Skin and Connective Tissue

Nick Levin
MS-II
children - Corneum
lazy - Lucidum
girls - Granulosum
slides - Spinosum
black hole - Basale
Corneum - Desquamating keratinocytes. Thick outer layers of flattened keratinized non-nucleated cells provide trauma and infection barrier.

Granular - lipids produced by keratinocytes secreted into extracellular space to form water barrier and keep water in skin. Filaggrin found here.

Spinosum - Center with ‘spiny’ appearance due to desmosomal junctions which hold keratinocytes together.

Basal - source of epidermal stem cells and keratinocytes move up. Cell division starts here.
**Dermis**

Flexible but tough structural support. Contains blood vessels, nerves and lymphatics. Sweat glands and hair follicles.

Fibroblasts and mast cells live in dermis.

Keloids (abnormal scars) from uncontrolled synthesis and excessive deposition of collagen at sites of dermal injury and wound repair.
2.
7.
COMMON SKIN DISORDERS
After completing the UWorld Question Bank for the second time, the now bored Gavin decides he will try and see if he has any of the physical manifestations of the disorders he reads about. Sure enough, when writing on himself with his own finger, Gavin elicits this hypersensitivity reaction illuminating the name of the same disorder. Presuming histamine is somehow involved in this reaction, which layer of skin would this reaction likely be elicited from?

a. Stratum Corneum
b. Stratum lucidum
c. Stratum Granulosum
d. Stratum Basale
e. Dermis
f. Hypodermis
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a. Stratum Corneum
b. Stratum lucidum
c. Stratum Granulosum
d. Stratum Basale
e. Dermis - Mast cells act here and this vascular reaction of Dermatographia Urticaria is from an excessive release of histamine forming wheals seen in 3-5% of teenagers.
f. Hypodermis
Erythema nodosum

Painful inflammatory lesions of subcutaneous fat, usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections, leprosy, Crohn disease.
Lichen Planus

Pruritic, Purple, Polygonal Planar Papules and Plaques are the 6 P’s of lichen Planus.

Mucosal involvement manifests as Wickham striae (reticular white lines). Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.
Pityriasis rosea

“Herald patch” followed days later by other scaly erythematous plaques, often in a “Christmas tree” distribution. Multiple plaques with collarette scale. Self-resolving in 6–8 weeks.
Psoriasis

- Unregulated proliferation of keratinocytes
  - Aggravated by Genetics, HIV, Drugs (lithium, B-blockers, NSAIDS)
  - Microcirculatory changes in superficial papillary dermis
  - Well-demarcated, flat, elevated, salmon-colored plaques with silver scales
  - Neutrophils collect in stratum corneum - Munro microabscesses
  - Rash in area of trauma (e.g. elbows), pitting of nails
A 27-year-old man comes to the physician's office with a 6-month history of low back pain and stiffness that wakes him up during the night and is worst in the morning. The patient was diagnosed with bilateral sacroiliitis 4 months ago because of his tenderness to percussion of the sacroiliac joints and pain on springing the pelvis up. He has severe limitation of motion of his lumbar spine. Laboratory test results are negative for antinuclear antibody and rheumatoid factor, and show the patient's human leukocyte antigen status is B27-positive. Which of the following is the most likely diagnosis?

(A) Ankylosing spondylitis

(B) Osteoarthritis

(C) Psoriatic arthritis

(D) Reiter's syndrome

(E) Rheumatoid arthritis

(F) Vertebral compression fracture
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Seronegative spondyloarthropathies

- No Rh Factor (no anti-IgG), HLA-B27 (codes for MHC-1), More often in **males**

**Psoriatic arthritis** - joint pain and stiffness, asymmetric, dactylitis

**Ankylosing spondylitis** - chronic inflammatory disease of spine and sacroiliac joints, uveitis, aortic regurgitation

**Inflammatory bowel disease** - chrohn’s and UC often accompany ankylosing spondylitis or peripheral arthritis

**Reactive arthritis**- Conjunctivitis, urethritis, arthritis - Post-GI Shigella, Salmonella, Yersinia, Campylobacter or Chlamydia
A 32-year-old woman presents to her physician complaining of “swollen lymph nodes” under her chin. Further questioning reveals that she has had a cough for the past 2 months and some increased shortness of breath. After completing a full physical examination, her physician orders an x-ray of the chest, which shows an abnormality. A lung biopsy is ordered, and a micrograph of the biopsy is shown in the image. What is her most likely diagnosis?

