

UNC SCHOOL OF MEDICINE Department of Pathology and Laboratory Medicine

Introduction to Pathology of Disease
NCA&T Biol 342, NCCU Special Course

Module 1: The Basics of Pathology

Introduction to Mechanisms of Disease

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Module 1: The Basics of Pathology

Pathology Bridges Science and Medicine

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Principles of Pathology

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Introduction to Mechanisms of Disease

What is pathology?

The term “pathology” is used in three different ways:

- The scientific and medical discipline that studies the structural, molecular and functional manifestations of disease, and the mechanisms that cause disease. *(A physician or scientist who knows and applies pathology is a pathologist.)*
- The structural and functional manifestations of a disease. *(The lung pathology is acute inflammation.)*
- A disease. *(The lung pathology is pneumonia.)*

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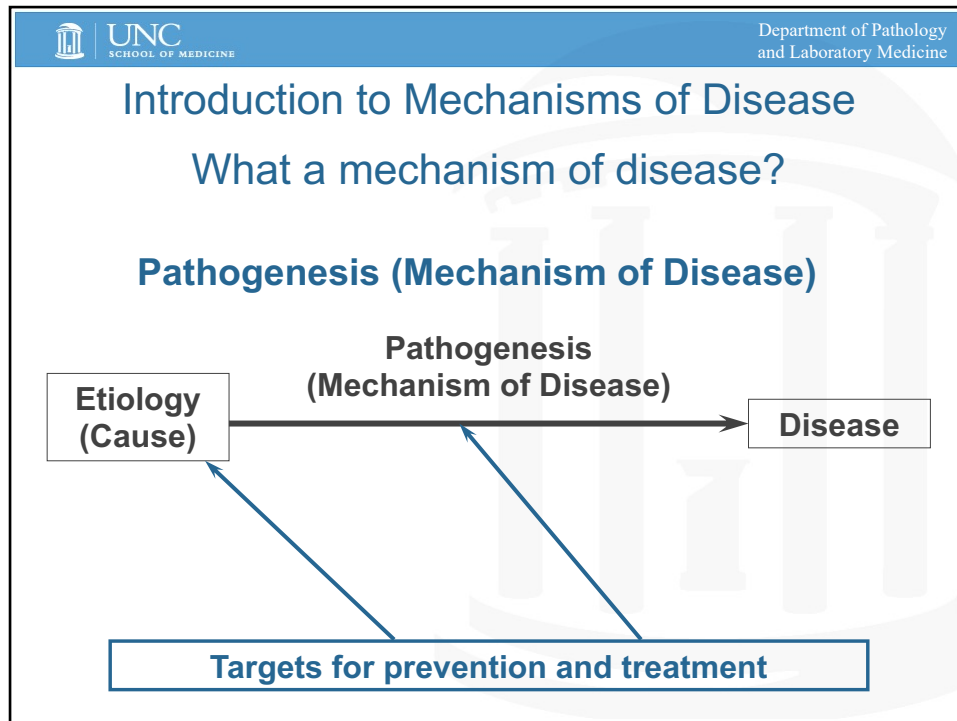
Introduction to Mechanisms of Disease

What is a disease?

Oxford Dictionary: A disorder of structure or function in a human, animal, or plant.

Biomedical Terminology: Molecular, cellular, tissue, organ or organismic disorder caused by an **etiology** and mediated by **pathogenic mechanisms**

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Introduction to Mechanisms of Disease



To discuss and understand mechanisms of disease one must know pathology terminology (terms and definitions) that are vital elements of the [language of biomedical science and clinical medicine](#).

You will encounter these terms and concepts repeatedly in any vocation or avocation involving biomedical science or clinical medicine.

Learning and understanding pathology terminology helps learn and understand mechanisms of disease.

- **This is the goal of this presentation**

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DEFINITIONS

Disease: molecular, cellular, tissue, organ and organismic **disorder** caused by an etiology and mediated by pathogenic mechanisms

Diagnosis: the **name** for a disease

Etiology: the **cause** of disease (many categories: infectious, physical, chemical, genetic, immune, etc.)



Pathogenesis: the **sequence of events** that leads from the etiology to the manifestations of disease

Symptom: disease manifestation **perceived and reported by the patient**

Sign: manifestation of disease that **can be identified** by physical examination, laboratory tests, imaging studies, and other methods.

