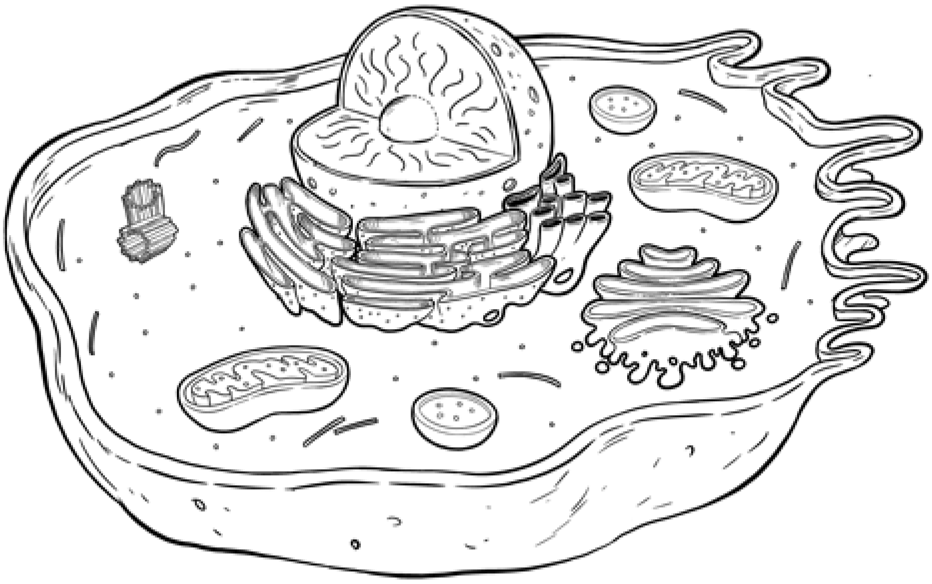
Pathology



USMLE PULSE

Index

1.Growth adaptations, cellular injury, and cell death

1)

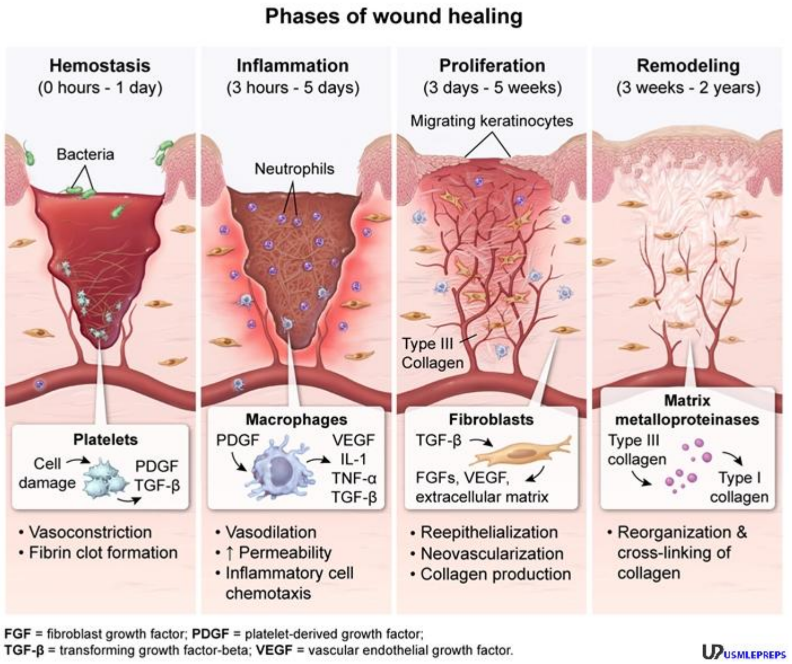
Major types of systemic amyloidosis				
	Primary	**Secondary**	**Age related**	**Dialysis related**
Disease association	Plasma cell dyscrasia	Chronic infection/ inflammation	Elderly men	ESRD on dialysis
Precursor protein ↓ **Misfolding mechanism** ↓ **Amyloid fibril type**	Immunoglobulin **light** chains ↓ Increased production ↓ A**L**	Serum **amyloid A** ↓ Increased production ↓ A**A**	Transthyretin (prealbumin) ↓ Accumulation over time ↓ ATTR*	β2-Microglobulin ↓ Decreased clearance ↓ Aβ2M
Clinical manifestations	Nephropathy, hepatosplenomegaly, cardiomyopathy (AL > AA), peripheral neuropathy, macroglossia, skin bruising		Cardiomyopathy, CTS, other peripheral neuropathy	Scapulohumeral arthritis, CTS
Amyloid names begin with "A" followed by the precursor protein abbreviation. *ATTR also occurs in a hereditary form that affects younger patients. CTS = carpal tunnel syndrome; ESRD = end-stage renal disease.				