(A) Goodpasture’s syndrome

(B) Sarcoidosis

(C) Small cell lung cancer

(D) Systemic lupus erythematosus

(E) Tuberculosis
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USMLE Step 1 Q&A, 2013
Sarcoidosis

- Immune-mediated, widespread noncaseating granulomas
- Elevated serum ACE levels and increased CD4+/CD8+ ratio
- Common in black females
- Asymptomatic except for enlarged lymph nodes

Polymyalgia rheumatica

SYMPTOMS Pain and stiffness in shoulders and hips, often with fever, malaise, weight loss. Does not cause muscular weakness.

More common in women > 50 years old; associated with temporal (giant cell) arteritis.

FINDINGS ESR, CRP, normal CK.

TREATMENT Rapid response to low-dose corticosteroids.

Fibromyalgia

S/S: Chronic, widespread musculoskeletal pain associated with stiffness, paresthesias, poor sleep, fatigue.

Most commonly seen in females 20–50 years old.

Tx: with regular exercise, antidepressants (TCAs, SNRIs), anticonvulsants.
Systemic Lupus Erythematosus (SLE)

- Malar Rash, Joint pain, Fever in reproductive age female and african descent
- Libman-Sacks endocarditis - nonbacterial, wart-like vegetations on both sides of the mitral valve.
- Lupus nephritis (type III hypersensitivity)
  - Nephritic - diffuse proliferative glomerulonephritis
  - Nephrotic - membranous glomerulonephritis

Dx: ANA, Anti-dsDNA antibodies (renal disease), Anti-Smith antibodies, Anti-histone antibodies (drug-induced), low complement levels due to immune complex.

Tx: NSAIDS, steroids, immunosuppressants, hydroxychloroquine
A 58-year-old man comes to the doctor complaining of arthralgias in his hands and knees and mild fever. Physical examination reveals hepatomegaly, but there is no rash or neurologic findings. Laboratory studies show no hematologic abnormalities or renal disease. The patient is positive for antinuclear antibody and negative for anti-DNA antibodies. The patient mentions that he started a new medication a few months ago. Which of the following medications is most likely be responsible for this patient’s symptoms?

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(B) Enalapril

(C) Haloperidol

(D) Hydralazine

(E) Rifampin
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(D) Hydralazine - also procainamide, isonazid, chlorapromazine, penicillamine, sulfasalazine, methyldopa, quinidine, Phenytoin

(E) Rifampin
Antiphospholipid Syndrome

-Primary or Secondary autoimmune disorder (in SLE)

Dx: Clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion with positive lupus anticoagulant, anticardiolipin, anti-B2 glycoprotein antibodies

Tx: systemic anticoagulation

NOTE: False positive VDRL and prolonged PTT with anticardiolipin antibodies and lupus anticoagulants
Polymyositis/Dermatomyositis

Both: increase CK, positive: ANA, anti-Jo-1, anti-SRP, anti-Mi-2 antibodies

Tx: Steroids with long-term immunosuppressive therapy (methotrexate)

**Polymyositis** → progressive symmetric **proximal muscle weakness** with endomysial inflammation with CD8+ T Cells. Most often involves shoulders.
Dermatomyositis

Also involves Malar Rash, Gotton papules, heliotrope (erythematous periorbital) rash, “shawl and face” rash, “mechanic’s hands”, increase risk of occult malignancy. Perimysial inflammation with atrophy with CD4+ T cells.
Myositis Ossificans

Metaplasia of skeletal muscle into bone following muscular trauma. Most often seen in upper or lower extremity. May present as “suspicious mass” at site of known trauma or as incidental finding on radiography.
Scleroderma (systemic sclerosis)

-Triad of autoimmunity, noninflammatory vasculopathy and collagen deposition with fibrosis.

s/s: sclerosis of skin (puffy and taut skin) without wrinkles, fingertip pitting. Also sclerosis of renal, pulm (most common cause of death), cardio and GI systems. - 75% Female

Diffuse→ widespread skin involvement, rapid, early visceral involvement. Associated with scl-70 antibody (anti-DNA topoisomerase I antibody)
CREST → limited Scleroderma

- Calcinosis
- Raynaud’s Syndrome
- Esophageal Dysmotility
- Sclerodactyly
- Telangiectasias

**Fingers and face skin involvement. More benign and associated with anti-centromere antibody**
Epithelial cell junctions

Tight junction (zonula occludens)—prevents paracellular movement of solutes; composed of claudins and occludins.

