HISTOLOGY CLINICAL

CHAPTER 2:

1. **Zonula occludens**:

Proteins of tight junctions provide the targets for certain common bacteria of medical importance.

- → The enterotoxin secreted by *Clostridium perfringens*, which causes "food poisoning," binds claudin molecules of intestinal cells, prevents insertion of these proteins during maintenance of tight junctions, and causes loss of tissue fluid into the intestinal lumen via the paracellular pathway.
- → Similarly, *Helicobacter pylori*, which is important in the etiology of gastric ulcers, binds the extracellular domains of tight-junction proteins in cells of the stomach and inserts a protein into these cells, which targets ZO-1 and disrupts signaling from the junction.
- → Defects in occludins may compromise the fetal blood-brain barrier, leading to severe neurologic disorders

2. **Zonula adherens:**
   - → Loss of E-cadherin in epithelial cell tumors (carcinomas) promotes tumor invasion and the shift to malignancy
3. **Desmosomes**:
   - → Various blistering (bullous) diseases, such as pemphigus vulgaris, involving the epidermis or stratified squamous epithelia of the oral mucosa, are due to abnormal desmosome function caused by autoimmune reactions against specific desmogleins that reduce cell-to-cell adhesion
4. **Hemidesmosomes:**
   - → Mutations in the integrin-β4 gene are linked to some types of epidermolysis bullosa, a skin blistering disorder
5. **Gap junctions:**
   - → Mutations in various connexin genes have been linked to certain types of deafness and peripheral neuropathy

CHAPTER 3:

Apical domain:

1. **Microvilli:**

→ Celiac disease, also called gluten-sensitive enteropathy or sprue, is a disorder of the small intestine in which one of the first pathologic changes is loss of the microvilli brush border of the absorptive cells. This is caused by an immune reaction against the wheat protein gluten during its digestion, which produces diffuse enteritis (intestinal inflammation), changes to the epithelial cells leading to malabsorption, and eventually to pathologic changes in the intestinal wall. The Malabsorption problems and structural changes are reversible when gluten is removed from the diet.

2. **Cilia:**

→ Several mutations have been described in the proteins of the cilia and flagella. They are responsible for the immotile cilia syndrome (Kartagener syndrome), whose symptoms are chronic respiratory infections caused by the lack of the cleansing action of cilia in the respiratory tract and immotile spermatozoa, causing male infertility.

Epithelium:

→ In individuals with chronic vitamin A deficiency, epithelial tissues of the type found in the bronchi and urinary bladder may gradually be replaced by stratified squamous epithelium

→ In chronic bronchitis, common among habitual smokers, the number of goblet cells in the lining of airways in the lungs often increases greatly. This leads to excessive mucus production in areas where there are too few ciliated cells for its rapid removal and contributes to obstruction of the airways. The ciliated pseudostratified epithelium lining the bronchi of smokers can also be transformed into stratified squamous epithelium by metaplasia.

→ Both benign and malignant tumors can arise from most types of epithelial cells. Malignant tumors of epithelial origin are called carcinomas (Gr. karkinos, cancer + oma, tumor). Malignant tumors derived from glandular epithelial tissue are called adenocarcinomas (Gr. adenos, gland + karkinos). Adenocarcinomas are by far the most common tumors in adults after age 45

CHAPTER 4

Glands:

- → The holocrine sebaceous glands are the primary structure involved in the common form of acne, acne vulgaris. Excessive holocrine secretion of sebum and keratin triggered by the surge of the steroid hormone testosterone that occurs in both genders at puberty frequently leads to blocked ducts within the gland. Activity of the normal commensal skin bacterium Propioni bacterium acnes within the blocked duct commonly produces localized inflammation
- → Some epithelial cells are prone to abnormal growth or dysplasia, which can progress to precancerous growth called neoplasia. Early neoplastic growth is often reversible and does not always result in cancer. Under certain abnormal conditions, one type of epithelial tissue may undergo transformation into another type in another reversible process called metaplasia. In heavy cigarette smokers, the ciliated pseudostratified epithelium lining the bronchi can be transformed into stratified squamous epithelium.

