following statements regarding the innate immune system are all true EXCEPT:
A. The innate immune response is rapid
B. Pattern recognition receptors are highly conserved in phagocytic cells
C. Activation of toll-like receptors result release of cytokines in monocytes
D. Defensins are important in attracting immature dendritic cells
E. Recognition of antigen leads to clonal expansion of lymphocytes

10. Which of the following statements regarding complement activation is false?
A. Activation can occur via the lectin pathway independent of antibodies
B. Generation of C3b is common to all pathways
C. Antibody-antigen complexes activate the classical pathway
D. C3a and C5b are anaphylatoxins
E. The MAC complex forms transmembrane channels in the cell membrane

**Answers**

1. E. Skin induration in response to a tuberculin test is a delayed type hypersensitivity (type IV) reaction which involves T cells.
2. D. A sunburn results in local immunosuppression allowing activation of herpes simplex eruption. This process is mediated by IL-10, an immunosuppressive and anti-inflammatory cytokine.
3. C. Protection against *Leishmania* infection is conferred by Th1 dominant reactions. In Th2 polarized and mixed Th1/Th2 responses, infection and progression of disease can occur. Studies have shown that IL-10 is strongly elevated in Th2 and mixed responses.
4. E. Interferon-gamma exerts pleiotropic functions.
5. C. Research has shown that Th2 cytokines have been associated with down-regulated expression of HBD-3. Antagonizing IL-4, IL-10, or IL-13 allows for increased expression of HBD-3 on skin surfaces of atopic patients and improved *S. aureus* killing.
6. B. In inflammatory responses, arachidonic acid can be metabolized by many enzymes including cyclooxygenase (involved in production of prostaglandins, prostacyclin, and thromboxane) and lipoxygenase (generates leukotrienes).

7. D. IL-5 is a TH2 cytokine that can be produced by mast cells, T-helper cells, and eosinophils. IL-5 is a key activator of eosinophils.

8. A. Several naturally occurring and experimental populations of regulatory T cells have been recently identified. Suppressive effects have been shown to be mediated by cell to cell contact, production of IL-10 or TGF-beta. They can be either CD4+ or CD8+ T cells. Answer A is false because TNF-alpha, a pro-inflammatory cytokine, is incorrect.

9. E. All of the answers with the exception of answer E describes innate immunity. Recognition of antigen resulting in clonal expansion of lymphocytes is a feature of adaptive immunity.

10. D. C3a and C5a are anaphylatoxins that can trigger rapid reactions and induction of local inflammatory responses. Functions of C5a include triggering mast cell release of histamines, activation of neutrophils and macrophages, and as a chemottractant for leukocytes. Complement C5b is not an anaphylatoxin but is part of the membrane attack complex.

REFERENCES


EPIDERMIS AND DERMIS

**Epidermis**
- Stratified squamous epithelium
- Approximately 0.4 to 1.5 mm thick and consisting mostly of keratinocytes (Fig. 28-1)
- Renewal of the epidermis takes approximately 26 to 28 days (13 to 14 days for maturation from basal layer to corneum and another 13 to 14 days for shedding)
- Divided into four main layers with characteristic cell shape, specialized intracellular structures, types of keratin, accessory cells, and proteins (Table 28-1): stratum corneum (SC), stratum granulosum, stratum spinosum, stratum germinativum
- **Stratum disjunction**: outer SC cells are more prone to desquamation
- **Stratum compactum**: cells of the lower stratum corneum; thicker cells and more densely packed, organized parallel arrays of keratin filaments, more fragile cornified envelope
- Stratum lucidum is an additional layer present between the strata granulosum and corneum in palmoplantar skin. It appears as an electronlucent zone and contains nucleated cells
- Differentiation from basal cell to corneocyte involves the loss of the nucleus and extrusion of cellular contents except for keratin filaments and filaggrin matrix

**Specialized Cells**
- Merkel cell
  - Type I mechanoreceptor (slow-adapting, low threshold)
  - Derived from ectoderm/neural crest
  - Mainly confined to basal layer
  - Present in areas with high tactile sensitivity (hairy and glabrous skin)
  - Typically found in epithelium of digits, lips, oral cavity, and outer root sheath of the hair follicle
  - Contain granules with neurotransmitter-like substances; nonspecific enolase present
  - Members of the amine precursor uptake and decarboxylation (APUD) system
  - Keratins found in merkel cells: K20 is specific; also contain K18, K8, K19

- Melanocytes
  - Neural crest–derived dendritic cell
  - Mainly confined to basal layer
  - Extend above and below basal layer but do not form junctions with keratinocytes
  - Contains two types of the pigment melanin
    - Eumelanin (brown and black coloration)
    - Pheomelanin (red or yellow coloration)

- Langerhans cell
  - Dendritic, bone marrow–derived (mesoderm) antigen-presenting cell
  - Involved in T-cell responses (i.e., contact hypersensitivity and graft-versus-host disease)
  - Process antigen and present it to T cells in the presence of major histocompatability complex (MHC) class II
  - Produces interleukin 1 (IL-1)
  - Contains distinctive racket-shaped Birbeck granules that are formed when an antigen is internalized by endocytosis
  - Ultraviolet B (UV-B) decreases number and antigen-presenting ability of Langerhans cell
  - Can be infected with HIV
  - Reduced numbers in patients with psoriasis, sarcoidosis, and contact dermatitis

**Specialized Structures**
- Desmosomes
  - Prominent in the stratum spinosum
  - Anchoring junctions that connect adjacent keratinocytes (Fig. 28-2)
  - Keratin filaments extend from desmosome to desmosome to form keratin cytoskeleton
### TABLE 28-1  Layers of the Skin and Characteristics

<table>
<thead>
<tr>
<th>Layer</th>
<th>Cell Shape</th>
<th>Types of Cells</th>
<th>Types of Keratin</th>
<th>Additional Structures</th>
<th>Associated Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratum corneum</td>
<td>Flattened polyhedral-shaped horny cells with loss of nucleus</td>
<td>Keratinocytes</td>
<td></td>
<td>Cornified cell envelope</td>
<td>Loricrin Profilaggrin Filaggrin Involucrin</td>
</tr>
<tr>
<td>Stratum disjunctum (outer stratum corneum cells)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratum compactum (cells of the lower stratum corneum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cornifin Trichohyalin TGM 1/2/3 Envolplakin SPR 1/2</td>
</tr>
<tr>
<td>Stratum granulosum</td>
<td>Diamond-shaped with characteristic dense basophilic granules</td>
<td>K2 K11</td>
<td>Basophilic keratohyaline granules</td>
<td></td>
<td>Profilaggrin Loricrin</td>
</tr>
<tr>
<td>Stratum spinosum</td>
<td>Polyhedral with round nucleus; “spiny appearance”</td>
<td>Keratinocytes Langerhans cell Transient amplifying cells</td>
<td>K1 K10 K9</td>
<td>Lamellar granules Desmosomes Gap junctions</td>
<td>Desmoglein II/III Desmocollin 1</td>
</tr>
<tr>
<td>Stratum germinativum</td>
<td>Columnar with round nucleus</td>
<td>Keratinocytes stem cells (10%) Transient amplifying cells (50%) Postmitotic differentiated cells (40%) Melanocytes Merkel cell Langerhans cell</td>
<td>K5 K14 K19</td>
<td></td>
<td>BPAG 1</td>
</tr>
</tbody>
</table>

![Image](image-url)  

**FIGURE 28-1**  Epidermis.  
(Reprinted with permission from Wolff, K et al. Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)
Actin attaches to cadherins via alpha, beta, and gamma catenins.

Lamellar granules (Odland bodies) first apparent in upper spinous layer, but primary site of action is the granular layer. 0.2 to 0.3 \( \mu \)m in diameter, membrane-bound secretory granules contain glycoproteins, glycolipids, phospholipids, free sterols, acid hydrolases, and glucosylceramides (precursors to ceramides that contribute to corneum lipid layer). Extrude their contents of lipids and enzymes into the intercellular space, where the lipid is rearranged to lipid sheets, creating a hydrophobic barrier between the granular and cornified layers.

Keratohyaline granules are dense basophilic granules containing electrondense proteins of profilaggrin, keratin, and loricrin. Filaggrin (cleaved from profilaggrin) becomes the major protein of keratohyaline granules. Involved in formation of cornified cell envelope rich in sulfur.

Cornified cell envelope (CCE) is an extremely durable protein-lipid polymer assembled on the interior of the keratinocyte. Eventually resides on the exterior of the corneocyte. Provides a mechanical and chemical barrier. CCE is 7 to 15 nm thick. Impermeability of this layer is achieved by the action of calcium-dependent transglutaminases that bind (cross-link) loricrin, keratin, desmosomal proteins, involucrin, elafin, and other proteins to the cell membrane, creating a proteinaceous and insoluble shield. Epsilon-gamma-glutamyl-lysine-isopeptide crosslinks make the CCE insoluble.
Specialized Proteins

- Profilaggrin/filaggrin (filament aggregate protein)
  - Profilaggrin is a protein made up of 10 to 12 tandem repeat units of filaggrin
  - Profilaggrin is converted to monomers of filaggrin in a stepwise conversion by three proteases and dephosphorylation
  - Filaggrin is thought to provide a protein matrix for keratin filament aggregation in corneocytes
- Loricrin
  - A protein composing 70% of the CCE
  - Hydrophobic, cysteine-rich protein
  - Gene is located on chromosome 1q21 as part of the epidermal differentiation complex
  - Encoded along with other proteins required for the terminal differentiation of epidermis
  - Loricrin is localized to the desmosome in association with desmoglein
- Involucrin
  - Glutamine-rich, acidic protein
  - Resistant to denaturing and unchanged by retinoic acids
  - Early marker of keratin differentiation
  - Serves as a scaffold for other proteins to bind during keratinization

Dermal-Epidermal Junction

- Also referred to as the basement membrane zone (BMZ)
- Thickness of 0.5 to 1.0 mm
- Visualized with periodic acid–Schiff (PAS) staining, not hematoxylin and eosin (H&E) stain
- Most components arise from basal keratinocytes or fibroblasts
- Function
  - Supportive structure to anchor the epidermis to the dermis: anchoring occurs through the cytoskeleton in keratinocytes that bind to laminin 5 in the lamina lucida, which, in turn, binds to type VII collagen in lamina densa
  - Regulates interactions between the dermis and epidermis
  - Provides a selective barrier between the dermis and epidermis
- Hemidesmosome (anchoring complex) (Fig. 28-3)
  - Attaches basal cells of epidermis to the basement membrane (link keratin cytoskeleton to laminin 5 in the lamina lucida)
  - Structurally different from desmosomes
  - Consists of a cytoplasmic portion (attachment plaque), transmembrane portion [bullous pemphigoid (BP) antigen 2 (180 KD) and integrin, and an extracellular portion (anchoring filaments and subbasal dense plate)
  - Cytoplasmic attachment plaque
    - Consists of BP antigen 1 (230 KD) and plectin (HD-1)
    - Keratin filaments (K5, 14) attach to plaque
    - Desmocalmin and desmoplakin bind keratin to plaque
    - Intracellular portion of BP antigen 2 (180 KD) (BPAG2) and collagen XVII are also present
  - Transmembrane portion
    - Consists of BP antigen 180 (BPAG2)—type II transmembrane configuration

Meissner corpuscles
- Located in dermal papillae
- Detect light pressure
- More prevalent in palms and soles
- “Pine cone” appearance
- Vater-Pacini corpuscles
- Located in deep dermis of palms, dorsum of hands, and soles; also skin of nipples and anogenital region
- Detect deep pressure and vibration
- “Pearl onion” appearance in cross section
- Mucocutaneous end organs (Krause end bulbs)
- Located in papillary dermis
- Found in skin at mucocutaneous junction (vermilion border of lips, glans penis, clitoris)
Contains $\alpha 6\beta 4$ integrin, which likely interacts with laminin 5 to form anchoring filaments

- Subbasal dense plate and anchoring filaments
  - Located below the hemidesmosome in the lamina lucida
  - Integrins and BPAG2 cross the membrane and attach to plate
  - Anchoring filaments then extend from the subbasal plate into the lamina densa, providing a point of deeper attachment

- Three zones of basement membrane zone
  - Lamina lucida
    - Named for appearance on electron microscopy (EM) as electron-lucent
    - 8 nm wide
    - Weakest of layers—able to split with heat or salt
    - Composed of laminin 1, nidogen (entactin), and fibronectin
    - Anchoring filaments cross lamina lucida
      - Filaments contain laminin-322 (composed of one $\alpha 3$, $\beta 3$, and $\gamma 2$ chain), formerly known as laminin 5 (aka. epiligrin, kalinin, and nicein)

    - One side connects to attachment plaque of plasma membrane; the other side connects to the subbasal dense plate
  - Lamina densa
    - Composed of type IV collagen (unique to dermal-epidermal junction)
    - Also contains entactin (nidogen): binds laminin, collagen IV, perlecan, and fibulins (calcium-binding extracellular matrix proteins)
    - Also contains fibulins (calcium-binding extracellular matrix proteins)
      - Fibulins function to support the structural network of different basement membranes by joining other supramolecular structures, elastic fibers, and aggregates
      - Can be found in basement membranes and vessel walls
      - Fibulin-1 mutation results in Marfan Syndrome
      - Fibulin-2 binds fibrinogen, fibronectin, nidogen, proteoglycans, aggrecan, and versican

- Contains heparan sulfate proteoglycan, which is negatively charged owing to disulfide bridges and renders the dermal-epidermal junction impermeable to negatively charged substances

- **Sublamina densa**
  - Contains network of anchoring fibrils composed of type VII collagen
  - Anchoring fibrils originate in lamina densa, dip down into the dermis, and attach to an anchoring plaque or loop back to reinsert into the lamina densa
  - Fibrils appear as “wheatstacks” on EM
  - Contains interstitial collagen fibers of types I, III, V, and VI
  - Contains microfibrils composed of fibrillin: two types of microfibrils
    ▲ Elaunins—horizontal
    ▲ Oxytalins—perpendicular to elaunins
  - Contains microthread-like fibers of the glyco-protein linkin

**TABLE 28-2 Classification of Keratins**

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidity (pK 4.5–5.5)</td>
<td>Basic or neutral (pK 5.5–7.5)</td>
</tr>
<tr>
<td>Smaller in size (40–56.5 kDa)</td>
<td>Larger in size (52–67 kDa)</td>
</tr>
<tr>
<td>Keratins K9–K20 Hal to Ha4, Hax</td>
<td>Keratins K1–K8 Hb1 to Hb4, Hbx</td>
</tr>
<tr>
<td>Chromosome 17q12-21</td>
<td>Chromosome 12q11-13</td>
</tr>
</tbody>
</table>

**KERATINS**

**Classification of Keratins**
- Members of the structural protein group of intermediate filaments (named for their assembled diameter of 10 nm)
- Six types of intermediate filaments (types I to VI)
- Keratins make up type I and type II intermediate filaments
- Approximately 40 varieties of keratin
- Spontaneously form pairs consisting of a type I and a type II; an acidic and a basic protein, respectively. (Table 28-2)

**Structure of Keratins**
- Polypeptides consisting of a central rod domain of approximately 310 amino acids (Fig. 28-4)
- Central domain is composed of four highly conserved alpha-helical regions (designated 1A, 2A, 1B, and 2B)
- Regions are connected by three nonhelical linking sequences thought to provide flexibility (designated L1, L12, and L2)
- Central domain is flanked by an amino head and carboxy tail
- Two keratin polypeptides (one type I and one type II) combine to form a parallel coiled coil
- Coil is stabilized by hydrophobic interactions between the two strands; structure is now a keratin heterodimer
- Keratin heterodimers form long chains in a head-to-tail sequence
- Two chains of keratin heterodimers then combine in antiparallel fashion to form a protofilament (2 to 3 nm)
- Two protofilaments combine to form a protofibril (4.5 nm)
- Protofibrils then assemble in groups of three or four strands to form a 10-nm intermediate filament of keratin

ADHESION MOLECULES

Keratins in Disease

- Mutations affecting the ends of the central domain prove the most deleterious (Table 28-3)

ADHESION MOLECULES

- Adhesion molecules contribute to
  - Cell-to-cell adhesion
  - Interaction between cells
  - Cell signaling
  - Inflammation
  - Migration of cells
  - Wound healing
  - Embryogenesis

- Families of adhesion molecules
  - Cadherins
    - Calcium-dependent cell-cell adhesion molecules
    - Main adhesion molecule in early embryogenesis
    - Structure: single-pass transmembrane glycoprotein
  - Classic cadherins—found at adherens junctions and interact with cytoplasmic anchoring structures
    - E cadherin: found on all epithelium; Chromosome 16q
    - N cadherin: found on nerve, muscle, epithelium
    - P cadherin: found on placenta and basal epithelium
  - Desmosomal cadherins—found in desmosomes; associate with keratin filaments via plakoglobin and desmplakin
    - Desmoglein—membrane-bound; pemphigus vulgaris—autoimmunity against desmoglein 3; pemphigus foliaceus—autoimmunity against desmoglein 1
    - Desmocollins—membrane bound

- Bind to catenins (link cytoskeleton to adherens junction)
- Two types

TABLE 28-3 Keratin Expression Patterns and Keratin-Associated Diseases

<table>
<thead>
<tr>
<th>Type II</th>
<th>Type I</th>
<th>Physiologic Location of Expression</th>
<th>Hereditary Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Suprabasal keratinocytes</td>
<td>Bullous congenital ichthyosiform erythroderma</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>Palmoplantar suprabasilar keratinocytes</td>
<td>Epidermolytic PPK Diffuse nonepidermolytic PPK Epidermolytic PPK with polycyclic psoriasiform plaques</td>
</tr>
<tr>
<td>2e</td>
<td>10</td>
<td>Upper spinous and granular layer</td>
<td>Ichthyosis bullosa of Siemens</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>Cornea</td>
<td>Meesmann's corneal dystrophy</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>Mucosal epithelium</td>
<td>White sponge nevus</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>Basal keratinocytes</td>
<td>Epidermolytic bulosa simplex</td>
</tr>
<tr>
<td>6a</td>
<td>16</td>
<td>Outer root sheath, hyperproliferative keratinocytes, palmoplantar keratinocytes</td>
<td>Pachyonychia congenita type I, focal nonepidermolytic PPK</td>
</tr>
<tr>
<td>6b</td>
<td>17</td>
<td>Nail bed, epidermal appendages</td>
<td>Pachyonychia congenita type II Steatocystoma multiplex</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>Simple epithelium</td>
<td>Cryptogenic cirrhosis</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>Embryonic</td>
<td></td>
</tr>
<tr>
<td>Hb, 1, 3, 5, 6</td>
<td>Ha 1, 2, 3a, 3b, 4–8</td>
<td>Hair follicle</td>
<td>Monilethrix (Hb1 and 6)</td>
</tr>
</tbody>
</table>

Δ **Plakoglobin**—cytoplasmic
Δ **Desmoplakin**—cytoplasmic: only molecule known to be present in both desmosomes and adherens junctions

- **Integrins**—integrate intracellular cytoskeleton with extracellular matrix
  - Large family of transmembrane molecules composed of two noncovalently bound polypeptide subunits (α, β)
  - Most integrins recognize and bind peptide sequence of arginine-glycine-aspartic acid (commonly found on matrix proteins like collagen)
  - Subfamily depends on β subunit:
    - β1—binds cells to extracellular matrix: This subfamily is also known as VLA (very late activation) 1–6
    - β2—binds leukocytes to endothelium or other inflammatory cells
      △ Three members: leukocyte function antigen-1 (LFA-1), macrophage activation antigen 1 (Mac 1), and p150, 95
      △ Abnormality leads to leukocyte adhesion problems and chronic infection/abscess
    - β3—interaction between platelets and neutrophils at sites of inflammation or vascular damage: contains two members: platelet glycoprotein IIb/IIIa and vitronectin receptor
    - β4—αβ4 is the most notable of this subfamily
      △ Localized to hemidesmosomes of basement membrane
      △ Binds to laminin 5 in anchoring filaments
      △ Plays an important role in junctional epidermolysis bullosa
  - **Selectins**
    - Family of proteins that function in cell-cell adhesion; mediate recruitment of inflammatory cells
    - Three classes
      △ **L-selectin** (leukocyte): expressed on leukocytes
      △ **P-selectin** (platelet)
        △ Stored preformed in Weibel-Palade bodies of endothelium; released rapidly to membrane in response to stimulation and then can be reinternalized
        △ Also found on alpha-granules of platelets and megakaryocytes
      △ **E-selectin** (endothelial): produced on endothelial cells in response to IL-1 and tumor necrosis factor (TNF)
  - **Immunoglobulin supergene family**
    - Extensive group of cell surface-binding proteins that contain one or more Ig/Ig-like domain (disulfide-bridged loops)
    - **Cellular adhesion molecule** (CAM)
      - Primary function is antigen recognition and cell-cell adhesion
      - Can be inducible or constitutively expressed on endothelium
      - **Members**
        △ **Intercellular adhesion molecule 1** (ICAM 1) CD 54
          △ Expressed constitutively on endothelial cells, certain epithelial cells, and antigen presenting cells
          △ Can be induced for surface expression on other cells by cytokines (αIFN)
          △ ICAM 1 allows inflammatory cells to attach and infiltrate lesions in skin (e.g., psoriasis)
          △ Ligand is LFA-1
          △ Interaction of LFA-1 and ICAM allows T cells to come into close contact with an antigen-presenting cell (APC), which is a key step in activating a T-lymphocyte
          △ ICAM 1 is the receptor for rhinovirus on respiratory epithelium
        △ **Intercellular adhesion molecule 2** (ICAM 2) CD 54
          - Constitutively expressed
          - A second ligand for LFA-1
        △ **Leukocyte function antigen 3** (LFA-3) CD 58
          △ Expressed on APCs and forms a ligand with CD2 receptor on T-cell surface
          △ This is a secondary signal in the activation of T cells
          △ Important target for current psoriasis therapies
        △ **Vascular cell adhesion molecule 1** (VCAM 1)
          △ Expressed on endothelial cells on activation
          △ Expression induced by IL-1 and TNF-α
          △ Directly involved in endothelium-lymphocyte interactions
          △ Mediates recruitment of lymphocytes into areas of inflammation

**COLLAGEN**
- Produced by ribosomes within fibroblasts
- Provides structural stability
- Represents 70% to 80% of dry weight of the dermis
- Basic collagen structure is three alpha chains combined in a triple-helix formation with cross-linking hydrogen bonds
Nineteen types of collagen

- Typical sequence of collagen: GLY—X—Y (Fig. 28-5)
  - GLY = glycine, always the third residue, 33% of amino acids in collagen
  - X = frequently proline
  - Y = frequently hydroxyproline or hydroxylysine

- Four classes of collagen
  - Fibrillar collagen—types I, II, III, and XI
  - Network-forming collagens (nonfibrillar)—type IV
  - Microfibrillar—VI, VII

- FACIT (fibril-associated collagens with interrupted triple helices)—IV, XII, XIV

- Collagen biosynthesis (Fig. 28-6)
  - Pretranslational
    - Occurs in the nucleus
    - Transcription of genes for procollagen
    - mRNA is formed
  - Cotranslational
    - mRNA is transferred to ribosomes of rich endoplasmic reticulum (RER)

### TABLE 28-4 Summary of Integrins

<table>
<thead>
<tr>
<th>Integrin</th>
<th>Alternate Name</th>
<th>Expressed on</th>
<th>Matrix Ligand</th>
<th>Endothelial Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>β1 Subfamily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1β1</td>
<td>VLA-1</td>
<td>T cells</td>
<td>Collagen I, IV Laminin</td>
<td></td>
</tr>
<tr>
<td>α2β1</td>
<td>VLA-2</td>
<td>T cells</td>
<td>Collagen I, IV Laminin</td>
<td></td>
</tr>
<tr>
<td>α3β1</td>
<td>VLA-3</td>
<td>T cells</td>
<td>Collagen Laminin 1, 5 Fibronectin Epiligrin</td>
<td></td>
</tr>
<tr>
<td>α4β1</td>
<td>VLA-4</td>
<td>T cells</td>
<td>Fibronectin</td>
<td>VCAM-1</td>
</tr>
<tr>
<td>α5β1</td>
<td>VLA-5</td>
<td>T cells</td>
<td>Fibronectin</td>
<td></td>
</tr>
<tr>
<td>α6β1</td>
<td>VLA-6</td>
<td>T cells</td>
<td>Laminin</td>
<td></td>
</tr>
<tr>
<td>β2 Subfamily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1β2</td>
<td>LFA-1</td>
<td>Neutrophils Monocytes</td>
<td></td>
<td>ICAM-1 ICAM-2</td>
</tr>
<tr>
<td>αmβ2</td>
<td>Mac-1</td>
<td>Neutrophils Monocytes</td>
<td>C3bi Fibronectin</td>
<td>ICAM-1</td>
</tr>
<tr>
<td>αxβ2</td>
<td>P150, 95</td>
<td>Neutrophils Monocytes</td>
<td>C3b Fibronectin</td>
<td></td>
</tr>
<tr>
<td>β3 Subfamily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Glycoprotein Iib/IIIa</td>
<td>Platelets</td>
<td>Fibrinogen Fibronectin von Willebrand factor Vitronecin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitronecin Receptor</td>
<td></td>
<td>Vitronecin Fibrinogen vWF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β4 Subfamily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α6β4</td>
<td></td>
<td>Keratinocytes (basal)</td>
<td>Laminin 1, 5</td>
<td></td>
</tr>
</tbody>
</table>

- Nineteen types of collagen
- Typical sequence of collagen: GLY—X—Y (Fig. 28-5)
  - GLY = glycine, always the third residue, 33% of amino acids in collagen
  - X = frequently proline
  - Y = frequently hydroxyproline or hydroxylysine
- Four classes of collagen
  - Fibrillar collagen—types I, II, III, and XI
  - Network-forming collagens (nonfibrillar)—type IV
  - Microfibrillar—VI, VII
**Postranslational**
- While in the RER, three procollagens are aligned and form disulfide bonds between chains to stabilize the structure; this occurs first on the amino end and then on the carboxy end
- Three procollagens form a triple helix (carboxy-to-amino end)
- Procollagen is transferred from the RER to the Golgi complex and is secreted continuously from the cell into the extracellular space
- Once excreted, neutral calcium-dependent proteinases cleave the extra peptide extensions on the end of the procollagen to form tropocollagen
- Tropocollagen then combines to form collagen fibrils, which are stabilized by cross-links
- Cross-linking is catalyzed by lysyl oxidase, which uses copper as a required cofactor (enzyme is defective in type IX Ehlers-Danlos syndrome)
- Fibrils combine to create a collagen fiber

**Factors that affect collagen production**
- Ascorbic acid—stimulates
- Transforming growth factor \( \beta \) (TGF-\( \beta \))—stimulates
- IL-1—inhibits by stimulating PGE2
- Glucocorticoids—inhibit collagen gene transcription
- Retinoic acid—increases collagen synthesis
- Interferon-\( \gamma \) (INF-\( \gamma \))—potent inhibitor of collagen gene transcription
- TNF-\( \alpha \)—inhibits gene transcription
- D-Penicillamine—interferes with collagen cross-linking
- Minoxidil—inhibits expression of lysyl hydroxylase
- Distribution of types of collagens (Table 28-5)
- Heritable connective tissue diseases (Table 28-6)

**ELASTIC TISSUE**

- Allows skin to return to normal shape after being deformed or stretched
- Composed of elastic fibers
- Elastic fibers are visualized with special stains: Verhoeff-van Gieson, Orcein, or Resorcin-Fuchsin
- Elastic fibers are made of protein filaments embedded in an amorphous matrix of mostly elastin; this elastin core is surrounded by microfibrils that contain fibrillin
- Papillary dermis—elastic fibers are thin and run perpendicular to the skin surface; named oxytalan fibers
- Reticular dermis—elastic fibers are thick and run parallel to the skin surface; named elaunin fibers
- Elastin
ELASTIC TISSUE

This is catalyzed by the enzyme lysyl oxidase, with copper and oxygen as cofactors.

Anetoderma = loss and fragmentation of skin owing to decreased desmosine.

Expression of elastin is activated early in embryogenesis and continues at a steady rate until age 40, when it drops off precipitously.

Degradation of elastic fibers occurs by elastases (proteolytic enzymes).

- Classic elastases—degrade insoluble elastic fibers at neutral or mildly alkaline pH; found in polymorphonuclear cells (PMNs); inhibited by $\alpha_1$-antitrypsin, $\alpha_2$-macroglobulin

- Secreted mainly by skin fibroblasts
- Elastin is mapped to chromosome 7
- Composed primarily of glycine, alanine, valine, proline, and lysine
- Elastin contains the unique amino acids of desmosine and isodesmosine
  - These amino acids provide sites for cross-linking (catalyzed by lysyl oxidase); cross-linking creates stability and insolubility
  - Desmosine is formed in the extracellular space by oxidative deamination of lysyl residues to allysine and then the fusion of three allysines with a lysyl residue

- This is catalyzed by the enzyme lysyl oxidase, with copper and oxygen as cofactors
- Anetoderma = loss and fragmentation of skin owing to decreased desmosine

- Expression of elastin is activated early in embryogenesis and continues at a steady rate until age 40, when it drops off precipitously
- Degradation of elastic fibers occurs by elastases (proteolytic enzymes)

A. Intracellular steps:
1. Translation of pre-pro $\alpha$ chains on the ribosomes of the rough endoplasmic reticulum
2. Cleavage of the signal sequence
3. Hydroxylation of selected prolyl and lysyl residues
4. Glycosylation of some hydroxylysyl residues
5. Formation of interchain disulfide bonds
6. Formation of triple helices

B. Secretion of procollagen

C. Extracellular modifications:
1. Cleavage of peptide extensions by specific proteases
2. Fibril formation
3. Cross-linking of collagen fibrils by deamination of hydroxylysine and lysine residues to give aldehydes, followed by cross-link formation by reaction of either (a) 2 aldehydes or (b) 1 aldehydes and 1 $\varepsilon$-amino group on adjacent molecules

FIGURE 28-6 Collagen biosynthesis. (Reprinted with permission from Wolff K et al. Fitzpatrick's Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)
TABLE 28-5 Distribution of Types of Collagens

<table>
<thead>
<tr>
<th>Collagen</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Skin, bone, tendon, dentin (80% of total adult collagen)</td>
</tr>
<tr>
<td>II</td>
<td>Cartilage, vitreous</td>
</tr>
<tr>
<td>III</td>
<td>Blood vessels, gut, fetal skin (predominant cartilage), chorioamnion</td>
</tr>
<tr>
<td>IV</td>
<td>Basement membrane (lamina densa), epidermal appendages, blood vessels</td>
</tr>
<tr>
<td>V</td>
<td>Wide spread except in hyaline cartilage</td>
</tr>
<tr>
<td>VI</td>
<td>Aortic intima, placenta</td>
</tr>
<tr>
<td>VII</td>
<td>Anchoring fibrils, amnion</td>
</tr>
<tr>
<td>VIII</td>
<td>Endothelial cells, cornea</td>
</tr>
<tr>
<td>IX</td>
<td>Cartilage</td>
</tr>
<tr>
<td>X</td>
<td>Cartilage (hypertrophic)</td>
</tr>
<tr>
<td>XI</td>
<td>Cartilage</td>
</tr>
<tr>
<td>XII</td>
<td>Cartilage, fibroblasts, FACIT collagen, perichondrium, periosteum, cornea</td>
</tr>
<tr>
<td>XIV</td>
<td>Cartilage, skin, tendons, muscle, placenta, FACIT collagen</td>
</tr>
<tr>
<td>XV</td>
<td>Placenta, basement membrane</td>
</tr>
<tr>
<td>XVI</td>
<td>Placenta</td>
</tr>
<tr>
<td>XVII</td>
<td>Hemidesmosomes (bullous pemphigoid antigen 2)</td>
</tr>
<tr>
<td>XVIII</td>
<td>Placenta, liver, kidney, basement membrane</td>
</tr>
<tr>
<td>XIX</td>
<td>Rhabdomyosarcoma, basement membrane</td>
</tr>
</tbody>
</table>

- Consists of several types of proteoglycans
- Proteoglycans (PGs)
  - Macromolecule with a core of protein and covalently attached glycosaminoglycans (GAGs)
  - Abundance of hydroxyl, carboxyl, and sulfate groups make proteoglycans hydrophilic and polyanionic; this creates an intensely hydrated molecule that can bind up to 1000 times of its own volume
  - This hydration affects volume and compressibility of the dermis
  - PGs also play a role in binding growth factors and acting as adhesion sites for other molecules
- Glycosaminoglycans—repeating units of disaccharides (Table 28-8)
- Skin conditions associated with GAG is:
  - Mucopolysaccharidoses (Hunter's, Hurler's, San Filipo) result from defective lysosomal enzymes; the defect causes accumulation of GAGs in many tissues
  - Aging results in increases of dermatan sulfate and decreases in chondroitin-6-sulfate
  - In wound healing, hyaluronic acid increases shortly after injury and then decreases as chondroitin sulfate increases

MELANOCYTES

- Melanocytes are derived from neural crest cells
- Melanocyte function, development, and differentiation are under the control of the paired box (PAX3) and the microphthalmia-associated transcription factor (MITF) genes. (Mutations in PAX3 and MITF results in Waardenburg syndrome.)
- Melanocytes migrate dorsoventrally in the eighth week of fetal development
- Melanin synthesis begins in the head region in the third month of fetal development
- Melanin is also found in the retina, uvea, cochlea/vestibular apparatus, and leptomeninges; therefore, diseases of skin pigmentation also may have abnormalities in these areas
- In all races, density of melanocytes is a consistent ratio of about one melanocyte for every ten keratinocytes
- Melanocytes reside in the basal layer and send dendrites containing melanosomes (containing the pigment melanin) into contact with keratinocytes
- Melanocytes do not form desmosomes with adjacent keratinocytes; they may form contact via E-cadherin adhesion molecules
- Melanocytes do not form hemidesmosomes with the basement membrane
- Melanosomes
  - Melanosomes are secretory organelles developed from specialized exocrine cells of neural crest origin

GROUND SUBSTANCE

- Component of connective tissue of dermis
- Consistency of a viscous solution or thin gel
- Stains with PAS or with toluidine blue

- Elastase-like metalloproteases—degrade soluble elastin, oxytalan, and elaunin fibers; cannot degrade insoluble elastases; requires calcium
- Diseases with elastic fiber abnormalities (Table 28-7)
Few filaments present

Stage II—melanosome
- Eumelanosomes with oval, lamellar structure
- Pheomelanosomes with round, irregular structure
- Start of melanin deposition
- Tyrosinase activity

Stage III—melanosome
- Partially melanized
- Decrease in tyrosinase activity
- Acid phosphatase present
- Stage IV—melanosome

Epidermal melanin unit: each melanocyte secretes melanosomes into a set number of keratinocytes (approximately 36)

Differences in skin pigmentation are due to differences in size and distribution of melanosomes
- Dark = small and single melanosomes
- Light = small and grouped melanosomes

Four stages of melanosome development
- Stage I—premelanosome
  ▲ Round in shape
  ▲ No organized structure
- Stage II—melanosome
- Stage III—melanosome
- Stage IV—melanosome

### TABLE 28-6 Heritable Connective Tissue Diseases With Cutaneous Involvement

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance*</th>
<th>Mutated Genes‡</th>
<th>Affected Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>AD, AR</td>
<td>COL1A1, COL1A2, COL3A1, COL5A1, COL5A2</td>
<td>α Chains of types I, III, and V collagens</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>AD, AR</td>
<td>COL1A1, COL1A2</td>
<td>α1 and α2 Chains of type I collagen</td>
</tr>
<tr>
<td>Cutis laxa</td>
<td>AD, AR, XR†</td>
<td>ELN MNK-1 (ATP7A)</td>
<td>Elastin ATP-dependent copper transporter</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>AR</td>
<td>CBS</td>
<td>Cystathionine β-synthase</td>
</tr>
<tr>
<td>Menkes’ syndrome</td>
<td>XR</td>
<td>MNK-1 (ATP7A)</td>
<td>ATP-dependent copper transporter</td>
</tr>
<tr>
<td>Focal dermal hypoplasia</td>
<td>XD</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis (shagreen patches)</td>
<td>AD</td>
<td>TSK-1 TSC 1 plus 2</td>
<td>Hamartin 1 Tuberen</td>
</tr>
<tr>
<td>Familial cutaneous collagenoma</td>
<td>AD</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Epidermolysis bullosa VII and XVII collagens</td>
<td>AD, AR</td>
<td>COL7A1, COL17A1</td>
<td>α1 Chains of types VII and XVII collagens</td>
</tr>
</tbody>
</table>

* AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XR, X-linked recessive; ND, not determined.
† Most cases involve abnormalities in the elastic fibers, and in some cases, mutations in the elastin gene (ELN) have been disclosed. Occipital horn syndrome, a copper deficiency syndrome, allelic to the Menkes’ syndrome gene (MNK-1), was previously known as X-linked cutis laxa and also Ehlers-Danlos syndrome IX (see Chap. 154).
‡ For detailed discussion on these genes, see Refs. 4 and 87.