Adherens junction (zonula adherens)—below tight junction, forms "belt" connecting actin cytoskeletons of adjacent cells with CADherins (Ca²⁺-dependent adhesion proteins). Loss of E-cadherin promotes metastasis.

Desmosome (macula adherens)—structural support via keratin interactions. Autoantibodies → pemphigus vulgaris.

Gap junction—channel proteins called connexons permit electrical and chemical communication between cells.

Integrins—membrane proteins that maintain integrity of basolateral membrane by binding to collagen and laminin in basement membrane.

Hemidesmosome—connects keratin in basal cells to underlying basement membrane. Autoantibodies → bullous pemphigoid. (Hemidesmosomes are down "bullow").
Psoriasis occurs in what level of the epidermis?
39 y.o. woman developed vesicular skin lesions over the past week. On PE, she has multiple, 0.2 to 1 cm vesicles and bullae on the skin of her scalp, axillae, groin and knees. Many lesions appear to have ruptured, and a shallow erosion with a dried crust of serum remains. A biopsy of an axillary lesion shows epidermal acantholysis and formation of an intraepidermal blister. The basal cell layer is intact. Which of the following additional tests can explain the pathogenesis of the patient’s disease?

a. Darkfield microscopy of vesicular fluid  
b. HLA genotyping  
c. Immunostaining with antidesmoglein  
d. Quantification of serum IgE level  
e. Viral culture of vesicular fluid
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Pemphigus vulgaris

Lesions caused by IgG autoantibodies directed at an intercellular cement substance called desmoglein, giving a netlike appearance with immunofluorescence microscopy. The antibody deposition disrupts intercellular bridges, causing the epidermal cells to detach from one another (acantholysis). This causes the formation of an intraepidermal blister. Staining with anti-IgG illuminates intercellular junctions at sites of incipient acantholysis.
65 y.o. man has developed pruritus followed by blistering skin lesions over the trunk, legs, and arms over the past month. On PE, there are 1- to 4-cm tense bullae, particularly over flexural surfaces of skin. Biopsy with immunofluorescence staining shows a subepidermal bulla, with both IgG and C3 deposited linearly along the dermal-epidermal junction. He is treated with topical corticosteroids and a month later his lesions are healed without scarring. Which component of skin was targeted by an autoantibody?

a. hemidesmosome  
b. keratinocyte cell membrane  
c. lamina densa  
d. nucleus  
e. reticulin
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Subepidermal bullae of bullous pemphigoid

- Usually heal without scarring
- Subsequent oral lesions may appear
- Most often seen in elderly

- Results from linear IgG deposition at the basal cell-basement membrane attachment plaques (hemidesmosomas) containing bullous pemphigoid antigen (BPAG). The lamina densa of the basement membrane is not directly involved, and the actual blister of bullous pemphigoid forms in the lumina lucida. In contrast, the antibodies in pemphigus vulgaris attack the desmosomes that attach the epidermal keratinocytes
The diagram shows a cross-section of normal human skin. Patients with pemphigus vulgaris suffer from production of autoantibodies against which of the following labeled layers in this image?
2.1-cm pigmented lesion with irregular borders and irregular brown to black areas. An excisional biopsy shows a malignant melanoma composed of epithelioid cells that extend 2 mm into the reticular dermis. There is a band of lymphocytes beneath the lesion. What is the most important determinant of prognosis?

a. age at diagnosis
b. depth of lesion
c. extent of radial growth
d. inflammatory response
e. location on the skin
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Elderly man with lesion on side of face that enlarges slowly over the past 5 years. The lesion is 3-cm with irregular borders, irregular brown to black pigmentation, and a central 2-mm blue-black nodule. Resection shows radial growth of round malignant cells and isolated nests in epidermis and superficial papillary dermis. Which gene is most likely mutated in this lesion?