2) The process of apoptosis is separated into an initiation phase and an execution phase. During the initiation phase, protein-hydrolyzing caspases are activated. In the execution phase, these caspases bring about the cell death by **cleaving cellular proteins and activating DNAses.**

The initiation of apoptosis occurs via signals from two separate pathways: the **intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway.** In the intrinsic pathway, the mitochondria become more permeable and pro-apoptotic substances are released into the cytoplasm in response to stress or the cessation of survival signals. Once the cell is exposed to stress or the cessation of survival signals, the anti-apoptotic proteins **Bcl-2 and Bcl-x** that reside in the mitochondrial membranes and cytoplasm are replaced with pro-apoptotic proteins such as **Bak, Bax, and Bim**. The pro-apoptotic proteins allow for the increased permeability of the mitochondria, which results in the release of caspase-activating substances like cytochrome c.

2. Inflammation, Inflammatory disorders, and wound healing

1. wound healing



A) This patient with a history of uncontrolled diabetes mellitus has a nonhealing wound with evidence of ongoing inflammation (eg, erythema). **Wound healing** normally progress through the inflammatory, proliferative, and remodeling phases. In the days after the initial injury, neutrophils and other immune cells are recruited to the wound and produce an **inflammatory response** that helps prevent bacterial overgrowth in the nutrient-rich environment of a healing wound. However, this inflammation also **impairs formation of granulation tissue** that is needed for normal wound healing. As healing progresses, release of growth factors and **anti-inflammatory cytokines** (eg, IL-10) by macrophages and regulatory T cells suppresses the inflammatory response, **facilitating fibroblast proliferation** and reepithelialization of the wound.

In patients with diabetes mellitus, constitutively **elevated blood glucose** increases inflammation by stimulating the release of **proinflammatory cytokines** and reactive oxygen species from neutrophils . Elevated glucose also leads to a marked **decrease in IL-10** production that contributes to the increased susceptibility for chronic, **nonhealing wounds** and ulcers in patients with uncontrolled diabetes.

- Bradykinin is a vasoactive inflammatory mediator that is normally produced by endothelial cells, macrophages, and platelets during the inflammatory phase of wound healing. Further upregulation of inflammatory mediators in patients with diabetes would most likely have a negative effect on fibroblast proliferation and reepithelialization.
- Although a baseline level of cortisol production is required for normal wound healing, excess cortisol can impair both the inflammatory and proliferative components of wound healing. Patients with diabetes tend to have elevated cortisol levels.
- Excess glucose inhibits fibroblast migration and results in the nonenzymatic glycation of collagen fibers, which can prevent collagen cross-linking and can impair the structural integrity of a healing wound.

Reepithelialization is triggered when injury to the skin disrupts most or all of the layers of the epidermis, resulting in loss of keratinocyte-to-keratinocyte contact. Contact with other keratinocytes typically limits cell division and/or motility (ie, contact inhibition). However, when this contact is lost due to injury, keratinocytes are stimulated to replicate and migrate until a continuous epithelial layer is restored.