TABLE 28-7  Clinical Features, Histopathology, Inheritance, Associated Biochemical Findings, and Predisposing Clinical Conditions in Cutaneous Diseases With Elastic Fiber Abnormalities*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance†</th>
<th>Clinical Manifestations</th>
<th>Histopathology of Skin</th>
<th>Biochemical Findings‡ Related to Elastic Fibers and Predisposing Clinical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>AR, sporadic§</td>
<td>Yellowish papules coalescing into plaques</td>
<td>Accumulation of pleomorphic and calcified elastic fibers in the mid-dermis</td>
<td>Deposition of calcium apatite crystals, excessive accumulation of glycosaminoglycans on elastic fibers; D-penicillamine treatment; mutations in the ABCC6 gene</td>
</tr>
<tr>
<td>Buschke-Ollendorf syndrome</td>
<td>AD</td>
<td>Dermatofibrosis lenticularis disseminata and osteopoikilosis</td>
<td>Accumulation of interlacing elastic fibers in the dermis</td>
<td>Increased desmosine content in the skin</td>
</tr>
<tr>
<td>Cutis laxa</td>
<td>AR, AD, or NH</td>
<td>Loose, sagging, inelastic skin Pulmonary emphysema Tortuosity of aorta Urinary and gastrointestinal tract diverticuli</td>
<td>Fragmentation and loss of elastic fibers</td>
<td>Decreased desmosine content and reduced elastin mRNA levels; increased elastase activity in some cases; D-penicillamine treatment, inflammatory and urticarial skin lesions (e.g., drug reaction); mutations in the ELN or FBLN5 gene in limited cases</td>
</tr>
<tr>
<td>DeBarys syndrome</td>
<td>AR</td>
<td>Cutis laxa-like skin changes Mental retardation Dwarfism</td>
<td>Rudimentary, fragmented elastic fibers</td>
<td>Reduced elastin mRNA levels</td>
</tr>
<tr>
<td>Wrinkly skin syndrome</td>
<td>AR</td>
<td>Decreased elastic recoil of the skin Increased number of palmar and plantar creases</td>
<td>Decreased number and length of elastic fibers</td>
<td></td>
</tr>
<tr>
<td>Mid-dermal elastolysis</td>
<td>NH</td>
<td>Fine wrinkling of the skin, primarily in exposed areas</td>
<td>Fragmentation and loss of elastin in the mid-dermis</td>
<td>Inflammatory; sun-exposure related</td>
</tr>
<tr>
<td>Anetoderma</td>
<td>NH</td>
<td>Localized areas of atrophic, saclike lesions</td>
<td>Loss and fragmentation of elastic fibers in the dermis</td>
<td>Reduced desmosine content in the lesions; often secondary to inflammatory lesions</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Clinical Manifestations</th>
<th>Histopathology of Skin</th>
<th>Biochemical Findings† Related to Elastic Fibers and Predisposing Clinical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastosis perforans serpiginosa</td>
<td>NH</td>
<td>Hyperkeratotic papules, commonly on the face and neck</td>
<td>Accumulation and transepidermal elimination of elastic fibers</td>
<td>D-Penicillamine–induced abnormalities in elastin cross-linking</td>
</tr>
<tr>
<td>Elastoderma</td>
<td>Unknown</td>
<td>Loose and sagging skin with loss of recoil</td>
<td>Accumulation of pleomorphic elastic material without calcification in the mid- and lower dermis and the subcutaneous tissue</td>
<td></td>
</tr>
<tr>
<td>Isolated elastomas</td>
<td>NH</td>
<td>Dermal papules or nodules</td>
<td>Accumulation of thick elastic fibers in the dermis</td>
<td></td>
</tr>
<tr>
<td>Elastofibroma dorsi</td>
<td>NH</td>
<td>Deep subcutaneous tumor, usually on subscapular area</td>
<td>Accumulation of globular elastic structures encased in collagenous meshwork</td>
<td>Trauma on the lesional area</td>
</tr>
<tr>
<td>Actinic elastosis</td>
<td>NH</td>
<td>Thickening and furrowing of the skin</td>
<td>Accumulation of irregularly thickened elastic fibers in upper dermis</td>
<td>Chronic sun exposure</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td>AD</td>
<td>Skeletal, ocular, and cardiovascular abnormalities, hyperextensible skin; striae distensae</td>
<td>Fragmentation of the elastic structure in the aorta</td>
<td>Mutations in the FBN1 gene Fibrillin 1 protein</td>
</tr>
<tr>
<td>Congenital contractural arachnodactyly</td>
<td>AD</td>
<td>Camptodactyly and joint contractures</td>
<td></td>
<td>Mutations in the FBN2 gene Fibrillin 2 protein</td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>AD</td>
<td>Supravalvular aortic stenosis; velvety skin; dysmorphic facies</td>
<td>Disruption of smooth muscle and matrix relationship affecting blood vessels</td>
<td>Allelic deletion of the ELN gene; contiguous gene deletion syndrome</td>
</tr>
</tbody>
</table>

*Most of these conditions represent a group of diseases with clinical, genetic, and biochemical heterogeneity.
†AD, autosomal dominant; AR, autosomal recessive; NH, not a heritable disease.
‡The biochemical abnormalities have been demonstrated in only a limited number of patients in each group, and it is not known whether the biochemical changes are the same in each patient with given disease.
§Rare cases with a distinct acquired form of pseudoxanthoma elasticum have been described.

**Control of melanin production**
- Pigmentation is either constitutive (level of pigment determined genetically) or facultative (inducible by UV exposure, “tan”)
- Stimulated by melanocyte-stimulating hormone (MSH), which is derived from the larger precursor proopiomelanocortin (POMC); POMC is also the precursor for adrenocorticotropic hormone (ACTH); this explains the hyperpigmentation of Addison’s disease
- Stimulated by estrogens and progesterones
- Melanocytic protein associated conditions: (see Chapter 9: Pigmentary Disorders)

**Endothelial Cells**

- Flattened epithelial-like cells
- Thickness < 10 μm
- Usually form a continuous monolayer with gap junctions between cells
- Endothelial cells rest on a basal lamina of laminin 1, collagens, fibronectin, nidogen (entactin), and heparan sulfate
- Endothelial cells have a polarized structure with differences between apical (lumen) aspect and basal surface
- Integrin receptors for ground substance/matrix molecules on basal surface
- Leukocyte receptors on apical (lumen) side
- Endothelial cells have a number of specialized structures
  - Weibel-Palade bodies (WPBs)
    - Contain von Willebrand factor (vWF), P selectin, and CD 63:
      - P selectin (CD62P) mediates leukocyte adhesion

**TABLE 28-8 Glycosaminoglycans**

<table>
<thead>
<tr>
<th>Glycosominoglycan</th>
<th>Distribution and Collagen Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid</td>
<td>Found in dermins, umbilical cord, synovial fluid, cartilage, vitreous No interaction with collagen High levels associated with nonscarring wound healing (i.e., fetal)</td>
</tr>
<tr>
<td>Dermatan sulfate</td>
<td>Found in structures formed by collagen fibers; dermins, tendon, ligaments, heart valves, arteries, fibrous cartilage Interaction with type I collagen Decorin—small dermataan sulfate, found along surface of collagen fibrils and assist with lateral fibrils into fibers; low levels in hypertrophic scars</td>
</tr>
<tr>
<td>Chondroitin 4- to 6-sulfate</td>
<td>Hyaline and elastic cartilage, arterial medial layer, nucleus pulposus Interact with type II collagen</td>
</tr>
<tr>
<td>Heparan sulfate</td>
<td>Basement membrane, structures with reticular fibers: smooth muscle, liver, spleen nerves Interact with type III collagen</td>
</tr>
</tbody>
</table>

- Complete melanization
- Very little tyrosinase activity
- Acid phosphatase present

**Pathway of melanin formation**
- Melanosome structure is formed within melanocytes
- Tyrosinase enzyme necessary for melanin formation is formed from Golgi apparatus of melanocyte
- Tyrosinase is transported to melanosome and begins melanin formation
- Melanosome is transferred to keratinocyte
- Melanosome is degraded during ascent to cornified layer
- Melanin is ultimately removed with loss of stratum corneum

**Melanin**
- Pigment that absorbs UV and visible light over a wide range of wavelengths without a distinct peak of absorption
- Able to absorb free radicals
- Tyrosinase is the main enzyme for melanin formation and catalyzes the first step: hydroxylation of tyrosine to dopa
- Tyrosinase is copper-dependent
- Tyrosine → dopa → dopaquinone: both these steps are catalyzed by tyrosinase
- The type of melanin produced depends on presence of other factors
  - Eumelanin—brown-black pigment
    - Formed if divalent cations are present with dopaquinone
    - Found in dark, oval melanosomes
  - Pheomelanin—yellow-red pigment
    - Formed if cysteine (or glutathione) is present with dopaquinone
    - Found in round, lamellar melanosomes

**Eumelanin**
- Formed if divalent cations are present with dopaquinone
- Found in dark, oval melanosomes

**Pheomelanin**
- Formed if cysteine (or glutathione) is present with dopaquinone
- Found in round, lamellar melanosomes

**Acid phosphatase present**
However, the desmosomal protein desmoplakin is located to complexus adherents and participates in a distinct type of cell contact separate from desmosomes.

Endothelial cells play a critical role in cutaneous inflammation.

Endothelial cells produce a number of cytokines.

- **IL-1**
  - Responsible for upregulation of ICAM-1, VCAM-1, and E-selectin
  - Induces platelet-activating factor, prosta-glandins, and nitric oxide
  - Activates T cells, serves as chemoattractant for lymphocytes, and stimulates proliferation of B cells

- **IL-6**: has few effects on normal endothelium but plays a critical role as a growth factor for Kaposi sarcoma neoplasms
- **IL-8**: likely plays a role as a chemoattractant for inflammatory cells

- **G-CSF**
- **M-CSF**
- **GM-CSF**

Endothelial cells express a variety of adhesion molecules that play a vital role in inflammation.

- **ICAM-1** (binds LFA-1 on leukocytes)
- **ICAM-2** (binds LFA-1 on leukocytes)
- **E-selectin** (binds memory T cells, especially in chronic inflammation)
- **P-selectin** (binds Lewis X, which is important in initial binding of PMNs to endothelium)
- **VCAM-1** (binds $\alpha_4\beta_1$ integrin of leukocytes)
- **MHC I, II** (bind CD8 and CD4 on T cells)
- **LFA-3** (binds CD2 on T cells)
- **CD 44** (binds hyaluronic acid)

**SWEAT GLANDS: ECCrine AND APOCRINE**

- **Eccrine glands**
  - Primary function of the eccrine unit is thermoregulation: cooling effects of evaporation of sweat on the skin surface
  - Highest density of eccrine glands is seen on the palms, soles, and axillae
  - Consists of two segments: secretory coil and a duct
  - Coil: composed of three distinct cell types: clear (secretory), dark (mucoid), and myoepithelial cells
  - Duct: outer ring of peripheral cells (basal) and an inner ring of luminal cells (cuticular); the coiled duct (proximal) is more active than the distal (straight) portion
Hypohidrosis: decreased eccrine sweating; anhidrosis: absent sweating seen in hereditary disorders such as the ectodermal dysplasias or in acquired conditions such as heat stroke or heat exhaustion

Miliaria crystalline: Excessive heat and humidity cause duct obstruction within the stratum corneum, asymptomatic superficial vesicles, and no surrounding inflammation

Miliaria rubra (prickly heat): Obstruction is found deeper in the epidermis; pruritic or tender red macules or papules that are often located on the thorax and neck

Miliaria profunda: duct obstruction at or below the dermal-epidermal junction; asymptomatic skin-colored papules

Apocrine miliaria: Inflammation follows intraepidermal rupture of apocrine ducts

Hidradenitis suppurativa: intense inflammation owing to follicular obstruction

Syringomas: most common benign sweat gland tumor; skin-colored papules on lower eyelids of adults

**MATRIX METALLOPROTEINASES**

Group of zinc-dependent enzymes (endopeptidases) that degrade varying components of the extracellular matrix in both normal and diseased tissue

Includes collagenases, gelatinases the stromelysins, the matrilysins, metalloelasstases, enamelysins, and the membrane-type matrix metalloproteinases (MMPs) (Table 28-9)

Synthesized as inactive proenzymes; limited proteolysis or treatment with an organomercurial compound sets up a chain of events causing conversion to the fully active form by complete removal of a propeptide (gelatinase A, MMP-2, can only be activated by the second mechanism)

Cells secrete extracellular matrix (ECM) metalloproteinases in a complex pattern of response to multiple growth factors and oncogenes

SCCs can secrete MMP-13 (collagenase-3), which preferentially cleaves type II collagen and gelatin, mediating their invasiveness

Tissue inhibitors of metalloproteinases (TIMPs) are considered to be the major tissue inhibitors; these are secreted proteins that are tightly regulated during tissue remodeling and physiologic processes

Inhibitors can modulate proteolysis once proenzymes have been activated

α2-Macroglobulin, a nonspecific antiproteinase, accounts for more than 95% of the inhibitory activity
### TABLE 28-9 Matrix Metalloproteinases

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>MMP Number</th>
<th>Alternate Name</th>
<th>Proenzyme Mol. Wt.</th>
<th>Known Matrix Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial collagenase</td>
<td>MMP-1</td>
<td>Type 1 collagenase</td>
<td>52,000</td>
<td>Collagens I, II, III, VII, VIII, X, entactin, tenascin, aggrecan, denatured collagens, IL-1β, myelin basic protein, L-selectin</td>
</tr>
<tr>
<td>Neutrophil collagenase</td>
<td>MMP-8</td>
<td></td>
<td>75,000</td>
<td>Collagens I, II, III, V, VII, VIII, X, gelatin, aggrecan, fibronectin</td>
</tr>
<tr>
<td>Collagenase-3</td>
<td>MMP-13</td>
<td></td>
<td>52,000</td>
<td>Collagens I, II, IV, IX, X, XIV, aggrecan</td>
</tr>
<tr>
<td>Gelatinase A</td>
<td>MMP-2</td>
<td>72-kDa type IV collagenase</td>
<td>72,000</td>
<td>Denatured collagens, collagens IV, V, VII, X, XI, XIV, collagen 1, species-dependent, elastin, fibronectin, laminin, aggrecan, myelin basic protein</td>
</tr>
<tr>
<td></td>
<td>MMP-9</td>
<td>92-Kd type IV collagenase</td>
<td>92,000</td>
<td>Denatured collagens, collagens IV, V, VII, X, elastin, entacin, aggrecan, fibronectin, osteonectin, IL-1β, plasminogen, myelin basic protein</td>
</tr>
<tr>
<td>Stromelysin-1</td>
<td>MMP-3</td>
<td>Proteoglycanase</td>
<td>57,000</td>
<td>Proteoglycan core protein, laminin, fibronectin collagens I, IV, V, IX, X, XI, gelatin, elastin, tenasin, aggrecan, myelin basic protein, entactin, decorin, osteonectin</td>
</tr>
<tr>
<td>Stromelysin-2</td>
<td>MMP-10</td>
<td>Transin-2</td>
<td>55,000</td>
<td>Proteoglycan core protein, collagens III, IV, V, laminin, fibronectin, elastin, aggrecan</td>
</tr>
<tr>
<td>Stromelysin-3</td>
<td>MMP-11</td>
<td></td>
<td>61,000</td>
<td>α1 Proteinase inhibitor</td>
</tr>
<tr>
<td>Martrilsyn</td>
<td>MMP-7</td>
<td>PUMP Matrilysin-1</td>
<td>28,000</td>
<td>Collagen IV, denatured collagens, laminin, fibronectin, elastin, aggrecan, tenascin, myelin basic protein</td>
</tr>
<tr>
<td>Matrilsyn-2</td>
<td>MMP-26</td>
<td>Endometase</td>
<td>28,000</td>
<td>Gelatin, α1 proteinase inhibitor</td>
</tr>
<tr>
<td>Membrane type matrix metalloproteinase-1</td>
<td>MMP-14</td>
<td>MT1-MMP</td>
<td>63,000</td>
<td>Progelatinase A, denatured collagen, fibronectin, laminin, vitronectin, entactin, proteoglycans</td>
</tr>
<tr>
<td>Membrane type matrix metalloproteinase-2</td>
<td>MMP-15</td>
<td>MT2-MMP</td>
<td>72,000</td>
<td>Progelatinase A</td>
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<tr>
<td>Membrane type matrix metalloproteinase-3</td>
<td>MMP-16</td>
<td>MT3-MMP</td>
<td>64,000</td>
<td>Progelatinase A</td>
</tr>
<tr>
<td>Membrane type matrix metalloproteinase-4</td>
<td>MMP-17</td>
<td>MT4-MMP</td>
<td>70,000</td>
<td>Unknown</td>
</tr>
<tr>
<td>Membrane type matrix metalloproteinase-5</td>
<td>MMP-24</td>
<td>MT5-MMP</td>
<td>73,000</td>
<td>Progelatinase A</td>
</tr>
</tbody>
</table>
TABLE 28-9 (Continued)

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>MMP Number</th>
<th>Alternate Name</th>
<th>Proenzyme Mol. Wt.</th>
<th>Known Matrix Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane type matrix metalloproteinase-6</td>
<td>MMP-25</td>
<td>MT6-MMP</td>
<td>63,000</td>
<td>Unknown</td>
</tr>
<tr>
<td>Metalloelastase</td>
<td>MMP-12</td>
<td></td>
<td>54,000</td>
<td>Elastin, collagen IV, vitronectin, plasminogen, laminin, entactin, fibrinogen, fibrin, fibronecint</td>
</tr>
<tr>
<td>Enamelysin</td>
<td>MMP-20</td>
<td></td>
<td>54,000</td>
<td>Amelogenin, aggrecan</td>
</tr>
<tr>
<td>MMP-19</td>
<td>MMP-19</td>
<td>RASI-1</td>
<td>57,000</td>
<td>Gelatin, aggrecan, fibronectin</td>
</tr>
<tr>
<td>MMP-21</td>
<td>MMP-21</td>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>MMP-22</td>
<td>MMP-22</td>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>MMP-23</td>
<td>MMP-23</td>
<td></td>
<td>44,000</td>
<td>Unknown</td>
</tr>
<tr>
<td>Epilysin</td>
<td>MMP-28</td>
<td></td>
<td>56,000</td>
<td>Unknown</td>
</tr>
</tbody>
</table>


HAIR DEVELOPMENT

See Chapter 1: Hair Findings.

NAIL DEVELOPMENT

See Chapter 3: Nail Findings.

QUIZ

Questions

1. Renewal of the epidermis takes approximately:
   A. 13–14 days
   B. 1–14 days
   C. 14–26 days
   D. 26–28 days
   E. 28–32 days

2. Fibulin-2 is capable of binding
   A. Fibrinogen
   B. Versican
   C. Aggrecan
   D. All of the above
   E. None of the above

3. Stratum lucidum is a layer present between the granular and cornified layer found in:
   A. Palmoplantar skin
   B. Mucosa
   C. Nail
   D. Axillary skin
   E. Scalp skin

4. Seventy percent of the cornified cell envelope consists of:
   A. Profillagrin
   B. Loricrin
   C. Involucrin
   D. Filaggrin
   E. Keratin

5. Krause end bulbs or mucocutaneous end organs are found in:
   A. Mucocutaneous junction
   B. Hands and soles
   C. Nipples/areola
   D. Scalp skin
   E. Nail apparatus

6. Which is the only protein known to be present in both desmosomes and adherens junctions:
   A. Desmplakin
   B. Integrin
   C. Desmocollins
   D. BP antigen 2 (180kd)
   E. BP antigen 1 (230kd)
7. The postganglionic neurotransmitter mediating eccrine sweat production is:
   A. Acetylcholine
   B. Epinephrine
   C. Dopamine
   D. Norepinephrine
   E. Serotonin

8. Matrix metalloproteinases can be upregulated during normal development and physiologic tissue repair. Under pathologic conditions, squamous cell carcinomas can secrete:
   A. Collagenase-1
   B. Stromelysin-3
   C. MMP-13
   D. Gelatinase-9
   E. Matrilysin-2

9. Which type of collagen is found in cartilage?
   A. I
   B. III
   C. XI
   D. XV
   E. XVII

10. At what week of development do neural crest derived melanocytes produce melanin?
    A. 8th week
    B. 10th week
    C. 12th week
    D. 16th week
    E. 18th week

**Answers**

1. D. It takes 13–14 days for maturation of keratinocytes from the basal layer to the corneum and another 13–14 days for shedding.

2. D. Fibulins are calcium-binding extracellular matrix proteins that do not form large aggregates but are capable of joining other supramolecular structures. Fibulin-2 is capable of binding fibrinogen, fibronectin, nidogen, proteoglycans, aggrecan, and versican.

3. A. The layer appears as an electronlucent zone and contains nucleated cells.

4. B. Loricrin accounts for the majority of proteins in the cornified cell envelope. It is insoluble and is highly hydrophobic. It is cross-linked by transglutaminase-3 to form homodimers and heterodimers with other proteins to increase solubilization.

5. A. These structures are found at the vermilion border of the lips, glans penis, and clitoris.

6. A. Desmoplakin bind intermediate filaments at their carboxy-terminal site. In adherens junctions, the N-terminus of desmoplakin can bind plakoglobin and plakophilin and in desmosomes, it can bind plakoglobin, plakophilin, and desmocollin.

7. A. Eccrine glands are highest in density in the palms, soles, and axillae. They are principally mediated by cholinergic stimulation.

8. C. Invasive SCCs can secrete MMP-13 (collagenase-3) which preferentially cleaves type II collagen and gelatin.

9. C. Many types of collagens can be found in cartilage including collagen II, IX, X, XI, XII, and XIV.

10. C. At the 8th week of fetal development melanocytes develop from the neural crest cells. It is not until the 12th week that melanocytes begin synthesis of melanin beginning in the head region.

**REFERENCES**


CHAPTER 29

BIOSTATISTICS

ALICE CHUANG
TAHNIAT S. SYED
ASRA ALI

VARIABLE

- In a clinic study, the outcome may or may not be a number, for example, the “success” or “failure” of a drug treatment. However, we often want to represent outcomes as numbers
- A random variable is a function that associates a unique numerical value with every outcome of a study. The value of the random variable will vary over time or vary from individual to individual
  - There are two types of random variable—discrete and continuous
  - A random variable has either an associated probability distribution (discrete random variable) or probability density function (continuous random variable)

BINOMIAL DISTRIBUTION

- The binomial distribution is the discrete probability distribution of the number of successes in a sequence of \( n \) independent “yes/no” or “success/failure” outcome of an individual, each of which yields “Yes” or “Success” with probability \( p \)

NORMAL (GAUSSIAN) DISTRIBUTION

- The normal distribution, also called the Gaussian distribution, is an important family of continuous probability distributions, applicable in many fields. It can be:
  - Graphically categorized by a bell-shaped curve (Fig. 29-1)
  - The most frequently occurring value is in the middle of the range, and other probabilities tail off symmetrically in both directions
  - The mean and median are identical

- The probability that a measurement will fall within 1.96 standard deviations of the mean is 0.95
- Many statistical tests rely on the assumption that analyzed data are derived from a population that has a normal (Gaussian) distribution. Regression, correlation, t tests, and analysis of variance all depend on a normal distribution assumption

STATISTICAL ANALYSIS

Descriptive Statistics

- Descriptive statistics are used to describe the basic features of the data in a study. They provide simple summaries about the study variables, such as central tendency, variability, skewness, kurtosis, and associations of variables

Continuous Variable

- Central tendency
  - Mean
    - Arithmetic average = sum of all the values divided by the number of observations
    - Outliers weigh heavily on the mean but it does provide a central value representative of the entire collection of numbers
  - Median
    - Middle value of a set of data; where 50% of the values are below this point, and 50% of the values are above it
    - It provides a central value that is not influenced by high and low extremes in the data
  - Mode
    - Represents the value occurring most frequently in a data set
    - A data set has no mode when all the values appear in the data with the same frequency. A data set has multiple modes when two or more values appear with the same frequency
• Variability
  • Variance
    – A measure of the spread or variability of a distribution
    – Variance \( V(X) \) or \( \sigma^2 \) equals the average value of the squared difference between measurements and their mean
    – Variance is small if many data points are close to their mean and is zero if all data points are equal
    – Variances are typically useful only when the measurements follow a normal or at least a symmetric distribution
  • Standard deviation (SD)
    – The standard deviation, also called the root-mean-square deviation, is equal to the square root of the variance
    – It is also a measure of the spread of a distribution and has the same measuring scale as the random variable
    – Standard deviation has a simple interpretation only if the distribution of the random variable is Gaussian (normal), the 95% of the outcomes is expected to be within 2 standard deviations of the mean; the 68% of outcomes is within 1 SD, and 3 SDs holds 99.7% of values (see Fig. 29-1)
  • Standard error of mean (SEM)
    – The standard deviation of sample mean is called standard error of mean (SEM)
    – Sample mean is an arithmetic average of set of samples. It is a random variable which has a distribution with the same mean as the samples and the standard deviation equal to standard deviation (SD) of samples divided by squared root of sample size
    – Standard error of mean falls as the sample size increases
    – Standard error of mean increases as standard deviation increases
  – Standard deviation versus standard error of mean: how widely scattered some measurements are versus evaluation of the accuracy around the estimate of the mean measurement
  • Range
    – A smallest length contains all the data
    – Range = largest measurement – smallest measurement
  • Skewness
    – Positively skewed data are represented by a distribution that has a long right tail while Negatively skewed data are represented by a distribution that has a long left tail (Fig. 29-1)
  • Kurtosis
    – Positive when the tails are narrow with a steep peak and is negative when the data distribution curve has wide tails with a flat peak
  • Association
    • Correlation coefficient
      – Measures how related two values are
      – The range of the coefficient is -1 to +1
      – The strength of the relationship between two variables is determined by how far the correlation coefficient is from zero (absolute value)
      – Zero equals no association, +1 equals a perfect positive correlation, and -1 equals a perfect negative correlation

Discrete Variable
• Frequency
  • The number of times the event occurred in a study
• Probability and percentage
  • A number, between 0 and 1, that indicates how likely an event is to occur on the basis of the number of events per the number of trials
  • Probability \( (p) = \frac{\text{frequency}}{\text{total number of trials}} \)
  • Percentage = \( p \times 100 \)
Odds
- Ratio of the probability of an event occurring (p) to the probability of the event not occurring (1−p)
- Odds = p / (1−p)

Odds ratio
- The ratio of the odds of an event occurring in one group to the odds of it occurring in another group
- These groups might be control and treated, or any other two groups classification
- If the probabilities of the event in each of the groups are \( p_1 \) (first group) and \( p_2 \) (second group), then the odds ratio is:

\[
\text{Odds ratio} = \frac{\frac{p_1}{1-p_1}}{\frac{p_2}{1-p_2}}
\]

Confidence Interval (Fig. 29-1)
- Estimated range of values which is likely to include an unknown population parameter
- The probability that the confidence interval produced will contain the true parameter value is through the selection of a confidence level for an interval
- Common choices for the confidence level are 0.90, 0.95 (most commonly used), and 0.99
- If the 95% confidence limits for an unknown quantity are \([a; b]\), then 95% of similarly constructed confidence limits in repeated samples from the same population would contain the unknown quantity
- Therefore, there is 95% confidence that the unknown value is in the interval \([a; b]\)
- Decreasing the level of confidence, results in a decrease in the size of the corresponding interval
- Increasing the sample size will decrease the length of the confidence interval without reducing the level of confidence

Hypothesis Testing (Table 29-1)

**Null Hypothesis (H₀)**
- The assumption that there is no difference in parameters (mean, ratio, variance, etc.) between two or more entities represents a theory that has not been proven
- Any observed difference in samples is due to chance or sampling error, while the alternative hypothesis asserts that there is a significant systematic association
- Assumes that a hypothesis may not be correct (i.e., no effect of a treatment) and attempts to gather evidence against that assumption (i.e., tries to reject \( H_0 \) and accept the alternative hypothesis)
- Statisticians often use \( H_0 \) to indicate the statistical hypothesis being tested

**Type I Error (Alpha)**
- In hypothesis testing, rejecting the null hypothesis when it is in fact true; results in a false positive study,
- For example, the testing result from observed data shows a difference where the true difference (unob servable) does not exist
- Probability of a type I error: \( P(\text{type I error}) = \text{significance level} = \alpha \)
- Alpha level is the probability of a type I error; the significance is usually set at 0.05

**Type II Error (Beta)**
- In hypothesis testing, failing to reject a false null hypothesis; results in a false-negative study that rejects a true alternative hypothesis
- For example, a study shows that no difference exists when in fact it does
- Probability of a type II error: \( P(\text{type II error}) = \beta \)
- May occur when the sample size is too small [it always occurs, but you can control (minimize) it by increasing sample size]
- Type I and type II errors are inversely related; for any set of data, the smaller the risk of one, the higher the risk of the other. In general, we fix the

<table>
<thead>
<tr>
<th>TABLE 29-1 Understanding Hypothesis Testing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Results</td>
</tr>
<tr>
<td>Treatments Are Really Not Different</td>
</tr>
<tr>
<td>Treatments Are Really Different</td>
</tr>
<tr>
<td>Treatments are not different</td>
</tr>
<tr>
<td>Treatments are different</td>
</tr>
</tbody>
</table>

*Note: Only pertains to outcomes of a randomized controlled trial.
probability of type I error and minimize the type II error by increasing sample size

**Power (Pw)**
- Definition: probability of finding a significant association if one truly exists (probability that the test will reject a false null hypothesis)
- \( 1 - \beta = Pw \) (therefore, as the power increases, the chances of a type II error decreases)
- Power is commonly set at 80 or 90%; maximum power a test can have is 1, the minimum is 0. The goal of a study is to have the power as close to 1 as possible
- The power of a study depends on: alpha, beta, effect size (small effect size decreases the power), and sample size (a small sample size, decreases the power of a study). The power is also affected by variance (large variance, decreases power of a study)

**Diagnostic Performance (Table 29-2)**
- A diagnostic test can result in the following outcomes:
  - **True positive**: the test is positive and the disease is present
  - **False positive**: the test is positive and the disease is absent
  - **True negative**: the test is negative and the disease is absent
  - **False negative**: the test is negative and the disease is present

**Test Sensitivity**
- General: assesses the validity of a test
- Definition: the ability of a screening test to identify correctly those who have the disease: \( \text{Sensitivity} = TP/(TP+FN) \)
- Properties: a test with high sensitivity has few false-negative results, independent of disease prevalence in the community

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>A (TP)</td>
</tr>
<tr>
<td>-</td>
<td>C (FN)</td>
</tr>
</tbody>
</table>

Note: TN, true negative; FN, false negative; TP, true positive; FP, false positive; sensitivity = TP/(TP + FN); specificity = TN/(TN + FP).

**Test Specificity**
- General: assesses the validity of a test
- Definition: the ability of a screening test to identify correctly those who do not have the disease: \( \text{Specificity} = TN/(TN + FP) \)
- Properties: a test with high specificity has few false-positive results, independent of disease prevalence in the community

**Positive Predictive Value (PPV)**
- General: assesses the reliability of a positive test
- Definition: the probability that a patient has a disease when the test for the disease is positive: \( \text{PPV} = TP/(TP + FP) \)
- Properties
  - Affected by two factors
    - Disease prevalence: higher disease prevalence results in a higher PPV
    - Specificity (only when disease is infrequent): higher specificity results in a higher PPV (with infrequent diseases)

**Negative Predictive Value (NPV)**
- General: assesses the reliability of a negative test
- Definition: probability that the patient does not have the disease when the results are negative: \( \text{NPV} = TN/(TN + FN) \)
- Properties
  - Affected by two factors
    - Disease prevalence: lower disease prevalence results in a higher NPV
    - Test sensitivity effect is minimized at a low prevalence and results in a more reliable negative test

**Measures of Effect**
- **Probability**: a number, between 0 and 1, that indicates how likely an event is to occur on the basis of the number of events per the number of trials
- **Odds**: ratio of the probability of an event occurring to the probability of the event not occurring
  - \( \text{Odds} = \text{probability}/(1 - \text{probability}) \)

**Relative Risk or Risk Ratio (RR)**
- Definition: ratio of the incidence of disease in exposed individuals to the incidence of disease in non-exposed individuals
- Can be determined in a prospective cohort study
- Relative risk may be the same as odds ratio for small probabilities
- Meaning of results:
  - If RR = 1: there is no evidence for increased risk in exposed individuals compared with nonexposed individuals
If RR > 1: the risk in exposed individuals is greater than the risk in nonexposed (i.e., there is a positive association).

