Basic cutaneous histology:

**Epidermis**: composed mainly of keratinocytes with melanocytes, merkel cells, and Langerhans cells interdispersed. Keratinocytes mature through a process called desquamatization where they rise from the basal layer to the cornified layer over approximately 25 days. The major layers have histologic differences that can be seen by light microscopy.

- Stratum Corneum
- Stratum Lucidum (thick skin only, palms and soles of feet)
- Stratum Granulosum
- Stratum Spinosum
- Stratum Basale

**Dermis**: directly beneath the epidermis. The dermis is composed of the papillary dermis and the reticular dermis. There are elastic fiber composition changes between the two types of dermis but there is no true anatomic separation. The papillary dermis is flanked by the epidermal rete and contains blood vessels and Meissner's corpuscles. The reticular dermis is everything beneath the papillary dermis up to the subcutaneous adipose tissue. The reticular dermis houses the adnexal structures of the skin as well as vessels and nerves.

**Subcutis**: beneath the dermis. Includes the adipose tissue, larger vessels and nerves including the Pacinian corpuscles.

Dermatology Vocabulary:

<table>
<thead>
<tr>
<th>Epidermal change</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkeratosis</td>
<td>Thickening of the stratum corneum</td>
</tr>
<tr>
<td>Parakeratosis</td>
<td>Flattened, keratinocyte nuclei within the stratum corneum, where nuclei are not normally present</td>
</tr>
<tr>
<td>Orthokeratosis</td>
<td>Hyperkeratosis of anuclear keratinocytes within the stratum corneum</td>
</tr>
<tr>
<td>Acanthosis</td>
<td>Thickened stratum spinosum</td>
</tr>
<tr>
<td>Acantholysis</td>
<td>Loss of cohesion between keratinocytes d/t dissolution of intercellular connections. Keratinocytes separate and “round up” (versus in spongiosis, where keratinocytes stretch and elongate)</td>
</tr>
<tr>
<td>Dyskeratosis</td>
<td>Abnormally or prematurely cornified (keratinized) keratinocytes in the epidermis that stain pink on H &amp; E</td>
</tr>
<tr>
<td>Spongiosis</td>
<td>Intercellular edema btwn keratinocytes. Edema may cause keratinocytes to become elongated and stretched, hallmark of eczema</td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>Irregular undulation of the epidermal surface</td>
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<tr>
<td>-------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Dermal Change</strong></td>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>Dermal atrophy</td>
<td>Decreased thickness of dermis</td>
</tr>
<tr>
<td>Edema</td>
<td>Accumulation of interstitial fluid</td>
</tr>
<tr>
<td>Solar Elastosis</td>
<td>Accumulation of basophilic (grey/blue) material in the upper dermis d/t sun damage</td>
</tr>
<tr>
<td>Hyalinization</td>
<td>Accumulation of dense, eosinophilic (stains pink/red) acellular material</td>
</tr>
<tr>
<td>Sclerosis</td>
<td>Hyalinized collagen w/ decreased fibroblasts</td>
</tr>
<tr>
<td>Mucin</td>
<td>Dermal mucin contains acid mucopolysaccharide and stains pale blue, smudgy, threadlike, or granular on H &amp; E</td>
</tr>
<tr>
<td><strong>Clinical Change</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Wheal</td>
<td>Transient papule/plaque</td>
</tr>
<tr>
<td>Papule</td>
<td>Elevated skin lesion &lt; 1cm</td>
</tr>
<tr>
<td>Disorder</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Macule</td>
<td>Flat discoloration &lt;1 cm</td>
</tr>
<tr>
<td>Patch</td>
<td>Macule &gt; 1 cm (same as picture above)</td>
</tr>
<tr>
<td>Plaque</td>
<td>Papule &gt; 1 cm</td>
</tr>
<tr>
<td>Excoriation</td>
<td>Small superficial defect involving epidermis and papillary dermis. Results from localized trauma like picking or scratching</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Loss of epidermis and dermis (and sometimes deeper tissue)</td>
</tr>
</tbody>
</table>

**Disorders of Desquamatization**

- **Ichthyosis vulgaris**: a disorder of dry, scaly skin. Often described as “fish scales,” and is diagnosed clinically just by looking at the skin. Is passed down through families in an autosomal dominant pattern, caused by a defect in the *FLG* gene, which synthesizes the microfilament filaggrin. Will be more prominent in winter, and can be treated with heavy duty moisturizers, usually creams and ointments over lotions.
- **Lamellar ichthyosis**: presents with severe, thick plates of scale that almost resemble reptile scales and **present at birth**. Mostly affects palms, soles, and flexures. Autosomal recessive inheritance, associated with a mutation in *keratinocyte transglutaminase*.
- **X-linked ichthyosis**: presents as more brownish and scaly eruption in males, usually in early childhood. More likely to involve flexural creases than ichthyosis vulgaris. Associated with deficiency in *STS gene* which makes *steroid sulfatase*.