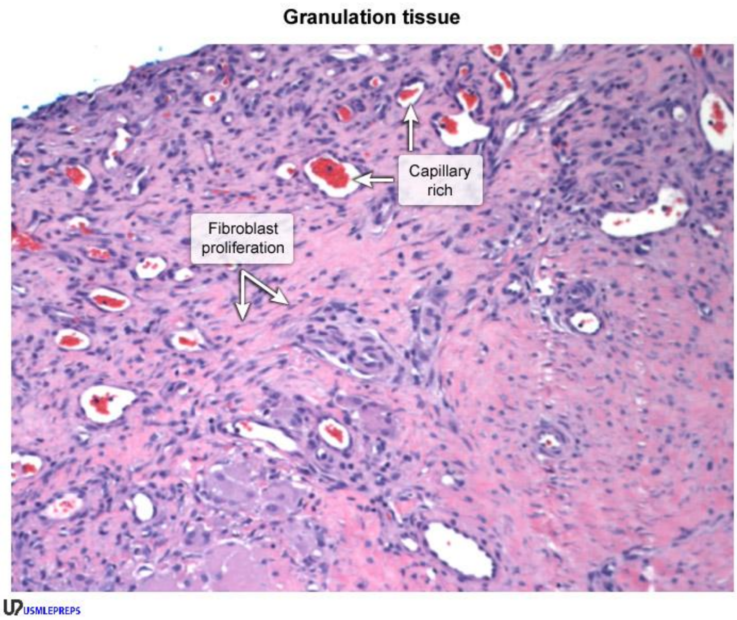
From the wound edges, keratinocytes migrate across newly formed granulation tissue at the wound base and are replenished via replication of basal keratinocytes in the stratum basale. This process continues until keratinocytes meet other keratinocytes (ie, contact inhibition), corresponding with completion of reepithelization (eg, wound covered in pearly pink epithelium). At this point, proliferation and migration signals cease, and the stratification process begins.

B. This patient has a lesion with **abundant capillaries and fibroblasts**, which is characteristic of **granulation tissue**. Raising of the lesion above the surrounding skin (tissue overgrowth) is further consistent with excessive proliferation of granulation tissue (ie, hypergranulation tissue) at the site of wound healing.

Granulation tissue is an essential component of the proliferative phase of normal wound healing, providing the nutrients and structure needed for a wound to fill and reepithelialize. Platelets and macrophages in and around a healing wound produce vascular endothelial growth factor (VEGF), which induces the vascular and fibroblast proliferation of granulation tissue. However, if **VEGF-induced tissue proliferation** continues unchecked, the resulting hypergranulation tissue prevents wound epithelialization and remodeling. These lesions most often occur at the site of nasogastric tubes or wounds left to **heal by secondary intention** (ie, the wound is purposely left open).

- During the remodeling phase of wound healing, fibroblasts and type III collagen in granulation tissue are gradually (ie, over weeks to years) replaced with myofibroblasts and type I collagen, forming a scar. Abnormalities in this process result in unchecked production of collagen fibers, forming a hypertrophic scar or keloid months after the initial wound.
- Neutrophils are essential to the normal inflammatory response in wound healing; they prevent infection and release cytokines and growth factors that allow wound healing to progress. However, protracted inflammation and excessive release of reactive oxygen species by neutrophils in a wound can cause tissue damage that delays wound healing, resulting in a chronic, nonhealing wound.

C.



D. Normally, during the proliferation phase of wound healing, **fibroblasts proliferate**, synthesize collagen and ground substance, and differentiate into myofibroblasts. These processes are promoted by **transformation growth factor beta (TGF beta)**, which typically diminishes upon completion of wound repair, when the wound transitions to the maturation phase. In keloids, however, TGF beta is **overexpressed**, with little regulation. As a result, keloids **extend beyond the borders** of the original wound, do not regress, and often recur after resection. In contrast, hypertrophic scars are limited to the original wound borders and may regress spontaneously. Matrix metalloproteinases (MMP) contribute to tissue remodeling through degradation of the extracellular matrix, typically in a regulated fashion. **Decreased MMP activity** (leading to decreased extracellular matrix degradation) may contribute to keloid formation. In contrast, MMP overproduction is often present in chronic (ie, nonhealing) wounds.

2.

Posttransplantation lymphoproliferative disorder	
Etiology	Immunosuppression following solid-organ or hematopoietic stem cell transplantation → suppressed cytotoxic T-cell immunosurveillance → Epstein-Barr virus–encoded proteins drive unchecked B-cell growth/expansion
Manifestations	Mononucleosis-like symptoms (eg, fever, night sweats, hepatosplenomegaly, lymphadenopathy) Extranodal mass in approximately 50% Biopsy findings: polyclonal or monoclonal B-cell proliferation

3. Nuclear factor-kappa B (NF-κB) is part of a family of transcription factors that perform a critical role in the **immune response to infection and inflammation.** In inflammatory cells, NF-κB is normally present in a latent, inactive state bound to its inhibitor protein, **IκB**. As part of the classical activation pathway, an extracellular signal, such as the binding of bacterial antigens to a toll-like receptor, causes activation of IκB kinase. This results in ubiquitination and subsequent destruction of IκB with the release of free NF-κB. Once free, NF-κB enters the nucleus and promotes the synthesis of a number of inflammatory proteins such as cytokines, acute phase reactants, cell adhesion molecules, and leukocyte-related growth factors. The inflammatory cascade is self-limiting as NF-κB also stimulates the transcription of more IκB, ultimately rebinding the freed NF-κB.