Chapter 5

Stem cells: (read if time)

- → Some cells in mesenchyme are multipotent stem cells potentially useful in regenerative medicine after grafting to replace damaged tissue in certain patients. Mesenchyme like cells remain present in some adult connective tissues, including that of tooth pulp and some adipose tissue, and are being investigated as possible sources of stem cells for therapeutic repair and organ regeneration.

Scar tissues:

- → The regenerative capacity of connective tissue is clearly observed in organs damaged by ischemia, inflammation, or traumatic injury. Spaces left after such injuries, especially in tissues whose cells divide poorly or not at all (eg, cardiac muscle), are filled by connective tissue, forming dense irregular scar tissue.

Myofibroblast: (read if time)

- → The healing of surgical incisions and other wounds depends on the reparative capacity of connective tissue, particularly on activity and growth of fibroblasts. In some rapidly closing wounds, a cell called the myofibroblast, with features of both fibroblasts and smooth muscle cells, is also observed. These cells have most of the morphologic characteristics of fibroblasts but contain increased amounts of actin microfilaments and myosin and behave much like smooth muscle cells. Their activity is important for the phase of tissue repair called wound contraction

Macrophages: (read if time)

→ Besides their function in turnover of ECM fibers, macrophages are key components of an organism's innate immune defense system, removing cell debris, neoplastic cells, bacteria, and other invaders. Macrophages are also important antigen-presenting cells required for the activation and specification of lymphocytes. When macrophages are stimulated (by injection of foreign substances or by infection), they change their morphologic characteristics and properties, becoming activated macrophages. In addition to showing an increase in their capacity for phagocytosis and intracellular digestion, activated macrophages exhibit enhanced metabolic and lysosomal enzyme activity. Macrophages are also secretory cells producing an array of substances, including various enzymes for ECM breakdown and various growth factors or cytokines that help regulate immune cells and reparative functions. When adequately stimulated, macrophages may increase in size and fuse to form multinuclear giant cells, usually found only in pathologic conditions.

Inflammation: (read if time)

→ Increased vascular permeability is caused by the action of vasoactive substances such as histamine released from mast cells during inflammation. Classically, the major signs of inflamed tissues include "redness and swelling with heat and pain" (rubor et tumor cum calore et dolore). Increased blood flow and vascular permeability produce local tissue swelling (edema), with increased redness and warmth. Pain is due mainly to the action of the chemical mediators on local sensory nerve endings. All these activities help protect and repair the inflamed tissue. Chemotaxis (Gr. chemeia, alchemy + taxis, orderly arrangement), the phenomenon by which specific cell types are attracted by specific molecules, draws much larger numbers of leukocytes into inflamed tissues.

CHAPTER 6

Collagen:

- → A **keloid** (origin: crab claw – due to its ability to expand into neighboring region)is a local swelling caused by abnormally large amounts of collagen that form in scars of the skin. Keloids occur most often in individuals of African descent and can be a troublesome clinical problem to manage. Not only can they be disfiguring, but excision is almost always followed by recurrence.
- → **Ehlers-Danlos type IV:** Faulty transcription or translation of collagen type III result in Aortic and/or intestinal rupture
- → **Ehlers-Danlos type VI**: Faulty lysine hydroxylation result in Increased skin elasticity, rupture of eyeball
- → **Ehlers-Danlos type VII**: Decrease in procollagen peptidase activity result in Increased articular mobility, frequent luxation

Elastic fibers: (already read in block 2 biochemistry)

- → Fibrillins comprise a family of proteins involved in making the scaffolding necessary for the deposition of elastin. Mutations in the fibrillin genes result in Marfan syndrome, a disease characterized by a lack of resistance in tissues rich in elastic fibers. Because the walls of large arteries are rich in elastic components and because the blood pressure is high in the aorta, patients with this disease often experience aortic swellings called aneurysms, which are life-threatening conditions

Ground substance:

- → The degradation of proteoglycans is carried out by several cell types and depends in part on the presence of several lysosomal enzymes. Several disorders have been described, including a deficiency in certain lysosomal enzymes that degrade specific GAGs, with the subsequent accumulation of these macromolecules in tissues. The lack of specific hydrolases in the lysosomes has been found to be the cause of several disorders, including the Hurler, Hunter, Sanfilippo, and Morquio syndromes. Because of their high viscosity, hyaluronan and proteoglycans tend to form a barrier against bacterial penetration of tissues. Bacteria that produce hyaluronidase, an enzyme that hydrolyzes hyaluronan and disassembles proteoglycans complexes, reduce the viscosity of the connective tissue ground substance and have greater invasive power.