a. ATM
b. BRAF
c. NF1
d. TYR
e. XPA
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a. ATM - ataxia-telangiectasia (dilated subepidermal blood vessels)
b. BRAF - Lentigo maligna melanoma (radial → vertical). Head and neck of elderly. Activating BRAF mutation downstream of RAS.
c. NF1 - neurofibromas
d. TYR - seen in albinism (TYR codes for tyrosinase for melanin production)
e. XPA - xeroderma pigmentosum (defect in DNA excision repair, CA in children from UV damage)
A 53-y.o. presenting with this skin lesion that appeared after 3 months on his upper arm likely worked where as a kid? *hint: ABCs stand for what?*

a. dip-n-dots  
b. century 24  
c. the beach water park  
d. in a mine near Grants, NM  
e. Copper indoor soccer arena as a mediocre referee
A 53-y.o. presenting with this skin lesion that appeared after 3 months on his upper arm likely worked where as a kid? *hint: ABCs stand for what?*

a. dip-n-dots  
b. century 24  
c. **the beach water park (s-100 tumor marker)**  
d. in a mine near Grants, NM  
e. Copper indoor soccer arena as a mediocre referee
Melanoma

At least 4 different types of melanoma, including superficial spreading, nodular, lentigo maligna, and acral lentiginous.

Often driven by activating mutation in BRAF kinase.

Primary treatment is excision with appropriately wide margins. Metastatic or unresectable melanoma in patients with BRAF V600E mutation may benefit from vemurafenib, a BRAF kinase inhibitor.
Elderly male notes changes in texture and color in skin in his armpits and groin over the past 3 months. On PE there is thickened, darkly pigmented skin in the axillae and flexural areas of neck and groin. Not painful or pruritic. Punch biopsy of axillary skin show undulating epidermal acanthosis with hyperkeratosis and basal layer hyperpigmentation. These are cutaneous markers of what underlying disease?

a. AIDS (stage 3 HIV)
b. Colonic adenocarcinoma
c. Langerhans cell histiocytosis
d. Mastocytosis
e. SLE
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a. AIDS (stage 3 HIV) - disseminated infections with papulosquamous dermatoses (NOT PIGMENTED)

b. Colonic adenocarcinoma - Acanthosis nigricans

c. Langerhans cell histiocytosis

d. Mastocytosis

e. SLE
The former owner of the beach water park is now 76y.o. and presents to your clinic with the most common type of skin cancer. While this type of cancer rarely metastasizes, it can be particularly dangerous in this presentation. on PE it is described as pink, pearly nodules. What kind of cancer does this man have?

a. actinic keratosis  
b. basal cell carcinoma  
c. dermatofibroma  
d. malignant melanoma  
e. nevocellular nevus
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a. actinic keratosis - premalignant scaly lesion to SCC, not invade
b. **basal cell carcinoma**
   c. dermatofibroma - benign lesion of dermis
d. malignant melanoma - pigmented (spindle cells)
e. nevocellular nevus - small, localized, benign
Basal cell carcinoma

Most common skin cancer. Found in sun-exposed areas of body. Locally invasive, but rarely metastasizes. Pink, pearly nodules, commonly with telangiectasias, rolled borders, central crusting or ulcer.
The many years of eating churros at the beach water park finally caught up with Nick to the point where he underwent an orthotropic heart transplantation. During the next 5 years he had 2 episodes of minimal cellular rejection, which were adequately treated by an increase immunosuppressive therapy. He has since developed multiple skin lesions on the face and upper trunk over the past 6 months. Some of the larger lesions have ulcerated.

a. dermatofibroma
b. erythema multiforme
c. lichen planus
d. psoriasis
e. squamous cell carcinoma
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a. dermatofibroma
b. erythema multiforme - HSR to drugs
c. lichen planus - purple, pruritic, polygonal papules
d. psoriasis
e. squamous cell carcinoma

Risk factors: UV, burn injuries, irradiation, immunosuppressed. DNA repair disorders (xeroderma pigmentosum)
S/S: Locally invasive with spread to lymph nodes, rarely metastasize. Ulcerative red lesions with frequent scales. Associated in draining sinuses.
Histo: keratin ‘pearls’
HIV-infected male has increasing fever, cough and dyspnea for the past 3 days which has culminated in acute respiratory failure. Upon admission he is diagnosed with *pneumocystis jiroveci* by DFA. After 1 week of therapy he develops target lesions of the skin composed of red macules with a pale, vesicular center. The 2- to 5-cm lesions are distributed symmetrically over the upper arms and chest. Which drug is culpable?

a. Dapsone  
b. Pentamidine  
c. Ritonavir  
d. Sulfamethoxazole  
e. Zidovudine
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Erythema Multiforme (EM), hypersensitivity to infections and some drugs such as sulfonamides and PCN. Also, herpes, mycoplasmal and fungal infections, malignant diseases, and collagen vascular diseases such as SLE.