If RR < 1: the risk in exposed individuals is less than the risk in nonexposed (i.e., there is a negative association; suggests a “protective” effect).

**Outcomes Assessment**

**Reliability**
- Precision of a test
- Measures the reproducibility and consistency of a test
- Reduced by random error

**Test Validity**
- Accuracy of a test
- Measures the trueness of measurement
- Reduced by systematic error
- Types
  - **Internal validity**: a study with no major methodological problems thus minimizing the error in correctly finding a causal relationship between the experimental treatment and the observed effect.
  - **Construct validity of cause**: infers that the observed effect is attributable to the specific experimental intervention and not other variables of effect; support for the intended interpretation of the variables.
  - **External validity**: relates to the generalizability of the study. Could the observed effect be produced in other settings, beyond the studied populations and at other times?
  - **Statistical conclusion validity**: are the conclusions reached justifiable on statistical grounds? Does the effect generalize to the population from which the sample was drawn?

**Study Design**

**Multivariable Model/Multivariate Analysis**
- A model relating multiple predictor variables (risk factors, treatments, etc.) to a single response or dependent variable
- It is used to examine the relationship between a single response and a dependent variable and multiple predictor variables
- One can ascertain the relationship between a predictor variable and the dependent variable independently and account for the effects of other predictor variables

**Intention to Treat**
- Subjects are analyzed according to the treatment group to which they were assigned, even if they did not receive the intended treatment or received only a portion of it
- This analysis reflects real-world nonadherence to treatment

---

**Odds Ratio (OR) (Table 29–3)**
- Used as a measurement in a retrospective case-control study
- Definition: Ratio of the odds of cases that have the disease to the odds that controls have the disease
- Measure of whether a certain exposure is associated with a specific disease
- The OR approximates the RR when
  - Cases studied are representative of people with disease in the population
  - Controls studied are representative of people without disease in the population
  - The disease being studied does not occur frequently

**Statistics Equations Review**
- Sensitivity = A/(A + C)
- Specificity = D/(B + D)
- PPV = A/(A + B)
- NPV = D/(C + D)
- Relative risk = [A/(A + B)]/[C/(C + D)]
- Odds ratio = (A × D)/(B × C)
- Attributable risk = [A/(A + B)]−[C/C + D)]

**P-Value (Probability Value)**
- The level of statistical significance
- Alpha or type I error (incorrect rejection of the null hypothesis)
- Definition: probability that a difference between two groups could have arisen by chance alone; the estimated probability of rejecting the null hypothesis of a study question when that hypothesis is true
- Commonly set at 0.05: this means that the probability that the difference between the two groups occurred by chance alone was 0.05, or 1 in 20

---

**TABLE 29-3 Calculating Odds Ratio**

<table>
<thead>
<tr>
<th>Disease Develops</th>
<th>Disease Does Not Develop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>A</td>
</tr>
<tr>
<td>Not exposed</td>
<td>C</td>
</tr>
</tbody>
</table>

Note: OR = AD/BC.
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Nonresponder bias: results if the survey results differ substantially from those that would have been generated if the response rate was 100%.

Interviewer bias: results from the personal prejudice of the individual conducting the interview.

The following characteristics of studies can decrease bias: randomization (minimizes selection bias), blinding, matching. Prospective studies may decrease the chance of patient selection bias.

**CONFOUNDING**

Variable that has independent associations with both the independent (predictor) and dependent (outcome) variables.

Examples include gender, age, socioeconomic status, and co-morbidities.

**RANDOMIZATION**

Best means of avoiding allocation bias.

Balances the groups for prognostic factors (i.e., disease severity).

Eliminates overrepresentation of any one characteristic within the study group.

Should be concealed from the clinicians and researchers of the study to help eliminate conscious or unconscious bias.

**BLINDING**

People involved in the study do not know which treatments are given to which patients.

With double blinding, neither the patient nor the clinician knows which treatment is being administered.

Eliminates bias and preconceived notions as to how the treatments should be working.

**SAMPLE SIZE**

A sample is a subgroup of the population (population consists of every person who fits a given set of respondent criteria).

Ideally the sample is selected randomly and is comparable with the population.

Inclusion criteria defines the survey’s target population.

Specifications needed to estimate sample size in a randomized trial:

- Differences in response rates to be detected.
- Estimate of the response rate in one of the groups.
- Level of statistical significance (alpha): the lower the significance level, the greater the required sample size.
- Level of power (1 – beta): the higher the power specification, the greater the required sample size.
- Whether test should be one- or two-tailed.

**DISEASE INCIDENCE**

- Number of new disease cases per population at risk.
- The number of new disease cases in the population during a specific time divided by the number of individuals at risk of developing the disease during that specific time.
- High incidence implies high disease occurrence.
- Low incidence implies low disease occurrence.
- Measured over a given time interval, data are usually obtained from a prospective cohort study.
- Determines probability of developing a specific disease.
- Used to detect etiologic factors.

**DISEASE PREVALENCE**

- Number of current cases per population at risk: the number of current disease cases at a specific time divided by the number of individuals in the population at that specific time.
- Old: persistent active disease contracted previously.
- New: onset of active disease.
- Point prevalence: disease prevalence at a point in time.
- Period prevalence: disease prevalence over a given period of time.
- Measures amount of illness in the community.
- Determines health care needs of the community.
- Data are usually obtained from a cross-sectional survey.

**RESEARCH ERROR**

Two types of research error:

- Random error: handled with the use of statistical tests and methods.
- Systematic error: uncontrolled error that may change the results and/or interpretation of research.

**SELECTION BIAS**

- Nonrandom systematic error in the design or conduct of a study.
- Types:
  - Sampling bias: results from failure to ensure that all members of the reference population have a known chance of being selected for inclusion in the sample.
  - Allocation bias: results from systematic differences in the characteristics of those assigned to treatment versus control groups in a controlled study.
  - Selection bias: results when the following occurs: (1) self-selection of individuals to participate in a survey or experimental study; (2) selection of samples or studies by researchers to support a particular hypothesis.

- Nonresponder bias: results if the survey results differ substantially from those that would have been generated if the response rate was 100%.
- Interviewer bias: results from the personal prejudice of the individual conducting the interview.
- The following characteristics of studies can decrease bias: randomization (minimizes selection bias), blinding, matching. Prospective studies may decrease the chance of patient selection bias.

**CONFOUNDING**

Variable that has independent associations with both the independent (predictor) and dependent (outcome) variables.

Examples include gender, age, socioeconomic status, and co-morbidities.

**RANDOMIZATION**

Best means of avoiding allocation bias.

Balances the groups for prognostic factors (i.e., disease severity).

Eliminates overrepresentation of any one characteristic within the study group.

Should be concealed from the clinicians and researchers of the study to help eliminate conscious or unconscious bias.

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Specifications needed to estimate sample size in a randomized trial:

- Differences in response rates to be detected.
- Estimate of the response rate in one of the groups.
- Level of statistical significance (alpha): the lower the significance level, the greater the required sample size.
- Level of power (1 – beta): the higher the power specification, the greater the required sample size.
- Whether test should be one- or two-tailed.
• Large enough number needed to reject a null result (i.e., to be sure that there is some treatment effect)

“GOLD STANDARD”
• Provides objective criteria (e.g., laboratory test not requiring interpretation) or a current clinical standard (e.g., a venogram for deep venous thrombosis) for diagnosis

CLINICAL TRIALS
• The type of study design chosen for a clinical trial depends on the purpose of the study (Table 29-4)

Steps for Conducting Clinical Trials Include
• Defining a relevant research question
• Selecting instrumentation
• Selecting an appropriate study design and method for statistical analysis
• Determining sample size and sampling procedure

Characteristics of Clinical Trials
• Clinical trials are ideally performed in a controlled setting
• They may evaluate any of the following
  • New drugs
  • Medical devices
  • Biologics
  • Other interventions on patients
  • Safety and efficacy of an experimental therapy
  • Whether a new intervention is better than standard therapy and/or
  • The efficacy of two standard or marketed interventions
• Examples of various trials include
  • Treatment trials: involves test treatments for a specific disease, new combination of drugs or new approaches to surgery or radiation therapy
  • Supportive care trials (quality-of-life trials): explores ways to improve comfort and the quality of life for individuals with a chronic illness
  • Prevention trials: looks for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning
  • Screening trials: includes the study of new ways of finding diseases or conditions in people who are at risk, before they have any signs or symptoms
  • Diagnostic trials: these are conducted to find better tests or procedures for diagnosing a particular disease

Cost-Identification Studies
• Evaluation of the cost of providing treatments
  • Cost-effectiveness analysis
    – Evaluates the costs and clinical outcome
    – Results are reported as cost per clinical outcome
  • Cost-benefit analysis
    – Evaluation of costs and benefits of a specific treatment
    – Results are reported in monetary units
  • Cost-utility analysis
    – Evaluation of cost and utility of a specific treatment
    – Results are reported as cost per quality-adjusted life-year (QALY)

Experimental Design (Study Design)
of Clinical Trials
• Observational study: investigator does not intervene in any way, but merely observes outcomes (case series, case-control studies, cross-sectional surveys, and cohort studies)
• Survey study: involves measuring a set of parameters in one pass through a sample of the population. Used for measuring frequency or magnitude of parameters, but can also be used to measure associations between variables. They can be repeated at time intervals and then combined to predict trends
• Experimental study: investigator intervenes in some way to effect the outcome, tests causal hypotheses where treatment can be given to patients. Biases include selection, informational, observer, and interviewer. The types include: simple experiment,

Table 29-4 Different Types of Study Designs

<table>
<thead>
<tr>
<th>Usual Purpose of Study</th>
<th>Type of Study Design</th>
<th>Sampling Procedure/Type of Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive</td>
<td>Survey study</td>
<td>One that uses the sample population</td>
</tr>
<tr>
<td>Hypothesis generating</td>
<td>Observational study</td>
<td>Case control, cohort or cross sectional</td>
</tr>
<tr>
<td>Hypothesis testing</td>
<td>Experimental or observational studies</td>
<td>Clinical trials, case control, cohort, or cross sectional</td>
</tr>
</tbody>
</table>
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Placebo
- Inert substance given to control subjects that are indistinguishable from the primary treatment, therefore, the only difference between groups is the specific intervention under study

Control Study
- Clinical study that includes a comparison (control) group which receives a placebo, another treatment, or no treatment at all compared to the study group

Sampling Procedure/Type of Surveys
RANDOMIZED CONTROLLED STUDY (PROSPECTIVE, EXPERIMENTAL)
- This type of trial has the following features
  - randomised allocation of participants to groups (treatment versus control)
  - blinding of the following: the participants to group allocation, the practitioner delivering the intervention, and/or the researcher assessing the outcome
  - use of a placebo control group
  - monitoring of the experimental conditions and interventions
- Also known as a parallel group design (“completely randomized”)
- Randomization is one of many components that help to reduce bias
- The goal is to decrease all possibilities for a difference in outcome to either the intervention or chance
- The likelihood that the intervention is the reason for a difference between groups (placebo versus treatment) depends on the level taken to indicate statistical significance (usually P < 0.05 or P < 0.01)
- Purpose of study can be characterized as either “explanatory” or “pragmatic”:
  - Explanatory approach: explains a biological principle
    - focus is efficacy: assessment of differences in effect between two or more conditions under ideal, highly controlled conditions
    - commonly have one specific outcome measure
  - Pragmatic approach: asks the question: “What is the better treatment in the particular clinical circumstances of the patients in the study?”
    - focus is effectiveness: assess differences in effect between two or more conditions when used in normal real-world clinical circumstances
    - not placebo controlled,
    - heterogeneous group of patients
- “Intention to treat” is a strategy for the analysis of randomised controlled trials that compares patients
in the groups to which they were originally randomly assigned; clinical effectiveness may be overestimated if an intention to treat analysis is not done

- Repeated measure study (prospective, experimental)
  - Used when significant baseline variation is expected. The outcome event is measured several times during the trial

- Factorial design study (prospective, experimental)
  - Evaluation of two interventions compared to a control in a single trial. Main disadvantage is the possibility of interaction and the diminution of the power of the trial. Therefore, a larger sample size is needed to compensate for the decrease in power

**CASE-CONTROL STUDY (RETROSPECTIVE, OBSERVATIONAL)**

- A group of individuals with the *condition/disease* (cases) and a group of people *without the condition* (controls) are identified
- Ideal study if the outcome is rare and/or the time period from exposure to outcome is long
- The effect of an individual’s exposure to various factors is evaluated in terms of the development of the outcome/disease being studied
- Information is collected about past exposure to suspected etiological factors in the case and control individuals by looking at their records or by questioning
- Both reporting bias and diagnostic bias may arise in this type of study (bias occurs when there is a systematic difference between the true results and those that are observed in the study)
- Less reliable than randomized controlled trials and cohort studies because a statistical relationship does not mean that one factor necessarily caused the other
- Can only determine odds ratio (OR) of developing the condition
- Case report (retrospective study)
  - A report on a single patient
  - Reports of cases with no control groups with which to compare outcomes; they have no statistical validity
- Case series (retrospective study)
  - Noncomparative study looking at the effect of treatment of individual patients and presentation of interesting or unusual observations

**COHORT STUDY (PROSPECTIVE OR RETROSPECTIVE, OBSERVATIONAL)**

- Large groups of *exposed* and *nonexposed* individuals are followed for long periods of time, to provide information on a range of outcomes, including incidence of disease, death from disease and other rare adverse events
- Ideal study when the outcome is frequent or the latency period is short
- The fact that individuals are not allocated by chance is the main difference between cohort studies and control randomized trials
- Since there are differences in baseline characteristics between the intervention and comparison groups, cohort studies are subject to selection bias and confounding.
- Types of cohort studies
  - Concurrent (concurrent prospective or longitudinal): original population is defined at the start of the study, and subjects are followed through time and the individuals are evaluated to see if the disease does or does not develop
  - Retrospective cohort (historical cohort, nonconcurrent prospective): exposed population is defined by historical records, and outcome is determined at the time the study begins
  - Types of comparisons in cohort study
    - Intervention versus alternative intervention
    - Intervention versus no intervention
  - Relative risk (RR) is used to assess the effect of a risk factor in a cohort study

**CROSSOVER TRIAL (PROSPECTIVE, EXPERIMENTAL)**

- Each subject receives both treatments being compared or the treatment and control
- Since a disease or process needs to persist long enough for the subjects to be exposed to each of the experimental treatments, crossover trials are generally restricted to the study of short term outcomes in chronic diseases or processes
- A washout (no treatment) period between consecutive treatments will help diminish the main disadvantage of the crossover trial: that the effects of one treatment may “carry over” and alter the response to subsequent treatments

**META-ANALYSIS (RETROSPECTIVE)**

- Observational study of the evidence that combines information from different studies to derive an overall estimate of a treatment’s effect
- Two issues exist with this type of study: (1) publication bias: an example is the possibility that studies showing an effect may be more likely to be published than studies showing no effect; (2) combinability of evidence due to varying quality and design of the studies being compared
- Uses statistical techniques to combine the results of several studies as if they were one large study

**Phases of Clinical Trials**

- There are four phases of clinical trials. Each phase can be viewed as an individual clinical trial
- The process of drug-development typically proceeds through all four phases, which could take several years
• Once a drug has passed the first three phases, it can be used by the general public.
• Prior to the initiation of clinical trials on a drug, pharmaceutical companies will perform pre-clinical studies. The purpose of these studies is to evaluate efficacy, toxicity and pharmacokinetic data on the drug being studied.
• Phase 0 (human microdosing studies)
  • Used to bring medications to the market faster based on data from preclinical studies.
• Phase 1: Typically, first stage of testing in healthy human subjects (occasionally in patients with actual disease).
  • Objective is to obtain preliminary information on dosage, absorption, pharmacokinetics, pharmacodynamics, and the relationship between toxicity and the dose-schedule of treatment.
  • Types of phase 1 studies:
    - Single ascending dose (SAD)
      ▲ Pharmacokinetic data, for a certain dose of a drug, is evaluated in a group of patients for a period of time.
      ▲ If no adverse side effects occur, a new group of patients is given a higher dose.
      ▲ Dose escalation continues until a pre-calculated pharmacokinetic safety level is reached, or an unacceptable side effect results (which is the Maximum tolerated dose (MTD)).
    - Multiple ascending dose studies (MAD)
      ▲ Evaluates the pharmacokinetics and pharmacodynamics of various doses of a drug.
      ▲ A group of patients receives multiple low doses of the drug, with collection and analysis of blood and/or other fluids, at various time points.
      ▲ Escalation of the dose in subsequent groups occurs.
• Phase 2: Evaluates efficacy and continues phase 1 safety assessments in groups of 100–300 individuals.
  • Studies are occasionally divided into either phase 2A (to assess dosing requirement) or phase 2B (to study efficacy).
• Phase 3: Comparative trial that determines the effectiveness and safety of a new treatment relative to standard therapy.
  • Randomized controlled multicenter trials on large patient group (1000–2000 or more).
  • Typically expected that there be at least two successful phase 3 trials.
  • The last stage before product licensing.
  • Other reasons for performing phase 3 trials include: “label expansion” (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved), obtain additional safety data, or to support marketing claims for the drug.
• Phase 4: postmarketing studies of licensed products.

Practice Guidelines
• Evidence-based developed statements to assist practitioners about appropriate health care for specific clinical circumstances.
• Guidelines review and evaluate the evidence and then make explicit recommendations for practice.
  • Safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population.
  • Adverse effects detected by this phase may result in the withdrawal or restriction of the drug.

Randomized Controlled Trials
• Study the effect of a therapy or test on patients with randomization and with large enough sample size to avoid confounding and selection bias.
• Include methodologies that reduce the potential for bias and that allow for comparison between intervention groups and control groups (no intervention).
• Evidence for questions of diagnosis is found in prospective trials that compare tests with a reference or “gold standard” test.
• From the results, an estimate of the number of patients who would need to be treated (NNT) to prevent one adverse outcome is calculated by:
  \[ \text{NNT} = \frac{1}{\text{Rate in untreated group} - \text{Rate in treated group}} \]
• NNT helps to estimate the effect that might be expected to be observed by using the new treatment or preventive measure but is limited by not taking into account quality of life.

Systematic Reviews
• Focus on a clinical topic and answer a specific question.
• Extensive literature searches are conducted to identify studies with sound methodology.
• The studies are reviewed, assessed, and summarized according to the predetermined criteria of the review question.

COMPARISON OF DATA

Analysis of Variance
• Used to determine if samples are actually from a single population.
• Does not allow you to compare which groups are more likely to differ from the other (that’s the $t$ test).
**Intention-to-Treat Analysis**
- All patients should be analyzed within the treatment group to which they were randomized in order to preserve the goals of randomization
- Minimizes nonresponder and transfer bias
- Statistical tests
  - Parametric tests are more likely to detect a difference if one exists
    - When using a parametric test, the following must be true: samples are obtained from a population that is normally distributed and that the sample variances are essentially equal
  - Nonparametric tests do not make any assumptions about the underlying distribution of the data; less powerful than parametric tests

**t-Test**
- Used to test for differences between the mean values of two treatment groups
- All t-tests are parametric tests
- Employs the statistic \( t \): \( t = \frac{\text{difference between sample means}}{\text{standard error of the difference in sample means}} \) (variability within groups)
- The larger the ratio, the more likely it is to demonstrate a statistical difference between the 2 groups

**Chi-Square Test**
- Used to determine if differences exist between observed and expected frequencies of results that are tabulated in a \( 2 \times 2 \) contingency table
- Statistical test that consists of three different types of analysis
  - Goodness of fit: determines if the sample under analysis was drawn from a population that follows some specified distribution
  - Test for homogeneity: answers the proposition that several populations are homogeneous with respect to some characteristic
  - Test of independence: tests the null hypothesis, which states that two criteria of classification, when applied to a population of subjects, are independent; if they are not independent, then there is an association between them

**Correlation Analysis**
- Evaluates the degree of association between two variables; the two variables are both treated equally, and neither is assumed to be the predictor or the outcome
- The null hypothesis for a correlations analysis is that the correlation coefficient is equal to zero (no relationship) or that variable 1 and variable 2 are not related
- Correlation coefficient (\( r \)): a statistical parameter quantifying the degree of association between the 2 variables

**Regression Analysis**
- Makes predictions of an outcome on one variable in relation to another variable based on the observed relationship between the variables
- The studied variables are either dependent (outcome) or independent (causative)
- Types of regression analysis: linear (most common), multiple, weighted, and logistic
- The assumptions for linear regression are that the dependent variable (Y) is adequately modeled as being linearly related to a single independent variable X

**Questions**
1. Your office has just purchased a new screening test for fungal infections. You decide to use the test along with the gold standard culture. Calculate the sensitivity and specificity of the test using the information below. What do these results mean to you?

<table>
<thead>
<tr>
<th>Results of Screening Test</th>
<th>Fungal Infection</th>
<th>No Fungal Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

2. You wish to find further information about this screening test. A trial has been performed in a clinic population similar to the one that you treat and produced the following results. Calculate the positive and negative predictive value of the test. What do these numbers tell you?

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Fungal Infection</th>
<th>No Fungal Infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>200</td>
<td>10</td>
<td>210</td>
</tr>
<tr>
<td>Negative</td>
<td>20</td>
<td>770</td>
<td>790</td>
</tr>
<tr>
<td>Total</td>
<td>220</td>
<td>780</td>
<td>1,000</td>
</tr>
</tbody>
</table>
3. Which is true for a normal (Gaussian) distribution?
   A. The graph normally has 2 peaks
   B. When the data are distributed normally, the mean and median are very close and may be identical
   C. It only applies to cross-sectional trials
   D. The most frequently occurring value is on either end of the curve

4. A study which is done in a very specific population that is not generalizable to the population that you treat, would be said have low:
   A. Construct validity
   B. Internal validity
   C. External validity
   D. Statistical validity

5. The results of a randomized controlled trial using a therapy to treat a severe skin malignancy showed a mortality rate of 18% in the untreated group and 5% in the treated group. Calculate the number needed to treat (NNT) to determine how many people would need to be treated in order to prevent one death.

6. When looking at the possible outcomes of a randomized controlled trial that compare two treatments, you generate a table based on your conclusions about treatment and what is the true outcome. Identify in the table, which would be a “correct decision,” “type II error,” and “type I error.” (Hint: two boxes are a “correct decision.”)

<table>
<thead>
<tr>
<th>Truth</th>
<th>Cases With Stroke</th>
<th>Cases Without Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments are not different</td>
<td>A 10</td>
<td>B 200</td>
</tr>
<tr>
<td>Correct decision</td>
<td>C 60</td>
<td>D 1000</td>
</tr>
<tr>
<td>Type II error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct decision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I error</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. What are characteristics of a phase 3 trial?
   A. These are small studies intended to provide preliminary information on dosage, metabolism, toxicity and absorption
   B. They involve fairly large comparative trials based on previous information from smaller trials to determine the effectiveness and safety of a new treatment relative to standard therapy
   C. They only provide information on feasibility
   D. They do not focus on generalizability to the population

Answers
1. Sensitivity: (True positive/[True positive + False negative]) 25/[25 + 2] = 93%. Of all the people with the disease, the number that will have a positive test.
   Specificity: (True negative/[True negative + False positive]) 100 / [100 + 1] = 99% Of all the people without the disease, the number that will have a negative test
2. Positive predictive value: (True positive/[True positive + False positive]) 200/[200 + 10] = 95%.
Of all the people with a positive test, the number that will have the disease.

Negative predictive value: (True negative/[True negative + False negative]) = 770/[770 + 20] = 97%.

Of all the people with a negative test, the number that will not have the disease.

3. B. A normal distribution is a bell shaped curve (1 peak) where approximately 68% of the results fall within 1 standard deviation and about 95% within 2 standard deviations. Since the mean is the average number and the median is the value that half the population falls below, these numbers can be very close when values follow a normal distribution.

4. C. One major objective of trials is to have the results apply to those outside of the study population. When a trial has low external validity, the therapy is found to be best for the population studied only. Internal validity takes into account whether the trial was done properly and had valid findings.

5. NNT = 1/[(Rate in untreated group) – (Rate in treated group)] = [1/(18% - 5%)] = 1/0.13 = 8

6. Your decision that a treatment is not different when it really is not different, is a correct answer. Similarly, concluding that the treatments are different when in reality they are different is also a true statement. A type I error is committed when there is no difference between treatments but on the basis of the study the investigators erroneously conclude that they are different. The probability of making this error is the P value (or alpha). A type II error occurs when there really is a difference between therapies but on the basis of the study, it is erroneously concluded that there is no difference. The probability of making this error is β. Since the total of all probabilities are equal to 1, the probability that the investigators correctly decide on the basis of their study that the treatments are correctly different is 1–β (or power).

7. C. The power of a study tells the investigator how good the study is at correctly identifying a difference between the treatments being tested, if in reality they actually are different. In other words, how likely is the study NOT to miss a difference if one really exists? Thus all are true statements except for C. The probability of making a type I error is the P value (or alpha).

8. D. A cohort design involves a study population that is followed for a long period of time to determine whether an outcome of interest has occurred i.e., it begins with exposed and non exposed subjects.

In a concurrent cohort study (also known as prospective or longitudinal) the study follows the subjects through time until the point at which the outcome develops or not. This is problematic when studying something that takes a long time to develop. Using data from 1980, the observation time will be shortened. For this reason it is called a retrospective cohort (or a historical cohort or nonconcurrent prospective study). In the end, exposed and nonexposed groups will be compared. In a cross sectional study both exposure and disease outcome are determined at the same time for each subject. It looks only at one point in time. Case control studies start with those who have the disease outcome and compares them to those without. Randomized controlled trials involve 2 groups that are randomized to an intervention and followed for the outcome.

9. OR = ([A x D] / [B x C])
   (10 x 1000) / (200 x 60) = 0.83

10. B. The U.S. Food and Drug Administration follows a standard protocol in testing new pharmaceutical agents. Phase 1 are small studies that evaluate the agent for toxic and pharmaceutical effects while phase 2 are larger that look for efficacy and safety. phase 3 are large randomized controlled trials that test for effectiveness and safety, which if successful would then be approved for marketing. phase 4 studies are postmarketing surveillance that will continue the study for safety and effectiveness as it is used by the public.

REFERENCES


HEMATOXYLIN AND EOSIN (H&E)

- Used for elucidation of basic histologic features, prior to the use of special stains or immunohistochemical studies as needed; among other features, calcification and microorganisms such as fungi and bacteria may be detected by H&E and confirmed by additional studies.

STAINS FOR CARBOHYDRATES

- Periodic-acid Schiff (PAS)
  - Stains glycogen red—diastase labile; therefore, diastase pretreatment will remove glycogen
  - Stains mucopolysaccharides red—diastase stable
  - Stains fungi red—diastase stable
  - Stains basement membrane red—diastase stable
- Colloidal iron
  - Stains mucin blue
- Alcian blue
  - Stains mucopolysaccharides blue
    - At pH 2.5: acid (carboxylated or sulfated mucopolysaccharides)
    - At pH 1.0: acid (sulfated mucopolysaccharides)
    - With hyaluronidase: only epithelial mucins will stain (connective tissue mucins will be digested and will not stain)
  - With PAS: acid mucopolysaccharides will stain blue and neutral polysaccharides will stain magenta; also, the yeast of Cryptococcus will stain red and the capsule will stain blue with this method
- Mucicarmine
  - Stains epithelial mucins red (also stains capsule of Cryptococcus red)

STAINS FOR PIGMENTS

- Fontana-Masson (Fig. 30-1)
  - Stains melanin and argentaffin granules black (nuclei will be red); useful for quantifying melanocytes (e.g. in vitiligo) and in cases of minocycline pigmentary alteration
  - Also stains Cryptococcus
- Grimelius argyrophil stain
  - Argentaffin and argyrophil substances will stain black
- Tyrosinase (DOPA-oxidase)
  - Requires fresh tissue
  - Stains melanin-containing cells brownish-black (due to tyrosinase acting on DOPA, the substrate for this reaction)

STAINS FOR MINERALS

- Von-Kossa
  - Stains calcium salts black; useful for detecting calcification of vessel walls and elastic tissue (calcinosis cutis, pseudoxanthoma elasticum, calciphylaxis, elastosis and elastofibroma)
- Alizarin red S
  - Stains calcium red
- Prussian blue stain (Fig. 30-2)
  - Stains iron blue (the Prussian blue reaction: tissue treated with dilute hydrochloric acid and potassium ferrocyanide)
- Gomori methenamine silver (GMS) (Fig. 30-3)
  - Stains urates black. {Note: urates are lost if tissue is processed in formalin}
Tissue must be processed with alcohol to prevent loss of urates. Also see Stains for Microorganisms below.

**STAINS FOR CONNECTIVE TISSUE COMPONENTS**

- Trichrome
  - Stains collagen blue or green and muscle red, depending on the type of reagents used
- Verhoeff-van Gieson
  - Stains elastic fibers black, collagen red, and muscle yellow (also red cells will stain yellow)

**STAINS FOR AMYLOID**

- Congo red
  - Stains amyloid pinkish-red; gives apple-green birefringence to amyloid (the most specific method for amyloid)
• Thioflavin T  
  • Amyloid shows yellow fluorescence  
• Crystal violet  
  • Stains amyloid purple-violet

### STAINS FOR FAT

• Oil red O  
  • Stains fat red; needs frozen/fresh tissue (once tissue is fixed and processed into paraffin blocks, this method does not work). This may be very helpful in seeing the fat globules in sebaceous carcinoma.
• Osmium tetroxide  
  • Paraffin-embedded tissue; stains fat black  
• Sudan black B  
  • Paraffin-embedded tissue; stains fat black

### STAINS FOR MICROORGANISMS

• H&E  
  • May demonstrate fungi, bacteria  
• Gram  
  • Stains gram-positive bacteria (also *Nocardia*) dark blue and gram-negative organisms red  
• Giemsa  
  • For *Leishmania* and granuloma inguinale  
• Gumori methenamine silver (GMS) (Fig. 30-3)  
  • Stains fungi, *Pneumocystis jiroveci* (formerly *carinii*), and protothecosis black  
• PAS  
  • Stains fungi and protothecosis pink  
• Fontana-Masson (Fig. 30-1)  
  • Stains *Cryptococcus*  
• Warthin-Starry  
  • Stains spirochetes black  
• Ziehl-Neelson stain  
  • Uses carbol fuchsin; stains mycobacteria red  
• Fite stain (Fig. 30-4)  
  • Modification of Ziehl-Neelson; stains *Mycobacterium leprae* and *Nocardia*  
  • It also detects atypical mycobacteria

### STAINS FOR MAST CELLS

• Giemsa and toluidine blue are metachromatic stains for mast cells; also chloroacetate esterase (Leder stain)

### IMMUNOHISTOCHEMICAL STUDIES

• Uses primary antibodies (polyclonal or monoclonal) to a particular antigen, followed by secondary antibody complexed to an enzyme; subsequently, a chromagen is added, which is acted on by the enzyme, releasing a colored product that is evaluated histologically

### STUDIES FOR EPITHELIA

• Cytokeratins (CK) are intermediate filaments found in epithelial cells; the following antibodies and cocktails are useful (Figs. 30-5 and 30-6)  
  • AE1/AE3—a cocktail antibody recognizing a broad spectrum of keratin; it labels most squamous cell carcinomas (SCC), basal cell carcinomas (BCC), adnexal tumors, and Merkel cell carcinomas but it may not label spindle cell SCC  
  • CAM5.2—useful for eccrine tumors, Paget’s disease (PD), extramammary Paget’s disease (EMPD), and will also label sebaceous carcinoma and a minority of BCC; SCC is mostly negative, however  
  • CK5/6—useful for SCC, including spindle cell SCC; it has been shown to label the majority of primary cutaneous adnexal neoplasms and may be useful in distinguishing these from metastatic adenocarcinoma to the skin (fewer of these are reactive with anti-CK5/6)(see also p63)  
  • CK7—Very useful for demonstrating PD and EMPD; present in less than a quarter cases of Merkel cell carcinoma  
  • CK20—Merkel cell carcinoma will typically exhibit perinuclear dot-like positivity

**FIGURE 30-4** Fite stain showing atypical mycobacteria pink inside giant cells (400x). This case was thought to be erythema nodosum clinically.
Chapter 30    HISTOLOGIC STAINS AND SPECIAL STUDIES

- CEA (carcinoembryonic antigen)
  - Antibody to CEA, which is an oncofetal antigen, will demonstrate glandular differentiation (helpful in eccrine and apocrine adnexal neoplasms)
  - It will also be positive in the ducts of sebaceous carcinoma
  - It is extremely useful to demonstrate EMPD but may not be as good for PD
- EMA (epithelial membrane antigen)
  - Positive in numerous tumors: EMPD, PD, adnexal neoplasms especially sebaceous neoplasms, perineuriomas, and focally positive in most SCC and in epithelioid sarcoma; also positive in plasma cells and some CD30 anaplastic large cell lymphomas
- GCDFP (gross cystic disease fluid protein)
  - Positive in PD, EMPD, and adnexal neoplasms; breast carcinomas are also labeled

STUDIES FOR NEUROECTODERMAL LESIONS

- S-100
  - Not very specific but extremely sensitive for primary melanoma (including desmoplastic melanoma), metastatic melanoma, and nevi; also positive in a variety of other tumors such as breast carcinoma, Rosai-Dorfman disease, granular cell tumor, neurofibroma, schwannoma, myxoid neurothekeoma, chondroid syringoma, syringoma, and Langherhans cell histiocytosis
- S-100A6 is positive in cellular neurothekeomas and some melanocytic lesions
- MART-1 (melanoma antigen recognized by T-cells) – Two main antibodies (M2 and A103)
  - Less sensitive and more specific than S-100 for melanocytic lesions; only a minority of cells in a proportion of desmoplastic melanoma label with this marker
  - It is also positive in adrenocortical carcinoma and angiomyolipoma (among others), particularly the clone A103

STUDIES FOR MESENCHYMAL TISSUE

- Actin antibodies (smooth muscle actin)
  - Useful in demonstrating leiomyoma/leiomyosarcoma, glomus tumors, and dematomyofibroma
  - Cellular neurothekeoma will also exhibit positivity in 50% of cases
- Desmin
  - For leiomyoma/leiomyosarcoma, angiomyofibroblastoma
- CD34
  - Very useful for dermatofibrosarcoma protuberans (DFSP); it is positive in vascular tumors such as hemangioma, angiosarcoma, Kaposi’s sarcoma, and lymphangioma and is also positive in nearly half the cases of epithelioid sarcoma
- CD31
  - It is positive in vascular neoplasms: angiosarcoma, hemangioma, lymphangioma, Kaposi’s sarcoma; also positive in macrophages (which is a possible pitfall)
HMB45 and Ki-67
- HMB45 is less sensitive and more specific than S-100 for melanocytic lesions; it reacts with gp100, a glycoprotein present in premelanosomes
- Only a minority of cells in a proportion of desmoplastic melanoma label with this marker
- This is a useful marker to demonstrate maturation in melanocytic lesions: i.e., melanocytic cells in the dermis label at the top of benign melanocytic lesions but not at the bottom; in suspicious lesions, demonstration of maturation may be helpful in arguing against a diagnosis of melanoma
- Ki-67 is an antigen present in all cells not in G0 (resting) phase. The most common antibody is Mib-1.
- Regarding blue nevi versus spindle cell melanoma, the former are strongly, diffusely positive with HMB45; HMB45 is especially useful in this context when used together with Ki-67, a marker of proliferation
- Melanocytic cells in the dermis that show maturation with HMB45 and show low proliferation (less than approximately 5% of cells reacting with Ki-67) are less likely to be melanoma; of course, it is not possible to be absolutely certain about this, but in the appropriate clinical context, it may provide helpful information
- CK20 (see above)
- Synaptophysin and chromogranin
  - Both of these markers may be positive in Merkel cell carcinoma
CD57
- Labels a small proportion of cellular neurothekeoma and neurofibroma
PGP9.5
- It is positive in cellular neurothekeoma; it is not very specific, though, and is positive in many other tumors, including Merkel cell carcinoma and dermatofibroma
NKI/C3
- It is a macrophage marker positive in cellular neurothekeoma, but is not very specific

STUDIES FOR HEMATOPOEITIC LESIONS

CD1a
- Marker for Langerhans cells (and therefore useful in Langerhans cell histiocytosis)
CD3
- Marks T cells
CD4
- Marks T cells (T-helper cells), Langerhans cells, and macrophages; in mycosis fungoides, typically CD4 predominates over CD8
CD5
- Marks T cells; it is also positive in B cells in chronic lymphocytic leukemia (CLL) and mantle zone lymphoma. CLL lymphocytes would be expected to be CD5 and CD20 positive.
CD7
- Marks T cells
  - It may be useful in MF in the following manner: it may not be present on epidermal lymphocytes that mark with CD4 and CD3, for example, suggesting loss of expression; however, inflammatory lesions may also exhibit this feature
CD8
- Marks T cells (T-cytotoxic/suppressor cells) (see CD4 above)
CD20 (Figs. 30-7 and 30-8)
- Marks B cells; may be useful, along with CD3, kappa and lambda in showing that a

FIGURE 30-7 Kappa immunoreactivity in cutaneous Marginal zone lymphoma (200x). The majority of the plasma cells were kappa positive and lambda negative.
CD35
- Marks follicular dendritic cells; positive in follicular dendritic cell sarcoma

CD45
- Marks most hematopoietic cells (ALCL may be negative)

CD56 (neuronal cell adhesion marker-NCAM)
- Marker for NK cell lymphoma
- Leukemic cells may be positive as well; also positive in neural neoplasms such as neurofibroma myxoid neurothekeoma and in desmoplastic melanoma

CD57 (see above)

Mast cell tryptase
- Positive in mast cells

MPO (myeloperoxidase)
- Antibody to MPO may label leukemic cells; also labels neutrophils and monocytes (note that there is a histochemical stain for MPO as well, with similar usefulness)

Kappa and lambda
- Presence of light-chain restriction, i.e., a plasmacytic infiltrate that is either kappa or lambda positive is seen in conditions such as myeloma and marginal zone lymphoma. Normally, a mixture of both with a kappa predominance is expected.