Tendon:

- → Overuse of tendon-muscle units can result in tendonitis, characterized by inflammation of the tendons and their attachments to muscle. Common locations are the elbow, the Achilles tendon of the heel, and the shoulder rotator cuff. The swelling and pain produced by the localized inflammation restricts the affected area's normal range of motion and can be relieved by injections of anti-inflammatory agents such as cortisone. Fibroblasts eventually repair damaged collagen bundles of the area.

Adipose tissue:

- → Unilocular adipocytes can generate benign tumors called lipomas that are relatively common, although malignant adipose tumors (liposarcomas) occur infrequently. Fetal lipomas of brown fat are sometimes called hibernomas
- → Leptin was discovered and is well studied in genetically obese mice, but such studies have not yet led to new treatments for human obesity. In most obese humans adipocytes produce adequate or excess quantities of leptin, but target cells are not responsive due apparently to insufficient or defective receptors or post-receptor signal transduction.
- → In addition to leptin, white adipose tissue secretes numerous other cytokines and other factors with paracrine and autocrine activity, including many proinflammatory cytokines. It is not clear whether these are produced by adipocytes or other cells of the tissue such as macrophages or fibroblasts. With its increased amounts of white adipose tissue, obesity is characterized by a state of chronic mild inflammation. Proinflammatory factors released from visceral fat are being investigated for links to the inflammation-related disorders associated with obesity, such as diabetes and heart disease.
- → Adult-onset obesity is very often associated with age-related metabolic changes and may involve reduced activity of the hormone-sensitive lipases of adipocytes, causing less effective fat mobilization out of the cells.
- → The increased number of adipocytes produced during childhood obesity predisposes an individual to obesity in later life. Despite claims of various fad diets, there is no evidence that any particular type of caloric restriction is more effective than others; rather, any intake of calories that is lower than the energy expenditure will result in loss of adipose tissue.

CHAPTER 7:

→ Many genetic conditions in humans or mice that cause defective cartilage, joint deformities, or short limbs are due to recessive mutations in genes for collagen type II, the aggrecan core protein, the sulfate transporter, and other proteins required for normal chondrocyte function.

→ Cells of cartilage can give rise to either benign (chondroma) or slow-growing, malignant (chondrosarcoma) tumors in which cells produce normal matrix components. Chondrosarcomas seldom metastasize and are generally removed surgically

Hyaline cartilage:

→ **Osteoarthritis**, a chronic condition that commonly occurs during aging, involves the gradual loss or changed physical properties of the hyaline cartilage that lines the articular ends of bones in joints. Joints that are weight-bearing (knees, hips) or heavily used (wrist, fingers) are most prone to cartilage degeneration. Fragments released by wear-and-tear to the articular cartilage trigger secretion of matrix metalloproteinases and other factors from macrophages in adjacent tissues, which exacerbate damage and cause pain and inflammation within the joint.

→ In contrast to other forms of cartilage and most other tissues, hyaline cartilage is susceptible to partial or isolated regions of calcification during aging, especially in the costal cartilage adjacent to the ribs. Calcification of the hyaline matrix, accompanied by degenerative changes in the chondrocytes, is a common part of the aging process and in many respects resembles endochondral ossification by which bone is formed

CHAPTER 8

→ Cancer originating directly from bone cells (a primary bone tumor) is fairly uncommon (0.5% of all cancer deaths), although a cancer called **osteosarcoma** can arise in osteoprogenitor cells. The skeleton is often the site of secondary, metastatic tumors, however, arising when cancer cells move into bones via small blood or lymphatic vessels from malignancies in other organs, most commonly the breast, lung, prostate gland, kidney, or thyroid gland.

→ **Osteoporosis**, frequently found in immobilized patients and in postmenopausal women, is an imbalance in skeletal turnover so that bone resorption exceeds bone formation. This leads to calcium loss from bones and reduced bone mineral density (BMD). Individuals at risk for osteoporosis are routinely tested for BMD by dual-energy x-ray absorptiometry (DEXA scans).