Differential Diagnosis: A **ranked list** of the most likely diagnoses based on the signs and symptoms of disease in a patient.

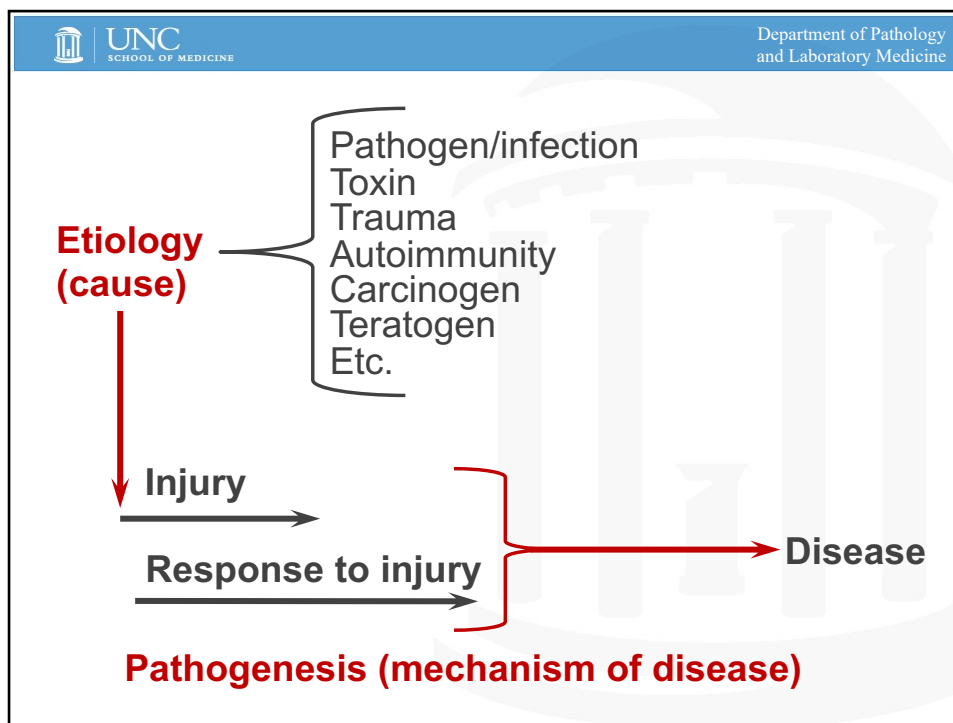
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The name used for a disease (**diagnosis**)
 can contain more or less information
 based on what is known about the
etiology, pathology, and pathogenesis

Myocarditis
 Viral myocarditis
 Coxsackievirus myocarditis
 Acute coxsackievirus myocarditis

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UNC SCHOOL OF MEDICINE **Mechanisms of Disease** Department of Pathology and Laboratory Medicine

- **Numerous etiologies** initiate a **limited number of pathogenic mechanisms** that produce a wide variety of diseases.
- Thus, a thorough understanding of the limited number of pathogenic mechanisms allows insight into myriad numbers of diseases, even ones you have never seen before.

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 **Mechanisms of Disease** Department of Pathology and Laboratory Medicine

Cellular responses to injury

- Intracellular response
- Cell death
- Hypertrophy
- Hyperplasia
- Atrophy
- Metaplasia
- Dysplasia
- Neoplasia

Tissue response to injury

- Inflammation
- Repair
- Hemostasis/thrombosis
- Ischemia


Abnormal morphogenesis

- Genetic
- Teratogenic

Biochemical disorder

- Genetic
- Acquired

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 **Mechanisms of Disease** Department of Pathology and Laboratory Medicine

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UNC SCHOOL OF MEDICINE **Subcellular responses to injury** Department of Pathology and Laboratory Medicine

Intracellular Changes Occur and May be Reversible

From *Essentials of Rubin's Pathology, 6th Edition, Lippincott Williams & Wilkins, Philadelphia, 2014*

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UNC SCHOOL OF MEDICINE **Hydropic Degeneration** Department of Pathology and Laboratory Medicine

Normal-appearing hepatocyte

Hepatocytes with abnormal swelling because of increased water within organelles (hydropic change) caused by injury by a toxin

Biopsy of liver with acute drug toxicity

From *Essentials of Rubin's Pathology, 6th Edition, LWW, 2014*

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Cell Death

Major pathways to cells death:

Apoptosis: regulated cell death caused by activation of internal molecular pathways leading to cell death (e.g., physiological tissue remodeling during embryonic development, renewal of epithelial layers).