**Epidermal Neoplasms:**

*Non-malignant:*
- **Seborrheic keratosis**: epidermal papillomatosis, acanthosis, and horn cyst formation. Present as stuck on plaques or verrucous lesions most common on the head / neck / trunk but can be seen anywhere. Considered a growth of aging these are benign lesions. Seldom seen in young patients. Multiple (as in hundreds) may be seen as part of a paraneoplastic syndrome in patients with metastatic cancer = Leser-Trélat sign.
- **Acanthosis nigricans**: may look similar to a seborrheic keratosis but lacks acanthosis and horn cyst. Seen in all ages of patients and can be associated with insulin resistance as well as malignancy. Clinically presents as a velvety plaque most common on the back of the neck or axilla.
- **Fibroepithelial polyp**: also called a skin tag or acrochordon. These are benign polypoid growths most common at sites of rubbing / friction. They are composed of an outgrowth of fibroblasts and collagen with vessels covered with normal or acanthotic epidermis.
- **Epidermal inclusion cysts / Wen**: Not epidermal neoplasms at all but categorized here because of the misnomer in their name. Actually are follicular cysts composed of the infundibular portion of the hair follicle which is quite similar to normal epidermis with the exception of a loss of rete pegs. Makes keratin (like epidermis) and thus appears as a keratin filled cystic structure lined by epidermis. Most do not communicate with the epidermis and are therefore dermal based nodules.

*Pre-malignant and Malignant:*
- **Actinic keratosis (AK)** - the earliest identifiable lesion that can eventually develop into an invasive squamous cell carcinoma (SCC). These lesions are diagnosed in 14% of all visits to dermatologists, following only acne and dermatitis in frequency. AK’s are typically produced by ultraviolet radiation, but ionizing radiation, arsenic, or polycyclic hydrocarbon exposure may also cause them. On physical examination, the typical AK is a poorly-demarcated, slightly erythematous papule or plaque found on sun-exposed areas such as the face, balding scalp, posterior neck, and dorsal upper extremity. Characteristically, AKs feel rough or "gritty" and may be difficult to see.
- **Squamous Cell Carcinoma (SCC)** - Squamous cell carcinomas are generally erythematous, scaly papules or plaques with ill-defined borders, and they may be confused with large, hypertrophic AKs. It is often difficult to differentiate these AKs from early SCCs without a biopsy. Microscopically, squamous cell carcinomas show a proliferation of pleomorphic keratinocytes confined to the epidermis (SCC in-situ) or extending into the dermis (invasive SCC).
  - **Etiology**
    - Actinic keratosis is the precursor lesion of SCC. However, some SCCs develop de novo and do not form from a previous AK. Keratinocytes with one mutation in p53 after UV radiation may undergo apoptosis. However, if these keratinocytes with mutated p53 suffer a second hit or mutation, then they become resistant to further apoptosis and instead experience clonal expansion, which is clinically evident as
AKs. Uncontrolled proliferation of these abnormal keratinocytes leads to the development of invasive SCC.

- **Clinical Manifestations**
  - SCCs usually present as firm, skin-colored to pink, papules or plaques, commonly found on the head and neck region of elderly individuals. Other locations include the trunk, arms, dorsal hands and legs. Hyperkeratosis, ulceration or crusting may be found on its surface. Symptoms such as itching, pain and bleeding may be associated with the lesion.

- **Histopathology**
  - Histopathologic evaluation of SCC reveals a proliferation of atypical keratinocytes that extends into the dermis. The proliferation of cells can be seen as slender, long strands or as bulky masses. Individual cells have a glassy eosinophilic cytoplasm, with large nuclei. Mitotic figures and keratin pearls are also seen. Various degrees of differentiation may be seen and is usually described as well-, moderately-, or poorly-differentiated. Increasing degrees of malignancy show less demarcation between the tumor masses and the stroma, greater atypia, less keratinization, and loss of intercellular bridges. Other histologic variants include acantholytic, adenosquamous, spindle-cell, verrucous, and desmoplastic SCC.