4)Chronic inflammatory conditions are characterized by the persistent stimulation of neutrophils and macrophages, leading to long-term elevation of circulating pro-inflammatory cytokines such as IL-1, IL-6, tumor necrosis factor-alpha, and interferon-gamma. The liver responds to these circulating cytokines (particularly IL-6) by generating acute phase reactants, proteins that modulate and influence the inflammatory response and play some role in innate immunity.

3. Principles of neoplasm

1. **Common hereditary cancer syndromes**

Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**
Lynch syndrome	MSH2, MLH1, MSH6, PMS2	Colorectal cancer Endometrial cancer Ovarian cancer	Autosomal dominant Inactivating mutation in corresponding tumor suppressor gene Deletion of remaining normal allele (second hit) leads to loss of heterozygosity & malignant transformation
Familial adenomatous polyposis	APC	Colorectal cancer Desmoids & osteomas Brain tumors	
von Hippel-Lindau syndrome	VHL	Hemangioblastomas Clear cell renal carcinoma Pheochromocytoma	
Li-Fraumeni syndrome	TP53	Sarcomas Breast cancer Brain tumors Adrenocortical carcinoma Leukemia	
Multiple endocrine neoplasia type 1	MEN1	Parathyroid adenomas Pituitary adenomas Pancreatic adenomas	
Multiple endocrine	RET	Medullary thyroid	Autosomal

neoplasia type 2		cancer Pheochromocytoma Parathyroid hyperplasia (MEN2A)	dominant Activating (gain-of-function) mutation in proto-oncogene Continuous stimulation of cell division predisposes to tumor growth

2) Retinoblastoma (Rb) protein

Retinoblastoma (Rb) protein is a regulator of the G1/S phase transition. The Rb protein has two forms, active (dephosphorylated) or inactive (phosphorylated). When the cell is stimulated by growth factors, activation of **cyclin D, cyclin E, and the corresponding cyclin kinases** (CDK 4 and 2) occurs and the Rb protein is phosphorylated (rendering it inactive). Phosphorylated Rb releases the E2F transcription factor, which allows progression through the G1/S checkpoint. After the cell divides, Rb protein is dephosphorylated (active) and remains so until the cell is ready to enter S phase again.

In terminally differentiated cells, the Rb protein stays in the dephosphorylated (active) state bound to E2F transcription factors, resulting in inhibited transcription of genes necessary for G1/S transition. Therefore, active Rb protein stops the cell from dividing and allows the cell to enter a quiescent (G0) phase

N.B. Cyclin D is a protein (encoded by CCND1) that regulates cell cycle. Its overexpression is seen in breast, lung, and esophageal cancers and certain types of lymphomas.

3)Epidermal growth factor receptor (EGFR)

Epidermal growth factor receptor (EGFR) is stimulated in a paracrine or autocrine fashion by its ligands, leading to the downstream activation of KRAS, a membrane-bound GTP-binding protein that stimulates cellular growth and proliferation. Many cancers (eg, colorectal, pancreas) leverage this system to drive unchecked cellular growth by overexpressing EGFR and its ligands or by developing constitutive activating mutations in the KRAS proto-oncogene.

The EGFR signaling system can be targeted for cancer treatment through the use of monoclonal antibodies (eg, cetuximab, panitumumab) that block EGFR, leading to reduced KRAS stimulation and decreased cellular growth. However, this treatment is only effective for tumors with wild-type (normal) KRAS. Tumors with KRAS-activating mutations are resistant to anti-EGFR agents as they have a constitutive activation of a downstream signal that is independent of EGFR stimulation or blockade. Prior to the use of anti-EGFR agents, genetic testing of tumor tissue is performed to see if KRAS is wild-type (eligible for treatment) or mutated (noneligible).