Necrosis: unregulated cell death caused by pathological lethal injury that often originates outside the cell (e.g., injury by hypoxia, inflammation, molecular toxin, burn, etc.).

Necroptosis: regulated necrosis caused by activation of internal molecular pathways leading to cell death (e.g., resulting from intracellular viral infections or inflammatory disease).

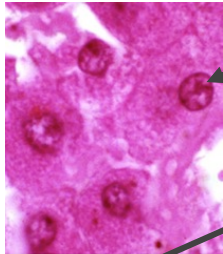
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Cell Death

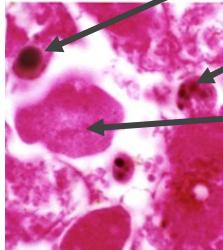
Cell death is demonstrated histologically by nuclear changes

Normal viable hepatocytes with normal nuclei



Normal nucleus: Dispersed chromatin and intact nuclear membrane.

Necrotic hepatocytes with absent or abnormal nuclei



Nuclei of Necrotic Cells

Pyknosis: The nucleus becomes smaller and stains deeply basophilic because of **chromatin clumping**.

Karyorrhexis: The pyknotic nucleus breaks up into **many smaller fragments**.

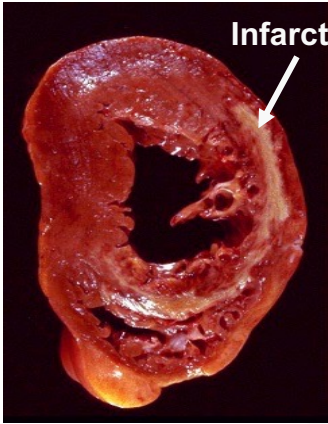
Karyolysis: The nucleus may be extruded from the cell or have progressive loss of chromatin staining resulting in the **disappearance of the nucleus**.

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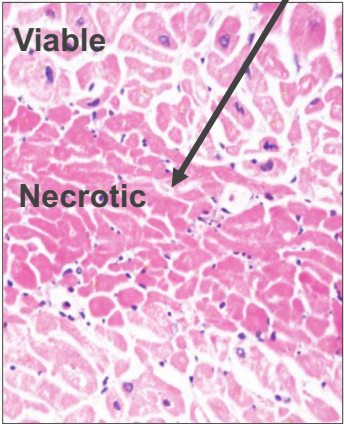
Infarction

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Necrosis caused by ischemia (low blood flow):
Nuclei disappear (karyolysis) and cytoplasm becomes more homogeneous resulting in residual ghosts of cells with **no nuclei**.



Infarct



Viable
Necrotic

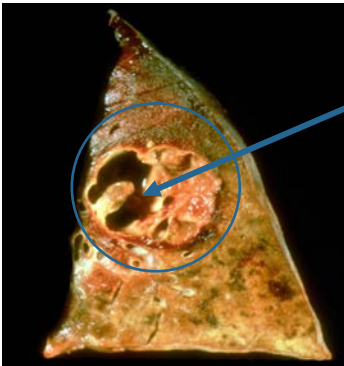
Myocardial infarction (“heart attack”) with ischemic necrosis

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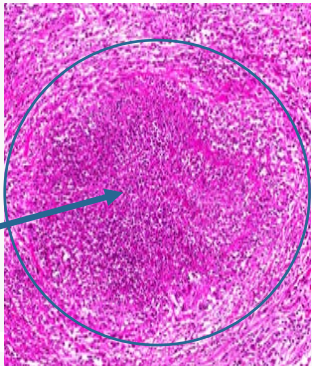
Liquefactive Necrosis

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Liquifactive necrosis caused by intense localized infiltration of neutrophilic polymorphonuclear leukocytes (neutrophils) at sites of severe acute inflammation (e.g. caused by bacterial infection). **Localized acute inflammation with liquifactive necrosis is called an abscess.**



Abscess with partial cavitation



Abscess containing numerous neutrophils (pus, purulence) that have liquefied the tissue

Liver abscess with liquifactive necrosis and cavitation caused by infection
Bacterial infection abscess with intense infiltration of neutrophils

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UNC SCHOOL OF MEDICINE | **Cellular responses to injury** | Department of Pathology and Laboratory Medicine

Cellular responses to injury (adaptation/maladaptation)

HYPERTROPHY is increased size of cells.