- **Treatment**
  - Excision for low risk SCCs (less than 2 cms in diameter, well differentiated)
  - Mohs micrographic surgery
  - Radiation therapy (used in combo with other modalities for aggressive, recurrent, or large inoperable tumors)
  - Cryotherapy (for small, superficial, or low-risk lesions)

- **Basal Cell Carcinoma (BCC)** – most common non-melanoma skin cancer (80%), more common in men (2:1). Risk factors include UV exposure, fair skin, immunosuppression, FH of skin cancer, radiation therapy, and genetic syndromes (neviod BCC syndrome, xeroderma pigmentosa)

  - **Etiology**
    - When UVB damages the DNA it produces C-T transition mutations. The p53 and PTCH (patch) genes are the major targets of UVB for the development of BCC. The p53 is a tumor-suppressor gene that regulates the cell cycle and apoptosis, and has been found to be mutated in approximately 56% of human BCC. The PTCH gene (located on chromosome 9q22) is involved in the Hedgehog signal transduction pathway and is found to be mutated in 30-40% of sporadic BCC. It is also responsible for the genetic defect in Gorlin syndrome. In approximately 50% of BCCs isolated from xeroderma pigmentosa both p53 and PTCH genes are mutated. UV radiation induces a state of relative immunosuppression (by altering antigen-presenting mechanisms and producing immunosuppressive cytokines) that ultimately compromises tumor rejection.

  - **Clinical Manifestation**
    - Sun-exposed areas are the most frequent location of BCCs, but it can be found in anywhere in the skin. There are several subtypes: The nodular BCC initially presents as a small, translucent, pearly papule with telangiectasias on its surface. As the lesion progresses, the center may become ulcerated and the borders become indurated, rolled and pearly. This variant is frequently found on the face. The superficial BCC is commonly located on the thorax and limbs, and appears as a pink, scaly plaque with a slight elevation pearly border. Crusting and ulceration may sometimes be present.
Gorlin syndrome (i.e. Nevoid Basal Cell Carcinoma syndrome) is characterized by the appearance of multiple BCCs during childhood, odontogenic keratocysts of the jaw and skeletal defects (i.e., macrocephaly, hypertelorism, frontoparietal bossing, spina bifida, or rib abnormality, among others). Tumors associated with this disease include medulloblastoma and meningioma. It is inherited in an autosomal dominant pattern.

**Melanocytic Neoplasms**

- **Freckle (ephelis)** - typically found on sun-exposed skin, usually on the face or dorsal forearms and hands of children or young adults with a fair-skinned phenotype. They darken in response to the sun and fade with UV abstinence. Histologically very subtle differences between a freckle and normal skin. A freckle may have larger-sized melanocytes (which are normal in number) with more prominent dendrites and an increased transfer of increased melanin to surrounding keratinocytes.

- **Lentigines** – two types. Solar lentigines (liver spots, age spots) occur in response to sunlight, but are more common in middle-aged or older patients, are thought to be caused by years of cumulative UV exposure, and tend to persist even in the absence of sunlight. They favor sites of maximum sun exposure such as the dorsal surface of the hands and the extensor forearms, vary in color from tan to dark brown, and can be up to 1cm in diameter. Simple lentigines, in contrast, occur at any age, have no predilection for sun-exposed areas or lighter skin types, and do not darken in response to sunlight. Solar lentigines typically have a normal number of melanocytes plus increased melanin in the basal layer of the epidermis, overlying a background of solar elastosis (abnormal elastic fibers in the dermis due to cumulative UV exposure). In contrast, simple lentigines typically have a mildly increased number of melanocytes, singly arranged along the basal layer of the epidermis.

- **Melanocytic nevi** - benign neoplasms, histologically distinguished from lentigines or ephelides by the presence of nest of nevus cells, which are melanocytes that group in well-demarcated nests. Acquired nevi tend to first appear in childhood as flat brown macules or minimally elevated papules, usually less than 6mm in diameter. They evolve during adulthood, becoming more elevated and dome-shaped and then eventually fleshy papules or nodules with loss of pigmentation. Further aging of a nevus can lead to a pedunculated skin tag-like lesion or even complete disappearance of the nevus. It is unusual to see melanocytic nevi in individuals older than 80 years of age. Congenital nevi, in contrast, are present at birth or become clinically apparent during early infancy. Congenital nevi may have irregular or serrated borders. Histologically, nevi are classified depending on the location of the melanocytic nests. In **junctional** nevi, the nevus cells are at the dermo-epidermal junction (DEJ) just above the basement membrane zone of the epidermis; the clinical correlate is a darkly pigmented flat or minimally elevated nevus. As nevi mature, the nests of melanocytes gradually are assimilated into the dermis; they are then classified as either **compound** when the nests are present at the DEJ and within the dermis or as **intradermal** when the nests are exclusively within the dermis. As the nests descend, they become uniformly smaller and are composed of smaller-sized melanocytes which produce less pigment.