Osteocytes:

→ The network of dendritic processes extending from osteocytes has been called a "mechanostat," monitoring areas within bones where loading has been increased or decreased, and signaling cells to adjust ion levels and maintain the adjacent bone matrix accordingly. Lack of exercise (or the weightlessness experienced by astronauts) leads to decreased bone density, due in part to the lack of mechanical stimulation of these cells.

Osteoclast:

In the genetic disease **osteopetrosis**, which is characterized by dense, heavy bones ("marble bones"), the osteoclasts lack ruffled borders and bone resorption is defective. This disorder results in overgrowth and thickening of bones, often with obliteration of the marrow cavities, depressing blood cell formation and causing anemia and the loss of white blood cells. The defective osteoclasts in most patients with osteopetrosis have mutations in genes for the cells' proton-ATPase pumps or chloride channels.

Bone growth:

Diagnostic technique:

The antibiotic tetracycline is a fluorescent molecule that binds newly deposited osteoid matrix during mineralization with high affinity and specifically labels new bone under the UV microscope (Figure 8–12). This discovery led to methods for measuring the rate of bone growth, an important parameter in the diagnosis of certain bone disorders.

In one technique tetracycline is administered twice to patients, with an intervening interval of 11-14 days. A bone biopsy is then performed, sectioned without decalcification, and examined. Bone formed while tetracycline was present appears as fluorescent lamellae and the distance between the labeled layers is proportional to the rate of bone appositional growth. This procedure is of diagnostic importance in such diseases as osteomalacia, in which mineralization is impaired, and osteitis fibrosa cystica, in which increased osteoclast activity results in removal of bone matrix and fibrous degeneration

Other diseases:

→ Calcium deficiency in children can lead to **rickets**, a disease in which the bone matrix does not calcify normally and the epiphyseal plate can become distorted by the normal strains of body weight and muscular activity. Ossification processes are consequently impeded, which causes

bones to grow more slowly and often become deformed. The deficiency can be due either to insufficient calcium in the diet or a failure to produce the steroid prohormone vitamin D, which is important for the absorption of Ca2+ by cells of the small intestine. In adults calcium deficiency can give rise to **osteomalacia** (osteon + Gr. malakia, softness), characterized by deficient calcification of recently formed bone and partial decalcification of already calcified matrix.

→ **Bone fractures** are repaired by a developmental process involving fibrocartilage formation and osteogenic activity of the major bone cells (Figure 8–19). Bone fractures disrupt blood vessels, causing bone cells near the break to die. The damaged blood vessels produce a localized hemorrhage or hematoma. Clotted blood is removed along with tissue debris by macrophages and the matrix of damaged, cell-free bone is resorbed by osteoclasts

→ In addition to PTH and calcitonin, several other hormones act on bone. The anterior lobe of the pituitary synthesizes growth hormone (GH or somatotropin), which stimulates the liver to produce insulin-like growth factor-1 (IGF-1 or somatomedin). IGF has an overall growth-promoting effect, especially on the epiphyseal cartilage. Consequently, lack of growth hormone during the growing years causes **pituitary dwarfism**; an excess of growth hormone causes excessive growth of the long bones, resulting in **gigantism**. Adult bones cannot increase in length even with excess IGF because they lack epiphyseal cartilage, but they do increase in width by periosteal growth. **In adults, an increase in GH causes acromegaly,** a disease in which the bones—mainly the long ones—become very thick

→ In **rheumatoid arthritis** chronic inflammation of the synovial membrane causes thickening of this connective tissue and stimulates the macrophages to release collagenases and other hydrolytic enzymes. Such enzymes eventually cause destruction of the articular cartilage, allowing direct contact of the bones projecting into the joint

Within an intervertebral disc, collagen loss or other degenerative changes in the annulus fibrosus are often accompanied by displacement of the nucleus pulposus, a condition variously called a **slipped or herniated disc.** This occurs most frequently on the posterior region of the intervertebral disc where there are fewer collagen bundles. The affected disc frequently dislocates or shifts slightly from its normal position. If it moves toward nerve plexuses, it can compress the nerves and result in severe pain and other neurologic disturbances. The pain accompanying a slipped disc may be perceived in areas innervated by the compressed nerve fibers—usually the lower lumbar region.