HYPERPLASIA is non-neoplastic increase in the number of cells in an organ or tissue.

ATROPHY is reduced size of cells or organs.

METAPLASIA is conversion of one differentiated cell type to another.

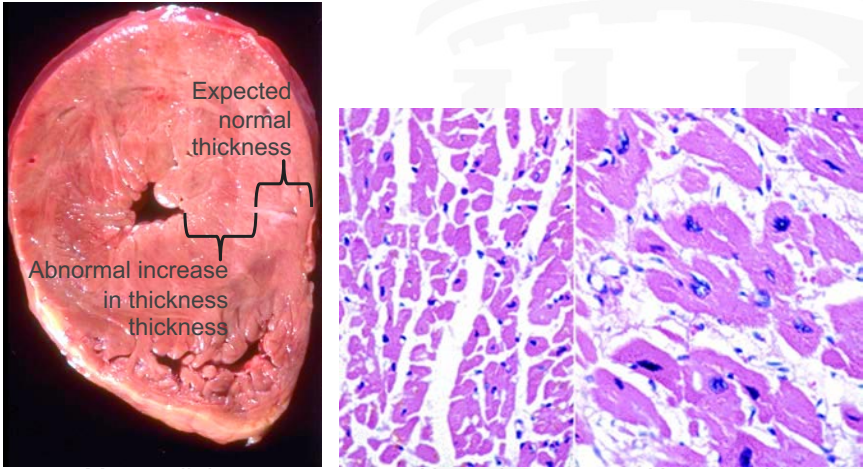
DYSPLASIA is disordered growth and maturation of the cellular components of a tissue. Dysplasia may be a precursor to malignant neoplasia.

NEOPLASIA is the autonomous growth of cells that have escaped normal regulation of cell proliferation. Neoplasms that remain localized are termed **benign**, whereas those that spread (or are capable of spreading) to distant sites (metastasize) are termed **malignant** (aka cancer).

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UNC SCHOOL OF MEDICINE | **Hypertrophy** | Department of Pathology and Laboratory Medicine

HYPERTROPHY is increased size of cells, which also results in increased organ or tissue size.



Myocardial hypertrophy

Normal cardiomyocytes

Hypertrophied cardiomyocytes

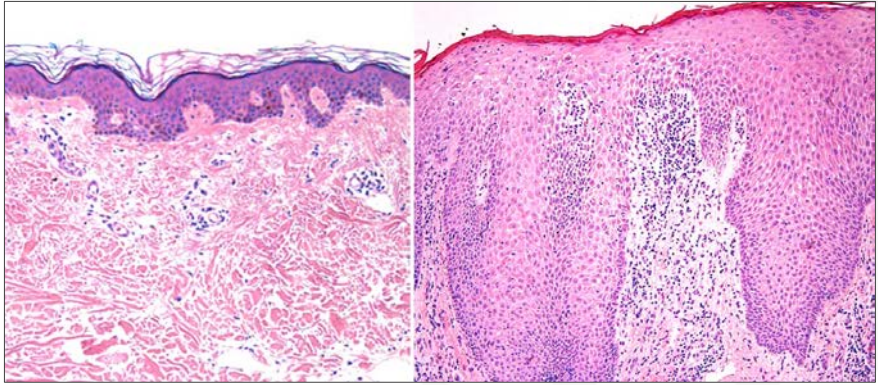
From Essentials of Rubin's Pathology, 6th Edition, LWW, 2014

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Hyperplasia

HYPERPLASIA is non-neoplastic increase in the number of cells in an organ or tissue.