- **Dysplastic Nevi** - are a subgroup of nevi which have an irregular outline, variable pigmentation, indistinct borders, and can be larger than 5 mm in diameter. Often described as having a "fried-egg" appearance, they typically have a dome-shaped central brown papular component surrounded by a flatter zone of light brown or tan pigmentation. They show disordered histological architecture, typified by less circumscription of the nevus cell nests and extension of the junctional nests beyond the intradermal component. Dysplastic nevi also show an increased number of single melanocytes in the basal layer of the epidermis, pleomorphism of cells, and nests that vary in size, shape, and spacing. The upper dermis usually shows fibrosis and contains a host response of lymphocytes.
When multiple dysplastic nevi are present in a patient with a family history of melanoma, there may be an increased risk for the development of melanoma in that patient. The presence of a single or few dysplastic nevi outside the context of a family history of melanoma may or may not portend an increased risk for that patient.

- **Melanoma** - may arise within a previously existing nevus or dysplastic nevus, but approximately 70% of the time, they arise de novo. Classically divided into subtypes based on their clinical and histopathologic features. Histologically, all are typified by large, pleomorphic, and hyperchromatic melanocytes with loss of orderly architecture and maturation. Most commonly, melanomas begin as minimally elevated, asymmetrical pigmented papules or plaques with irregular, sometimes scalloped, borders and variations in color. At this stage they may be difficult to distinguish from dysplastic nevi. Superficial spreading melanomas typically show the ABCDE’s of melanoma (Asymmetry, Border irregularity, Color variegation and Diameter greater than 6mm, Evolving). If neglected, the depth of tumor invasion can continue to increase; a clinical correlate would be the development of nodularity within the melanoma. Nodular melanoma classically does not have a macular or plaque phase and presents as a blue or black papule or nodule.

  - The superficial spreading and nodular types of melanoma together account for approximately 80% of all melanomas. Both types occur most commonly in patients with lighter skin phenotypes, and may occur anywhere, but have a predilection for the upper back in men and women and the lower legs in women. Risk factors for developing these variants of melanoma include a family history of melanoma (with or without the presence of multiple dysplastic nevi), the presence of numerous common acquired nevi, and a history of blistering sunburns. The most important indicator of prognosis for all subtypes of melanoma is the Breslow’s depth, which is the maximal thickness of tumor invasion as measured by an ocular micrometer, from the top of the granular layer of the epidermis to the base of the neoplasm. Breslow’s depth is recorded in millimeters with lesions less than 1.0 mm having an excellent prognosis with infrequent metastases and melanomas thicker than 4 mm having a rather poor prognosis with a 5-year survival of approximately 50%. The most common sites of local and/or regional metastases are the draining lymph node basins and the skin between the primary site and these lymph nodes whereas the most common sites of systemic metastases are the lung, liver, brain, and gastrointestinal tract.

**Dermal Neoplasms**

- **Dermatofibroma** - pink papule common on the extremities.
  - Histopathological features:
    - Scattered boomer-rang shaped cells of varying degree of cellularity with infiltration of the surrounding collagen at the border "trapping"
    - Hyperpigmented basal layer that “tables” (flattened rete ridges)

- **Dermatofibrosarcoma Protuberans** – most commonly seen on youngish patients on the trunk.
  - Presents as papules or nodules (often multi-nodular) DFSP is an uncommon cutaneous soft tissue neoplasm, characterized by a slow, infiltrative growth pattern. DFSP has considerable morbidity because of its aggressive local invasiveness.
    - Histopathological features
      - Monomorphic spindle cells arranged in a “storiform” or “cartwheel” pattern.
      - CD 34 positive

- **Keloid Scar** - Nodular fibroblastic proliferation and the presence of hypocellular, glassy, eosinophilic, hyalinized and disordered collagen fibers in dermis.
Tumors of Cellular Immigrants

- **Cutaneous T-cell lymphoma** – neoplasm of helper T-cells (CD4+) that originate in the skin. Mycosis Fungoides is the most common variant. Etiology has not been established, though it has been postulated that patients with atopic dermatitis have an increased risk of developing CTCL due to chronic stimulation of T-cells that may induce its clonal proliferation. Other etiologic factors such as viral infections (HTLV-1) and chemical exposure have also been suggested.
  - Histopathological features
    - Mild epidermal hyperplasia
    - Papillary dermis has a band-like mononuclear cell infiltrate composed of hyperchromatic cerebriform cells with hyperchromatic cerebriform nuclei (known as mycosis cells)
    - Pautrier’s microabscesses may be seen in the epidermis, which are just aggregations of atypical lymphocytes
    - Dense infiltrate of lymphocytes that “line up” along DEJ