CHAPTER 10

Cardiac muscle:

→ The most common injury sustained by cardiac muscle is that due to ischemia, or tissue damage due to lack of oxygen when coronary arteries are occluded by heart disease. Lacking muscle satellite cells, adult mammalian cardiac muscle has little potential to regenerate after injury. However, certain fish and amphibians, as well as newborn mice, do form new muscle when the heart is partially removed, despite the lack of satellite cells. Research on the possibility of mammalian heart muscle regeneration builds on work with the animal models, focusing primarily on the potential of mesenchymal stem cells to form new, site-specific muscle

Smooth muscle:

→ Benign tumors called **leiomyomas** commonly develop from smooth muscle fibers but are seldom problematic. They most frequently occur in the wall of the uterus, where they are more commonly called **fibroids** and where they can become sufficiently large to produce painful pressure and unexpected bleeding.

CHAPTER 13

→ The normal vascular endothelium is antithrombogenic, allowing adhesion of no blood cells or platelets and preventing blood clot formation. When endothelial cells of the microvasculature are damaged by tissue injury, collagen is exposed in the subendothelial tissues and induces the aggregation of blood platelets. These platelets release factors that initiate a cascade of events that produce fibrin from circulating plasma fibrinogen.

An intravascular clot, or **thrombus** (plural, thrombi), with a fibrin framework quickly forms to stop blood loss from the damaged vessels.

From large thrombi, solid masses called **emboli** (singular, embolus) may detach and be carried by the blood to obstruct distant vessels. In both cases vascular flow may be blocked, producing a potentially life-threatening condition. Thus, the integrity of the endothelial layer preventing contact between platelets and the subendothelial connective tissue is an important antithrombogenic mechanism.

Treatment:

Individuals in the initial stages of medical conditions involving thrombus formation, such as myocardial infarct, stroke, or pulmonary embolism, are treated intravenously with tissue plasminogen activator, commonly abbreviated as tPA. This is a serine protease that breaks down fibrin and quickly dissolves the clot.

→ **Atherosclerosis** (Gr. athero, gruel or porridge, and scleros, hardening) is a disease of elastic arteries and large muscular arteries that may play a role in nearly half of all deaths in developed parts of the world. It is initiated by damaged or dysfunctional endothelial cells oxidizing low-density lipoproteins (LDLs) in the tunica intima, which induces adhesion and intima entry of monocytes/macrophages to remove the modified LDL. Lipid-filled macrophages (called foam cells) accumulate and, along with the free LDL, produce a pathologic sign of early atherosclerosis called **fatty streaks**. During disease progression these develop into fibro-fatty plaques, or **atheromas**, consisting of a gruel-like mix of smooth muscle cells, collagen fibers, and lymphocytes with necrotic regions of lipid, debris, and foam cells.

Predisposing factors:

- ✓ Include dyslipidemia (> 3:1 ratios of LDL to HDL [high-density lipoprotein])
- ✓ hyperglycemia of diabetes,
- ✓ hypertension, and
- ✓ The presence of toxins introduced by smoking.

In elastic arteries atheromas produce localized destruction within the wall, weakening it and causing arterial bulges or aneurysms that can rupture. In muscular arteries such as the coronary arteries, atheromas can occlude blood flow to downstream vessels, leading to ischemic heart disease.

→ The **hyperglycemia or excessive blood sugar** that occurs with diabetes commonly leads to diabetic microangiopathy, a diffuse thickening of capillary basal laminae and concomitant decrease in metabolic exchange at these vessels, particularly in the kidneys, retina, skeletal muscle, and skin

→ Lymphatics and larger lymphatic vessels are clinically important because (among other reasons) they facilitate the spread of pathogens, parasites, and malignant cells in the body. Surgical removal of lymph nodes, standard procedure to determine the occurrence of cancer metastasis, can disrupt the lymphatic drainage and produce swelling or **lymphedema**, in tissues of the affected region.