Normal epidermis Epidermal hyperplasia in psoriasis

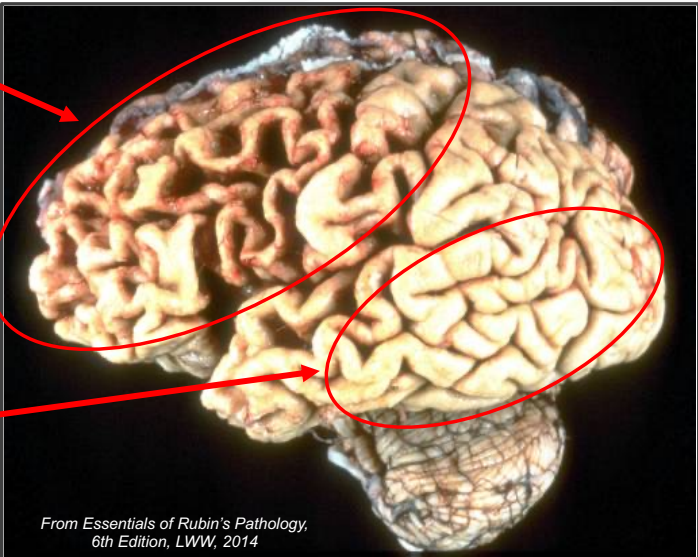
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Atrophy

ATROPHY is reduced size of cells or organs.



Frontal lobe **atrophy** with thinned gyri and widened sulci

Normal gyri and sulci

From Essentials of Rubin's Pathology, 6th Edition, LWW, 2014

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Atrophy

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Causes (etiologies) of Atrophy:

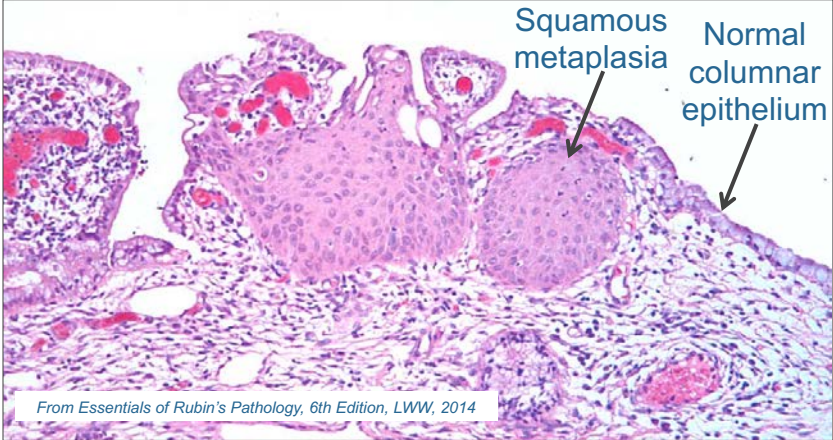
- **Reduced Functional Demand** (e.g. skeletal muscle atrophy caused by denervation)
- **Inadequate Oxygen Supply** (e.g. kidney atrophy caused by renal artery stenosis)
- **Insufficient Nutrients** (e.g. skeletal muscle and fat atrophy caused by starvation)
- **Interrupted Trophic Signals** (e.g. endometrial atrophy after menopause)
- **Persistent Cell Injury** (e.g. gastric mucosal atrophy caused by chronic gastritis)
- **Increased Pressure** (e.g. localized skin atrophy caused by prolonged bed rest)
- **Chronic Disease** (e.g. cachexia caused by chronic disease)

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Metaplasia

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METAPLASIA is conversion of one differentiated cell type to another.



From Essentials of Rubin's Pathology, 6th Edition, LWW, 2014

Squamous metaplasia in the endocervix with normal columnar epithelium at both margins and squamous metaplasia in the center.

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Dysplasia

DYSPLASIA is disordered growth and maturation of the cellular components of a tissue. Dysplasia may be a precursor to malignant neoplasia.

Normal polarized epithelium

Unpolarized dysplastic epithelium

From Essentials of Rubin's Pathology, 6th Edition, LWW, 2014

Dysplastic epithelium of the uterine cervix lacks normal polarity, and cells have large hyperchromatic nuclei.

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Neoplasia

NEOPLASIA is the autonomous growth of cells that have escaped normal regulation of cell proliferation.

- **Benign neoplasm:** localized and unable to spread (metastasize)
- **Malignant neoplasm (aka cancer):** invasive and capable of spreading (metastasizing)

Thyroid follicular adenoma

Colonic adenocarcinoma metastatic to liver

Tumor: swelling or mass

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Neoplasia

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Uterus with multiple leiomyomas

In general, malignant neoplasms have less well differentiated cells that have larger nuclei that are pleomorphic, atypical, hyperchromatic and more often undergoing mitosis.