STUDIES FOR INFECTIOUS DISEASES

- The following is a list of useful antibodies:
  - HHV-8: kaposi’s sarcoma
  - Spirochetal antibody: syphilis
  - Herpes-simplex antibody: for demonstrating Herpes simplex virus
  - Herpes-zoster antibody: for demonstrating zoster

QUIZ

Questions

1. Biopsy of a lesion on the scrotum of a 65-year-old male shows pagetoid cells in the epidermis. Which of the following combinations of studies may be helpful in diagnosing this case?
   A. CK20, S-100, Mart-1, CK7 and CEA
   B. CD1a, CD5, S-100, PAS and GMS
   C. CK20, CD1a, PAS, GMS and CD1a
   D. EMA, CD1a, CD5, CD3 and GMS

2. A biopsy shows small lymphocytes in dense aggregates in the subcutaneous tissue. Immunohistochemical studies reveal that these are CD5 and CD20 positive. The best diagnosis is:
A. Acute myeloid leukemia
B. Chronic myeloid leukemia
C. Acute lymphocytic leukemia
D. Chronic lymphocytic leukemia

3. Which of the following may be helpful in evaluating mast cells?
A. Anti-trypsin antibody
B. Anti-tryptase antibody
C. GMS
D. Gram

4. In a case of suspected Merkel cell carcinoma, which of the following studies may be negative?
A. CK20
B. Cytokeratin
C. CEA
D. CD56

5. An immunocompromised patient presents with pulmonary lesions and a widespread papular eruption. Biopsy of a skin lesion reveals probable fungal organisms that are GMS and Fontana-Masson positive. The most likely diagnosis is:
A. Coccidioidomycosis
B. Cryptococcosis
C. Histoplasmosis
D. Systemic candidiasis

6. A biopsy of a papule on the arm shows lymphoid aggregates with apparent germinal centers with a cuff of plasma cells around them. Immunohistochemical studies show the following: CD3 – positive; CD20 – positive; kappa – negative; lambda – numerous positive plasma cells. The best diagnosis is:
A. Secondary syphilis
B. Mantle cell lymphoma
C. Marginal zone lymphoma
D. Lupus

7. A 2-year-old boy has crusted, ulcerated lesions on the scalp and forehead. The dermatopathologist informs you that an immunohistochemical study shows numerous CD1a positive cells in the epidermis. Which other immunohistochemical study may be positive in this case?
A. S-100
B. Mart-1
C. CK7
D. CD5

8. A 14-year-old Caucasian male has hypopigmented patches on the elbows. You suspect vitiligo and perform a biopsy. Which of the following studies may be useful in this case?
A. Fontana-Masson
B. PAS
C. Giemsa
D. Prussian blue

9. One of your colleagues, a Mohs surgeon, removes a lower eyelid lesion. He shows you the frozen section and you see somewhat clear cells in the epidermis. Which of the following studies may be useful in evaluating the frozen section slide and arriving at a diagnosis?
A. Giemsa
B. Oil red O
C. GMS
D. Leder stain

10. A 23-year-old HIV-positive male presents with reddish lesions on his leg. The dermatologist performs a biopsy and writes a note to the dermatopathologist. Which of the following may be helpful in evaluating mast cells?
A. Anti-trypsin antibody
B. Anti-tryptase antibody
C. GMS
D. Gram

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C. GMS
D. Gram

Answers

1. A. In EMPD, CK7 and CEA should be positive. CK20 positivity is seen less frequently, but may be seen associated with underlying gastrointestinal malignancy. Of course, in a pagetoid lesion, it is important to rule out melanoma in situ, and S-100 and Mart-1 will be expected to be negative.
2. B. Chronic lymphocytic leukemia/small lymphocytic lymphoma tumor cells have both CD5 and CD20 positivity.
3. C. Antibody to mast cell tryptase can highlight the mast cells. Mast cells may be evaluated with Giemsa and Leder stains as well.
4. D. Merkel cell carcinoma shows characteristic dot-like CK20 positivity, cytokeratin positivity and also CD56. CEA is not typically positive.
5. E. Cryptococcus, like other fungi, is GMS and PAS positive. Interestingly, it is also Fontana-Masson positive.
6. C. Marginal zone lymphoma can look deceptively like cutaneous lymphoid hyperplasia because of the presence of reactive appearing lymphoid aggregates and germinal centers. A clue to the diagnosis on H&E is the presence of plasma cells around the
aggregates of lymphocytes. Therefore, kappa and lambda immunohistochemical studies to show light chain restriction can be very helpful in arriving at the correct diagnosis.

7. A. The presentation is that of Langerhans cell histiocytosis. The tumor cells are CD1a and S-100 positive. This is an important thing to remember since S-100 positive intraepidermal cells are not always melanocytic cells—they may be Langerhans cells.

8. A. The absence of any melanin (which would be detected by Fontana-Masson) would be expected in vitiligo.

9. B. In cases of sebaceous carcinoma, a fat stain (such as an Oil red-O stain that gives fat a red-orange color) is very useful. It generally works in the frozen section setting, since the process of fixation leads to loss of fat.

10. C. Since the most likely diagnosis is Kaposi’s sarcoma, an HHV-8 would be expected to be positive in the lesion.

REFERENCES


SYNONYMS

- Dermatoscopy
- Skin surface microscopy
- Epiluminence microscopy (ELM)
- Digital dermoscopy/digital ELM
- Auflichtmikroskopie (German)
- Dermoscopia/dermatoscopia (Spanish)
- Dermoscopy is the term used by experienced dermoscopists and is most commonly used in the literature

DEFINITION

- Dermoscopy is an in-vivo, non-invasive technique in which oil or fluid (e.g., mineral oil, gels, alcohol and water) is placed on the lesion
  - Fluid eliminates reflection of light from the surface of the skin allowing visualization of color and structure in the epidermis, dermo-epidermal junction and papillary dermis
  - The color and structure visualized cannot be seen with the naked eye or with typical magnification that clinicians use
  - Polarizing light and digital instrumentation do not require fluid
- When using polarized light dermoscopy
  - Light from a polarized light source penetrates the stratum corneum with less scatter
  - A second polarizer screens out scattered surface light resulting in the physician seeing primarily light from the deeper structures
  - This removes the need for contact with the skin and the need for immersion fluids, resulting in faster examination times

BENEFITS OF DERMOSCOPY

- Helps to differentiate melanocytic from non-melanocytic skin lesions
- Helps to differentiate benign from malignant skin lesions
- With dermoscopy the diagnostician’s sensitivity to diagnose melanoma is 85% and better compared to 65–80% when the technique is not used
- Increases the diagnosis of early melanoma
- Increases the diagnosis of melanoma incognito (false negative melanoma)
- Helps to avoid unnecessary surgery
- Helps to plan surgery
- Helps to work better with a pathologist (asymmetrical high risk criteria, dermoscopic – pathologic correlation)
- Patient reassurance
- Allows for follow up of patients with multiple nevi digitally to find changes over time

DERMOSCOPIC DIGITAL MONITORING

- There are pigmented skin lesions that are not high risk enough to warrant immediate histopathologic diagnosis, yet not so banal that there is no concern at all
- There are melanomas that do not appear to be high risk clinically or with dermoscopy
- They are only diagnosed after monitoring for dermoscopic changes over time when comparing baseline with subsequent digital images
- Short-term monitoring is performed every three or four months
  - Any change over time could be a melanoma
- Long term monitoring is done at 6-month to yearly intervals
  - Important changes include asymmetrical enlargement, the appearance of high risk criteria, new colors, or regresssion
- Single or multiple suspicious pigmented skin lesions can be chosen for digital monitoring
THE TWO STEP ALGORITHM

- The analysis of a suspicious skin lesion is a two-step process
  - Step one: determine if it is melanocytic or non-melanocytic
  - Step two: if it has the criteria for a melanocytic lesion, the second step is to determine if it is low, intermediate or high risk using the melanocytic algorithm of your choice
- Pattern analysis was the first melanocytic algorithm developed for this purpose and is most often used by experienced dermoscopists. Variations of pattern analysis (the simplified algorithms) have also been developed, including:
  - The ABCD rule of dermatoscopy (the second algorithm developed) (Table 31-1)
  - The Seven Point Checklist (Table 31-2)
  - Menzies Method (eleven point checklist) (Table 31-3)
  - The newest three-point checklist (Table 31-4)

Step One: Identification of Criteria

Look for the criteria associated with a melanocytic lesion (Table 31-5). If one does not find them, the search is on for the criteria associated with seborrheic keratosis, basal cell carcinoma, dermatofibromas, vascular lesions and others
- Not all of the possible criteria are needed to make a diagnosis
- When there is absence of criteria for a melanocytic lesion, seborrheic keratosis, basal cell carcinoma, dermatofibroma or vascular lesion, you are now dealing with a melanocytic lesion by default
- The “default category” is the last criterion used to diagnose a melanocytic lesion (Fig. 31-1)

CRITERIA DEFINED

- Melanocytic Lesion
  - Pigment network/network/reticulation
    - On the trunk and extremities
    - Black, brown or gray
    - Honeycomb-like, reticular, web-like line segments (elongated and hyperpigmented rete ridges) with hypopigmented holes (dermal papilla)
  - Pseudonetwork/Pseudopigment network
    - Because the skin of the head and neck is thin and does not have well developed rete ridges, one sees
      ▲ Appendageal openings/adnexal structures (sebaceous glands, hair follicles)
      ▲ Uniform, round white or yellowish structures
    - When they penetrate areas of diffuse pigmentation, reticular like structures are formed that is referred to as the pseudonetwork
    - Monomorphous appendageal openings can often be seen on the skin of the face without any pigmentation
    - They should not be confused with the milia-like cysts seen in seborrheic keratosis
    - It is not always possible to make the differentiation
    - Consequences could be misdiagnosing lentigo-maligna for a seborrheic keratosis
    - This criterion can also be seen with non-melanocytic lesions
    - In the strictest sense of the definition it is not 100% diagnostic of a melanocytic lesion
  - Dots and Globules
    - Roundish structures distinguished only by their relative sizes

### Table 31-1  ABCD Rule of Dermatoscopy: Identify Criteria and assign Points to Determine Total Dermatoscopy Score (TDS)

<table>
<thead>
<tr>
<th>Dermoscopic Criterion Definition Score Weight Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetry: In 0, 1, or 2 perpendicular axes; assess contour, colors and structures 0-2</td>
</tr>
<tr>
<td>Border: Abrupt ending of pigment pattern at periphery in 0-8 segments 0-8</td>
</tr>
<tr>
<td>Color: Presence of up to 6 colors (white, red, light-brown dark-brown blue-gray, black) 1-6</td>
</tr>
<tr>
<td>Dermoscopic structures: Presence of network, structureless (homogeneous) areas, branched streaks, dots, and globules 1-5</td>
</tr>
</tbody>
</table>

Formula for calculating total dermatoscopy score (TDS): \((A \times 1.3) + (B \times 0.1) + (C \times 0.5) + (D \times 0.5) = TDS\). Interpretation of total score: 
- \(< 4.75\): Benign melanocytic lesion
- \(4.75-5.45\): suspect lesion (close follow-up or excision recommended)
- \(> 5.45\): lesion highly suspect for melanoma.
TABLE 31-2  Menzies Scoring Method: 11 Point Check List

<table>
<thead>
<tr>
<th>Dermoscopic Criterion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Negative features</td>
<td></td>
</tr>
<tr>
<td>2. Symmetry of pattern</td>
<td></td>
</tr>
<tr>
<td>3. Presence of single color</td>
<td></td>
</tr>
<tr>
<td>4. Positive features</td>
<td></td>
</tr>
<tr>
<td>5. Blue-white veil</td>
<td></td>
</tr>
<tr>
<td>6. Multiple brown dots</td>
<td></td>
</tr>
<tr>
<td>7. Pseudopods (streaks)</td>
<td></td>
</tr>
<tr>
<td>8. Radial streaming (streaks)</td>
<td></td>
</tr>
<tr>
<td>9. Scar-like depigmentation</td>
<td></td>
</tr>
<tr>
<td>10. Peripheral black dots/globules</td>
<td></td>
</tr>
<tr>
<td>11. Multiple (5 or 6) colors</td>
<td></td>
</tr>
<tr>
<td>12. Multiple blue/gray dots</td>
<td></td>
</tr>
<tr>
<td>13. Broadened network</td>
<td></td>
</tr>
</tbody>
</table>

For melanoma to be diagnosed, both negative features must be absent and one or more of the 9 positive features must be present.

TABLE 31-3  7-Point Checklist

<table>
<thead>
<tr>
<th>Dermoscopic Criterion</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Atypical pigment network (major criteria)</td>
<td>2</td>
</tr>
<tr>
<td>2. Blue-whitish veil</td>
<td>2</td>
</tr>
<tr>
<td>3. Atypical vascular pattern</td>
<td>2</td>
</tr>
<tr>
<td>4. Irregular streaks (minor criteria)</td>
<td>1</td>
</tr>
<tr>
<td>5. Irregular dots/globules</td>
<td>1</td>
</tr>
<tr>
<td>6. Irregular blotches</td>
<td>1</td>
</tr>
<tr>
<td>7. Regression structure</td>
<td>1</td>
</tr>
</tbody>
</table>

By simple addition of the individual scores a minimum total score of 3 is required for the diagnosis of melanoma, whereas a total score of less than 3 is indicated of non melanoma.

TABLE 31-4  Three Point Checklist to Diagnose High-Risk Lesions (Melanoma, Basal Cells)

1. Asymmetry of color and or structure
2. Irregular pigment network
3. Blue and / or white color

2 out 3, 3 out 3 → Excise

The three point check list is based on simplified pattern analysis and is intended to be used by non-expert dermoscopists as a screening technique. It’s aim is to diagnose melanocytic and non-melanocytic potentially malignant pathology.

- Dots (0.1 mm) are smaller than globules (greater than 0.1 mm)
- Black, brown, gray or red
  - When black, they can represent atypical melanocytes in the epidermis
  - Regular brown dots and globules represent nests of melanocytes at the dermo-epidermal junction
  - Irregular brown dots and globules represent nests of atypical melanocytes at the dermo-epidermal junction
  - Grayish dots (“peppering”) represent free melanin and melanophages in the papillary dermis, which can be seen in regression areas or alone in benign pathology such as late stage lichen planus-like keratosis or post traumatic
  - Reddish globules can be seen in melanoma (neovascularization)

- It is written and taught that aggregated globules identify a melanocytic lesion with no mention of the smaller dots. The reality is that both dots and globules define a melanocytic lesion (Fig. 31-2)

  - **Homogeneous blue pigmentation**
    - Structureless blue color in the absence of local criteria such as pigment network, dots or globules (Fig. 31-3)
    - Many variations of homogeneous blue color usually represents a blue nevus
    - The history is important because there is a differential diagnosis which could include
      - A lesion as banal as a radiation tattoo to one more ominous such as nodular or cutaneous metastatic melanoma

  - **Parallel patterns/ acral patterns**
    - Fissures and ridges on the skin of the palms and soles (dermoglyphics)
    - Can create parallel patterns
Table 31-5 Criteria for Various Lesions

<table>
<thead>
<tr>
<th>Criteria for a melanocytic lesion:</th>
<th>Pigment network (trunk and extremities)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pseudopigment network/pseudo network (head and neck)</td>
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<tr>
<td></td>
<td>Aggregated globules</td>
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<tr>
<td></td>
<td>Homogeneous blue color of a blue nevus</td>
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<tr>
<td></td>
<td>Parallel patterns on acral sites</td>
</tr>
<tr>
<td></td>
<td>By default</td>
</tr>
<tr>
<td>Criteria for a seborrheic keratosis:</td>
<td>Milia-like cysts</td>
</tr>
<tr>
<td></td>
<td>Follicular openings</td>
</tr>
<tr>
<td></td>
<td>Fissures and ridges</td>
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<td>Fingerprint pattern</td>
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<td></td>
<td>Hairpin shaped vessels</td>
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<td></td>
<td>Moth-eaten borders</td>
</tr>
<tr>
<td></td>
<td>Sharp demarcation</td>
</tr>
<tr>
<td>Criteria for a basal cell carcinoma:</td>
<td>Absence of criteria for a melanocytic lesion</td>
</tr>
<tr>
<td></td>
<td>Arborizing blood vessels</td>
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<tr>
<td></td>
<td>Pigmentation</td>
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<td></td>
<td>Ulceration</td>
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<tr>
<td></td>
<td>Spoke-wheel structures</td>
</tr>
<tr>
<td>Criteria for a dermatofibroma:</td>
<td>Central white patch</td>
</tr>
<tr>
<td></td>
<td>Peripheral pigment network</td>
</tr>
<tr>
<td>Criteria for a vascular lesion:</td>
<td>Vascular spaces called lacunae</td>
</tr>
</tbody>
</table>

**FIGURE 31-1** Amelanotic melanoma. This is a melanocytic lesion by default because there is an absence of criteria for a melanocytic lesion, seborrheic keratosis, basal cell carcinoma, dermatofibroma or hemangioma. The blue-white color (arrow) is a clue that this might be a melanocytic lesion. There are pinpoint/dotted (yellow boxes) and irregular linear (black boxes) vessels plus a general milky-red background color. Note: This interdigital melanoma was mistakingly treated as a tinea for two years.

**FIGURE 31-2** Acquired nevus. This is a melanocytic lesion because it has pigment network (black boxes) and aggregated globules (circles). There is a small hemangioma adjacent to the nevus (arrow).
THE TWO STEP ALGORITHM

• Parallel-furrow pattern (benign pattern)
  - Thin brown parallel lines in the furrows of the skin (crista superficialis limitans)
  - Variations include two thin lines with or without dots and globules (Fig. 31-4)

• Lattice-like pattern (benign pattern)
  - Thin brown parallel lines in the furrows
  - Running perpendicular to the furrows forming a ladder-like picture (Fig. 31-5)

• Fibrillar pattern (benign pattern)
  - Fine brown lines
  - Run in an oblique (/////) direction
  - Pressure can change the lattice-like pattern into a fibrillar pattern

• Globular pattern (benign)
  - Brown globules without a parallel component

FIGURE 31-3 Blue nevus. The classic homogenous blue color of a blue nevus.

FIGURE 31-4 Acral nevus. This is a melanocytic lesion on acral skin with the benign parallel-furrow pattern. Pigmentation is in the thin furrows (arrows) with globules (boxes) in the ridges (stars).

• Reticular pattern (benign)
  - A lesion with only pigment network

• Homogeneous pattern (benign)
  - Brown homogeneous patch of color

• Parallel-ridge pattern (thin/early melanoma)
  - Pigmentation is in the thicker ridges of the skin (crista profunda intermedia) (Fig. 31-6)
  - Sometimes there are monomorphous round white structures in the ridges that represent the acrosyringia of the sweat ducts “string of pearls”

FIGURE 31-5 Acral nevus. Brown lines in the furrows (black arrows) and perpendicular to the furrows (yellow arrows) characterize the lattice-like pattern. Pressure on the foot can change this into the fibrillar pattern with fine oblique (/////) lines.

FIGURE 31-6 Acral melanoma. The parallel-ridge pattern diagnoses this acral melanoma with pigmentation in the thicker ridges (black arrows). The thin white lines are the furrows (yellow arrows).
Chapter 31  DERMOSCOPY

Seborrheic keratosis
• Milia-like cysts
• Variously sized white or yellow structures
• Small or large, single or multiple
• They can appear opaque or bright like “stars in the sky” (epidermal horn cysts)

Follicular openings/ pseudofollicular openings/ comedo-like openings
• Sharply demarcated roundish structures
• Pigmented or nonpigmented
• Shape can vary, not only within a single lesion, but from lesion to lesion in an individual patient or in different patients
• When pigmented, they can be brownish-yellow or even dark brown and black (keratin-filled invaginations of the epidermis)
• Pigmented follicular openings can be hard to differentiate from the pigmented dots and globules of a melanocytic lesion (Fig. 31-9)

Fissures and ridges
• Fissures (sulci/crypts) and ridges (gyri) seen in papillomatous seborrheic keratosis can create several patterns
  ▲ Cerebriform or brain-like in which they resemble a sagittal section through the cerebral cortex
  ▲ Mountain-like with variously sized or uniformly roundish structures representing mountains (ridges) and fine pigmented lines representing valleys (fissures)

Pearls
• There can be exceptions to every dermoscopic rule
• The history and clinical appearance of the lesion are important and should not be ignored
• If a pigmented lesion on the soles is rapidly changing yet has a typical benign parallel furrow pattern, it still could be melanoma
• A supposedly benign acral pattern with irregularity to the components could be high risk
• The presence of blood at acral sites (palms, soles, nails) may or may not be associated with melanoma
• Look carefully for other important criteria
• If in doubt, cut it out!

FIGURE 31-7  Acral hemorrhage. The parallel-ridge pattern created by blood (white arrows).

FIGURE 31-8  Acquired nevus. There is an increased incidence of acral melanoma in darker skinned races. This nevus on the palm of an African-American was without change and demonstrates the benign parallel-ridge pattern. Pigmentation is seen in the ridges of the nevus (yellow arrows) and in the ridges of the entire palm (white arrows).

• Diffuse variegated pattern (melanoma)
  - Pigmented blotches
  - Black, brown or gray
• Multicomponent pattern (melanoma)
  - Filled with regular and irregular criteria
  - Multiple colors plus areas with acral patterns (fibrillar, parallel-furrow)
• Non-specific pattern (melanoma)
  - If one cannot determine any of the above benign or malignant patterns; this represents a “red flag” of concern

FIGURE 31-9  Multiple colors plus areas with acral patterns (fibrillar, parallel-furrow).
Well demarcated, concave borders that are felt – to resemble a “moth-eaten” garment

Sharp demarcation

• The majority of seborrheic keratoses have – sharp, well-demarcated borders
• Not always indicative of melanoma in a pigmented lesion (Fig. 31-9)

Basal cell carcinoma

• Absence of the criteria seen in a melanocytic lesion
  ▲ Specifically, absence of a pigment network

Possible to confuse the mountain and valley pattern with the cobblestone pattern of a melanocytic lesion

▲ Pigmented lines should not be confused with an atypical pigment network
▲ Hypo- and hyperpigmented ridges can be digit-like (straight, kinked, circular or branched) and are referred to as “fat fingers”
  – All of these patterns are commonly seen in this ubiquitous benign skin lesion (Fig. 31-10)

Fingerprint pattern

• Brown fine/thin parallel line segments that resemble fingerprints
• Differ from the pigment network where the line segments are honey comb-like or reticular
• Fingerprint pattern can be seen in flat seborrheic keratosis or in solar lentigines
• Some authors believe that solar lentigines are flat seborrheic keratosis (see below and Fig. 31-23)

Hairpin vessels

• Elongated vessels (capillary loops) resembling hairpins (Fig. 31-11)
• May or may not be surrounded by hypopigmented halos
• Light halo indicates a keratinizing tumor and may be found in keratoacanthomas
• Irregular and thick hairpin vessels can be seen in melanoma

Moth-eaten borders

• Flat or slightly raised brown seborrheic keratoses

▲ Possible to confuse the mountain and valley pattern with the cobblestone pattern of a melanocytic lesion

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• Irregular and thick hairpin vessels can be seen in melanoma

Moth-eaten borders

• Flat or slightly raised brown seborrheic keratoses
Dots and globules plus homogeneous blue color found in some basal cell carcinomas
- Raises the issue of dermoscopic differential diagnosis of individual criterion

**Arborizing vessels**
- One of the most sensitive and specific vascular structures seen with dermoscopy
  - Red tree-like branching telangiectatic blood vessels
  - Can be thick or thin lines that are in focus because of their superficial location
  - Most often there are different caliber vessels in a single lesion
- Can also be found in
  - Benign nevi
  - Sebaceous gland hyperplasia
  - Scars
  - On sun-damaged skin
  - Melanoma

**Pigmentation**
- Basal cell carcinoma may or may not contain pigment (pigmented nests or island of basal cell carcinoma in the dermis) that can range from
  - Fine dots to large leaf-like structures (bulbous extensions forming a leaf-like pattern)
  - Blue-gray ovoid nets
  - Multiple blue-gray globules

**Colors that can be seen**
- Black
- Brown
- Gray
- Blue
- Red
- White
- Not necessary to try to determine if “leaf-like” structures (“maple leaf-like areas”) are present since in reality this is a difficult task (Fig. 31-12)

**Ulceration**
- Single or multiple areas where there is loss of epidermis with oozing blood or congealed blood and crusts (Fig. 31-13)
- There should be no recent history of trauma

**Spoke-wheel structures**
- Spoke-wheel structures are the only criterion with dermoscopy that are 100% diagnostic
- Can be found in up to 10% of basal cell carcinomas
- May or may not be associated with the other criteria used to make the diagnosis
- Well-defined pigmented radial projections meeting at a darker central globule/central axle/hub
- Complete or incomplete variations of this structure can be seen and one often has to use their imagination to make the identification
- Finding spoke-wheel structures might be the only clue to the correct diagnosis

![FIGURE 31-12](image1) Basal cell carcinoma. This pigmented basal cell carcinoma has classic arborizing vessels (black arrows), gray blotches (boxes), blue globules (yellow arrows) and fine gray dots (circles). The three different presentations of pigmentation point out how variable this criterion can be.

![FIGURE 31-13](image2) Basal cell carcinoma. Arborizing vessels (black arrows) and ulceration (yellow arrows) characterize this nonpigmented basal cell carcinoma.
Pearl
- A nonhealing area in an adult that bleeds spontaneously is a basal cell carcinoma until proven otherwise

- Dermatofibroma
  - Central white patch
    - Most typical presentation of this criterion is:
      ▲ Centrally located
      ▲ Scar-like
      ▲ Bony or milky white
      ▲ Homogeneous area (scarring in this fibro-histiocytic tumor)
    - Several variations such as white network-like structures (negative pigment network, reticular depigmentation) which can also be seen in Spitz nevi and melanoma
    - Telangiectatic vessels with different shapes can also be found anywhere in the lesion
    - Not all dermatofibromas have a central white patch
    - The clinically firm feel should be used to help make the diagnosis
  - Pigment network
    - Dermatofibromas are one of the nonmelanocytic lesions that can have a pigment network; solar lentigines are another
      ▲ In most cases, a fine peripheral pigment network with thin brown lines is seen
      ▲ Not all dermatofibromas have a pigment network
    - Ring-like structures which are a variation of a hyperpigmented network (Fig. 31-14)
    - Atypical dermatofibromas with the following features are melanoma mimics that warrant a histopathologic diagnosis:
      ▲ Irregular pigment network
      ▲ Irregular dots/globules/ blotches
      ▲ Pink color
      ▲ Irregular regression-like white color
      ▲ High-risk vascular structures (Fig. 31-15)
  - Vascular lesions
    - Lacunae/lagoons/saccules
      - Sharply demarcated bright red to bluish round or oval structures (dilated vascular spaces in the dermis) (Fig. 31-16)
      ▲ Different colors can be seen in a single hemangioma
      ▲ Lacunae should not be mistaken for the milky-red color seen in pigmented and amelanotic melanoma which can have “out-of-focus” reddish globular-like structures
      ▲ Black homogeneous structureless areas represent thrombosis
      ▲ Significant scale or dryness (hyperkeratosis) can be seen in angiokeratomas
    - Patchy white color or blue-white veil (blue and or white color) is commonly seen in hemangiomas

**FIGURE 31-14** Dermatofibroma. A classic central white patch (black arrow) and pigment network (black boxes) characterize this dermatofibroma. In this instance, ring-like structures (white arrows) make up the pigment network.

**FIGURE 31-15** Atypical dermatofibroma. Regressive melanoma is in the dermoscopic differential diagnoses of this atypical dermatofibroma. There is asymmetry of color and structure, the multicomponent global pattern, irregular pigment network (box), irregular globules (red arrows) and irregular blotches (yellow arrows). This warrants a histopathologic diagnosis.
Even though pattern analysis is considered a melanocytic algorithm, the same principles are used to diagnose all of the lesions that can be identified with the technique.

- Blue
- Dysplastic
- Spitz
- Melanoma
  - In situ
  - Superficial spreading
  - Nodular
  - Amelanotic
  - Nail apparatus
  - Acral

Even though pattern analysis is considered a melanocytic algorithm, the same principles are used to diagnose all of the lesions that can be identified with the technique.