- **Urticaria Pigmentosa** - Typically presents in early childhood. 50% of cases occurring before 6 months of age
  - Few to numerous macules, papules, nodules and vesicles with variable tan to grey pigmentation
  - Pruritus, diarrhea, shortness of breath, joint pains and fatigue variably present
  - Urtication upon stroking (Darier’s sign) is usually positive
  - Mast cell degranulation must be avoided in extensive cases to prevent possible anaphylaxis:
    - Aspirin, alcohol, opiates, polymyxin B, quinine, scopalmine, amphotericin B and tubocurarine
  - Histology: early spongiotic and later verrucous phases. Characteristic early phase shows eosinophilic spongiosis with dyskeratosis.

- **Solitary mastocytoma** – both familiar and sporadic types. Appears as one or two fuzzy bordered tan to brown macules/patches. Histology shows numerous mast cells.

Adnexal Neoplasms

- **Trichilemmoma** – a proliferation of the outer root sheath, with small solitary lobules or groups of lobules connected to the epidermis with vertical growth.
  - Cowden’s disease: multiple trichilemmomas, sclerotic fibromas, acral keratosis, oral fibromas. Also has an increased risk of breast/endometrial/thyroid cancer. Autosomal dominant pattern of inheritance, caused by a mutation in the PTEN gene.

- **Cylindroma** – thought to be apocrine in origin, will see histopathologically multiple puzzle-like basaloid lobules in a mosaic or puzzle pattern. Clinically appears as a “turban” around the head or forehead

- **Sebaceous Neoplasms**
  - **Sebaceous adenoma** – individual lobules where >50% of the lobule contains mature sebaceous cells. On the rim there will be increase in thickness of the basal cells of the sebaceous glands in comparison to normal glands. Associated with Muir-Torre syndrome (sebaceous neoplasm of skin and a visceral malignancy, usually GI or GU carcinoma). Muir-Torre is autosomal dominantly inherited, and is associated with an inherited defect in a copy of a DNA mismatch repair gene, either MLH1 or MSH2, which leads to microsatellite instability.

Vascular Neoplasms

- **Pyogenic granuloma (Lobular capillary hemangioma)** - common benign vascular lesion, may arise at any age in either sex and shows a predilection for head, neck (especially the mucous membranes) and limbs (especially the hands). It evolves rapidly, reaching its maximum size in a matter of months.
Histologically consists of a usually exophytic, lobulated, dermal mass consisting of many small capillaries.

- **Bacillary angiomatosis** - benign vasoproliferative lesions presenting as widespread, numerous blood-red, smooth surfaced, superficial papules and skin-colored or dusky subcutaneous nodules. Cause by *Bartonella henselae*, histology reveals lobules of capillaries with prominent, often cuboidal vascular endothelial cells with intervening neutrophils and bacilli (identified on Warthin-Starry stain). Associated with HIV/AIDS.

- **Cherry hemangioma** - Common benign lesions that present as tiny red papules on the trunk and upper extremities of the middle aged and elderly. Pathogenesis is unknown. Histology shows a small collection of dilated and congested capillaries in the papillary dermis.

- **Strawberry hemangioma (infantile hemangioma)** - common benign vascular tumor that occurs most often as a congenital lesion or infantile lesion arising at any site, with the head and neck benign most common. Females >>> males. Clinically, the lesions are flat red or purple lesions, frequently less than 5 cm, that gradually enlarge and develop a raised surface. They can involute spontaneously. Histologically, they have a uniform appearance characterized by an intradermal or subcutaneous multilobular proliferation of numerous small vascular spaces lined by plump endothelial cells, which may be mitotically active. GLUT-1+

- **Cystic hygroma** - benign lesion of infancy presenting as a large cystic mass, most often in the neck, axillae or inguinal region, histologically presents as an ill-defined lesion in the dermis or subcutaneous fat consisting of numerous thin walled lymphatic channels with gross cystic dilation. Associated with Turner Syndrome.

- **Glomus tumor** - benign tumor arising from the glomus body, which is a specialized arteriovenous anastomosis found most often in the fingers. These are relatively common lesions that arise most often in the third and fourth decades and are predominantly seen on the hands, particularly the fingers in the subungual region. Histologically, the lesions are well circumscribed and composed of small vessels with normal endothelium surrounded by a dense, rather organoid, mantle of uniformly round glomus cells with pale eosinophilic cytoplasm, clearly defined cell margins, and central nuclei.