4. **Human papillomavirus (HPV)**
Oncoviruses can induce cancer-forming mutations through the expression of proteins that activate protooncogenes or inactivate tumor suppressor genes. **Human papillomavirus (HPV)** is implicated in several types of cancer, including head and neck, cervical, anal, and penile cancer. **HPV produces viral oncoproteins E6 and E7, both of which affect tumor suppressors:**

- HPV viral protein E6 binds to p53, a tumor suppressor protein that normally inhibits the proliferation of cells with genetic abnormalities. Ubiquitination of the E6-p53 complex induces degradation of p53, leading to unregulated cellular growth.
- HPV viral protein E7 binds to retinoblastoma (Rb) protein, which results in the displacement of E2F (a transcription factor that induces cell cycle activation), promoting unregulated DNA replication and cyclin-mediated cell cycling.

5)Progression from normal mucosa to a small adenomatous polyp (adenoma). The initial appearance of small adenomatous polyps is attributed to mutation of the **APC tumor suppressor gene**. APC is located on chromosome 5, and its mutation leads to β-catenin accumulation and uncontrolled cell proliferation. Increase in the size of the adenoma mutation of the **KRAS protooncogene** is thought to facilitate this step by leading to a protein that also stimulates unregulated cell growth. Malignant transformation of adenoma into carcinoma requires mutation of **TP53.**

6) Tumor necrosis factor-α (TNF-α) is a cytokine that causes necrosis of some tumors in vitro and produces symptoms of cachexia in experimental animals. TNF-α is also called **cachectin** and is considered a main mediator of paraneoplastic cachexia (along with interleukin [IL]-1β, and IL-6).

7) Decreased activity of a tumor suppressor gene would predispose to neoplasms. In normal individuals, p53 regulates cell proliferation. It acts during phase G1 of the cell cycle to detect abnormalities of the cellular genome. If there is damaged DNA, p53 will prevent the cell from progressing to mitosis, causing the cell to be arrested in the G1 phase. If the DNA can be repaired, the cell will subsequently be allowed to divide, but if the damage is so severe that repair is impossible, the cell will proceed instead to apoptosis. p53 is nicknamed "the molecular policeman" because of its important role in guarding the integrity of genetic material.

8)Most cases of hereditary breast and ovarian cancer are associated with mutations in the tumor suppressor **genes BRCA1 and BRCA2.** Tumor suppressor genes are involved in multiple processes, including:

- DNA repair
- Cellular differentiation
- Checkpoint control of the cell cycle
- Transcription factor regulation

9.

Specific cancer risk factors			
Pancreas	Tobacco smoke Obesity	**Renal**	Tobacco smoke Obesity Hypertension
Gastric	Dietary nitrates Alcohol & tobacco use Helicobacter pylori	**Bladder**	Tobacco smoke Occupational exposures (rubber, plastics, aromatic amine–containing dyes, textiles, leather)
Liver	Hepatitis B & C Liver cirrhosis (any cause) Hemochromatosis Aflatoxin	**Breast**	Early menarche Late menopause Nulliparity BRCA mutations
Colorectal	Hereditary CRC	**Prostate**	Increasing age

	syndromes Inflammatory bowel disease Obesity Charred or fried foods		African American

10. Oxidative phosphorylation is the primary driver of energy metabolism in most terminally differentiated cells during normal conditions. However, rapidly dividing cells such as stem cells and cancer cells generate most of their energy through anaerobic glycolysis despite the presence of adequate oxygen (Warburg effect) (Choice D). These cells produce significantly more lactate than a normal terminally differentiated cell as almost all glucose is converted to lactate and excreted.

The alteration of cellular metabolism from oxidative phosphorylation to anaerobic glycolysis is a crucial part of oncogenesis, and is thought to benefit cancer cells due to the following:

- Shunting glucose away from oxidative phosphorylation increases the concentration of glucose metabolic products (eg, ribulose 5-P, serine, glycine, glycerol) for the synthesis of nucleic acids, amino acids, and lipids.
- Lactic acid excretion promotes production of vascular endothelial growth factor by stromal cells, which improves blood flow to the tumor. It also creates an acidic tumor microenvironment, which impairs antitumor cytotoxic T cells.

Because anaerobic glycolysis generates only 2 molecules of ATP per molecule of glucose, tumor cells uptake much more glucose than normal cells. Therefore, areas of tumor activity can usually be visualized by positron emission scanning with radiolabeled glucose.