- Melanocytic
- Nonmelanocytic
- Benign
- Malignant
- Inflammatory

**Pearls**

- Do not focus on one or two criteria and make a diagnosis before checking for all the criteria. You could be lead astray.
- Try to identify all of the criteria in a lesion.
- High risk criteria that are present are not always easy to find. Beware!
**THE TWO STEP ALGORITHM**

**PATTERN ANALYSIS METHOD**

- **Step #1:**
  - Determine symmetry or asymmetry of color and or structure using the mirror image technique
  - Contour of the lesion is not important with this algorithm
  - The lesion is bisected by two lines that are placed 90 degrees to each other
  - The first line attempts to create the most symmetry as possible
  - Is the color and or the structure on the left half of the lesion a mirror image of the right half
  - Repeat the analysis for the upper and lower half of the lesion
  - Perfect symmetry of color and structure is not often found in nature, and inter observer agreement is not good with this assessment even among experienced dermoscopists
  - Symmetry or asymmetry can also be determined along any axis through the center of the lesion (Menzies method)
  - Significant asymmetry of color and or structure is a very important clue that you might be dealing with high risk pathology
  - Raise a “red flag” of concern and proceed with focused attention to what else you might find

- **Step #2:**
  - Determine the global/overall pattern of the lesion
  - The predominant criteria seen throughout the lesion could be:
    - Reticular
    - Globular
    - Cobblestone
    - Homogeneous
    - Parallel
    - Starburst
    - Multicomponent
    - Nonspecific
  - There can be combinations of criteria in a single lesion such as reticular and homogeneous or reticular and globular
  - The “reticular homogeneous pattern” or “reticular globular pattern”

- **Step #3:**
  - Identify the local criteria in the lesion:
    - Pigment network
    - Dots and globules
    - Streaks (also called pseudopods and radial streaming)
    - Blotches
    - Blue-white veil
    - Regression
    - Colors
    - Vascular structures

- **Step #4:**
  - Determine if the criteria seen are:
    - Regular or irregular (typical or atypical)
    - Good or bad
    - Low or high risk
  - Melanoma specific criteria are defined as criteria that can be seen in benign and malignant lesions but are more specific for high risk pathology such as:
    - Dysplastic nevi
    - Spitzoid lesions
    - Melanoma
  - All of the high risk criteria can be seen in benign pathology and one should never tell a patient that they have melanoma 100%
  - Due to the different characteristics of the skin in these locations the criteria are different on:
    - Trunk and extremities
    - Head and neck
    - Palms and soles
  - Thinner skin on the head and neck versus the trunk and extremities and thicker skin on the palms and soles with fissures and ridges
  - The criteria found on the head, neck, palms and soles are referred to as site specific criteria (Table 31-6)

**GLOBAL PATTERNS**

- **Reticular**
  - Pigment network filling most of the lesion
- **Globular**
  - Dots and globules filling most of the lesion
- **Cobblestone**
  - Larger angulated globules resembling street cobblestones filling most of the lesion (Fig. 31-18)
- **Homogeneous**
  - Diffuse pigmentation in the absence of local criteria such as pigment network, dots and globules
- **Starburst (Spitzoid)**
  - Streaks and/or dots and globules at the periphery of the lesion
- **Multicomponent**
  - Three or more different areas within a lesion
  - Each zone can be composed of a single criterion or multiple criteria
- **Nonspecific**
  - None of the above global patterns can be identified

**LOCAL CRITERIA**

- **Regular (typical) pigment network:**
  - Various shades of brown
  - Honeycomb-like (web-like, reticular) line segments
  - Uniform color, thickness and holes
Irregular (atypical) pigment network:
- Black, brown or gray
- Line segments that are thickened, branched and broken up (enlarged, fused rete ridges)
- There may be a diffuse distribution or foci of irregular pigment network

Regular dots and globules:
- Brown roundish structures
- Usually clustered
- Dots (0.1 mm) are smaller than globules (greater than 0.1 mm)
- Size, shape and color are similar with an even distribution in the lesion (nest of melanocytes at the dermo epidermo junction)
- Dots and/or globules only found at the periphery can be seen in Spitz or actively changing nevi
- Actively changing means if followed digitally the nevus will invariably enlarge within a short period of time
- Peripheral dots and globules are usually seen in younger patients with benign pathology
- Beware of this pattern in a newly acquired nevus in an adult

Irregular dots and globules:
- Black, brown, gray or red roundish structures
- Different sizes and shades of color

### TABLE 31-6 Melanoma-Specific Criteria in Different Body Regions

<table>
<thead>
<tr>
<th>Trunk and Extremities</th>
<th>Head and Neck</th>
<th>Palm and Soles</th>
<th>Nail Apparatus</th>
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</thead>
<tbody>
<tr>
<td>Global criteria:</td>
<td>Asymmetrical pigment around follicular openings</td>
<td>Parallel ridge pattern</td>
<td>Loss of parallelism of pigmented bands/ melanonychia striata</td>
</tr>
<tr>
<td>Asymmetry of color and or structure</td>
<td>Annular granular structures/pattern</td>
<td>Diffuse variegated pigmentation</td>
<td>Hutchinson and Micro-Hutchinson’s sign</td>
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<tr>
<td>Multicomponent pattern</td>
<td>Rhomboid structures</td>
<td>Multicomponent pattern</td>
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<tr>
<td>Non-specific pattern</td>
<td>Dark homogeneous areas</td>
<td>Atypical reticulated/ lattice-like pattern</td>
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<tr>
<td>Local criteria: Irregular pigment network</td>
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<tr>
<td>Irregular dots and globules</td>
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<tr>
<td>Irregular streaks (pseudopods/radial streaming)</td>
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<tr>
<td>Irregular blotches</td>
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<tr>
<td>Blue-white veil</td>
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<tr>
<td>Regression</td>
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<tr>
<td>5 or 6 colors</td>
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<tr>
<td>Atypical vascular pattern (vessels associated with melanoma)</td>
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</table>

**FIGURE 31-18** Acquired nevus. Small dots and globules (boxes) and larger angulated globules (arrows) characterize this benign nevus. The mountain and valley pattern seen in seborrheic keratosis is in the dermoscopic differential diagnosis. A positive wobble sign in which the soft nevus moves from side to side with movement of instrumentation versus a stiff immoveable seborrheic keratosis helps to make the differentiation.
Atypical melanocytes in the dermis
• The white color should be lighter than the surrounding skin
• Regression by itself is an independently potentially high risk criterion
• The more regression seen, the greater the chance the lesion is a melanoma

Blue-white color:
• It is not always possible to identify classic regression on blue-white veil
• Blue and/or white color of any intensity, shape or distribution
• A “red flag” of concern should be raised

Hypopigmentation:
• Commonly seen featureless areas of light brown color in all types of melanocytic lesions both benign and malignant
• Inexperienced dermoscopists can have trouble differentiating hypopigmentation from the white color seen with true regression

Colors seen with dermoscopy:
• Eumelanin has a brown color
• Its location in the skin will determine the colors one sees with dermoscopy
• Black indicates melanin is superficially located in the epidermis (i.e., in the stratum corneum)
• Black is not always an ominous color but can be seen in benign pathology as well as in melanoma
• Light and dark brown indicates pigment is at the dermo-epidermal junction
• Gray in the papillary dermis represents free melanin and melanophages (“peppering”) as the pigment gets into the deeper dermis it looks blue (the Tyndall effect)
• Red and or pink color can be created by inflammation or neovascularization
• Sebaceous material and hyperkeratosis can look yellow
• The more colors seen, the greater chance one is dealing with high risk pathology (Figs. 31-19, 31-20, 31-21)

Atypical vascular pattern/polymorphous vascular pattern:
• Vessels that can be seen in melanoma are nonspecific; they can also commonly be found in other lesions including
  – Benign
  – Malignant
  – Inflammatory
• When identified they should raise a “red flag” of concern including
  – Dotted/pinpoint (dots resembling the head of a pin)
Irregular linear
- Irregular tortuous/corkscrew (irregular, thick, coiled)
- Irregular hairpin (irregular and thick hairpin shaped)
- Glomerular
- One must focus his/her attention to make out the shapes of these small vessels (Fig. 31-22)

Milky-red areas:
- Localized or diffuse (amelanotic melanoma) pinkish-white color
- With or without reddish and or bluish out of focus/ fuzzy globular structures (neovascularization)
- Not to be confused with the in focus lacunae seen in hemangiomas

Glomerular vessels:
- Diffuse or clustered fine coiled vessels that can be seen in
  - Bowen disease (Fig. 31-22)
  - Melanoma
  - Pink lichen planus – like keratosis
  - Stasis dermatitis
  - Psoriasis

FIGURE 31-19 Melanoma. This is a melanocytic lesion because there is a pigment network (red arrows) and aggregated globules (circles). There is asymmetry of color and structure (+) plus the multicomponent global pattern (1,2,3). Local criteria includes; irregular pigment network (red arrows), irregular dots and globules (circles), irregular blotches (black arrows) and blue-white color (stars). The classic blue-white veil is not seen. Pepperling (yellow box) and gray blotches (yellow arrows) are part of the regression. More than five colors are seen including red.

FIGURE 31-20 Melanoma. There is a melanocytic lesion because there are aggregated globules (circle). There is asymmetry of color and structure (+) plus the multicomponent global pattern (1,2,3). Local criteria includes; irregular dots and globules (circle), blue-white color (stars) and pepperling (boxes). The classic blue-white veil is not seen. More than five colors, including red, are another melanoma specific criterion.

FIGURE 31-21 Melanoma. This is a melanocytic lesion because there are aggregated globules (circles). There is an atypical starburst (spitzoid) global pattern with foci of streaks at the periphery (boxes). Local criteria includes; irregular dots and globules (circles), irregular streaks (boxes) and regression. The white and gray blotches (yellow arrows) make up the regression. The black arrows point out where there are no streaks. Five colors, including red, round off the melanoma specific criteria.
- **Asymmetrical pigmentation around follicular openings:**
  - Seen only on the head and neck
  - Irregular brown color outlining parts of the round follicular openings
  - The color does not completely encircle the openings (early proliferation of atypical melanocytes)

- **Annular-granular pattern/structures:**
  - Seen only on the head and neck
  - Brown or gray fine dots that surround follicular openings (melanophages and or atypical melanocytes)
  - This criterion can be seen in
    - Lentigo maligna, lentigo maligna melanoma
    - Pigmented actinic keratosis
    - Post traumatic
    - Late stage lichen planus-like keratosis (Figs. 31-23, 31-24)

- **Rhomboid structures:**
  - Seen only on the head and neck
  - Rhomboid is a parallelogram with unequal angles and sides
  - Black, brown, or gray thickening around the follicular openings
  - In reality true rhomboids are not regularly formed
  - Any pigmented thickening around follicular openings is worrisome

- **Dark homogeneous areas:**
  - On the head and neck
  - Irregular in size and shape
  - Black or brown homogeneous blotches of color
  - Complete occlusion of follicular openings due to invasive melanoma (lentigo maligna melanoma)

**Pearls**
- Actinic keratosis and actinic lentigines can be associated with lentigo-maligna on the head and neck
- Use the areas where the high risk criteria are located to perform a biopsy, or the malignant diagnosis could be missed. There should be a good dermoscopic-pathologic correlation
- If you think the lesion is lentigo maligna yet the pathology report does not make the diagnosis, seek another histopathologic opinion or biopsy another area of the lesion

- **Benign pigmented nail bands (melanonychia striata):**
  - Single or multiple nail involvement with brown longitudinal parallel lines
  - Uniform color, spacing and thickness
  - A single band in a lighter skinned person with these findings is still worrisome

- **Malignant pigmented nail bands (atypical melanonychia striata):**
  - Loss of parallelism with brown, black, or gray
Darker skinned races multiple nails involved

Nail-apparatus blood/subungual hematoma:
- The color of blood seen in the nail apparatus depends how long the blood has been there
  - Fresh blood looks red or purple/violaceous
  - Older blood can look yellowish brown or black
- A well demarcated homogeneous area with parallel lines at the distal edge and globule-like blood spots/pebbles (Fig. 31-26)
- Digital dermoscopy is helpful to follow nail apparatus blood that should slowly move distally over several months

High risk dermoscopic criteria at this location in adults are usually not associated with high risk pathology when seen in children
- Disfiguring nail matrix biopsies can usually be avoided
- Any rapidly changing scenario warrants a histopathologic diagnosis no matter how old or young the patient
- Digital monitoring is helpful to monitor pigmentation in the nail apparatus

Micro-Hutchinson’s sign: Hutchinson’s sign
- Pigmentation of the cuticle that can only be seen clearly with dermoscopy
- Pigmentation of the cuticle easily seen without dermoscopy

Non-melanocytic nail apparatus bands:
- Uniform grayish lines on a gray background can be seen in lentigo
- Drug induced pigmentation multiple nails involved

- Darker skinned races multiple nails involved
- Nail-apparatus blood/subungual hematoma:
  - The color of blood seen in the nail apparatus depends how long the blood has been there
    - Fresh blood looks red or purple/violaceous
    - Older blood can look yellowish brown or black
  - A well demarcated homogeneous area with parallel lines at the distal edge and globule-like blood spots/pebbles (Fig. 31-26)
- Digital dermoscopy is helpful to follow nail apparatus blood that should slowly move distally over several months

Pearls
- Presence of blood in a nail does not rule out melanoma
- Search carefully for high risk criteria that might also be present
**THE TWO STEP ALGORITHM**

- Symmetry of color and structure
- Comma-shaped blood vessels
- Hypopigmentation
- Milia-like cysts and follicular openings can be seen
- Pink nevi can be featureless or feature poor
- A solitary flat pink lesion is more worrisome than multiple soft and compressible pink lesions

**Finding the Hutchinson’s sign and the parallel-ridge pattern on the surrounding skin adjacent to the nail can help make the diagnosis of nail apparatus melanoma**

**COMMON DERMOSCOPIC PATTERNS**

- *Congenital nevi*:
  - Diffuse homogeneous brown color
  - Patchy or diffuse pigment network (target network may or may not be seen as network holes each with a small centrally located brown dot or pinpoint vessel)
  - Globular and/or cobblestone pattern (target globules may or may not be seen as globules with a smaller centrally located dot or vessel)
  - Islands of normal skin and islands of criteria such as network dots and globules
  - Multicomponent pattern with three or more distinct areas of criteria
  - Dark coarse terminal hairs (hypertrichosis) with or without surrounding hypopigmentation (perifollicular hypopigmentation) (Fig. 31-27)
  - Milia-like cysts and follicular openings most often found in seborrheic keratosis can be seen

- *Acquired nevi*:
  - Light/dark brown or pink color
  - Regular pigment network
  - Lacks sharp demarcation at the borders
  - Globular or cobblestone pattern (the most common pattern seen in children)

**Pearl**

- Dermoscopy might not be helpful to diagnose pink macules and papules which can be melanocytic, nonmelanocytic, benign, malignant or inflammatory (Fig. 31-28)

- *Blue nevi*:
  - Blue, blue-gray or blue-black homogeneous color (Fig 31-3)
  - Variable number of subtle blue globular-like structures
  - Regression with white or gray areas commonly seen
  - Radiation tattoo, nodular and metastatic melanoma is in the dermoscopic differential diagnosis
  - The history is essential to make the differential diagnosis

- *Combined nevi*:
  - Light or dark brown homogeneous color +/– other local criteria (regular nevus) and central
Patients with multiple dysplastic nevi usually do not have many that look very atypical with dermoscopy. Look for the clinical and/or dermoscopic “ugly duckling” to consider for biopsy or digital follow-up.

Pink dysplastic nevi can be feature poor or featureless with low or high grade histopathology.

- Blue blotch (blue nevus) with a “fried egg” clinical appearance
- Diffuse brown homogeneous color with a blue border
- Diffuse blue homogeneous color with a brown border
- Variable combinations of blue and brown color

**Recurrent nevi/pseudomelanoma:**
- Sharp border
- Irregular pigment network; irregular streaks
- Irregular dots and globules
- White scar-like areas with arborizing vessels
- Any combination of criteria can be seen
- Pigmentation centrally located in the scar; if the pigmentation goes out of the scar rule out melanoma
- The history of previous surgery and histopathology is important (Fig. 31-29)

**Dysplastic nevi:**
- ABCDE clinical lesions can look banal or high risk with dermoscopy
- Being indistinguishable from melanoma
- Evolving/changing might be the only clue that a lesion is melanoma
- Asymmetry of color and structure
- Irregular pigment network
- Irregular blotches
- Irregular dots and globules
- Multifocal hypopigmentation (Fig. 31-30)
- Regression, blue-white color/ blue-white veil, atypical vessels and streaks are not usually seen

**FIGURE 31-28** Pink lichen planus-like keratosis. This small papule was only found after a complete skin examination. There are different shades of pink color, pinpoint (boxes) and comma shaped vessels (yellow arrows) plus a milky-red area (black arrow).

**FIGURE 31-29** Recurrent nevus. Asymmetry of color and structure (+), the multicomponent global pattern (1,2,3) irregular globules (boxes), irregular blotches (yellow arrows), and scar tissue (stars) with arborizing vessels (black arrows) characterize this recurrent nevus.

**FIGURE 31-30** Dysplastic nevus. There are foci of irregular dots and globules (boxes), irregular blotches (black arrows) and multifocal hypopigmentation (red arrows).

- Patients with multiple dysplastic nevi usually do not have many that look very atypical with dermoscopy
- Look for the clinical and/or dermoscopic “ugly duckling” to consider for biopsy or digital follow-up
- Pink dysplastic nevi can be feature poor or featureless with low or high grade histopathology
THE TWO STEP ALGORITHM

Pearl
- “Anything pink, stop and think!”

An atypical starburst/spitzoid pattern with foci of dots/globules and/or streaks at the periphery can be seen in melanoma
- Symmetrical and asymmetrical starburst patterns can be seen in melanoma
- Homogeneous light brown or reddish featureless pattern
- Globular pattern with central blue-white color
- Diffuse black irregular pigment network pattern
- Atypical pattern similar to superficial spreading melanoma
- Spitz nevi:
  - There are six patterns seen in Spitz nevi
    - Starburst
    - Globular
    - Homogeneous
    - Pink
    - Black pigment network
    - Atypical
  - Spitzoid is the term used when any of the different six patterns is seen
  - Starburst is the most common pattern (Fig. 31-31)
    - Streaks and / or dots and globules at the periphery
    - Light /dark brown, black or blue color centrally

Pearl
- Any spitzoid pattern requires a histopathologic diagnosis especially in adults

- Regular or irregular pattern depends on the location of the streaks
  - Regular starburst pattern has symmetrical streaks around the lesion
  - Irregular starburst pattern has foci of streaks at the periphery
- Symmetrical and asymmetrical starburst patterns can be seen in melanoma
- Globular is the second most common Spitzoid pattern
  - Filled with regular or irregular dots/and or globules
  - Blue color seen centrally is the clue that the lesion might be a Spitz nevus
- Homogeneous pattern
  - Featureless brown color
- Pink pattern
  - Feature-less pink papule
- Black network pattern
  - The lesion is composed totally of a prominent black pigment network
  - Ink-spot lentigo and melanoma are in the differential diagnosis
- Atypical pattern
  - This can have any combination of melanoma-specific criteria
  - The histopathologic diagnosis is usually a surprise
- White pigment network/ negative pigment network/reticular depigmentation
  - This is an important clue that the lesion is Spitzoid

FIGURE 31-31 Spitz nevus. A central regular blotch (stars) plus globules (black arrows) and a few streaks (red arrows) at all points of the periphery characterize this classic starburst/spitzoid pattern.

In-situ melanoma (trunk and extremeties)
- May or may not demonstrate the clinical ABCD clinical criteria
- Flat or slightly raised lesion
- Asymmetry of color and structure
- Black and/or dark brown irregular pigment network
- Irregular dots and globules
- Irregular dark blotches
- Hypopigmentation
- Lacks the criteria for deeper melanoma (pink, red, gray or blue color, atypical vessels or regression
- Looks more malignant than benign but not definitely malignant (Fig. 31-32)

Superficial spreading melanoma:
- Starts in an existing nevus or de novo
- Demonstrates the clinical ABCD criteria
Amelanotic melanoma:
• Flat, palpable or nodular
• Hypopigmented, pink or red
• May or may not have the melanoma specific criteria typically seen in pigmented melanomas
• Different shades of pink color and atypical vascular pattern
• Milky-red areas are important clues to the correct diagnosis
• Pediatric patients have a high proportion of amelanotic melanomas (Fig. 31-33)
• Amelanotic melanoma should always be in the differential diagnosis of a pyogenic granuloma

Cutaneous metastatic melanoma:
• Dermoscopy might not be as helpful to make the diagnosis as the history of a melanoma being previously excised
• Single or multiple
• Pigmented or non-pigmented

Pearls
• The clinical appearance of a lesion (flat, palpable or nodular, presence or absence of the ABCD criteria) plus the colors and structures seen with dermoscopy can help estimate if you are dealing with a thin, intermediate or thick melanoma
• Flat melanomas are usually in-situ with black and brown color plus well developed local criteria
• Thick melanomas tend to be elevated or nodular and can have a paucity or absence of local criteria such as pigment network, plus blue-white veil/color, multiple colors and the atypical vascular pattern

FIGURE 31-32 In-situ melanoma. This is a melanocytic lesion because there is a pigment network (black box) and aggregated globules (circles). There is asymmetry of color and structures (+), the multicomponent global pattern (1,2,3), irregular pigment network (black box), irregular dots and globules (circles), irregular blotches (yellow arrows), and reticular depigmentation (white box). The hypopigmentation (black stars) should not be confused with regression. There is diffuse erythema (red stars) and only three other colors.

FIGURE 31-33 Amelanotic melanoma (feature poor melanoma). This is a melanocytic lesion because it has aggregated globules (boxes). There is an absence of melanoma specific criteria found on the face with different shades of pink and brown color plus ulceration (yellow arrows). Follicular openings (black arrows) should not be confused with the milia-like cysts of a seborrheic keratosis.
• All different sizes, shapes and colors can be seen in each patient with or without atypical vessels
• Any combination of criteria can be seen
• Benign patterns such as a hemangioma-like cutaneous metastatic melanoma (Fig 31-17)

• **Feature poor melanoma:**
  • Melanoma with subtle non diagnostic criteria (Fig. 31-33)
• **Featureless melanoma:**
  • Melanoma without dermoscopic criteria at all
• Melanoma incognito/false negative melanoma:
  • Clinically the lesion does not look like melanoma
  • With dermoscopy there are obvious or subtle clues to make the diagnosis
  • Clues to help make the diagnosis
    – History of dermoscopic change over time
    – A Spitzoid pattern in a lesion that does not look Spitzoid clinically
    – Areas of regression as the major high risk criterion
    – High risk vessels in a pink lesion
• The "Little Red Riding Hood Sign" is when the lesion looks clinically benign from a distance but not close up with dermoscopy

**Pearl**

- Dermoscopy should not only be used on clinically suspicious lesions if one wants to diagnose melanoma incognito

• **Nail apparatus melanoma:**
  • Amelanotic reddish diffuse color/amelanotic tumor
  • Diffuse melanonychia with different shades of black, brown or gray color
  • Irregular pigmented bands (Fig. 31-25)
  • A single uniform band does not rule out melanoma
  • Irregular dots and globules
  • Blood in 25% of lesions
  • Nail plate destruction with advanced disease
  • +/- Hutchinson sign
  • The parallel -ridge pattern can be seen on the adjacent skin

• **Ink spot lentigo:**
  • Black macule or macules on sun exposed areas
  • Prominent thickened black pigment network
  • Usually a very easy clinical and dermoscopic diagnosis
  • Melanoma could be in the clinical and dermoscopic differential diagnosis
  • Look for melanoma specific criteria that should not be present in an ink spot lentigo

• Solar lentigo:
  • Macules and/or patches
  • Different shades of homogeneous brown color
  • Moth- eaten concave borders
  • Fingerprint-like wavy linear line segments

• **Actinic keratosis:**
  • Nonpigmented actinic keratosis
    – Scaly surface
    – Pinkish-red pseudopigment network
  • Pigmented actinic keratosis
    – Mimics lentigo maligna
      ▲ Asymmetrical follicular pigmentation
      ▲ Annular-granular structures
      ▲ Rhomboid structures

**Pearl**

- Multiple scaly lesions favors the diagnosis of actinic keratosis over lentigo maligna. Both can have pigmented and non-pigmented variants.

• Bowen’s disease (in situ squamous cell carcinoma):
  • Pink or reddish scaly macules, papules, patches, plaques
  • Pinpoint and/or glomerular vessels
  • Clusters and/or diffuse distribution of vessels throughout the lesion
  • With or without homogeneous brown color

• Keratoacanthoma:
  • Centrally located yellowish keratinous material
  • Peripheral whitish background
  • Hairpin vessels at the periphery

• Sebaceous gland hyperplasia:
  • Delled yellow papules seen clinically
  • Multiple grouped white or yellow globules
  • Small caliber basal cell carcinoma-like vessels
    – The vessels have been termed crown or wreath-like vessels
      ▲ Supposedly never to reach the center of the lesion
      ▲ This is a misnomer because in reality the vessels rarely meet this criterion and can be found anywhere in the lesion

**Pearl**

- The globules are the main feature used to differentiate sebaceous gland hyperplasia from basal cell carcinoma

• **Collision tumor:**
  • Lesion with the dermoscopic criteria for two different pathologies
  • One can find a triple collision lesion with three different pathologies
**Pediculosis Pubis**
- It is possible to easily see the parasite attached to adjacent pubic hairs or hairs at other sites

**Lichen Planus**
- peppering  
- brown blotches  
- white reticular areas (Wickham's striae)  
- negative pigment network/reticular depigmentation is in the dermoscopic differential diagnosis of Wickham’s striae

**Warts**
- red and or black dots (thrombosed capillaries)  
- with or without a white halo

**Psoriasis**
- red scaly plaque or plaques  
- diffuse distribution of glomerular vessels identical to Bowen’s disease  
- distribution of lesions will help differentiate Psoriasis from Bowen’s disease  
- both can have single or multiple lesions

**Nail Folds**
- normal capillary loops are hairpin shaped and run parallel to the axis of the nail  
- the main value of nail fold dermoscopy is the early diagnosis of scleroderma before there are positive clinical and serologic findings

**Scleroderma Pattern**
- the triad of:  
  - rarefied capillaries (less than 6 loops per mm)  
  - thin loops, megacapillaries  
  - pearly shining sclerosis “cotton balls”

**Dermatomyositis**
- mega, twisted, branched loops, microhemorrhage

**Lupus Erythematosus**
- considerable variation of loops, branching, twisted, microhemorrhage

**Scabies**
- Burrows appear as discrete linear areas  
- Mites can be seen as a small triangle/gray delta structure that corresponds to the front section of the body with its mouth/biting apparatus and legs  
- Higher magnification and oil increase the visibility of the mite, stool and eggs

**Pediculosis Capitis**
- Direct visualization of the parasite and nits  
- It is possible to see if the nits are full (vital nits) or empty which helps determine the success or failure of treatment

**OTHER DIAGNOSES MADE WITH DERMOSCOPY**

**Scabies**
- Burrows appear as discrete linear areas  
- Mites can be seen as a small triangle/gray delta structure that corresponds to the front section of the body with its mouth/biting apparatus and legs  
- Higher magnification and oil increase the visibility of the mite, stool and eggs

**Trichoscopy**
- The use of dermoscopy to evaluate scalp skin and hair follicles  
- Structures that can be visualized include  
  - Hair shafts  
  - Hair follicle openings  
  - Perifollicular epidermis  
  - cutaneous microvasculature  
- Higher magnifications (20 to 70-fold) with digital systems and fluid (70% ethanol) are preferred  
- Hand held instrumentation with lower magnification and other fluids such as emersion oil or gels can also be used

**FIGURE 31-34** Collison tumor – squamous cell carcinoma and seborrheic keratosis. A rapidly growing nodule (arrow) representing a squamous cell carcinoma and the mountain and valley pattern of a seborrheic keratosis (box) characterize this lesion. The cobblestone pattern of a nevus is in the dermoscopic differential diagnosis.
**Genetic Hair Shaft Abnormalities**

**Monilethrix**
- Multiple constrictions of the hair shaft alternating with elliptical nodosities that look like a “pearl necklace”
- A high tendency to fracture which gives hair a stubble-like appearance
- Hair shafts bend regularly in multiple places and curve in different directions “regularly bended ribbon sign”

**Netherton Syndrome**
- Trichorrhexis invaginata/bamboo hair/ golf tee type characterized by invagination of the distal portion of the hair shaft into its proximal portion forming a ball in cup appearance
- Diagnosis can easily be made without the need for hair sampling and microscopic examination

**Pili Annulati**
- Alternating light and dark bands are seen clinically
  - Light bands represent cavities within the cortex
  - Cavities appear as whitish areas within a darker hair shaft
  - The opposite is true with light microscopy

**Acquired Hair Diseases**

**Androgenic Alopecia**
- Variable hair shaft diameter
- Digital systems allow the precise measurement and monitoring of hair shaft thickness
- Identify and count vellus hairs (thin hairs less than 0.03 mm in width)
- Terminal to vellus hair ratio can be calculated without skin biopsies
- Increased percentage of thin hairs
- Decreased average hair diameter
- Predominance of hair follicle units with single hairs
- Hyperkeratotic plugs
- Perifollicular pigmentation

**Alopecia Areata**
- Regularly distributed hyperkeratotic plugs in hair follicles (yellow dots)
- Cadaverized hairs (black dots)
- Dystrophic hairs
- Micro-exclamation point hairs
- Fibrosis with white dots in long standing cases

**Cicatricial Alopecia**
- Scarring alopecia of different etiologies looks the same with fibrosis of follicular ostia visible as white dots
- With more advanced disease the dots coalesce to form bony white areas without visible ostia

**Questions**

1. Which criteria can be used to diagnose a melanocytic lesion?
   A. Milia-like cysts and pigmented follicular openings
   B. Arborizing vessels, ulceration and pigmentation
   C. A central white patch plus fine peripheral pigment network
   D. Lacunae and black homogenous blotches
   E. Pigment network, brown globules, homogeneous blue color, or parallel patterns

2. Diagnosing a melanocytic lesion by default means that:
   A. There are high risk criteria at the periphery of the lesion that are hard to identify
   B. There are criteria for a seborrheic keratosis or basal cell carcinoma associated with pigment network and brown globules
   C. There is an absence of criteria to diagnose a melanocytic lesion, seborrheic keratosis, dermatofibroma, pyogenic granuloma or ink-spot lentigo, therefore the lesion should be considered melanocytic
   D. There is an absence of criteria to diagnose a melanocytic lesion, seborrheic keratosis, basal cell carcinoma, dermatofibroma or hemangioma, therefore the lesion should be considered melanocytic
   E. None of the above

3. Which criteria can be used to diagnose a seborrheic keratosis?
   A. Milky-red areas, irregular streaks, and pigmented follicular openings
   B. Streaks, irregular blotches and regression
   C. Fissures, ridges, sharp border demarcation, milia-like cysts, follicular openings, fat fingers and hairpin vessels
   D. Rhomboid structures and/or circle within a circle
   E. Diffuse brown color, glomerular vessels and milia-like cysts

4. Which criteria can be used to diagnose a basal cell carcinoma?
   A. Pigment network and arborizing vessels
   B. Arborizing and pinpoint vessels plus multifocal hypopigmentation
   C. The absence of a pigment network, arborizing vessels, pigmentation, ulceration, spoke-wheel structures
   D. Glomerular vessels, ulceration and blue ovoid nests of pigmentation
   E. Islands of black blotches, arborizing vessels and moth-eaten borders
5. Vascular lesions can contain the following criteria:
   A. Out of focus lacunae-like globules
   B. A variable number of red, sharply demarcated vascular spaces called lacunae and fibrous septae
   C. Ten to twenty major and minor lacunae and thromboses
   D. A minimal of two well-developed glomerular vessels
   E. Fibrous septae, peppering, and blue dark lacunae

6. Dermatofibromas can be associated with the following criteria:
   A. Pigment network, arborizing vessels and central white patch
   B. A central white patch that is never located at the periphery
   C. A central white patch and peripheral pigment network
   D. A complete absence of blood vessels and a few milia-like cysts
   E. Multifocal hypopigmentation, arborizing vessels and a central bluish-white veil

7. Melanoma-specific criteria on the trunk and extremities can contain this combination of criteria:
   A. Asymmetry of color and structure, a cobble-stone global pattern and regular globules or blotches
   B. A multicomponent global pattern, symmetry of color and structure, regular network, regular globules and regression
   C. Polymorphous vessels, arborizing vessels, two colors and regular streaks
   D. Irregular network, irregular globules, irregular blotches and regression
   E. Rhomboid structures and the parallel-ridge pattern

8. Dysplastic nevi typically have the following combination of criteria:
   A. Symmetry of color and structure and no melanoma-specific criteria
   B. Asymmetry of color and structure, irregular network, regular blotches and regular streaks
   C. Multifocal regression, peppering, regular pigment network, regular dots and globules
   D. Pinpoint, arborizing and glomerular vessels plus several melanoma-specific criteria
   E. Asymmetry of color and structure plus several melanoma-specific criteria

9. Which statement is true about Spitz nevi?
   A. They can have ten different patterns
   B. A Spitzoid lesion only refers to the starburst or pink patterns
   C. Melanoma is not in the differential diagnosis of regular starburst pattern
   D. In an adult, most Spitzoid lesions do not need to be excised
   E. Symmetrical and asymmetrical starburst patterns can be seen in melanoma

10. The following statement best describes the criteria seen in superficial spreading melanomas.
    A. Criteria associated with a benign nevus are never seen
    B. They contain several well developed melanoma-specific criteria such as symmetry of color and structure and one prominent color
    C. Usually they have several well developed melanoma-specific criteria such as asymmetry of color and structure, multicomponent global pattern, regular network, regular globules and regular streaks
    D. They contain a variable number of melanoma-specific criteria such as asymmetry of color and structure, multicomponent global pattern, irregular local criteria, five or six colors and polymorphous vessels
    E. Are usually feature poor or featureless

Answers

1. E. Criteria to diagnose a melanocytic lesion include any variation of pigment network (regular and/or irregular), multiple brown dots and/or globules, homogeneous blue color of a blue nevus and parallel patterns seen on acral skin. The default category is the last way to diagnose a melanocytic lesion. Milia-like cysts, and follicular openings can be seen in melanocytic lesions but are not primary criteria to make the diagnosis. Answers A, B and C diagnose a basal cell carcinoma, dermatofibroma and hemangioma.

2. D. Diagnosing a melanocytic lesion by default means that one does not see criteria for a melanocytic lesion, seborrheic keratosis, basal cell carcinoma, dermatofibroma or hemangioma. Default is an absence of criteria. One has to memorize all of the criteria from each specific potential diagnosis to be able to diagnose a melanocytic lesion by default. Dermoscopy cannot be mastered by osmosis. It is essential to study and practice the technique routinely in one’s daily practice. Ink-spot lentigo and pyogenic granuloma are not in this algorithm.
3. C. All of the criteria used to diagnose seborrheic keratosis are commonly seen in daily practice. Melanoma-specific criteria can also be seen in atypical seborrheic keratosis. Beware of seborrheic keratosis-like melanomas. Milky red areas, irregular streaks, regression, rhomboid structures and circle within a circle are all melanoma-specific criteria that are more sensitive and specific for melanoma but could be found in seborrheic keratosis. Glomerular vessels are a primary criterion to diagnose Bowen’s disease and are not seen in seborrheic keratosis.

4. C. Basal cell carcinomas are usually a clinical diagnosis and dermoscopy is used to confirm ones clinical impression. By definition, if one sees pigment network the lesion could not be a basal cell carcinoma. A subset of melanomas can be indistinguishable from basal cell carcinoma with pigmentation and arborizing vessels. Pinpoint and glomerular vessels could be seen but they would be out shadowed by arborizing vessels. If not, one could be dealing with a basal cell-like melanoma. Moth-eaten borders are seen in lentigines and flat seborrheic keratosis, never in basal cell carcinomas.

5. B. The hallmark of vascular lesions are lacunae, vascular spaces with well-demarcated sharp borders. There is no set number of lacunae needed to make the diagnoses. At times one has to use their imagination to decide if the margins fit the criteria for vascular spaces. Different shades of red, blue and even black are typically seen. Black homogeneous color usually represents thrombosis. Major and minor lacunae do not exist. Fibrous whitish septae and/or bluishwhite color are routinely seen in typical hemangiomas. At times it is not possible to differentiate lacunae and red color of a hemangiom from the milky-red areas that can contain out-of-focus reddish globules seen in melanoma.