- **Kaposi Sarcoma (Malignant)** - Malignant tumor spindle cell tumor associated with HIV and HHV-8 presenting as small, reddish-blue macules or flat plaques, which are often multiple and often enlarge. There are 4 types of Kaposi sarcoma:
  - **Classic (endemic)** - arises most often in elderly males of Mediterranean and Jewish descent in the distal extremities
  - **AIDS-related** - presenting in young adults, mostly males, especially in the trunk, limbs, and mucosae and disseminates widely and rapidly
  - **Immunosuppression-associated** - rare, presents in patients receiving immunosuppressive therapy, especially after kidney transplant, indolent course
  - **African Kaposi sarcoma** - cases arising largely in sub-Saharan Africa (1) on the limbs of middle-aged men (indolent) and (2) in young children with visceral or lymph node involvement (usually fatal).

Histologically there are three stages (*ALL HHV-8 POSITIVE*):

- **Patch stage** - mild increase in the number of dermal vessels showing minimal endothelial atypia, vessels arranged parallel to the epidermis and may dissect between collagen bundles and surround adnexal structures and vessels (the promontory sign)
- **Plaque stage**: obvious dermal vascular proliferation, presence of eosinophilic spindled cells in the dermis around these vessels and ill defined margins
Nodular stage: relatively well-circumscribed dermal mass of variably eosinophilic spindle cells with numerous irregular slit-like vascular spaces which lack an endothelial lining but contain extravasated red blood cells

Angiosarcoma (Malignant)

Inflammatory Dermatosis

Lichenoid Dermatitis

- Lichen Planus - Prototypical lichenoid inflammatory condition with a band-like infiltrate of lymphocytes sometimes obscuring the DEJ, with hyperkeratosis, wedge-shaped areas of hypergranulosis, irregular acanthosis, saw toothing of the basal layer with squamatization of basal cells. Clinically will have the 5 P’s: polygonal, purplish, pruritic, papules and plaques. Also involves the oral mucosa.
- Erythema Multiforme – subepidermal blister, with necrotic keratinocytes at all levels of the epidermis. Clinically is a targetoid lesion with a pale/dusky center.
- Lupus erythematosus – lesions can be localized (above neck like scalp, nose, malar cheeks, lips, ears) or generalized (thorax and upper extremities, less common than localized). Abnormal labs such as ANA, dsDNA, leukopenia, hematuria, or albuminuria can help identify those patients who progress.
- Lichen Sclerosis et Atrophicus – Presents as a whitish macule described as a cigarette paper lesion most common on the genitalia. Histologically first presents as a lichenoid dermatitis. The lichenoid infiltrate gets "pushed down" leaving hyalinized collagen in its place.
- Dermatomyositis – clinically presents as proximal symmetrical muscle weakness, periorbital edema with heliotrope discoloration, Gottron’s papules/Gottron’s sign on the distal fingertips, periungual telangiectasia, and cuticular dystrophy. Violaceous erythema in shawl or photodistribution hyperkeratosis/scale over palms and soles, and psoriasiform scalp dermatitis. Can diagnose clinically with elevated muscle enzymes, muscle biopsy with evidence of inflammation or perifascicular atrophy, and thorough history and physical.

Psoriasiform Dermatitis

- Psoriasis - Psoriasis is an inflammatory disorder of the skin in which activation of T lymphocytes results in release of cytokines that leads to proliferation of keratinocytes. In normal skin, the cells of the epidermis are regenerated every 28 days, while in psoriatic skin epidermis is regenerated every two to four days. Affects about 2% of the US population, and usually begins in the third decade of life (early onset predicts more severe disease, and is more likely with positive family history). Increased incidence of psoriasis is seen in offspring of parents in which one or both affected, as well as in MZ twins (HLA-B/C accordance). Clinically, psoriasis appears as sharply demarcated papules and plaques, with non-coherent silvery scales. Auspitz sign is evident which is bleeding upon removal of scale (due to dilated superficial blood vessels). Some trigger factors have been postulated to be cold weather or lack of sun, physical trauma, as well as infection.

Spongiotic Dermatitis: A general category of dermatitis encompassing allergic contact and atopic dermatitis, fungal infections, nummular dermatitis. All have same histology of edema in between keratinocytes with variable amount of epidermal change and some superficial dermal infiltrate of lymphocytes and often eosinophils.

- Allergic contact dermatitis – a type IV hypersensitivity reaction (delayed, cell-mediate), when a hapten combines with a protein within a Langerhans cell to produce a reaction. Many plants are causes of allergic contact dermatitis. Some of the most common include carriers of the rhus antigen pentadecacatechol (found in poison ivy, oak and sumac). Rhus antigen causes an acute,
often streaky or linear reaction with an erythematous and edematous possibly vesicular dermatitis.