CHAPTER 14

→ Some pathogenic bacteria, such as Haemophilus influenza and Streptococcus pneumoniae, avoid phagocytosis by granulocytes and macrophages of innate immunity by covering their cell walls with a "capsule" of polysaccharide. The capsule inhibits recognition and binding to the phagocytes' receptors. Eventually such bacteria can be removed by antibody-based mechanisms, including phagocytosis after opsonization, but in the interim of several days the cells proliferate undisturbed and establish a more dangerous infection. Elderly or immunocompromised patients, with reduced adaptive immunity, are particularly susceptible to infections with such bacteria.

Tissue grafts and organ transplants: (read if time already in physio)

→ Tissue grafts and organ transplants are classified as **autografts** when the donor and the host are the same individual, such as a burn patient for whom skin is moved from an undamaged to the damaged body region; **isografts** are those involving identical twins. Neither of these graft types is immunologically rejected. **Homografts** (**or allografts**), which involve two related or unrelated individuals, consist of cells with MHC class I molecules and contain dendritic cells with MHC class II molecules, all presenting peptides that the host's T cells recognize as "foreign," leading to immune rejection of the graft. Development of immunosuppressive drugs such as the **cyclosporins** that inhibit the activation of cytotoxic T cells has allowed the more widespread use of allografts or even **xenografts** taken from an animal donor if allografts are in short supply. Such immunosuppression can however lead to other immune-related problems, such as certain opportunistic infections or cancers.

Adenoids:

→ Chronic inflammation of the pharyngeal lymphoid tissue and tonsils of children often produces hyperplasia and enlargement of the tonsils to form "adenoids," which can obstruct the eustachian tube and lead to middle ear infections.

Lymph nodes:

→ Metastatic cancer cells detached from a primary tumor can enter lymphatics and are carried to nearby lymph nodes, especially the **sentinel lymph node** that is the first one downstream of the region with the tumor. Cells from well-established tumors are often immunosuppressive themselves and may continue growth as a secondary tumor within lymph nodes. During cancer surgery lymph nodes in the lymphatics draining the tumor area are examined by pathologists for the presence of cancer cells. The presence of such metastatic cells in lymph nodes is a key determinant in most staging systems for various types of cancer and an important prognostic indicator.

→ **Neoplastic** proliferation of lymphocytes, producing a malignant lymphoma, may occur diffusely but is often located in one or more lymph nodes. Such growth can completely obliterate the normal architecture of the node and convert it to an enlarged, encapsulated structure filled with lymphocytes, a condition called **lymphadenopathy**.

Spleen:

→ Enlargement of the spleen, **splenomegaly**, can occur from a variety of causes, including lymphoma or other malignant growth, infections such as mononucleosis, or sickle cell disease and other types of anemia. The splenic capsule is relatively thin, and an enlarged spleen is susceptible to traumatic rupture, a potentially life-threatening occurrence due to loss of blood into the abdominal cavity. Such rupture may require prompt surgical removal of the spleen, **splenectomy**, after which most functions of the organ are carried out by other lymphoid organs, with erythrocyte removal occurring in the liver and bone marrow.

CHAPTER 15

→ **Friction blisters** are lymph-filled spaces created between the epidermis and dermis of thick skin by excessive rubbing, as with ill-fitting shoes or hard use of the hands. If continued, such activity produces protective thickening and hardening of the outer cornified epidermal layers, seen as **corns** and **calluses.**

→ In adults, one-third of all cancers originate in the skin. Most of these derive from cells of the basal or spinous layers, producing, respectively, basal cell carcinomas and squamous cell carcinomas. Fortunately, both types of tumors can be diagnosed and excised early and consequently are rarely lethal. Skin cancer shows an increased incidence in fair-skinned individuals residing in regions with high amounts of solar radiation.

→ In the chronic skin condition called **psoriasis**, keratocytes are typically produced and differentiate at accelerated rates, causing at least slight thickening of the epidermal layers and increased keratinization and desquamation. Psoriasis is caused by overactive T lymphocytes that trigger an autoimmune reaction in the skin, which can also lead to inflammation with redness, irritation, itching, and scaling, with a defective skin barrier.

→ **Albinism** is a congenital disorder producing skin hypopigmentation due to a defect in tyrosinase or some other component of the melanin-producing pathway.