6. C. Dermatofibromas are ubiquitous benign tumors and in most cases dermoscopy is not needed to make the diagnosis. A central white patch and pigment network the primary criteria to make the diagnosis may or may not be present. It might not be possible to differentiate an atypical dermatofibroma from a melanoma if melanoma-specific criteria are identified. There are innumerable ways that the central white patch can appear, and in many cases it is not centrally located. Telectangietatic vessels with polymorphous shapes are commonly seen but basacell-like arborizing vessels would make the diagnosis of a dermatofibroma unlikely.

7. D. Irregularity is the name of the game if criteria are to be considered melanoma-specific. Melanoma-specific criteria can be seen in both benign and malignant pathology but are more sensitive and specific for melanoma. There is not a single melanoma-specific criterion that is pathognomonic for melanoma. One should learn their definitions and study as many classic textbook examples as possible. Rhomboid structures help diagnose melanoma on the face and the parallel-ridge pattern can be seen in acral melanomas.

8. E. Dysplastic nevi are ubiquitous in the light skinned population and can be indistinguishable clinically and dermoscopically from melanoma. They usually look more benign than malignant with dermoscopy; however, there are melanomas that do not have well developed melanoma-specific criteria. Vessels of any kind are not typically seen except in pink feature poor dysplastic nevi. They can have a variable number of melanoma-specific criteria (e.g., irregular pigment network, irregular dots and/or globules, irregular blotches) that are not as well developed as those seen in melanoma. Streaks, regression and many colors are not usually seen and should raise a “red flag “ of concern that the lesion might be a melanoma.

9. E. Spitzoid lesions are always a “red flag” for concern. Even symmetrical patterns can be seen in melanoma. There are only six patterns (starburst, globular, homogeneous, pink, black network, atypical). One often has to use their imagination to diagnose a Spitzoid lesion. Since symmetrical and asymmetrical Spitzoid patterns can be found in melanoma, they should all be excised in children as well as in adults. A dermatopathologist that specializes in melanocytic lesions is good, while one that has expertise in Spitzoid lesions is ideal. Even experienced dermatopathologists have trouble differentiating atypical Spitzoid lesions from melanoma, and atypical Spitzoid lesions have the potential to metastasize to regional lymph nodes.

10. D. Superficial spreading melanoma can have it all as far as the spectrum of melanoma-specific criteria goes. The criteria can be well developed or difficult to identify. Criteria associated with benign melanocytic lesions can also be seen. The more high risk criteria identified in the lesion, the greater the chance that one is dealing with a melanoma. Nodular and amelanotic melanoma are more likely to be feature poor or featureless.

REFERENCES

Altamura D, Avramidis M, Menzies SW: Assessment of the optimal interval for and sensitivity of short-term sequential


Radiologic findings of various cutaneous disorders are organized and presented as follows (Table 32-1):

- Bullous
- Connective tissue
- Cornification
- Hair and nails
- Hematologic
- Infectious
- Infectious, fungal
- Inflammatory
- Malignant potential
- Metabolic
- Pigmentation
- Vascular
- Other
### TABLE 32-1 Radiological Findings in Skin Diseases and Related Conditions

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<td>Junctional epidermolysis bullosa (Herlitz/Letals)</td>
<td>Autosomal recessive</td>
<td>Generalized bullae, perioral granulation tissue, absent/shed nails, dysplastic teeth, respiratory edema</td>
<td>Pyloric atresia</td>
</tr>
<tr>
<td></td>
<td>Defect in α6β4-integrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Connective Tissue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bushke-Ollendorf (connective tissue nevus syndrome)</td>
<td>Autosomal dominant</td>
<td></td>
<td>Asymptomatic oval opacities on x-ray (osteopoikilosis) may be mistaken for bone metastases</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Autosomal dominant, Autosomal recessive (kyphoscoliosis type VI; dermatosparaxis type VIIIC)</td>
<td>Skin hyperextensibility, cigarette paper texture to scars, hypermobile joints; congenital dislocation of the hip (types I, IV, VIIC and VIIIB)</td>
<td>Mitral valve prolapse and aortic root dilatation; wide joint spaces</td>
</tr>
<tr>
<td></td>
<td>Collagen and proteins involved in collagen production</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goltz syndrome (focal ectodermal dysplasia)</td>
<td>X-linked dominant</td>
<td>Fat herniation, cutaneous papillomas</td>
<td>Osteopathia striata (linear vertical opacities in metaphyses of the bones); lobster claw deformity of the hand</td>
</tr>
<tr>
<td>Lipoid proteinosis (hyalinosis cutis et mucosae, Urbach-Wiethe disease)</td>
<td>Autosomal recessive Defect of ECM gene</td>
<td>Hoarse cry at birth; early bullae with later pearly papules on face, eyelid, neck, mucosa, and extremities; alopecia, parotiditis, large wooden tongue, abnormal teeth, seizures</td>
<td>“Bean bag” hippocampal calcifications in the temporal lobe; deposits may also be found in the vocal cords and other laryngeal structures.</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Autosomal dominant Defect of fibrillin-1</td>
<td></td>
<td>Kyphoscoliosis; pectus excavatum (depression of sternum), pectus carinatum (projection of sternum); mitral valve prolapse and aortic root dilation</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>Autosomal recessive Autosomal dominant Defect in ABCC6 gene</td>
<td>Yellow pebbling of skin</td>
<td>Mitral valve insufficiency, artery calcification, coronary artery disease, peripheral vascular disease; gastric or duodenal hemorrhage</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Radiologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cornification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondrodysplasia punctata (Conradi-Hunermann-Happle syndrome)</td>
<td>X-linked dominant Defect in emopamil binding protein (EBP) (AKA 3beta-hydroxysteroid-Δ8-Δ7-isomerase)</td>
<td>Ichthyosiform erythroderma in Blashko’s lines, patchy alopecia, asymmetric focal cataracts</td>
<td>Stippled epiphyses (chondrodysplasia punctata), unilateral limb shortening, scoliosis</td>
</tr>
<tr>
<td>Congenital hemidsyplasia with ichthyosiform and limb defects (CHILD)</td>
<td>X-linked dominant Defect in NSDHL gene encoding 3beta-hydroxysteroid-dehydrogenase</td>
<td>Unilateral ichthyosiform erythroderma</td>
<td>Ipsilateral hypoplasia of limbs, bones, organs</td>
</tr>
<tr>
<td>Epidermal nevus syndrome (Ichthyosis hystrix)</td>
<td>Unknown</td>
<td>Epidermal nevi; tumors of fibrous and vascular tissue; seizures</td>
<td>Skeletal abnormalities associated with location of nevi; cerebral angiomas; systemic malignancies</td>
</tr>
<tr>
<td>Palmoplantar keratoderma with periodontosis (Papillon-Lefèvre syndrome)</td>
<td>Autosomal recessive Defect in cathepsin C</td>
<td>Palmoplantar keratoderma, psoriasiform hyperkeratotic plaques on elbows and knees, periodontitis, gingivitis</td>
<td>Calcification of dura mater, exfoliation of teeth</td>
</tr>
<tr>
<td><strong>Hair and Nails</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome)</td>
<td>X-linked recessive (extodysplasin gene) Autosomal dominant (NEMO)</td>
<td>Smooth, dry skin; hypo/anhidrosis with concomitant pyrexia</td>
<td>Jaw radiographs: hypodontia or dental abnormalities (peg shaped teeth)</td>
</tr>
<tr>
<td>Menkes syndrome (occipital horn syndrome)</td>
<td>X-linked recessive Defect of ATP7A gene</td>
<td>Pili torti, doughy skin; occipital horns develop from ectopic bone formation with in the aponeuroses of the posterior neck muscles</td>
<td>Elongated and tortuous vessels, subdural hematomas, tumors and cysts of the epidermis and epidermal appendages, occipital horns (exostoses); delayed myelination of white matter.</td>
</tr>
<tr>
<td>Nail patella syndrome</td>
<td>Autosomal dominant Defect in LMX1B gene</td>
<td>Dysplastic nails (triangular lunula), nephropathy (may be subclinical), Lester iris</td>
<td>Hypoplastic or absent patellae; posterior iliac horns (Fong’s syndrome when isolated finding)</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>Sporadic zinc finger anomaly TBX1 gene</td>
<td>Congenital absence of thymus and parathyroid; abnormal aorta, hypocalcemia, tetany; recurrent fungal and viral infections, cardiac problems most common cause of death</td>
<td>Absent thymic shadow</td>
</tr>
<tr>
<td>Disease</td>
<td>Etiology</td>
<td>Clinical Features</td>
<td>Radiologic Findings</td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Fanconi's syndrome (familial pancytopenia)</td>
<td>Autosomal recessive Mutation in 1 of the Fanconi anemia complementation group genes (FANC)</td>
<td>Pigment abnormalities, severe anemia, thrombocytopenia, hyperreflexia, retinal hemorrhage, testicular hypoplasia</td>
<td>Aplasia of the radius, absent thumbs</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital syphilis, early</td>
<td><em>Treponema pallidum</em></td>
<td>Clinical manifestations exhibit at birth or shortly thereafter</td>
<td>Epiphysitis of long bones (pain on motion, Parrot pseudoparalysis), osteochondritis, sawtooth lesion on x-ray in the metaphysic, onion-peel periosteum sign (multiple layers of new bone)</td>
</tr>
<tr>
<td>Congenital syphilis, late</td>
<td><em>Treponema pallidum</em></td>
<td>Late skeletal findings usually manifest in the latter half of the first decade or in the second decade</td>
<td>Knee perisynovitis (Clutton joints), bulldog jaw: mandibular protuberance, gummas (skull, long bones), saber shins: anterior bowing of tibia, Higoumenaki sign (unilateral hyperostosis of the medial clavicle), scaphoid scapulae: concavity of vertebral border of scapulae</td>
</tr>
<tr>
<td><strong>Infectious, Fungal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillosis</td>
<td><em>Aspergillus</em> species</td>
<td>Disseminated disease seen in immunocompromised patients; saprophytic colonization in immunocompetent hosts</td>
<td>Aspergilloma (pulmonary cavitary lesions), alveolar infiltrates</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td><em>Blastomyces dermatitidis</em></td>
<td>Atypical pulmonary disease with skin and bone involvement</td>
<td>Alveolar infiltrates (reticulonodular pattern), pleural effusion, similar to that of tuberculosis</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td><em>Coccidioides immitis</em></td>
<td>Desert rheumatism, arthalgia; erythema multiforme or erythema nodosum may occur</td>
<td>Infiltrates, nodules, cavity, mediastinal or hilar adenopathy, pleural effusion</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td><em>Cryptococcus neoformans</em></td>
<td>Found in avian excreta and soil, may coexist with sarcoid</td>
<td>Patchy pneumonitis, granulomas; may also be found in the bones and urologic organs</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td><em>Histoplasma capsulatum</em></td>
<td>Oral disease, Addison disease from adrenal infiltration</td>
<td>Patchy pulmonary infiltrates, upper lobe cavitations, healed lesions that appear as residual pulmonary nodules, lesions simulate that of tuberculosis; adrenal calcification</td>
</tr>
</tbody>
</table>

*TABLE 32-1 (Continued)*
<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Radiologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucormycosis</td>
<td><em>Rhizomycor absidia</em>&lt;br&gt;<em>Rhizomycor rhizopus</em></td>
<td>Patients are oftentimes immunocompromised (organ transplantation, diabetic)</td>
<td>Sinus disease, bone erosion</td>
</tr>
<tr>
<td>Mycetoma (Madura foot)</td>
<td>Fungal or bacterial infection of the subcutaneous tissue</td>
<td>Characteristically on the foot, follows implantation with draining sinus and gross deformity</td>
<td>Honeycomb bone destruction in the foot, extension to underlying bone and joints leads to osteomyelitis and arthritis</td>
</tr>
<tr>
<td>Nocardiosis</td>
<td><em>Nocardia asteroidis</em></td>
<td>Opportunistic infection</td>
<td>Pulmonary lesion simulates tuberculosis</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td><em>Paracoccidioides brasiensis</em></td>
<td>Most common in Latin American countries, poor hygiene, malnutrition</td>
<td>Confluent nodular infiltrates in the lung; adrenal lesions</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis (Fig. 32-1)</td>
<td>Unknown</td>
<td>Cutaneous findings with proximal muscle weakness, Gottron’s papules, heliotrope rash, periungual telangiectasias</td>
<td>Osteoporosis, calcinosis; interstitial pneumonia</td>
</tr>
<tr>
<td>Kawasaki’s syndrome (mucocutaneous lymph node syndrome)</td>
<td>Unknown</td>
<td>Mostly commonly in Japan; 5 of 6 criteria need to be met for diagnosis (fever unresponsive to antibiotics, conjunctivitis, erythema/edemas of palms, oral lesions, polymorphous eruption, cervical lymphadenopathy</td>
<td>Echocardiogram—coronary artery aneurysm; coronary artery calcifications</td>
</tr>
<tr>
<td>Morphea</td>
<td>Unknown</td>
<td>Localized scleroderma</td>
<td>Melorheostosis (dense linear pattern of hyperostosis resembling candle wax flowing)</td>
</tr>
<tr>
<td>Reiter’s syndrome</td>
<td>Unknown</td>
<td>Develops after enteric infections(eactive arthritis); seronegative spondyloarthritides; sacroiliitis, spondyloarthritides</td>
<td>Enthesopathy, bone lucency, new bone formation; feet are involved with relative sparing of hands</td>
</tr>
<tr>
<td>SAPHO syndrome</td>
<td>Unknown</td>
<td>Eponym for the combination of synovitis, acne, pustulosis, hyperostosis, and osteitis</td>
<td>Hyperostosis, osteitis, “bullhead” sign in sterno-costoclavicular region on bone scan (sternoclavicular hyperostosis); may be indistinguishable from chronic osteomyelitis, hypervitaminosis A, retinoid use</td>
</tr>
</tbody>
</table>
### TABLE 32-1 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Radiologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoidosis</td>
<td>Unknown</td>
<td>Granulomatous multisystem disorder</td>
<td>Bilateral hilar adenopathy, interstitial pulmonary infiltrates, osteolytic lesions; splenomegaly, renal and bone involvement may be seen, as well as neurosarcoid</td>
</tr>
<tr>
<td><strong>Malignant Potential</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cockayne syndrome</strong></td>
<td>Autosomal recessive</td>
<td>“Cachectic dwarf”: long limbs, contractures, cool acral extremities, photosensitivity, progressive neural degeneration, deafness, retinitis pigmentosum, cataract, dental caries</td>
<td>Intracranial calcifications (Fig. 32-2)</td>
</tr>
<tr>
<td><strong>Cowden disease</strong></td>
<td>Autosomal dominant</td>
<td>Tricholemmomas, oral papillomas</td>
<td>Mammogram to identify breast lesions; barium swallow, upper and lower GI endoscopy for hamartomatous polyps; ovarian cysts; goiter</td>
</tr>
<tr>
<td><strong>Dyskeratosis congenita</strong></td>
<td>X-linked recessive</td>
<td>Reticulated pigmentation of skin, dystrophic nails, premalignant oral leukoplakia</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td><strong>Gardner’s syndrome</strong></td>
<td>Autosomal dominant</td>
<td>Epidermoid cysts, fibroma, desmoids tumor</td>
<td>Osteomas; odontomas/supernumerary teeth, hyperostosis, thyroid tumors, intestinal adenomatous polyps</td>
</tr>
<tr>
<td><strong>Gorlin-Goltz (basal cell nevus syndrome)</strong> (See also Chap. 23)</td>
<td>Autosomal dominant</td>
<td>Basal cell carcinomas, palmoplantar pits, frontal bossing, medulloblastoma, ovarian fibromas, fibrosarcoma; Albright’s sign: short fourth metacarpal (Figure 32-3)</td>
<td>Odontogenic jaw cysts, calcification of falx cerebri (Fig. 32-4), rib deformities, bifid ribs, kyphoscoliosis, long bone cysts</td>
</tr>
<tr>
<td><strong>Peutz-Jeghers syndrome</strong></td>
<td>Autosomal dominant</td>
<td>Periorificial mucocutaneous melanocytic macules (lentigenes)</td>
<td>Intestinal hamartomatous polyps most numerous in the jejunum and ileum</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alkaptonuria</strong></td>
<td>Autosomal recessive</td>
<td>Blue-black discoloration of sclera and cartilage, dark sweat/urine/cerumen, arthropathy (large joints); deafness</td>
<td>Aortic and intervertebral disk calcification (Fig. 32-5); renal stones, prostate concretions; spinal x-rays are diagnostic.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Radiologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcinosis cutis</td>
<td>Calcium deposition without bone formation</td>
<td>Three main types: dystrophic (damaged tissue with normal calcium/phosphorus levels); metastatic (normal tissue with abnormal calcium and phosphorous levels); idiopathic (no tissue damage or metabolic disorder)</td>
<td>Visceral and nonvisceral calcification; depends on type of cutaneous calcinosi</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Autosomal recessive Deficiency in glucocerebrosidase</td>
<td>Type I: manifests in adults as hyperpigmentation, hepatosplenomegaly, lymphadenopathy, pancytopenia. Type II: manifests in infancy as hepatosplenomegaly, rapid neurologic deterioration, chronic aspiration, pneumonia. Bone marrow: Gaucher cells (“crumpled tissue paper”)</td>
<td>Splenomegaly, osteoporosis from infiltration by Gaucher cells, bone infarcts, avascular necrosis of femoral head, Erlenmeyer flask deformity of long bones, periosteal new bone formation</td>
</tr>
<tr>
<td>Gout</td>
<td>Deposition of monosodium urate</td>
<td>Tophi on helix of ears, elbows, fingers and toes</td>
<td>Soft tissue tophi may calcify; punched out cystic lesions on articular surfaces without osteoporosis.</td>
</tr>
<tr>
<td>Hepatolenticular degeneration (Wilson disease)</td>
<td>Autosomal recessive Defect of ATB7B gene</td>
<td>Liver failure</td>
<td>On MRI, changes in the putamen and caudate nuclei may be found from copper deposition; osteoporosis and “fringed” appearance of articular surfaces; cirrhosis</td>
</tr>
<tr>
<td>Pigmentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albright's hereditary osteodystrophy (McCune-Albright syndrome)</td>
<td>Postzygotic mutation Defect in GNAS1 gene encoding alpha subunit of the G stimulatory protein that regulates adenylate cyclase</td>
<td>“Coast of Maine” cafe-au-lait macules, precocious puberty, endocrine abnormalities (hyperthyroidism); dimpling over the metacarpophalangeal joints (Albright sign)</td>
<td>Polyostotic fibrous dysplasia, recurrent fractures, bowing of the limbs, limb-length discrepancies, bone cysts, sclerosis at the skull base; findings often seen associated with area of pigmentation</td>
</tr>
<tr>
<td>Hypomelanosis of Ito (incontinentia pigmenti achromians)</td>
<td>Unknown</td>
<td>Marbled cake hypopigmentation in Blaschko’s lines, seizures</td>
<td>Musculoskeletal abnormalities asymmetry</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
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<th>Clinical Features</th>
<th>Radiologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinentia pigmenti (Bloch-Sulzberger syndrome)</td>
<td>X-linked dominant Defect on NEMO gene</td>
<td>Linear arrangement of lesions, appearance depends on stage of development (vesicular, verrucous, hyperpigmentation)</td>
<td>Peg or conical shaped teeth; brain atrophy</td>
</tr>
<tr>
<td>Neurofibromatosis I</td>
<td>Autosomal dominant Defect in neurofibromin</td>
<td>Diagnose optic glioma with MRI, occurs during the first 4 years of life; bilateral in 4%. It is the most common intracranial tumor associated with neurofibromatosis type 1</td>
<td>Sphenoid wing dysplasia, cortical thinning of long bones, bowing of the tibia (Fig. 32-6), tibial pseudoarthrosis, scoliosis, optic glioma</td>
</tr>
<tr>
<td>Neurofibromatosis II</td>
<td>Autosomal dominant Defect in merlin</td>
<td>Café-au-lait with hair</td>
<td>Acoustic neuromas, cranial nerve schwannomas, brain tumors</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Autosomal dominant Defect in hamartin (ch 9) or tuberin (ch 16)</td>
<td>Ash-leaf hypo-pigmented patches, connective tissue tumors</td>
<td>Hamartomas at multiple sites. Phalangeal cysts, periosteal thickening, paraventricular calcifications, cortical tubers, subependymal hamartomas; angiomyolipoma, pulmonary lymphangiomatosis, cardiac rhabdomyoma</td>
</tr>
</tbody>
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**Vacular**

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<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Radiologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary hemorrhagic telangiectasia (Osler-Weber-Weber-Rendu disease)</td>
<td>Autosomal dominant Defect in endoglin gene or ALK1 gene</td>
<td>Telangiectasias, epistaxis</td>
<td>CT scan: pulmonary arteriovenous malformations, liver, kidney, and splenic lesions</td>
</tr>
<tr>
<td>Proteus syndrome</td>
<td>PTEN</td>
<td>Symmetrical overgrowth; capillary malformations and subcutaneous masses</td>
<td>Bony overgrowth of the cranium of facial structures, soft tissue and bony hypertrophy</td>
</tr>
<tr>
<td>Ataxia-teleangiectasia (Louis-Bar syndrome)</td>
<td>ATM gene</td>
<td>Telangiectasias, café-au-lait macules</td>
<td>Sinopulmonary infections, thymus maldevelopment, subnormal bone age</td>
</tr>
<tr>
<td>Blue rubber nevus syndrome (Bean syndrome)</td>
<td>Unknown</td>
<td>Venous malformations</td>
<td>GI venous malformation with endoscopy</td>
</tr>
<tr>
<td>Klippel-Trenaunay-Weber</td>
<td>Unknown</td>
<td>Capillary malformation, usually on lower extremity. Parkes-Weber variant: atrioventricular fistulas, high-output heart failure</td>
<td>Underlying bone and soft tissue hypertrophy, varicosities, thromboses, destructive bone lesions, limb hypertrophy and abnormalities, compensatory scoliosis</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Radiologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maffucci syndrome (enchondromatosis with hemangioma)</td>
<td>Unknown</td>
<td>Grapelike superficial and deep venous malformations (rarely malignant). Between 15% and 30% of enchondromas transform to chondrosarcoma</td>
<td>Multiple enchondromas (phalanges, long bones), fractures, bowing, limb length discrepancies; phleboliths in hemangiomas; Ollier disease: multiple enchondromas without hemangiomas</td>
</tr>
<tr>
<td>Sturge-Weber (encephalotrigeminal angiomatosis)</td>
<td>Unknown</td>
<td>Facial capillary malformation, seizures, hemiparesis, choroidal malformations, glaucoma</td>
<td>Tram track (double contour) calcifications of cerebral cortex, leptomeningeal angiomatosis; underlying soft tissue and skeletal hypertrophy</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td>Sequestration of skin along embryonic closure lines.</td>
<td>Present at birth on the head and neck most commonly</td>
<td>MRI to diagnose intracranial or intramedullary cysts</td>
</tr>
<tr>
<td>Langerhans’ cell histiocytosis</td>
<td>Unknown</td>
<td>Crusted purpuric papules and a scaly seborrheic-like eruption in the scalp and groin</td>
<td>Letterer-Siwe: honeycomb lung involvement with cystic cavities (Fig. 32-7); floating teeth, osteolytic bone lesions. Hand-Schüller-Christian: “punched out” osteolytic skull lesions (Fig. 32-8); eosinophilic granulomas: granulomatous bone lesion (Fig. 32-9)</td>
</tr>
<tr>
<td>Multicentric reticulohistiocytosis</td>
<td>Unknown</td>
<td>Destructive polyarthritis</td>
<td>Resorption of subchondral bone, arthritis mutilans, accordion hand (shortening of fingers and mutilation)</td>
</tr>
</tbody>
</table>


**FIGURE 32-5** Radiologic findings in an alkaptonuric patient showing aortic and vertebral disk calcification. (Reprinted with permission from Wolff, et al., Fitzpatrick's Dermatology in Internal Medicine, 7th edition, Mcgraw-Hill; 2008.)

FIGURE 32-7 Letterer-Siwe disease, “honeycomb lung”. (Reprinted with permission from Wolff, et al., Fitzpatrick’s Dermatology in Internal Medicine, 7th edition, McGraw-Hill; 2008.)


FIGURE 32-9 Eosinophilic granulomas. (Reprinted with permission from Wolff, et al., Fitzpatrick’s Dermatology in Internal Medicine, 7th edition, McGraw-Hill; 2008.)
**Answers**

1. C. Osteopathia striata. The condition is Goltz syndrome, characterized by fat herniations, cutaneous papillomas, and lobster claw deformity of the hand. In contrast, osteopoikilosis and stippled epiphyses are seen in Bushke-Ollendorf and Conradi-Hunnerman-Happle syndromes, respectively.

2. M. Sphenoid wing dysplasia. The condition is neurofibromatosis, type I, characterized by neurofibromas, café-au-lait spots and optic gliomas. Neurofibromatosis type II is caused by a defect in merlin. Angiomyolipomas and rhabdomyomas are found in tuberous sclerosis, defects in hamartin and tuberin.

3. P. Tram track calcification of cerebral cortex. The condition is Sturge-Weber syndrome, characterized by facial capillary malformation, seizures, hemiparesis, choroidal malformations, and glaucoma. Radiologic findings include tram track calcification of cerebral cortex. In contrast, bean bag hippocampal calcification is found in lipoid proteinosis. When calcification is found on intervertebral disks, this is characteristic for alkaptonuria.

4. O. Enchondromas. The condition is Mafucci, characterized by enchondromas. Ollier disease, in contrast, is the presence of multiple enchondromas without hemangiomas.

5. Q. Arthritis mutilans and accordion hand. The condition is multicentric reticulohistiocytosis, characterized by destructive polyarthritis that may progress to arthritis mutilans and accordion hand.

6. A. Pyloric atresia. The condition is junctional epidermolysis bullosa, characterized by generalized bullae, perioral granulation tissue, absent/shed nails, dysplastic teeth, and respiratory edema.

7. F. Absent thymic shadow. The condition is DiGeorge syndrome, characterized by congenital absence of thymus and parathyroid, hypocalcemia, tetany, recurrent fungal and viral infections, and cardiac problems.

8. H. Coronary artery aneurysm and coronary artery calcifications. The condition is Kawasaki syndrome (mucocutaneous lymph node syndrome), characterized by coronary artery aneurysms on echocardiogram. Coronary artery calcifications may also be seen.

9. E. Absent patella and posterior iliac horns. The condition is nail patella syndrome, characterized by hypoplastic or absent patellae and posterior iliac horns. When posterior iliac horns are present without other abnormalities, this is called Fong syndrome.

10. I. Odondogenic jaw cysts and calcification of falx cerebri. Basal cell nevus syndrome is characterized...
by defects in the PTCH gene. McCune-Albright is associated with postzygotic mutation in GNAS1 gene encoding alpha subunit of the G stimulatory protein that regulates adenylate cyclase. Deficiency in glucocerebrosidase is associated with Gaucher disease. Mutation in one of the Fanconi anemia complementation group genes (FANC) is seen in Fanconi disease.

REFERENCES

INDICATIONS FOR ELECTRON MICROSCOPY

Ancillary to standard techniques (i.e., light microscopy) to resolve diagnostic difficulties in human histopathology through examination of ultrastructural findings at the cellular and organelle level

- Unclassifiable, undifferentiated neoplasms
- Supporting a diagnosis from a list of differential diagnosis
- Supporting a light microscopic diagnosis
- Determination of the primary site in metastatic neoplasms
- Medical disease of kidney
- Metabolic storage diseases
- Other congenital disorders
- Infectious agents
- Autoimmune diseases
- Certain cutaneous diseases
- Identification of foreign material in tissues

TECHNIQUE AND TISSUE PREPARATION

- Tissue preparation is similar to conventional wax embedding light microscopy: aldehyde fixation, dehydration, embedding, sectioning and examination of sections exposed to some form of radiation
- Electron microscopy differences include:
  - Image is formed by the scattering of electrons by heavy metal atoms (introduced as solutions of uranyl acetate and osmium tetroxide or lead citrate) selectively adherent to tissue sections
  - Tissue is embedded in epoxy, allowing for sectioning to a thickness of 100 nm
  - Tissue should be submitted in appropriate media (i.e., 2.5% glutaraldehyde; Karnovsky’s [universal] solution)
  - Fixation with glutaraldehyde provides the best structural preservation; unlike formaldehyde, glutaraldehyde is slowly penetrating. Therefore, only very small pieces of tissue are processed (i.e. 0.5 to 1 mm³ or 2–3 mm² and thickness of about 0.5 mm)
  - Although processing and staining are labor intensive, turn around time can be as short as 24 to 48 hours
  - Electron microscopy may also be performed on formalin fixed material from deparaffinizing a wax block. Preservation may be sufficient for diagnostic purposes although results may be variable

DIAGNOSTIC CELLS AND ORGANELLES

Langerhans Cell (Fig. 33-1)
- Bone marrow-derived
- Antigen-processing and -presenting cells
- Indented nucleus with ropey nucleolus
- Rod- and racket-shaped (terminal expansion) cytoplasmic granules (Birbeck granules) with central dotted line
- Often seen at the cell surface when membrane-bound antigen is internalized by endocytosis
- Cytoplasm contains dispersed vimentin intermediate filaments

Merkel Cell (Fig. 33-2)
- Slowly adapting type I mechanoreceptors located in sites of high tactile sensitivity
- Present among basal keratinocytes
- Nucleus is lobulated
- Cytoplasm is electron-lucent with prominent Golgi
- Margins of cells project cytoplasmic spines toward keratinocytes
- Typical granules (80 to 200 nm) have a dense core, halo, and a slightly ruffled membrane
Granules contain neurotransmitter-like substances.
Intermediate filaments are numerous and assume a parallel or whorled arrangement near the nucleus (dot-like pattern).

**Lamellar Granules (Fig. 33-3)**
- In the intercellular space and cytoplasm of the granular cell
- 0.2 to 0.3 nm in diameter
- Membrane-bound secretory organelles containing a series of alternating thick and thin lamellae (folded sheets/disk-like/liposome-like structures)
- Contain glycoproteins, glycolipids, phospholipids, free sterols, acid hydrolases, and glucosylceramides

**Dermal-Epidermal Junction (Fig. 33-4)**
- Interface between epidermis and dermis
- LL = lamina lucida
- LD = lamina densa
- AFib = anchoring fibrils

**Desmosome (Fig. 33-5)**
- Calcium-dependent cell surface structures that function to promote adhesion of epidermal cells and aid in resistance to mechanical stresses
- Regularly organized submembrane plaque associated with intermediate filaments (see below)
- Intermediate line in the intercellular space
- Components of desmosome
- Desmosomal plaque
- Transmembrane glycoproteins (part of cadherin family)
- Desmosomal core

**Intermediate Filaments [Fig. 33-4 (Upper Left Corner): Dense Bundle of Tonofibrils]**
- About 8 to 12 nm thick
- There are five main classes (cytokeratin, vimentin, desmin, neurofilament, and glial filament)
- Only cytokeratin filaments have a distinctive ultrastructure: bundle together to form tonofilaments or tonofibrils
- Other intermediate filaments are generally non-bundling
- Fibrin may closely resemble tonofibrils, appearing as masses of short fibers that on higher magnification demonstrate periodicity
FIGURE 33-3 Lamellar granules. (Reprinted with permission from Wolff et al., Fitzpatrick's Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)

Stage IV melanosomes are enriched with electron dense melanin; the lattice is obscured.