- **Vesiculo-Bullous Dermatitis**
  - **Bullous Pemphigoid (BP)** – histopathological appears as subepidermal separation with eosinophils. A clue to early BP is eosinophilic spongiosis and eosinophils lined up along the DEJ. Rarely BP can be neutrophilic or “cell-poor” (non-inflammatory). Linear IgG and C3 at the DEJ on direct immunofluorescence (DIF) against hemidesmosomes. Two antigens: Bullous pemphigoid antigen-1 (BPAg-1) (230 kDa) and Bullous pemphigoid antigen-2 (BPAg -2) (180 kDa); the BPAg-2 is thought to be the pathogenic antigen.
  - **Pemphigus Vulgaris (PV)** – Clinically presents as flaccid, thin-walled bullae that are easily ruptured, with erosions, crusts, and healing with hyperpigmentation. May be Nikolsky’s sign positive. Histopathology demonstrates suprabasilar acantholysis with “tombstoning” of the basal layer which may involve hair follicles/adnexa, and eosinophils and neutrophils in the infiltrate. DIF will show IgG antibodies against desmogleins with “net-like” distribution
  - **Dermatitis Herpetiformis (DH)** – Clinically appears as patients in the 4th decade, with severely grouped vesicles symmetrically on extensor surfaces. Pruritus causes vesicles to be transient, as scratching results in erosions. DIF shows granular IgA in dermal papillae. Linear IgA disease (or chronic bullous disease of childhood) can look histologically the same, but DIF shows linear IgA at the DEJ. Has an association with celiac disease or other GI malignancy, and responds to a gluten-free diet.
  - **Porphyria Cutanea Tarda** - Caused by a deficiency in uroporphyrinogen decarboxylase (UROD); may be inherited, sporadic or associated with Hepatitis C. Sporadic form may occur in association with HCV; in one study 82% of patients with PCT had HCV-antibodies. Other environmental triggers include alcohol, estrogens, and polyhalogenated hydrocarbons. Skin findings include vesicles and bullae on sun-exposed areas, and atrophic scarring with milia formation. Histopathological findings demonstrate a subepidermal bulla lined by well-preserved dermal papillae (festooning), thickening of basement membrane zone and factors.
  - **Epidermolysis Bullosa** - May present at birth or childhood. Numerous subtypes. Result in a subepidermal separation. Can look histologically like BP or like DH (with neutrophils) or non-inflammatory. Salt-split skin differentiates EB from BP. Antibodies to type VII collagen (290 kDa).

- **Granulomatous Dermatitis**: A general term for granulomas within the skin.
  - **Sarcoidosis** – fairly normal epidermis, with naked, non-caseating granulomas (sparse lymphocytic infiltrate) located through the mid- and deep dermis. Can look identical to foreign body reaction. On histology may see Schaumann body (basophilic, rounded structure composed of calcium carbonate, phosphate, and iron) or asteroid body (star-shaped), though neither body is specific for sarcoid (also seen in TB, leprosy, and berylliosis). This is a diagnosis of exclusion and must rule out infectious causes.

- **Vasculopathic Dermatitis**
  - **Urticaria** - popularly called "hives", represents a common vascular reaction pattern of the skin which affects as many as 15 to 20% of the population at some time during their lives. The lesions are erythematous to pale edematous papules and plaques that are often annular. Pruritus is a constant feature but varies in intensity among affected persons. Individual urticarial lesions are transient, usually lasting less than twenty-four hours, representing the single most important diagnostic criterion. One classification of the disorder is based on its duration, with episodes persisting less than six weeks arbitrarily termed acute urticaria, and those persisting longer termed chronic urticaria. Lesions represent transudation of fluid from small cutaneous blood
vessels into the dermis; they can result from either IgE-mediated hypersensitivity to an antigen with release of histamine and other mediators from mast cells and basophils, or from other immunologic or non-immunologic mechanisms. Foods, drugs, insect bites, or acute infections are usually found to be the cause of acute urticaria. Any drug may be responsible, but penicillins are the most common class of drugs that induce IgE-mediated acute urticaria. Foods that may be implicated include nuts, shellfish, eggs, milk, chocolate, wheat, tomatoes and berries. Foods, drugs, and chronic infections are occasionally implicated as causes of chronic urticaria, but in the large majority of cases no definite etiology can be identified. Special forms of urticaria exist which are precipitated by physical stimuli such as brisk stroking of the skin (dermographism), exercise, pressure, cold, heat, vibration, sunlight exposure and contact with water. The mainstays of treatment for most types of urticaria are oral antihistamines and avoidance of triggers.