S/S: multiple macules, papules, vesicles, target lesions
44-y.o. woman has developed skin lesions on her elbows and knees over the past year. Lesions start as 4-mm pustules with surrounding erythema but then evolve into 1 to 5cm plaques covered in silvery-white scale. Lesions appear in areas of local trauma and sunlight makes them regress. Biopsy shows thinning of stratum granulosum with marked parakeratotic scale containing microabscesses. What other symptoms may be this patient have?

a. Friction rub  
b. Guaiac-positive stool sample  
c. Hyperreflexia  
d. Hypertension  
e. Nail changes and arthritis
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References

Robbins and Cotran, REVIEW OF PATHOLOGY, 4th Edition
First Aid for the USMLE STEP 1, 2014
First Aid Q&A for USMLE STEP 1
Images courtesy of Google Images public domain
<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Description</th>
<th>Disease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale</td>
<td>Macule &gt; 1 cm</td>
<td>Large birthmark (congenital nevus)</td>
</tr>
<tr>
<td>Macule</td>
<td>Elevated solid skin lesion &lt; 1 cm</td>
<td>Mole (nevus), acne</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Large fluid-containing blister &gt; 1 cm</td>
<td>Eczema, psoriasis, SCC</td>
</tr>
<tr>
<td>Papules</td>
<td>Flat lesion with well-circumscribed change in skin color &lt; 1 cm</td>
<td>Pustular psoriasis</td>
</tr>
<tr>
<td>Plaque</td>
<td>Dry exudate</td>
<td>Impetigo</td>
</tr>
<tr>
<td>Bulla</td>
<td>Small fluid-containing blister &lt; 1 cm</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>Patch</td>
<td>Transient smooth papule or plaque</td>
<td>Chickenpox (Varicella)</td>
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<tr>
<td>Pustule</td>
<td>Vesicle containing pus</td>
<td>Psoriasis</td>
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<tr>
<td>Wheal</td>
<td>Flaking off of stratum corneum</td>
<td>Hives (urticaria)</td>
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<tr>
<td>Crust</td>
<td>Papule &gt; 1 cm</td>
<td>Freckle, labial</td>
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</tbody>
</table>
Atopic Dermatitis (eczema)
Erythematous papules and pustules but no comedones, may be associated with facial flushing (ETOH, heat). Chronic → rhinophyma

Allergic Contact Dermatitis
Flat, greasy, pigmented squamous epithelial proliferation with keratin-filled cysts (horn cysts)
Looks “stuck on.” Lesions occur on head, trunk, and extremities.
Common benign neoplasm of older persons.

Psoriasis
Warts; caused by HPV. Soft, tan-colored, cauliflower-like papules

Rosacea
Type IV hypersensitivity reaction following exposure to allergen.

Seborrheic Keratosis
Papules and plaques with silvery scaling on knees and elbows, increases stratum spinosum, Auspitz sign (bleeding at spots of dermal papillae scraped off). Can be associated with arthritis and nail pitting

Verrucae
Hives. Pruritic wheals that form after mast cell degranulation

Urticaria
Pruritic eruption, commonly on skin flexures, associated with atopic disease (asthma, allergic rhinitis). Usually starts in face in infants.

Hyperkeratosis
increased thickness of stratum corneum
Psoriasis, calluses

Parakeratosis
Hyperkeratosis with retention of nuclei in stratum corneum
Psoriasis

Spongiosis
Separation of epidermal cells
Pemphigus vulgaris

Acantholysis
Epidermal hyperplasia (increased spinosum)
Eczematous dermatitis

Acanthosis
Epidermal accumulation of edematous fluid in intercellular spaces
Acanthosis nigricans