**Macrophage (Fig. 33-7)**
- Part of the mononuclear phagocytic system
- Derived from precursor cells of bone marrow that differentiate into monocytes in the blood
- Skin macrophages express CD11c, CD6, and KiM8 antigens
- On electron microscopy: melanosomes within phagosomes

**Mast cell (Fig. 33-8)**
- Specialized secretory cells: originate in bone marrow from CD34 positive stem cells
- Proliferation depends on c-kit receptor and the stem cell factor (SCF) ligand
- Round/ovoid nucleus
- Granules can be secretory or lysosomal (0.2 to 0.5 nm)
- Mediators can be preformed and stored in granules (histamine, heparin, tryptase, chymase)
- Lattice-like structure of granules: found in mast cells of skin and intestinal submucosa
- Scroll-like structure of granules: found in mast cells of lung and intestinal mucosa

**Collagen (Fig. 33-9)**
- Fibers have regular banding pattern (periodicity) at approximately 70-nm intervals
- Regularly oriented fibers composed of fibrils and microfibrils
- Fibrils are aligned in a parallel manner, resulting in a pattern of cross-striations

**Elastic Tissue (Figs. 33-10 and 33-11)**
- Amorphous branching structures forming continuous sheets in some connective tissues
- Fibers composed of elastin with an electron-lucent core surrounded by thin, longitudinally oriented electron-dense microfibrils (Fig. 33-11)
- F = fibroblast; E = elastic tissue; C = collagen fibers (Fig. 33-10)

**Eosinophil (Fig. 33-12)**
- Nucleus has a deep groove and segment
- Granules contain electron-dense staining zone that is usually angulated or rectangular in shape surrounded by a lucent matrix
- Granules that contain the eosinophil basic proteins
  - Major basic protein (MBP)—only protein located in core
  - Eosinophilic cationic protein (ECP)—located in matrix


FIGURE 33-9 Collagen. (Reprinted with permission from Wolff et al., Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)

FIGURE 33-10 A fibroblast surrounded by elastic tissue. (Reprinted with permission from Wolff et al., Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)
- Eosinophil-derived neurotoxin (EDN)—located in matrix
- Eosinophil peroxidase (EPO)—located in matrix

**Amyloid**
- Composed of nonfibrillary protein known as amyloid P component and a fibrillary component that is derived from various sources
- Has an antiparallel beta-pleated sheet configuration
- Amorphous moderately dense material located in extracellular spaces
- At higher magnification, short and haphazardly arranged filaments (7–15 nm) can be observed, like straw strewn on the ground

**Fabry Disease (Fig. 33-13)**
- Deficient activity of lysosomal enzyme alpha-galactosidase-A
- Inherited as X-linked recessive; heterogenous females are generally asymptomatic, but may have characteristic corneal opacities
- Manifestations include: angiookeratoma in bathing suit distribution, acroparesthesia, acute attacks of pain, cardiovascular and renal disease
- Accumulation of neutral glycosphingolipids in most visceral tissues and body fluids, in particular endothelial cells

**FIGURE 33-11** Elastic fibers in normal human skin. *(Reprinted with permission from Wolff et al., Fitzpatrick’s Dermatology in General Medicine, 7th Ed. New York: McGraw-Hill; 2008.)*


• Concentric lamellar inclusions in lysosomes of fibrocytes

**Mycosis Fungoides, Sézary Cell (Fig. 33-14)**
• CD4+ T-helper lymphocytes
• Convoluted nucleus that is deeply indented (cerebriform)

**Granular Cell Tumor**
• Schwann cell origin
• Cytoplasmic granular appearance from numerous lysosomes, contain granular and membranous debris

**INFECTIONS**

**Pox Virus (Fig. 33-15)**
• Single molluscum contagiosum virus virion
• Size = 240 × 300 nm, no envelope
• dsDNA virus, capsid assembly in cytoplasm
• Also known to cause Orf, milker’s nodules, variola, and vaccinia

**Herpes Family of Viruses (Fig. 33-16)**
• Size = 120 to 200 nm
• Icosahedral, enveloped dsDNA
• Replicates in nucleus
• Herpes simplex (types 1 and 2) (human herpes virus (HHV) 1, HHV2), varicella-zoster (HHV3), Epstein-Barr virus (HHV4), cytomegalovirus (HHV5), HHV6 (roseola infantum), HHV8 (Kaposi sarcoma, body cavity lymphoma, Castleman disease)

**Papillomavirus (Fig. 33-17)**
• Multiple nonenveloped virions
• Size: 50 to 55 nm, icosahedral with capsid subunits (capsome)
• Nonenveloped dsDNA replicates in nucleus
QUIZ

Questions

1. Which study(s) should be performed to determine the precise location of separation in vesiculobullous conditions?
   A. Hematoxylin and eosin stained tissue sections
   B. Polarized light
   C. Heat induced epitope retrieval
   D. Electron microscopy
   E. Laser microdissection

2. You have just seen a male patient that has numerous angiokeratomas and acroparesthesias. To confirm the diagnosis, a biopsy is performed. For optimal tissue preservation of cellular detail, how should the tissue be submitted to pathology?
   A. In formalin
   B. In sterile saline
   C. In bacteriostatic saline
   D. In water
   E. In glutaraldehyde
   F. In Bouin solution

3. Which description matches the ultrastructural appearance of a patient with a brown macule that hives when stroked?
   A. Rod- and/or racquet-shaped cytoplasmic granule
   B. Homogenous dense core cytoplasmic granule
   C. Organized subepidermal plaque between two cells associated with keratin
   D. Organized subepidermal plaque between one cell and the dermis
   E. Scroll Like structure of granule
   F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
   G. Granules with angulated or rectangular electron dense area
   H. Convoluted nucleus with deep indentions (cerebriform)

4. Which description matches the ultrastructural appearance of a child with crusted purpuric papules and a scaly seborrheic-like eruption in the scalp and groin?
   A. Rod- and/or racquet-shaped cytoplasmic granule
   B. Homogenous dense core cytoplasmic granule
   C. Organized subepidermal plaque between two cells associated with keratin
   D. Organized subepidermal plaque between one cell and the dermis
   E. Scroll-like structure of granule

5. Which description matches the ultrastructural appearance of an elderly person with tense bullae located on intertriginous areas and lower extremities that may be preceded by a hive without scarring?
   A. Rod- and/or racquet-shaped cytoplasmic granule
   B. Homogenous dense core cytoplasmic granule
   C. Organized subepidermal plaque between two cells associated with keratin
   D. Organized subepidermal plaque between one cell and the dermis
   E. Scroll-like structure of granule
   F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
   G. Granules with angulated or rectangular electron dense area
   H. Convoluted nucleus with deep indentions (cerebriform)

6. Which description matches the ultrastructural appearance of a fair-skinned, male, 70-year-old patient with a solitary erythematous nodule on the face?
   A. Rod- and/or racquet shaped cytoplasmic granule
   B. Homogenous dense core cytoplasmic granule
   C. Organized subepidermal plaque between two cells associated with keratin
   D. Organized subepidermal plaque between one cell and the dermis
   E. Scroll-like structure of granule
   F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
   G. Granules with angulated or rectangular electron dense area
   H. Convoluted nucleus with deep indentions (cerebriform)

7. Which description matches the ultrastructural appearance of a patient with persistent scaly patches in sun protected areas that respond poorly to topical steroids?
   A. Rod- and/or racquet-shaped cytoplasmic granule
   B. Homogenous dense core cytoplasmic granule
   C. Organized subepidermal plaque between two cells associated with keratin
   D. Organized subepidermal plaque between one cell and the dermis
   E. Scroll-like structure of granule
F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
G. Granules with angulated or rectangular electron dense area
H. Convoluted nucleus with deep indentions (cerebriform)

8. Which description matches the ultrastructural appearance of a patient with hyperextensibility of the skin, easy bruising, poor healing with fish mouth scars?
   A. Rod- and/or racquet-shaped cytoplasmic granule
   B. Homogenous dense core cytoplasmic granule
   C. Organized subepidermal plaque between two cells associated with keratin
   D. Organized subepidermal plaque between one cell and the dermis
   E. Scroll like structure of granule
   F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
   G. Granules with angulated or rectangular electron dense area
   H. Convoluted nucleus with deep indentions (cerebriform)

9. In which stage of development does the melanin appear in the melanosome?
   A. Stage I
   B. Stage II
   C. Stage III
   D. Stage IV
   E. Stage V

10. Which protein is not an intermediate filament?
    A. Desmin
    B. Actin
    C. Vimentin
    D. Keratin
    E. Neurofilament

Answers

1. D. Electron microscopy. Electron microscopy is an ancillary technique to resolve diagnostic difficulties in human histopathology through examination of ultrastructural findings at the cellular and organelle level, such as meticulous examination of the dermal-epidermal junction to determine the location of separation in vesiculobullous diseases. Immunofluorescence is also helpful. Hematoxylin and eosin stained tissue sections is the standard method of preparation of tissue for light microscopy. Polarized light is used to confirm the presence of polarizable material (i.e., amyloid). Heat induced epitope retrieval may be necessary for immunohistochemistry of formalin fixed tissue.

2. E. Glutaraldehyde. Fixation with glutaraldehyde provides the best structural preservation; unlike formaldehyde, glutaraldehyde is slowly penetrating. Therefore, only very small pieces of tissue are processed (i.e., 0.5 to 1 mm³ or 2–3 mm² and thickness of about 0.5 mm). Electron microscopy may also be performed on formalin fixed material from deparaffinizing a wax block. Preservation may be sufficient for diagnostic purposes although results may be variable. Formalin is used for routine tissue fixation. Sterile saline is often used to submit tissue for microbiology studies. Bouin solution may be used to help tissue dyes adhere.

3. E. Scroll-like structure of granule. The patient has a mastocytoma that demonstrates Darier sign (hives when stroked). The characteristic cell is mast cells that contain scoll like structure of granules on electron microscopy.

4. A. Rod- and/or racquet-shaped cytoplasmic granule. The patient has findings that suggest Langerhans cell histiocytosis. The characteristic cell is the Langerhans cell that contains rod- and/or racquet-shaped cytoplasmic granules on electron microscopy.

5. D. Organized subepidermal plaque between one cell and the dermis. The patient has findings that suggest bullous pemphigoid, which affects proteins in the hemidesmosome.

6. B. Homogenous dense core cytoplasmic granule. The patient has findings that suggest Merkel cell carcinoma. The characteristic cell is the Merkel cell that contains homogenous dense core cytoplasmic granule on electron microscopy.

7. H. Convoluted nucleus with deep indentions (cerebriform). The patient has findings that suggest mycosis fungoides. The characteristic cell is the Sézary cell that contains a convoluted nucleus with deep indentions (cerebriform) on electron microscopy.

8. F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner. The patient has findings that suggest Ehlers-Danlos syndrome, which is a congenital abnormality of collagen. On electron microscopy, collagen appears as fibers with periodicity of approximately 70 nm and aligned in a parallel manner.

9. C. Stage III. There are only four stages of melanosome development. Melanosomes become elongated and form ordered, cross-striated lattice in stage II of development. Melanin does not appear until stage III. In stage IV, melanosomes are enriched with electron dense melanin; the lattice is obscured.

10. B. Actin. There are five main classes of intermediate filaments: cytokeratin, vimentin, desmin,
neurofilament, and glial filament. Actin is a protein involved in the contractile apparatus of cells.

REFERENCES


The purpose of this chapter is to present information that may be considered “high yield” for the dermatology board exam, mock boards, and recertification exam. Table 34-1 identifies common factoids relating to genetic inheritance of diseases. Table 34-2 focuses on important disease-associated viruses. Table 34-3 focuses on histologic bodies. Table 34-4 discusses infectious diseases for which there are known vectors. Table 34-5 presents common contact allergens. Tables 34-6, 34-7, and 34-8 focus on common findings of the bones, eyes, and nails, respectively.

The information included herein should not be considered complete or exhaustive. Detailed descriptions of the topics are found in other chapters.

**TABLE 34-1 Genes to Know**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene/Protein</th>
<th>Gene Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinentia Pigmenti</td>
<td>XLD (NEMO)</td>
<td>NF-κB essential modulator Transcription factor</td>
</tr>
<tr>
<td><strong>AUTOSOMAL DOMINANT INHERITANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioedema, hereditary (Quinke’s)</td>
<td>(CIINH) C1 esterase inhibitor</td>
<td>Inhibits first component of complement</td>
</tr>
<tr>
<td>Bannayan-Riley-Ruvalcaba</td>
<td>(PTEN) phosphatase and tensin homolog</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>Bart’s syndrome</td>
<td>(COL7A1) type VII collagen</td>
<td>Anchoring fibril</td>
</tr>
<tr>
<td>Bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis)</td>
<td>Keratins 1 and 10</td>
<td>Intermediate filament</td>
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</tbody>
</table>

*Continued*
TABLE 34-1  (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene/Protein</th>
<th>Gene Function</th>
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</thead>
<tbody>
<tr>
<td>Bullous ichthyosis of Siemens</td>
<td>Keratin 2e</td>
<td>Intermediate filament</td>
</tr>
<tr>
<td>Carney complex (LAMB [lentigines, atrial myxoma, mucocutaneous myxomas, blue nevi], NAME [nevi, atrial myxoma, myxoid neurofibroma, ephilides])</td>
<td>(PRKAR1A)</td>
<td>R1 regulatory subunit of protein kinase A</td>
</tr>
<tr>
<td>Cowden’s syndrome (multiple hamartoma syndrome)</td>
<td>(PTEN)</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>Darrier-White disease (keratosis follicularis)</td>
<td>(SERCA2) calcium ATPase2A2</td>
<td>Calcium dependent ATPase</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>(DKC1 gene) dykerin (TERC) telomerase, RNA component</td>
<td>rRNA processing Telomerase RNA component</td>
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<td>Ectodermal dysplasia, hidrotic (Clouston’s)</td>
<td>Connexin 30/ED2 gene, HED gene</td>
<td>Gap junction protein</td>
</tr>
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<td>Ectodermal dysplasia with skin fragility</td>
<td>Plakophilin 1</td>
<td>Structural</td>
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<td>Epidermolysis bullosa, dominant dystrophic (EB)</td>
<td>(Col7A1) Type VII collagen</td>
<td>Anchoring fibril</td>
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<tr>
<td>Epidermolysis bullosa simplex (EBS)</td>
<td>Keratins 5 and 14</td>
<td>Intermediate filament</td>
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<tr>
<td>Erythrokeratoderma variabilis (EKV)</td>
<td>Connexin 31</td>
<td>Gap junction protein</td>
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<tr>
<td>Gardner’s syndrome</td>
<td>(APC) adenomatosis polyposis coli</td>
<td>Cleaves β-catenin</td>
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<td>Hailey-Hailey disease</td>
<td>(ATPase2C1)</td>
<td>Calcium-dependent ATPase</td>
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<td>Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)</td>
<td>Endoglin Alk-1 gene activin receptor binding kinase</td>
<td>TGF-β binding protein TGF-β receptor</td>
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<tr>
<td>MEN I</td>
<td>(MEN1) menin gene</td>
<td>Binds nuclear junD</td>
</tr>
<tr>
<td>MEN IIa and IIb</td>
<td>(RET) receptor tyrosine kinase</td>
<td>Proto-oncogene</td>
</tr>
<tr>
<td>Milroy’s disease (Nonne-Milroy-Meige Syndrome)</td>
<td>(FLT-4) a.k.a (VEGFr-3)</td>
<td>Growth factor receptor</td>
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<td>Monilethrix</td>
<td>KRT hHb6 and hHb1 Type II human hair keratins, 6 &amp; 1</td>
<td>Intermediate filament</td>
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<td>Muir-Torre syndrome</td>
<td>(hMSH2)</td>
<td>Mismatch repair gene</td>
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<td>Nail-Patella syndrome</td>
<td>LMX1B gene</td>
<td>Homeobox domain transcription factor</td>
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<th>Disease</th>
<th>Gene/Protein</th>
<th>Gene Function</th>
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<tr>
<td>Naxos disease</td>
<td>Junctional plakoglobin&lt;br&gt;Keratin 9</td>
<td>Structural protein&lt;br&gt;Intermediate filament</td>
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<td>Neurofibromatosis I</td>
<td>NF-1 (neurofibromin)</td>
<td>Increases GTPase activity of ras</td>
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<tr>
<td>Neurofibromatosis II</td>
<td>NF-2 (schwannomin or Merlin)</td>
<td></td>
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<td>NOMID syndrome (neonatal onset multisystem inflammatory disease); also called CINCA syndrome</td>
<td>CIAS1 gene</td>
<td>Cryopyrin gene, role in innate immune response.</td>
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<td>Pachyonychia congenuita</td>
<td>K6, K16, or K17</td>
<td>Intermediate filament</td>
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<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
<td>Tumor suppressor</td>
</tr>
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<td>Piebaldism</td>
<td>(C-ki)</td>
<td>Proto-oncogene (tyrosine kinase)</td>
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<td>Porphyria cutanea tarda</td>
<td>Uroporphyrinogen decarboxylase</td>
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<td>Porphyria, acute intermittent</td>
<td>Porphobilinogen deaminase</td>
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<td>Porphyria, erythropoietic protoporphyria (EPP)</td>
<td>Ferrochelatase</td>
<td>Mitochondrial gene</td>
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<td>Porphyria, variegate</td>
<td>Protoporphyrinogen oxidase</td>
<td>Mitochondrial gene</td>
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<tr>
<td>Reed syndrome (cutaneous and uterine leiomyomatosis)</td>
<td>Fumarate hydratase</td>
<td>Tumor suppressor</td>
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<tr>
<td>Rubenstein-Taybi syndrome</td>
<td>(CBP) CREB-Binding Protein</td>
<td>Involved in cAMP regulated gene expression</td>
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<tr>
<td>Striate PPK 1</td>
<td>Desmoglein-1</td>
<td>Structural protein</td>
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<tr>
<td>Striate PPK 2</td>
<td>Desmoplakin</td>
<td>Structural protein</td>
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<td>Tuberous sclerosis</td>
<td>(TSC1) on Chrom. 9 hamartin gene&lt;br&gt;(TSC2) on Chrom. 16 tuberin gene</td>
<td>GTPase activating protein domain</td>
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<td>Vohwinkel</td>
<td>Loricrin gene</td>
<td>Structural</td>
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<td>Vohwinkel with deafness</td>
<td>Connexin 26</td>
<td>Gap junction protein</td>
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<td>Vorner syndrome</td>
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<td>Intermediate filament</td>
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<td>Waardenburg syndrome</td>
<td>(PAX3) (MITF) (EDN3/SOX10) – with Hirschprung’s</td>
<td>Transcription factor&lt;br&gt;Transcription factor&lt;br&gt;endothelin</td>
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<tr>
<td>White sponge nevus</td>
<td>KERATIN 4 and 13</td>
<td>Intermediate filament</td>
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<tr>
<td>Disease</td>
<td>Gene/Protein</td>
<td>Gene Function</td>
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</tr>
<tr>
<td><strong>Autosomal Recessive Inheritance</strong></td>
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</tr>
<tr>
<td>Atrichia with papules (&quot;alopecia universalis&quot;)</td>
<td>(HR) hairless gene</td>
<td>Zinc finger</td>
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<tr>
<td>Albinism I, oculocutaneous</td>
<td>TYR-tyrosinase</td>
<td>Melanin pathway</td>
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<td>Albinism II, oculocutaneous</td>
<td>P gene—pink protein</td>
<td>Unknown</td>
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<tr>
<td>Albinism III, oculocutaneous (rufous)</td>
<td>(TYRP1) tyrosinase-related protein 1</td>
<td>Stabilizes tyrosinase</td>
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<tr>
<td>Alkaptonuria</td>
<td>(HGO) homogentisic acid oxidase</td>
<td>Phenylalanine and tyrosine breakdown pathway</td>
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<td>Ataxia-telangiectasia (Louis-Bar)</td>
<td>(ATM/ATM protein) ataxia-telangiectasia mutated</td>
<td>Phosphatidylinositol-3-kinase like domain</td>
</tr>
<tr>
<td>Basal cell carcinoma syndrome, nevoid (Gorlin)</td>
<td>(PTCH) patched homolog (Drosophila)</td>
<td>Inhibits “smoothened” signaling; this inhibition blocked by “hedgehog”</td>
</tr>
<tr>
<td>Bloom’s syndrome</td>
<td>(BLM)</td>
<td>DNA helicase</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>LYST/CHS1 gene/CHS protein</td>
<td>Lysosomal transport</td>
</tr>
<tr>
<td>Citrullinemia</td>
<td>(ASS) arginosuccinate synthetase gene</td>
<td>Enzyme in urea cycle</td>
</tr>
<tr>
<td>Cockayne’s syndrome</td>
<td>(CKN1) (ERCC6) XPB DNA helicase</td>
<td>DNA helicase—DNA repair</td>
</tr>
<tr>
<td>Epidermolysis bullosa, generalized atrophic benign (GABEB)</td>
<td>(BPAg2) collagen XVII (LAMB3) laminin</td>
<td>Structural protein</td>
</tr>
<tr>
<td>Epidermolysis bullosa, junctional (EB with pyloric atresia)</td>
<td>Integrin α6,β4/ITGB6 gene, ITBG4 gene</td>
<td>Structural</td>
</tr>
<tr>
<td>Epidermolysis bullosa, junctional (EB letalis, Herlitz)</td>
<td>Laminin 5 LAMA3, LAMB3, LAMC2 genes</td>
<td>Structural</td>
</tr>
<tr>
<td>EBS with muscular dystrophy</td>
<td>Plectin/PLEC1 gene</td>
<td>Structural</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>(MEFV) marenstrin</td>
<td>PMN inhibitor</td>
</tr>
<tr>
<td>Farber’s disease (lipogranulomatosis)</td>
<td>Acid ceramidase</td>
<td>Deficiency leads to ceramide accumulation</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
<td>β-Glucocerebrosidase</td>
<td></td>
</tr>
<tr>
<td>Griscelli syndrome</td>
<td>(MTO5a) myosin Va</td>
<td>Melanosome transport to keratinocytes</td>
</tr>
</tbody>
</table>

*Continued*
### Table 34-1 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene/Protein</th>
<th>Gene Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocystinuria</td>
<td>Cystathione synthetase</td>
<td>Condensation of homocysteine and serine</td>
</tr>
<tr>
<td>Hurler’s syndrome</td>
<td>Alpha-L-uronidase</td>
<td></td>
</tr>
<tr>
<td>Hypotrichosis, localized autosomal recessive</td>
<td>(DSG4) desmoglein 4</td>
<td>Desmosomal cadherin</td>
</tr>
<tr>
<td>Ichthyosis, lamellar</td>
<td>Transglutaminase-1</td>
<td></td>
</tr>
<tr>
<td>Lhermite-Duclos syndrome</td>
<td>(PTEN)</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>Neimann-Pick disease</td>
<td>Sphingomyelinase</td>
<td></td>
</tr>
<tr>
<td>Netherton’s syndrome</td>
<td>SPINK5 gene</td>
<td>Serine protease inhibitor</td>
</tr>
<tr>
<td>Papillon-Lefevre syndrome</td>
<td>Cathepsin C</td>
<td>Lysosomal protease</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Phenylalanine hydroxylase</td>
<td></td>
</tr>
<tr>
<td>PIBIDS syndrome</td>
<td>(XPD) (TFIIH) xeroderma pigmentosa D</td>
<td>DNA helicase</td>
</tr>
<tr>
<td>Porphyria, congenital erythropoietic (Gunther)</td>
<td>Uroporphyrinogen III cosynthase</td>
<td></td>
</tr>
<tr>
<td>Porphyria, erythropoietic protoporphyria (EPP)</td>
<td>Ferrochelatase</td>
<td>Mitochondrial gene</td>
</tr>
<tr>
<td>Refsum syndrome</td>
<td>Phytanoyl Co-A hydroxylase</td>
<td></td>
</tr>
<tr>
<td>Richner-Hanhart syndrome</td>
<td>Tyrosine aminotransferase</td>
<td></td>
</tr>
<tr>
<td>Rothman-Thompson (poikiloderma congenital)</td>
<td>(RECQL4) DNA helicase</td>
<td>DNA helicase</td>
</tr>
<tr>
<td>Sjögren-Larsson syndrome</td>
<td>Fatty aldehyde dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>Takahara disease</td>
<td>Catalase</td>
<td>Bacterial defense</td>
</tr>
<tr>
<td>Tangier disease</td>
<td>(CERP)</td>
<td>Cholesterol efflux regulatory protein</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>(WRN) (ERCC) (XPB, D, and G)</td>
<td>DNA helicase</td>
</tr>
</tbody>
</table>

**X-Linked Dominant Inheritance**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene/Protein</th>
<th>Gene Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects)</td>
<td>(EBP gene) emopamil binding protein/ (NSDHL gene) 3-beta hydroxy sterol dehydrogenase</td>
<td>Cholesterol biosynthetic pathway</td>
</tr>
<tr>
<td>Conradi-Hünermann syndrome</td>
<td>(EBP) (PEX7)</td>
<td>Sterol isomerase peroxisomal gene</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td>(NEMO) NF-κB essential modulator</td>
<td>Transcription factor</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene/Protein</th>
<th>Gene Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X-Linked Recessive Inheritance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruton’s agammaglobulinemia</td>
<td>((BTK) gene)</td>
<td>Tyrosine kinase</td>
</tr>
<tr>
<td>Ectodermal, dysplasia, hypohidrotic (Christ-Seimens-Touraine syndrome)</td>
<td>Ectodysplasin</td>
<td></td>
</tr>
<tr>
<td>Fabry’s disease (angiokeratoma corporis diffusum)</td>
<td>Alpha-galactosidase A</td>
<td>Hydrolyzes glycolipids and glycoproteins</td>
</tr>
<tr>
<td>Granulomatous disease of childhood, chronic</td>
<td>((CYBB) gene) cytochrome B</td>
<td>NADPH-oxidase complex component (respiratory burst) needed to kill catalase-positive bacteria</td>
</tr>
<tr>
<td>Hunter’s syndrome</td>
<td>Iduronate sulfatase</td>
<td></td>
</tr>
<tr>
<td>Ichthyosis, X-linked</td>
<td>Aryl sulfatase C</td>
<td>Steroid sulfatase</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>((HGPRT))</td>
<td>Purine salvage pathway enzyme</td>
</tr>
<tr>
<td>Menke’s kinky hair syndrome</td>
<td>MNK</td>
<td>Copper transporting ATPase</td>
</tr>
<tr>
<td>SCID (severe combined immunodeficiency disease)</td>
<td>((ADA)) adenosine deaminase II-2 receptor</td>
<td></td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>((WASP)) sialoglycoprotein</td>
<td>Binds GTPase and actin</td>
</tr>
<tr>
<td><strong>Unknown or No Inheritance Pattern</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Fillagrin (FLG)</td>
<td>Filament aggregating protein</td>
</tr>
<tr>
<td>Baere-Stevenson syndrome</td>
<td>((FGFr2)) FGF receptor 2</td>
<td></td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
<td>((Gs-\alpha))</td>
<td>Stimulates G protein increasing cAMP</td>
</tr>
</tbody>
</table>
### TABLE 34-2 Viruses

<table>
<thead>
<tr>
<th>Associated or Causative Virus</th>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxsackie virus A-16</td>
<td>Hand-foot-and-mouth disease</td>
<td>Fever, ulcerovesicular stomatitis, acral erythematosus vesicles, buttock lesions</td>
</tr>
<tr>
<td>Coxsackie viruses (A-10)</td>
<td>Herpangina</td>
<td>Fever, painful ulcerations in mouth</td>
</tr>
<tr>
<td>EBV (Epstein-Barr virus)</td>
<td>Oral hairy leukoplakia</td>
<td>Corrugated white plaque on lateral tongue common in AIDS</td>
</tr>
<tr>
<td>EBV, HBV, echovirus 6</td>
<td>Unilateral laterothoracic exanthem</td>
<td>Simulates zoster</td>
</tr>
<tr>
<td>Echovirus 16</td>
<td>Boston exanthema</td>
<td>Mild exanthematous febrile illness with aseptic meningitis</td>
</tr>
<tr>
<td>Echovirus 25 and 32</td>
<td>Eruptive pseudoangiomatosis</td>
<td>As per syndrome name</td>
</tr>
<tr>
<td>Enterovirus 71</td>
<td>Herpangina</td>
<td>Fever, painful ulcerations in mouth</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Gianotti-Crosti syndrome</td>
<td>Children with sudden onset of lichenoid papules on face, extremities, and buttocks, sparing trunk</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Lichen planus</td>
<td>Purple polygonal, plateau-shaped, pruritic, papules</td>
</tr>
<tr>
<td>HHV (human herpesvirus)-8</td>
<td>Castleman disease</td>
<td>Angiolymphoid hyperplasia usually plasmacytoid in lymph nodes</td>
</tr>
<tr>
<td>HHV-6</td>
<td>Rosai-Dorfman</td>
<td>Sinus histiocytosis with massive lymphadenopathy</td>
</tr>
<tr>
<td>HHV-6 and 7</td>
<td>Roseola infantum (exanthem subitum, sixth disease)</td>
<td>Infants with high fever followed by exanthema</td>
</tr>
<tr>
<td>HHV-7?</td>
<td>Pityriasis rosea</td>
<td>Usually asymptomatic well-known exanthema</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi sarcoma</td>
<td>Vascular tumor, various types</td>
</tr>
<tr>
<td>HPV (human papilloma virus) 16 and 18, mostly HPV 1</td>
<td>Bowen disease</td>
<td>Squamous cell carcinoma in situ</td>
</tr>
<tr>
<td>HPV (papovavirus-dsDNA)</td>
<td>Condyloma acuminata</td>
<td>Genital warts</td>
</tr>
<tr>
<td>Low risk: Types 6 and 11 High risk: Types 16 and 18</td>
<td>Myrmecia</td>
<td>Large cup-shaped palmoplantar warts</td>
</tr>
<tr>
<td>HPV 13 and 32</td>
<td>Verruca plantaris</td>
<td>(Plantar warts)</td>
</tr>
<tr>
<td></td>
<td>Heck disease (focal epithelial hyperplasia)</td>
<td>Small white and pink papules in mouth</td>
</tr>
<tr>
<td>Associated or Causative Virus</td>
<td>Disease</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>HPV 16</td>
<td>Bowenoid papulosis</td>
<td>Genital papules and plaques resembling Bowen’s disease</td>
</tr>
<tr>
<td>HPV 2</td>
<td>Verruca vulgaris</td>
<td>Common warts</td>
</tr>
<tr>
<td>HPV 23b</td>
<td>Stucco keratoses</td>
<td>White hyperkeratotic plaques on legs</td>
</tr>
<tr>
<td>HPV 3</td>
<td>Verruca plana</td>
<td>(Flat warts)</td>
</tr>
<tr>
<td>HPV 5, 8, 12, and others as well as common types</td>
<td>Epidermodysplasia verruciformis</td>
<td>Inherited disorder of HPV infection and SCCs</td>
</tr>
<tr>
<td>HPV 6 and 11</td>
<td>Buschke and Löwenstein</td>
<td>Giant condyoma</td>
</tr>
<tr>
<td>HPV 60</td>
<td>Ridged wart</td>
<td>Wart with preserved dermatoglyphics</td>
</tr>
<tr>
<td>HPV 7b</td>
<td>Butcher’s wart</td>
<td>Warty lesions seen in people who handle raw meat</td>
</tr>
<tr>
<td>HSV (herpes simplex virus)</td>
<td>Kaposi varicelliform eruption (eczema herpeticum)</td>
<td>Diffuse HSV ulcerations in eczematous dermatitis</td>
</tr>
<tr>
<td>MCV (molluscum contagiosum virus) -1 to MCV-4; MCV-2 in HIV</td>
<td>Molluscum contagiosum</td>
<td>Umbilicated lesions common in children and HIV</td>
</tr>
<tr>
<td>Nonspecific: hep. B, parvovirus B19, rubella</td>
<td>STAR complex</td>
<td>Sore throat, arthritis, rash</td>
</tr>
<tr>
<td>Paramyxovirus (RNA)</td>
<td>Measles (rubeola)</td>
<td>Viral prodrome, then enanthem (Koplick spots), then maculopapular rash spreading craniocaudally</td>
</tr>
<tr>
<td>Parapoxvirus</td>
<td>Orf</td>
<td>Umbilicated nodule after farm animal exposure</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Erythema infectiosum (fifth disease)</td>
<td>Slapped cheeks, reticular exanthem, anemia</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Papular/purpuric stocking-glove syndrome</td>
<td>As named</td>
</tr>
<tr>
<td>Poxvirus (DNA)</td>
<td>Molluscum contagiosum</td>
<td>Umbilicated lesions common in children and HIV</td>
</tr>
<tr>
<td>Togavirus (RNA)</td>
<td>Rubella</td>
<td>Viral prodrome, prominent lymphadenopathy, pain with superolateral eye movements, morbilliform rash, exanthem (Forschheimer’s spots)</td>
</tr>
<tr>
<td>Variola (poxvirus) (DNA)</td>
<td>Variola major (smallpox)</td>
<td>12-day incubation, fever and malaise, then centrifugal vesiculopustular rash</td>
</tr>
<tr>
<td>Disease</td>
<td>Histologic Finding</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>----------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>A-HSV, CMV (cytomegalovirus), and VZV (varicella zoster virus) B-polio</td>
<td>Cowdry type A and B inclusion bodies</td>
<td>Type A: intranuclear eosinophilic, amorphous bodies surrounded by a clear halo Type B: in neuronal cells</td>
</tr>
<tr>
<td>Amiodarone hyperpigmentation</td>
<td>Lipofuscin granules</td>
<td>Yellow-brown granules in macrophages</td>
</tr>
<tr>
<td>Androgenic alopecia</td>
<td>Arao-Perkins bodies</td>
<td>Elastin bodies seen within “streamers” beneath vellus follicles</td>
</tr>
<tr>
<td>Benign cephalic histiocytosis</td>
<td>Comma-shaped bodies</td>
<td>Cytoplasmic bodies seen on EM</td>
</tr>
<tr>
<td>Café-au-lait macules, neurofibromatosis, Chediak-Higashi</td>
<td>Macromelanosomes</td>
<td>Large melanosomes</td>
</tr>
<tr>
<td>Chediak-Higashi</td>
<td>Giant liposomes in neutrophils</td>
<td>Large liposomal granules</td>
</tr>
<tr>
<td>Chromomycosis</td>
<td>Medlar/sclerotic bodies</td>
<td>Large (5-12 µm round, thick walled brown cells seen in and out of giant cells)</td>
</tr>
<tr>
<td>Cutaneous meningioma</td>
<td>Psammoma bodies</td>
<td>Concentrically laminated calcified basophilic bodies</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>Pautrier microabscess</td>
<td>Clusters of lymphocytes within epidermis</td>
</tr>
<tr>
<td>Darier’s, Grover’s, warty dyskeratoma (Hailey-Hailey)</td>
<td>Corps grains</td>
<td>Dyskeratotic keratinocytes with elongated nuclei seen in the granular zone</td>
</tr>
<tr>
<td></td>
<td>Corps ronds</td>
<td>Dyskeratotic keratinocytes with perinuclear halo and surrounding basophilic dyskeratotic material</td>
</tr>
<tr>
<td>Ehrlichiosis</td>
<td>Morulae</td>
<td>Leukocyte intracytoplasmic inclusions</td>
</tr>
<tr>
<td>Farber’s disease</td>
<td>Farber bodies</td>
<td>Curvilinear bodies seen in the cytoplasm of fibroblasts and endothelial cells on EM</td>
</tr>
<tr>
<td>Farber’s disease and other ganglioside storage diseases</td>
<td>Zebra bodies</td>
<td>Vacuoles with transverse membranes in endothelial cells on EM</td>
</tr>
<tr>
<td>Granular cell tumors</td>
<td>Pustulo-ovoid bodies</td>
<td>Round cytoplasmic eosinophilic inclusions</td>
</tr>
<tr>
<td>Granuloma inguinale</td>
<td>Donovan bodies</td>
<td>Intrahistiocyte inclusions comprised of organisms that stain positively with Warthin-Starry stain or Giemsa</td>
</tr>
<tr>
<td>Disease</td>
<td>Histologic Finding</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>HTLV-1 (human T-cell lymphotrophic virus-1) and ATL (adult T-cell lymphoma/leukemia)</td>
<td>Flower bodies/cells</td>
<td>Atypical CD4+ T cells</td>
</tr>
<tr>
<td>Interface dermatitis</td>
<td>Civatte/colloid bodies</td>
<td>Apoptotic keratinocytes that may be found in epidermis or extruded into papillary dermis</td>
</tr>
<tr>
<td>Interface dermatitis, especially LP</td>
<td>Max-Joseph space</td>
<td>Artifactual separation between dermis and epidermis</td>
</tr>
<tr>
<td>Langerhans cells</td>
<td>Birbeck granules</td>
<td>Racquet-shaped bodies seen on EM</td>
</tr>
<tr>
<td>Lepromatous leprosy</td>
<td>Globi</td>
<td>Collections of AFB (acid fast bacilli) seen in foamy macrophages with Fite stain</td>
</tr>
<tr>
<td>Lipoid proteinosis</td>
<td>Onion skinning</td>
<td>Hyaline material surrounding blood vessels</td>
</tr>
<tr>
<td>Malakoplasia</td>
<td>Michaelis-Gutman bodies</td>
<td>Calcified lamellar eosinophilic bodies in foamy “von Hansemann” macrophages</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>Henderson-Patterson bodies</td>
<td>Cytoplasmic eosinophilic inclusions in keratinocytes</td>
</tr>
<tr>
<td>Normal endothelial cells</td>
<td>Weibel-Palade bodies</td>
<td>Organelles seen on EM</td>
</tr>
<tr>
<td>Normal skin, absent in harlequin fetus</td>
<td>Lamellar/Odland bodies</td>
<td>Free fatty acid, ceramide, and cholesterol containing vacuoles released from the Golgi in the stratum granulosum seen on EM</td>
</tr>
<tr>
<td>Ochronosis</td>
<td>Banana bodies</td>
<td>Crescentic banana-shaped pigmented bodies in the upper dermis</td>
</tr>
<tr>
<td>Ovarian neoplasms</td>
<td>Psammoma bodies</td>
<td>Concentrically laminated calcified basophilic bodies</td>
</tr>
<tr>
<td>Plasmacytoid proliferations (e.g., multiple myeloma)</td>
<td>Dutcher bodies</td>
<td>Intranuclear inclusions of immunoglobulins</td>
</tr>
<tr>
<td>Pleomorphic lipoma</td>
<td>Floret cells</td>
<td>Multinucleated giant cells with radially arranged nuclei</td>
</tr>
<tr>
<td>Porphyria cutanea tarda, pseudoporphyria, and erythropoietic protoporphyria</td>
<td>Caterpillar bodies</td>
<td>Eosinophilic wavy collection in basal layer of epidermis, found on roof of blister</td>
</tr>
<tr>
<td>Protothecosis</td>
<td>Mulberry bodies</td>
<td>Thick-walled spherical body containing organisms</td>
</tr>
<tr>
<td>Rabies</td>
<td>Negri bodies</td>
<td>Eosinophilic bodies within large neurons</td>
</tr>
<tr>
<td>Rhinoscleroma</td>
<td>Mikulicz cell</td>
<td>Foamy macrophage containing bacteria</td>
</tr>
<tr>
<td>Rhinoscleroma</td>
<td>Russel bodies</td>
<td>Immunoglobulin inclusions in plasma cells</td>
</tr>
</tbody>
</table>
### TABLE 34-3  (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Histologic Finding</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoidosis, botryomycosis, sporotrichosis, actinomycosis, other</td>
<td>Asteroid bodies</td>
<td>Stellate collections of eosinophilic spicules and giant cells</td>
</tr>
<tr>
<td>Sarcoidosis and other granulomatous diseases</td>
<td>Conchoidal bodies (Schaumann bodies)</td>
<td>Shell-like calcium complexes within giant cells</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>Antoni A tissue</td>
<td>Cellular areas with Verocay bodies</td>
</tr>
<tr>
<td></td>
<td>Antoni B tissue</td>
<td>Loose stromal area with relative paucity of cells</td>
</tr>
<tr>
<td></td>
<td>Verocay bodies</td>
<td>Palisading nuclei arranged in rows with peripheral eosinophilic cytoplasm</td>
</tr>
<tr>
<td>Sclerema neonatorum and subcutaneous fat necrosis of the newborn</td>
<td>Cholesterol clefts</td>
<td>Needle-like crystals in fat cells</td>
</tr>
<tr>
<td>Spitz nevus</td>
<td>Kamino bodies</td>
<td>Eosinophilic bodies composed of BMZ (basement membrane zone) material</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>Cigar bodies</td>
<td>Budding cigar-shaped PAS+ yeast (rarely seen)</td>
</tr>
<tr>
<td>Thyroid neoplasms</td>
<td>Psammoma bodies</td>
<td>Concentrically laminated calcified basophilic bodies</td>
</tr>
<tr>
<td>Well’s syndrome, arthropod bites, other</td>
<td>Flame figures</td>
<td>Dermal eosinophils and eosinophilic granules surrounding central masses of brightly pink amorphous collagen</td>
</tr>
</tbody>
</table>