→ **An acquired condition called vitiligo** involves skin depigmentation, often only in affected patches, due to the loss or decreased activity of melanocytes. The causes of melanocyte loss are not clear, but they may include environmental, genetic, or autoimmune conditions

→ Melanocytes can normally proliferate in skin to produce **moles**, or **benign melanocytic nevi** of various types. Changes in the size or appearance of moles are sometimes indicative of dysplasia that can progress further to malignant melanoma. Dividing rapidly, malignantly transformed melanocytes often penetrate the basal lamina, enter the dermis, and metastasize by invading blood and lymphatic vessels.

→ Merkel cells are of clinical importance because Merkel cell carcinomas, though uncommon, are very aggressive and difficult to treat. Merkel cell carcinoma is 40 times less common than malignant melanoma but has twice the mortality of that disease

→ Abnormalities of the dermal-epidermal junction can lead to one type of blistering disorder (**bullous pemphigoid**). Another type of blistering disorder (pemphigus) is caused by autoimmune damage to intercellular junctions between keratinocytes.

→ With age, changes in the dermal ECM are normal: thickening of collagen fibers, less collagen synthesis, and loss of hyaluronan and other GAGs. In old age extensive cross-linking of collagen fibers and the loss of elastic fibers, especially after excessive exposure to the sun (solar elastosis), cause the skin to become more fragile, lose its suppleness, and develop wrinkles. The epidermis also normally thins and becomes more transparent during aging. In several disorders, such as **cutis laxa and Ehlers-Danlos syndromes**, there is a considerable increase in skin and ligament extensibility caused by defective collagen-fibril processing.

→ The **density of tactile Meissner corpuscles in skin** can be determined approximately by two-point discrimination tests. Such neurologic measurements indicate that the number of tactile corpuscles in skin normally declines during adult life. Loss of tactile corpuscles or reduction in

their activity can also be detected in scleroderma and certain other connective tissue disorders that lead to sclerosis (hardening) of the dermis and tightening of the skin

→ **Loss of hair to produce baldness or alopecia** results from a complex combination of genetic and hormonal factors that is not well understood.

→ Arresting mitotic activity in the hair matrix during **cancer chemotherapy** disrupts both the function and the structural integrity of hair follicles and usually leads to rapid, reversible **alopecia.**

→ **Acne vulgaris** is an inflammatory disorder of the pilosebaceous unit, which can be expected to occur during adolescence. It involves excessive keratinization within this unit and excess sebum production, both of which contribute to the blockage of ducts in the follicle. Anaerobic bacteria, typically Propioni bacterium acnes, grow in the accumulated sebum, leading to localized inflammation and neutrophil infiltration. The resulting enlarged follicle is called a **comedone**.

CHAPTER 17

→ The chronic presence or accumulation of toxins that occur with heavy cigarette smoking or industrial air pollution affects the respiratory epithelium beginning in the nasal cavities. Immobilization of the cilia causes failure to clear mucus containing filtered material and exacerbates the problem, leading eventually to the likelihood of squamous metaplasia of the epithelium. A change from pseudostratified ciliated columnar to stratified squamous epithelium can occur, particularly in the mucosa of bronchi. This can produce precancerous cell dysplasia in this tissue.

→ The loss or reduction of the ability to smell, **anosmia or hyposmia**, respectively, can be caused by traumatic damage to the ethmoid bone that severs olfactory nerve axons or by damage to the olfactory epithelium caused by intranasal drug use. The olfactory neurons are the best-known neurons to be replaced regularly because of regenerative activity of the epithelial stem cells from which they arise. For this reason, loss of the sense of smell due to toxic fumes or physical injury to the olfactory mucosa itself is usually temporary

→ **Sinusitis** is an inflammatory process of the sinuses that may persist for long periods of time, mainly because of obstruction of drainage orifices. Chronic sinusitis and bronchitis are components of primary ciliary dyskinesia, or Kartagener syndrome, an inherited genetic disorder characterized by defective ciliary action.

→ **Inflammation of the larynx**, or laryngitis, is typically due to viral infection and is usually accompanied by edema or swelling of the organ's lamina propria. This changes the shape of the vocal folds or other parts of the larynx, producing hoarseness or complete loss of voice.