Leukocytoclastic vasculitis: Numerous clinical causes. Presents as non-blanchable macules. Perivascular mixed inflammation with neutrophils and fibrin deposition in the vessel.

Infections of the Skin

- **Verruca vulgaris** - HPV causes verruca, more commonly referred to as warts. Warts are rare in infants, but the incidence rises during school years. About 10% of children between the ages of 2 and 12 have warts. In general there is an incidence peak between the ages of 12-16. Condylomata acuminata (genital and peri-anal warts), however, are more common in an older populations. Verrucae vulgaris (common warts) are hyperkeratotic dome shaped papules or nodules located most commonly on the hands. Verruca plana (warts on the bottom of feet) can cause great discomfort. Anogenital warts, condylomata acuminata, are discrete, sessile, smooth surfaced papillomas that can be flesh colored, brown or whitish. They are most commonly found on the external genitalia, perineum or peri-anal areas, and the most commonly implicated cause is HPV types 6 and 11. Warts are transmitted by contact. The virus infects the basal cells of the epidermis, thus a breach in the skin barrier is an important predisposing factor. Host immune function is extremely important in the infectious process as well. Once an immunocompetent patient has been infected with a specific HPV type, it is very unlikely that he/she will experience infection with that same type in the future. Patients who are immunosuppressed for any reason, however, can present with numerous, treatment resistant warts as well as recurrent infections with the same HPV type.
  - Histopathological features
    - Hyperkeratosis, hypergranulosis, papillomatosis
    - Koilocytes in vacuolated keratinocytes with raisin-like nuclei
    - Rete ridges often slope inward at borders of lesion (arborization)

- **Molluscum contagiosum** – caused by a poxvirus. Usually affects children and adults.
  - Histopathological features
    - Lobulated, endophytic hyperplasia
    - Keratinocytes contain very large intracytoplasmic inclusions that compress the nucleus against the cell membrane (Henderson-Patterson bodies) which pushes the nucleus aside

- **Bullous impetigo** - characterized by localized bullae arising on normal skin. The bullae are easily ruptured and form shallow erosions with an adjacent yellow-brown crust. Bullous impetigo is typically caused by *Phage II Staphylococcus aureus*. The bullous lesion is caused by an exfoliative toxin produced by the bacteria that causes cleavage within the granular cell layer of the epidermis. In children who lack antibodies or in adults with immunodeficiency or renal failure, systemic absorption of this toxin can cause the staphylococcal scalded skin syndrome, a generalized eruption characterized by painful erythema and superficial skin separation. Histopathologically presents as a subcorneal blister
with pustular dermatitis. Children, as opposed to adults, usually do not appear seriously ill. Treated with topical mupirocin (Bactroban).

- **Superficial Fungal (Dermatophytosis)** - Superficial fungal infections caused by a dermatophyte (species of fungi belonging to the genera *Trichophyton*, *Microsporum*, or *Epidermophyton*) are referred to as "tinea." Dermatophytes digest and invade keratin and may infect skin, nails, and hair. Infections may be acquired through human-to-human (anthropophilic) spread, animal-to-human (zoophilic) spread, or soil-to-human (geophilic) spread. The latter two categories tend to produce a more severe cutaneous inflammatory response in immunocompetent hosts. Infections of scalp hair and general body surfaces are most frequent during childhood; hand, foot, or nail infections are much more common after puberty. Dermatophyte infections are more common in association with hot, humid environments, sweating or softening of the skin, occlusive footwear, use of hair greases or oils, diabetes mellitus, and defects of cellular immunity (e.g., AIDS).

  - **Onychomycosis** - dermatophyte infection of the nail plate and is often found in association with tinea pedis. Toenails (especially the great toenail) are affected more frequently than fingernails. The clinical findings include yellow discoloration, thickening, subungual debris and loss of attachment of the nail plate to the nail bed. The diagnosis of a dermatophyte infection can be easily confirmed by obtaining material from an actively infected site (i.e., skin, hair, or nail), dissolving it in a potassium hydroxide (KOH) solution, and examining the material under a microscope. A KOH preparation that is positive for the presence of dermatophytes will demonstrate septate hyphae that branch at various angles in skin and nail specimens; in infected hairs, spores are generally present either on the hair surface or within the hair shaft. Nail clippings or tissue biopsy may also be performed. PAS stain is used to highlight the wall of the fungus. Direct antibody test in the microbiology lab and culture may also be performed on Sabouraud's agar. A two- to four-week period is usually required for growth and identification of the dermatophyte species.