### TABLE 34-4  Infectious Diseases and Their Vectors

<table>
<thead>
<tr>
<th>Organism</th>
<th>Vector</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ancylostoma brazilienses</em></td>
<td>Feces, animal</td>
<td>Cutaneous larva migrans</td>
</tr>
<tr>
<td><em>Arbovirus, RNA-virus</em></td>
<td>Food, contaminated</td>
<td>West Nile fever</td>
</tr>
<tr>
<td><em>Bartonella bacilliformis</em></td>
<td><em>Lutzomyia verrucarum</em> (sandfly)</td>
<td>Carrion disease</td>
</tr>
<tr>
<td><em>Bartonella quintana</em></td>
<td><em>Pediculosis humanus</em> (louse)</td>
<td>Trench fever</td>
</tr>
<tr>
<td><em>Borrelia afzelii</em></td>
<td><em>Ixodes ricinus</em></td>
<td>Acrodermatitis chronica atrophicans</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td><em>Ixodes scapularis</em> (dammini) (Northeast and Midwest U.S.) <em>Ixodes pacificus</em> (Western U.S.)</td>
<td>Lyme disease</td>
</tr>
<tr>
<td><em>Borrelia duttonii, B. recurrentis</em></td>
<td><em>Orrithodorus tholozanii</em> (pick) <em>Pediculosis humanus</em> (louse)</td>
<td>Relapsing fever</td>
</tr>
<tr>
<td><em>Borrelia garinii and B. afzelii</em></td>
<td><em>Ixodes ricinus</em> (Europe)</td>
<td>Lyme disease</td>
</tr>
</tbody>
</table>

*Continued*
### TABLE 34-4 (Continued)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Vector</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Burkholderia pseudomallei</em></td>
<td>Swamp water</td>
<td>Melioidosis (Whitmore disease)</td>
</tr>
<tr>
<td><em>Cercariae of Schistosomes</em></td>
<td>Snails</td>
<td>Cercarial dermatitis</td>
</tr>
<tr>
<td>(nonhuman)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Dermatobia hominis</em> (botfly)</td>
<td>Mosquito</td>
<td>Myiasis</td>
</tr>
<tr>
<td>and <em>Cordylobia</em> species</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Dracunculus medinensis</em></td>
<td><em>Cyclops</em> water flea in drinking</td>
<td>Dracunculiasis (guinea worm disease, medina worm)</td>
</tr>
<tr>
<td>water</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ehrlichia chaffeensis</em></td>
<td>Tick bites</td>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td><em>Erysipalothrix rhusiopathiae</em></td>
<td>Found on pigs, shellfish, and</td>
<td>Erysipeloid of Rosenbach</td>
</tr>
<tr>
<td></td>
<td>turkeys</td>
<td></td>
</tr>
<tr>
<td><em>Francisella tularensis</em></td>
<td><em>Amblyomma americanum</em> (lone star</td>
<td>Tularemia (Ohar disease, deer fly fever)</td>
</tr>
<tr>
<td></td>
<td>tick)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Chrysops discalis</em> (deer fly)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Dermacentor andersonii</em> (tick)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(from handling wild rabbits)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Leishmaniasis mexicana</em></td>
<td><em>Lutzomyia</em> (sandfly)</td>
<td>Leishmaniasis, new world</td>
</tr>
<tr>
<td><em>L. braziliensis braziliensis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. braziliensis guyanensis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. braziliensis panamensis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. tropica</em>; <em>L. major</em>; *L.</td>
<td><em>Phlebotomus perniciosus</em> (sandfly)</td>
<td>Leishmaniasis, old world</td>
</tr>
<tr>
<td>aethiopia*; <em>L. infantum</em></td>
<td>Reservoir: Rodents (gerbils)</td>
<td></td>
</tr>
<tr>
<td><em>Leishmaniasis mexicana</em></td>
<td><em>Lutzomyia flaviscutellata</em></td>
<td>Chiclero ulcer</td>
</tr>
<tr>
<td><em>Leptospira interrogans</em></td>
<td><em>Rat urine</em></td>
<td>Weil disease</td>
</tr>
<tr>
<td>icterohemorrhagiae*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Loa loa</em></td>
<td><em>Chrysops</em> species (mango fly or</td>
<td>Loaiaasis (Calabar, tropical and fugitive</td>
</tr>
<tr>
<td></td>
<td>deer fly)</td>
<td>swelling)</td>
</tr>
<tr>
<td><em>Nocardia farcinica</em></td>
<td><em>Cattle</em></td>
<td>Bovine farcy</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td><em>Simulium</em> species (black fly)</td>
<td>Onchocerciasis (river blindness)</td>
</tr>
<tr>
<td><em>Pseudomonas mallei</em></td>
<td><em>Horses, mules, and donkeys</em></td>
<td>Glanders (Farcy)</td>
</tr>
<tr>
<td><em>Rickettsia akari</em></td>
<td><em>Alldermanyssus sanguineus</em></td>
<td>Rickettsialpox</td>
</tr>
<tr>
<td></td>
<td>(house mouse mites)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Liponyssoides sanguineus</em> (house</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mouse mites)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reservoir: <em>Mus musculus</em> (house</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mouse)</td>
<td></td>
</tr>
<tr>
<td><em>Rickettsia conorii</em></td>
<td><em>Rhipicephalus sanguinous</em> (dog</td>
<td>Mediterranean fever (boutonneuse fever, South</td>
</tr>
<tr>
<td></td>
<td>tick)</td>
<td>African tick bite fever)</td>
</tr>
<tr>
<td><em>Rickettsia prowazekii</em></td>
<td><em>Pediculus humanus</em> (body louse)</td>
<td>Typhus, epidemic</td>
</tr>
<tr>
<td></td>
<td>Reservoir: <em>Glaucomys volans</em> (flying</td>
<td></td>
</tr>
<tr>
<td></td>
<td>squirrel)</td>
<td></td>
</tr>
</tbody>
</table>

*Continued*
### TABLE 34-4  (Continued)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Vector</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rickettsia rickettsii</td>
<td>Amblyomma americanum (lone star tick)</td>
<td>Rocky Mountain spotted fever</td>
</tr>
<tr>
<td></td>
<td>Dermacentor andersoni, D. variabilis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isxid ticks</td>
<td></td>
</tr>
<tr>
<td>Rickettsia tsutsugamushi</td>
<td>Trombiculid red mite (chigger)</td>
<td>Scrub typhus (tsutsugamushi fever)</td>
</tr>
<tr>
<td>Rickettsia typhi</td>
<td>Xenopsylla cheopis (rat flea)</td>
<td>Typhus, endemic</td>
</tr>
<tr>
<td>S. mansoni, S. haematobium, and</td>
<td>Snails</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>S. japonicum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirillium minor, Streptobacillus montiliformis</td>
<td>Rat bites</td>
<td>Rat-bite fever (Haverhill fever, Sodoku)</td>
</tr>
<tr>
<td>Spirometra (dog and cat tapeworm larvae)</td>
<td>Frogs and snakes (application or ingestion)</td>
<td>Sparganosis</td>
</tr>
<tr>
<td>Taenia solium</td>
<td>Contaminated food</td>
<td>Cystercercosis cutis</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>Cat feces and undercooked meat</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Trichinella spiralis</td>
<td>Pig, bear, and walrus meat</td>
<td>Trichinoses</td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td>Reduviid bug (assassin bug, kissing bug)</td>
<td>Chagas disease (American trypanosomiasis)</td>
</tr>
<tr>
<td>Trypanosoma gambiense, Trypanosoma rhodesiernse</td>
<td>Tsetse fly (Glossina morsitans)</td>
<td>African trypanosomiasis</td>
</tr>
<tr>
<td>Wuchereria bancrofti, Brugia malayi, Brugia timori</td>
<td>Culex, Aedes, and Anopheles mosquitos</td>
<td>Elephantiasis tropica</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>Xenopsylia cheopis (rat fleas)</td>
<td>Plague</td>
</tr>
</tbody>
</table>

### TABLE 34-5  Contact Allergens

<table>
<thead>
<tr>
<th>Common Sources</th>
<th>Allergen</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals</td>
<td>Bermuda fire sponge</td>
<td>Contact erythema multiforme</td>
</tr>
<tr>
<td>Cement</td>
<td>Potassium dichromate</td>
<td>permanent-press textile products</td>
</tr>
<tr>
<td>Clothing</td>
<td>Formaldehyde</td>
<td>Eyelid dermatitis, dimethylglyoxime test (pink)</td>
</tr>
<tr>
<td>Clothing snaps</td>
<td>Nickel sulfate</td>
<td>Nickel plating, hair dye, metal, vitamin B₁₂, cement,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>construction</td>
</tr>
<tr>
<td>Coloring, blue</td>
<td>Cobalt dichloride</td>
<td>Nickel plating, hair dye, metal, vitamin B₁₂, cement,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>construction</td>
</tr>
<tr>
<td>Cosmetics</td>
<td>Ammonium persulfate</td>
<td>Hair bleach</td>
</tr>
<tr>
<td></td>
<td>Benzalkonium chloride (Quaternium 15)</td>
<td>Shampoos</td>
</tr>
<tr>
<td></td>
<td>Formaldehyde</td>
<td></td>
</tr>
</tbody>
</table>

Continued
TABLE 34-5 (Continued)

<table>
<thead>
<tr>
<th>Common Sources</th>
<th>Allergen</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glyceryl thioglycolate</td>
<td>Permanent (hair) wave solutions</td>
</tr>
<tr>
<td></td>
<td>Methyl methacrylate</td>
<td>Artificial nails, dental work</td>
</tr>
<tr>
<td></td>
<td>Paraphenylenediamine</td>
<td>Dark hair dye, henna tattoo additive</td>
</tr>
<tr>
<td></td>
<td>toluenesulfonamide/formaldehyde resin</td>
<td>Nail lacquer/hardener: eyelid dermatitis</td>
</tr>
<tr>
<td></td>
<td>Imidazolidinyl urea (Germall 115)</td>
<td>Formaldehyde releaser found in cosmetics</td>
</tr>
<tr>
<td></td>
<td>Cyanoacrylate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethyl cyanoacrylate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flavoring; additives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cinnaminic aldehyde</td>
<td>Pastries, toothpaste, chewing gum, beverages, Bitters, lipstick</td>
</tr>
<tr>
<td></td>
<td>Food</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ammonium persulfate</td>
<td>Bleaching agent in flour</td>
</tr>
<tr>
<td></td>
<td>Benzoyl peroxide</td>
<td>Bleaching agent in flour</td>
</tr>
<tr>
<td></td>
<td>Diallyl disulfide</td>
<td>Garlic</td>
</tr>
<tr>
<td></td>
<td>Eugenol</td>
<td>Cloves</td>
</tr>
<tr>
<td></td>
<td>Sesamine</td>
<td>Sesame oil</td>
</tr>
<tr>
<td></td>
<td>Fragrance, adhesives, flavoring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Balsam of Peru</td>
<td>Cross reacts with cinnamon, clove, orange peel, benzoin</td>
</tr>
<tr>
<td></td>
<td>Glues, plastics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epoxy resin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jewelry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Na gold-thiosulfate</td>
<td>Best screen for allergy to gold; Late and persistent positive reactions</td>
</tr>
<tr>
<td></td>
<td>Jewelry, clothing snaps</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nickel sulfate</td>
<td>Eyelid dermatitis, dimethylglyoxime test (pink)</td>
</tr>
<tr>
<td></td>
<td>Leather</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chromates potassium dichromate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzocaine</td>
<td>Topical amide anesthetics</td>
</tr>
<tr>
<td></td>
<td>Benzoyl peroxide</td>
<td>Acne medication</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
<td>Screening for Group B and D corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Ethylenediamine</td>
<td>Stabilizer in Mycolog; cross-reacts with aminophylline and hydroxyzine</td>
</tr>
<tr>
<td></td>
<td>Glutaraldehyde</td>
<td>Cold sterilant</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone-17-butyrate</td>
<td>Group B and D corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Neomycin sulfate</td>
<td>Topical antibiotic</td>
</tr>
<tr>
<td></td>
<td>Tixocortol pivalate</td>
<td>Group A corticosteroids</td>
</tr>
</tbody>
</table>
### TABLE 34-5  (Continued)

<table>
<thead>
<tr>
<th>Common Sources</th>
<th>Allergen</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plants</td>
<td>Allylisothiocyanate</td>
<td>Mustard, radish</td>
</tr>
<tr>
<td></td>
<td>Calcium oxalate crystals</td>
<td>Dieffenbachia (“dumb cane”)</td>
</tr>
<tr>
<td></td>
<td>D-Usnic acid</td>
<td>Lichen</td>
</tr>
<tr>
<td></td>
<td>Furocoumarin</td>
<td>Celery, dill, fig, lime, parsley, parsnip, meadow grass, St. John’s wort (Umbelliferae family)</td>
</tr>
<tr>
<td></td>
<td>Limonene</td>
<td>Orange and lemon peel, tea tree oil</td>
</tr>
<tr>
<td></td>
<td>Primin</td>
<td>Primrose (<em>Primula obonica</em>)</td>
</tr>
<tr>
<td></td>
<td>rcin</td>
<td>Castor bean (<em>Ricinus communis</em>)</td>
</tr>
<tr>
<td></td>
<td>Sesquiterpene lactone</td>
<td>Compositae family members (chrysanthemum, ragweed, artichoke)</td>
</tr>
<tr>
<td></td>
<td>Tuliposide A</td>
<td>Peruvian lily, tulip</td>
</tr>
<tr>
<td></td>
<td>Urushiol</td>
<td>Poison ivy, poison oak, poison sumac, Japanese lacquer tree, cashew nut, mango, ginkgo tree</td>
</tr>
<tr>
<td>Plaster</td>
<td>Potassium dichromate</td>
<td></td>
</tr>
<tr>
<td>Preservatives</td>
<td>Kathon CG (methylchloroisothiazolinone)</td>
<td>Found in cosmetics, formaldehyde-like</td>
</tr>
<tr>
<td></td>
<td>Methylchloroisothiazolinone (Kathon CG)</td>
<td>Used in cosmetics</td>
</tr>
<tr>
<td></td>
<td>Paraben mix</td>
<td>Low incidence of contact dermatitis</td>
</tr>
<tr>
<td></td>
<td>Quatennium-15 (most common preservative cause of AD)</td>
<td>Formaldehyde releasing preservative, found in hair care products, moisturizers</td>
</tr>
<tr>
<td></td>
<td>Thimerosal</td>
<td>Cosmetic preservative in vaccines, contact lens solution, tuberculin skin test</td>
</tr>
<tr>
<td>Resin</td>
<td>p-tert-butylphenol</td>
<td>Formaldehyde resin adhesive in leather/rubber products</td>
</tr>
<tr>
<td>Rosin</td>
<td>Colophony (rosin) (abeitic acid)</td>
<td>Solder, paper products, adhesives, paints, varnishes</td>
</tr>
<tr>
<td>Rubber products</td>
<td>2-Meroaptobenzothiazole (MBT)</td>
<td>Adhesive, pesticide, animal repellents, shoe allergy</td>
</tr>
<tr>
<td></td>
<td>Black rubber mix (N-Phenyl-N’ isopropyl p-phenylenediamine, N-Phenyl-N’ cyclohexylphenylenediamine, N,N-diphenylphenylenediamine)</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 34-5  (Continued)

<table>
<thead>
<tr>
<th>Common Sources</th>
<th>Allergen</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamates (zinc diethylidithiocarbamate, zinc dibutylidithiocarbamate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercapto mix (4-morpholinyl-2-benzothiazyl disulfide, N-cyclohexyl-2-benzothiazole sulfenamide, 2,2-benzothiazyl disulfide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed dialkyl thioureas</td>
<td>Rubber accelerator, neoprene, tape, mouse pads, wet suits</td>
<td></td>
</tr>
<tr>
<td>Tetramethylthiuram disulfide</td>
<td>Rubber accelerator, gloves, antimicrobial antioxidant in rubber products.</td>
<td></td>
</tr>
</tbody>
</table>

**Sunsceen**  
Oxybenzone  
Padimate O (PABA)

**Turpentine**  
Carene

### TABLE 34-6  Common Bone Findings in Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne fulminans</td>
<td>Osteolytic lesions</td>
</tr>
<tr>
<td>Albright’s osteodystrophy</td>
<td>Bradymetacarpalism</td>
</tr>
<tr>
<td>Apert’s syndrome</td>
<td>Synostosis</td>
</tr>
<tr>
<td>Bushke-Ollendorf syndrome</td>
<td>Osteopoikolosis</td>
</tr>
<tr>
<td>Cockayne’s syndrome</td>
<td>Dwarfism</td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>Osteochondritis, saber shins, saddle nose, mulberry molars, Hutchinson’s teeth</td>
</tr>
<tr>
<td>Conradi-Hünermann syndrome</td>
<td>Unilateral limb shortening, chondrodysplasia punctata</td>
</tr>
<tr>
<td>Ehler’s-Danlos IX</td>
<td>Occipital horns</td>
</tr>
<tr>
<td>Fanconi’s syndrome</td>
<td>Absent radius or thumb</td>
</tr>
<tr>
<td>Franceschetti-Jadassohn syndrome</td>
<td>Malaligned great toes</td>
</tr>
<tr>
<td>Gardner’s syndrome</td>
<td>Craniofacial osteomatosis</td>
</tr>
<tr>
<td>Goltz’s syndrome</td>
<td>Osteopathia striata, lobster- claw deformity, scoliosis</td>
</tr>
<tr>
<td>Gorlin’s syndrome</td>
<td>Bifid rib, mandibular keratocysts, kyphoscoliosis, calcified falx cerebri, frontal bossing, etc.</td>
</tr>
<tr>
<td>Hallerman-Streiff syndrome</td>
<td>Bird-like facies, natal teeth</td>
</tr>
</tbody>
</table>

Continued
### TABLE 34-6  (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocystinuria</td>
<td>Marfanoid habitus, genu valgum</td>
</tr>
<tr>
<td>Linear morphea</td>
<td>Melorheostosis</td>
</tr>
<tr>
<td>Maffucci’s syndrome</td>
<td>Enchondromas, chondrosarcoma</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td>Marfanoid habitus</td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
<td>Polyostotic fibrous dysplasia</td>
</tr>
<tr>
<td>MEN III</td>
<td>Marfanoid habitus</td>
</tr>
<tr>
<td>Multicentric reticulohistiocytosis</td>
<td>Mutilating arthritis</td>
</tr>
<tr>
<td>Nail-Patella syndrome</td>
<td>Posterior iliac horn, absent patella</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>Fragile bones</td>
</tr>
<tr>
<td>Papillon-Lefévre syndrome</td>
<td>Tentorial and chondroid plexus calcification</td>
</tr>
</tbody>
</table>

### TABLE 34-7  Common Eye Findings in Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaptonuria</td>
<td>Pingueculae, Osler’s sign</td>
</tr>
<tr>
<td>Allezandrini syndrome</td>
<td>Unilateral retinitis pigmentosa</td>
</tr>
<tr>
<td>Argyria</td>
<td>Blue sclera</td>
</tr>
<tr>
<td>Ataxia-telangiectasia (Louis-Bar’s)</td>
<td>Bulbar telangiectasia</td>
</tr>
<tr>
<td>Behçet’s syndrome</td>
<td>Retinal vasculitis, uveitis, and hypopyon</td>
</tr>
<tr>
<td>CHIME syndrome (colobomas of eye; heart defects, ichthyosiform dermatosis, mental retardation, ear defects)</td>
<td>Colobomas of retina</td>
</tr>
<tr>
<td>Cicatricial pemphigoid</td>
<td>Symblepharon</td>
</tr>
<tr>
<td>Cockayne’s syndrome</td>
<td>Salt and pepper retinitis pigmentosa with optic atrophy</td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>Keratitis</td>
</tr>
<tr>
<td>Conradi-Hünermann syndrome</td>
<td>Asymmetric focal cataracts</td>
</tr>
<tr>
<td>Ehler’s-Danlos VI</td>
<td>Keratoconus</td>
</tr>
<tr>
<td>Fabry’s disease</td>
<td>Whorl-like corneal opacities, spokelike cataracts</td>
</tr>
<tr>
<td>Fanconi’s syndrome</td>
<td>Strabismus, retinal hemorrhages</td>
</tr>
<tr>
<td>Gardner’s syndrome</td>
<td>Congenital hypertrophy of retinal pigmented epithelium</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
<td>Pingueculae</td>
</tr>
<tr>
<td>Goltz’s syndrome</td>
<td>Colobomas</td>
</tr>
<tr>
<td>Hallerman-Streiff syndrome</td>
<td>Microopthalmia, congenital cataracts, strabismus</td>
</tr>
</tbody>
</table>

Continued
### TABLE 34-7  (Continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocystinuria</td>
<td>Downward lens displacement</td>
</tr>
<tr>
<td>Incontinentia pigmenti (Bloch Sulzberger’s)</td>
<td>Strabismus, atrophy, cataracts, optic coloboma</td>
</tr>
<tr>
<td>JXG</td>
<td>Hyphema, hypopyon</td>
</tr>
<tr>
<td>KID</td>
<td>Keratitis</td>
</tr>
<tr>
<td>Lamellar Ichthyosis</td>
<td>Ectropion</td>
</tr>
<tr>
<td>LEOPARD</td>
<td>Hypertelorism</td>
</tr>
<tr>
<td>Lipoid Proteinosis (Urbach-Wiethe)</td>
<td>Eyelid “string of pearls”</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td>Upward lens displacement</td>
</tr>
<tr>
<td>Nail-patella syndrome</td>
<td>Lester iris</td>
</tr>
<tr>
<td>NF-2</td>
<td>Posterior subcapsular lenticular cataracts</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>Blue sclera</td>
</tr>
<tr>
<td>PXE (Gronblad-Strandberg)</td>
<td>Angioid streak</td>
</tr>
<tr>
<td>Refsum syndrome</td>
<td>Salt and pepper retinitis pigmentosa</td>
</tr>
<tr>
<td>Richner-Hanhart</td>
<td>Pseudoherpetic keratitis</td>
</tr>
<tr>
<td>Sjögren-Larsson syndrome</td>
<td>Glistening dots, retinitis, pigmentosa</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Astrocytic hamartomas</td>
</tr>
<tr>
<td>vonRecklinghausens’s (NF-1)</td>
<td>Lisch nodules</td>
</tr>
<tr>
<td>Waardenburg’s syndrome</td>
<td>Dystopia, canthorum, heterchromia, irides</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Kayser-Fleischer ring</td>
</tr>
<tr>
<td>X-linked ichthyosis</td>
<td>Posterior comma-shaped corneal opacities (Descemet’s membrane)</td>
</tr>
</tbody>
</table>

### TABLE 34-8  Common Nail Findings in Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nails</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU and AZT</td>
<td>Blue lunula</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>Nail pits, red and spotted lunula</td>
</tr>
<tr>
<td>Apert’s syndrome</td>
<td>One large fingernail</td>
</tr>
<tr>
<td>Argyria</td>
<td>Slate blue lunula</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Mee’s lines</td>
</tr>
<tr>
<td>CHF, connective tissue disease</td>
<td>Red lunula</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Terry’s nails</td>
</tr>
<tr>
<td>Coffin-Siris syndrome</td>
<td>Fifth-nail dystrophy</td>
</tr>
</tbody>
</table>

Continued
TABLE 34-8  (Continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nails</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue disease and trauma</td>
<td>Pterygium inversum unguis</td>
</tr>
<tr>
<td>Darier-White disease</td>
<td>Red and white bands, V-nicking</td>
</tr>
<tr>
<td>Fe$^{2+}$ deficiency</td>
<td>Koilonychia</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Koilonychia</td>
</tr>
<tr>
<td>High fever, surgery, and meds (chemo)</td>
<td>Beau’s lines</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Koilonychia</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Muehrcke’s nails</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>Dorsal pterygium</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Lindsay’s nails</td>
</tr>
<tr>
<td>Retinoids, indinavir, and estrogen</td>
<td>Pyogenic granuloma</td>
</tr>
<tr>
<td>Trichinosis, endocarditis, and trauma</td>
<td>Splinter hemorrhages</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Koenen’s tumor</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Blue lunulae</td>
</tr>
<tr>
<td>Yellow nail syndrome</td>
<td>Yellow curved nails</td>
</tr>
</tbody>
</table>

Quiz Questions

1. Which of the following contact allergens would be most likely to have a persistent positive patch test?
   A. Thimerosal
   B. Gold
   C. Nickel
   D. Paraphenylenediamine

2. Which desmoglein is associated with hypotrichosis?
   A. Desmoglein 1
   B. Desmoglein 2
   C. Desmoglein 3
   D. Desmoglein 4

3. The gene responsible for Goltz syndrome is:
   A. Myosin Va
   B. PORCN
   C. Endoglin
   D. BP Ag2

4. Griscelli syndrome results from a defect in:
   A. TGF-binding proteins
   B. The innate immune response
   C. β-catenin
   D. Melanosome transport to keratinocytes

5. Oral hairy leukoplakia is related to which virus?
   A. HHV6
   B. EBV
   C. VZV
   D. Pox

6. Castleman’s disease is caused by which virus?
   A. HHV1
   B. EBV
   C. CMV
   D. HHV8

7. On skin biopsy, clusters of lymphocytes are seen within the epidermis in which disease?
   A. Cutaneous T-cell lymphoma
   B. Lipoid proteinosis
   C. Ichthyosis vulgaris
   D. Schwannoma

8. Michaelis-Gutman Bodies are seen in:
   A. Rhinoscleroma
   B. CTCL
   C. Atopic dermatitis
   D. Malakoplakia

9. The Reduviid bug is the vector for which disease?
   A. Trypanosomiasis
   B. Leishmaniasis
   C. Cutaneous larva migrans
   D. Lyme disease
10. Rickettsialpox is caused by bites from the:
   A. House mouse (Mus musculus)
   B. Rodent mite (Allodermanyyssus sanguineus)
   C. Pediculosis humanus
   D. Xenopsylla cheopis

11. What is the allergen in henna tattoos?
   A. p-Phenylenediamine
   B. Quaternium 15
   C. Neomycin
   D. Ricin

12. Which of the following is NOT a formaldehyde-releasing preservative used in cosmetics and toiletries?
   A. Diazolidinyl urea
   B. DMDM hydantoin
   C. Quaternium 15
   D. Paraben

13. Which of the following nail finding is associated with lichen planus?
   A. Triangular lunulae
   B. Dorsal pterygium
   C. Ventral pterygium
   D. Blue lunulae

14. A patient with lobster-claw deformity may have which of the following bone findings?
   A. Osteopathica striata
   B. Bifid ribs
   C. Occipital horns
   D. Chondrodysplasia punctata

15. A patient with multiple polyps of the GI tract and multiple epidermoid cysts may have what eye finding?
   A. Coloboma
   B. Lester iris
   C. Herpetic keratitis
   D. Congenital hypertrophy of retinal pigment epithelium (CHRPE)

**Answers**

1. B. Gold allergy can be seen at all sites of jewelry contact and as eyelid dermatitis. In addition, oral lichenoid lesions can be seen. It can cause late patch test reactions and persistent patch test reactions that can last for months after testing.

2. D. Desmoglein 4. The desmoglein 4 gene (DSG4) is associated with localized autosomal recessive hypotrichosis (LAH). LAH is an autosomal recessive form of hypotrichosis affecting the scalp, trunk, and extremities, and usually sparing the facial, pubic, and axillary hair.

3. B. Goltz syndrome results from a defect in the gene known as PORCN, which encodes the protein, porcupine. The porcupine protein was first identified in fruit flies and named for the porcupine-like spikes projecting from the fly’s body. Porcupine is an important Wnt signaling protein.

4. D. Griscelli syndrome is autosomal recessive and characterized by silver gray pigmentation of hair, pigmentary dilution of skin, and increased pyogenic infections. Patients have progressive neurologic deterioration. It is caused by mutations in the gene encoding for myosin Va or RAB27a. These proteins are involved in melanosome transport to keratinocytes.

5. B. EBV infection of mucosal keratinocytes is associated with oral hairy leukoplakia. It is characterized by white plaques on the lateral surfaces of the tongue that can not be scraped off. Oral hairy leukoplakia typically occurs in HIV infected or in other immunocompromised patients.

6. D. Castlemen’s disease is caused by HHV8. It is a lymphoproliferative disorder that usually presents as a mediastinal mass. It can also be associated with POEMS syndrome. HSV 8 has also been associated with Kaposi’s sarcoma and primary effusion lymphoma.

7. A. These lymphocyte clusters are known as Pautrier’s microabscesses and are seen in CTCL.

8. D. Michaelis-Gutman bodies are seen histologically in malakoplakia. They are calcified lamellar eosinophilic bodies found in foamy macrophages. Malakoplakia is an inflammatory condition that usually affects immunocompromised people. It presents as a plaque or a nodule that usually affects the genitourinary tract but may rarely involve the skin.

9. A. American trypanosomiasis (Chagas disease) is spread by T. cruzi which is found in the feces of infected reduviid bugs. American Trypanosomiasis presents with an erythematous nodule at the site of inoculation. Inoculation is common through the conjunctiva which results in conjunctivitis and edema of the orbital area known as Romana’s sign.

10. B. The rodent mite (Allodermanyyssus sanguineus) or Liponyssoides sanguineus) is the vector for rickettsialpox. The reservoir is the house mouse (Mus musculus). The rodent mite bite is painless and is usually not recognized by the victim. A primary lesion occurs at the site of the bite and develops into an eschar. Systemic symptoms such as fever, chills, sweats, and headache evolve 1-2
weeks later. Two to three days later a generalized papulovesicular eruption occurs.

11. A. p-Phenylenediamine (PPD) is combined with henna to make the tattoo darker. PPD has many potential cross reactions to chemicals such as PABA, sulfonamides, thiazides, benzocaine and related anesthetics, and sulfonylectures.

12. D. Parabens are not formaldehyde releasing and are not common causes of allergic contact dermatitis. Nonformaldehyde releasing preservatives include iodopropynyl butyl carbamate, vitamin E (alpha-tocopheryl), thimerosal, benzalkonium chloride, and triclosan.

13. B. LP is associated with dorsal pterygium. Connective tissue disease can be associated with ventral pterygium.

14. A. The question describes Goltz syndrome (focal dermal hypoplasia), which is associated with lobster-claw deformity of the fingers, short stature, and asymmetric trunk and limbs. Osteopathica striata refers to vertical striations in long bones on x-ray. Patients also have coloboma, strabismus, and microphthalmia.

15. D. CHRPE. Patients with Gardner syndrome have polyposis with a high predisposition to adenocarcinoma. A congenital marker for diagnosis of this autosomal dominant syndrome is CHRPE. Patients also present with multiple epidermoid cysts, osteomas, desmoid tumors, odontomas, and supernumerary teeth.
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