→ **Croup** is a similar syndrome in young children in which edema of the laryngeal mucosa is accompanied by both hoarseness and coughs that typically are loud and harsh.

→ Benign reactive polyps, called **singer's nodules**, are frequent in the stratified squamous epithelium of the true vocal cords, affecting the voice.

→ **Coughing** is a reflex action produced most often by viral infection or other irritation of the trachea or other region of the respiratory tract. A persistent dry cough, in which no mucus (phlegm) is produced, can be treated by cough suppressants that act on the brain stem and vagus nerve, while productive coughs are often treated with expectorants (increase sputum production) that help loosen mucus covering the respiratory mucosa

→ Bronchioles constitute the air passages affected most often, especially in young children, by the measles virus or adenovirus, both of which can cause **bronchiolitis**. If persistent, the inflammation produced by either infection can lead to obliterative bronchiolitis, complete or partial closure of the airway lumen due to fibrosis in the wall.

→ Most types of **lung cancer are carcinomas** involving epithelial cells lining the larger segments of bronchi, not bronchioles.

→ **Asthma** is a common condition produced by chronic inflammation within the bronchial tree of the lungs. The disorder is characterized by sudden constrictions of the smooth muscle in bronchioles called bronchospasms, or bronchial spasms. Constriction is caused by mast cell degranulation triggered by the presence of specific antigens. The resulting difficulty in breathing can be very mild to severe. Epinephrine and other sympathomimetic drugs relax the muscle and

increase the bronchiole diameter by stimulating the sympathetic nervous system, and they are administered during asthma attacks.

→ When the thickness of the bronchial walls is compared with that of the bronchiolar walls, the bronchiolar muscle layer is seen to be proportionately greater.

→ Obstruction of the air supply in bronchi due to excess mucus or to aspirated material can lead to collapse of pulmonary lobules as circulating blood absorbs gases from the affected alveoli. This condition, called **atelectasis**, is normally reversible when the blockage is relieved but, if persistent, can cause fibrosis and loss of respiratory function.

→ **Diffuse alveolar damage or adult respiratory distress syndrome** can be produced by various types of injuries to the alveolar epithelial and the capillary endothelial cells. Common causes of such injuries include viral and bacterial respiratory tract infections; inhalation of toxic gases, chemicals, or air with excessive oxygen; and fat embolism syndrome, in which adipocytes enter the blood during surgery, circulate, and later block the capillary beds. With removal of the initiating factors, normal alveolar wall components can often be restored and at least partial function restored

→ **In congestive heart failure**, the lungs become congested with blood, and erythrocytes pass into the alveoli, where they are phagocytized by alveolar macrophages. In such cases, these macrophages are called heart failure cells when present in the lung and sputum; they are identified by a positive histochemical reaction for iron pigment (hemosiderin).

→ **Emphysema**, a chronic lung disease most commonly caused by cigarette smoking, involves dilation and permanent enlargement of the bronchioles leading to pulmonary acini. Emphysema is accompanied by loss of cells in the alveoli and other parts of the airway walls, leading to an irreversible loss of respiratory function. Any type of infection in the respiratory regions of the lung produces the local inflammatory condition called pneumonia

→ The condition **pneumothorax** is a partially or completely collapsed lung caused by air trapped in the pleural cavity, typically resulting from blunt or penetrating trauma to the chest and producing shortness of breath and hypoxia.

→ Inflammation of the pleura, a condition called either **pleuritis or pleurisy**, is most commonly caused by an acute viral infection or pneumonia. Pleural effusion or fluid buildup in the pleural cavity produces shortness of breath and can be one result of inflamed pleura.

→ **Lung cancer** is one of the most common forms of this disease. Squamous cell carcinoma, which is closely correlated with a history of smoking, arises most often from epithelial cells of segmental bronchi.

→ **Adenocarcinoma,** the most common lung cancer in nonsmokers, usually arises from epithelial cells more peripherally, in bronchioles and alveoli.

→ **Small cell carcinoma,** a less common but highly malignant form of lung cancer, develops after neoplastic transformation of small granule Kulchitsky cells in bronchial respiratory epithelium.