Normal myometrium

Leiomyoma (benign)

Leiomyosarcoma (malignant)

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Mechanisms of Disease

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- Repair
- Hemostasis/thrombosis
- Ischemia

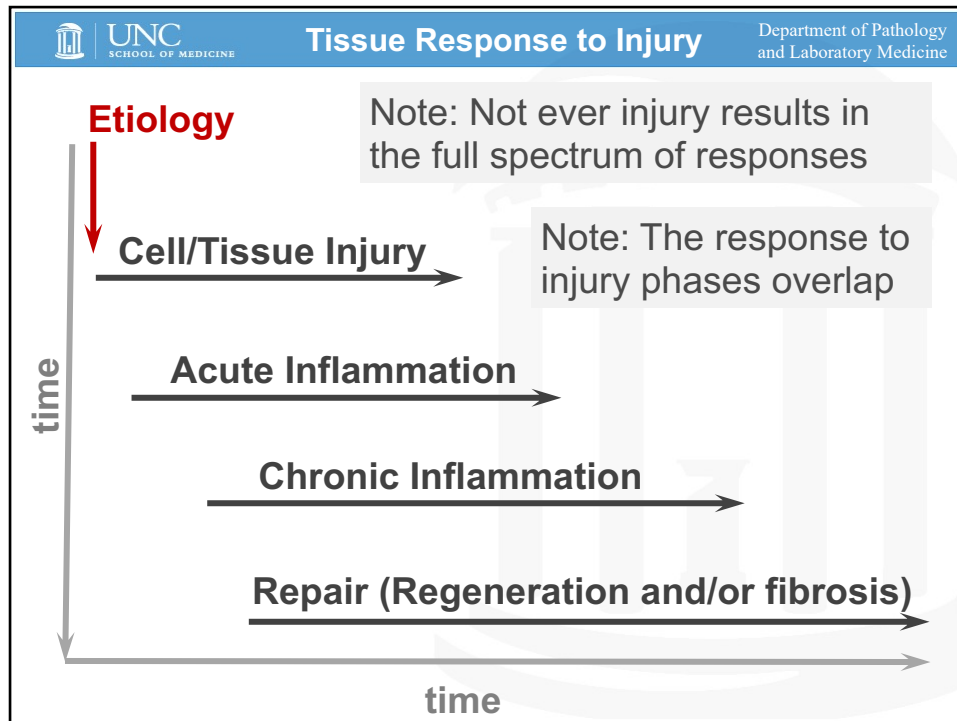
Abnormal morphogenesis

- Genetic
- Teratogenic

Biochemical disorder

- Genetic
- Acquired

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Inflammation Department of Pathology and Laboratory Medicine

Inflammation is a reaction of tissue to a pathogenic insult.

Inflammation is mediated by extracellular molecular signals that activate humoral and cellular inflammatory pathways and cause the movement of fluid and leukocytes from blood into the extravascular compartment.



Inflammation:

- Localizes or eliminates the cause of injury
- Removes injured tissue components
- Leads to repair

- redness
- swelling
- heat
- pain
- dysfunction

Inflammation is a double-edged sword that usually is beneficial but can cause morbidity (disease) and mortality (death).

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UNC SCHOOL OF MEDICINE **Inflammation** Department of Pathology and Laboratory Medicine

Neutrophil Monocyte Macrophage Lymphocyte

The diagram illustrates the process of inflammation. At the top, four types of leukocytes are identified: Neutrophil (green with multi-lobed nucleus), Monocyte (green with kidney-shaped nucleus), Macrophage (green with large kidney-shaped nucleus), and Lymphocyte (purple with round nucleus). Below, a cross-section of a blood vessel is shown. Red blood cells (red) and various leukocytes are in the lumen. Some leukocytes are shown migrating through the vessel wall into the extravascular space, where they are seen interacting with tissue cells.

Inflammation is mediated by extracellular molecular signals that activate humoral and cellular inflammatory pathways and cause the movement of fluid and leukocytes from blood into the extravascular compartment.

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The slide compares acute and chronic inflammation. On the left, a microscopic image shows a dense infiltrate of neutrophils, with an arrow pointing to one. Below it, a diagram shows a blood vessel with many neutrophils migrating into the tissue. On the right, a microscopic image shows a less dense infiltrate of mononuclear cells. Below it, a diagram shows a blood vessel with fewer leukocytes migrating into the tissue, which is populated by a larger number of macrophages and lymphocytes.

Acute inflammation has tissue infiltrating of predominantly polymorphonuclear neutrophils (PMNs) with multilobed nuclei.

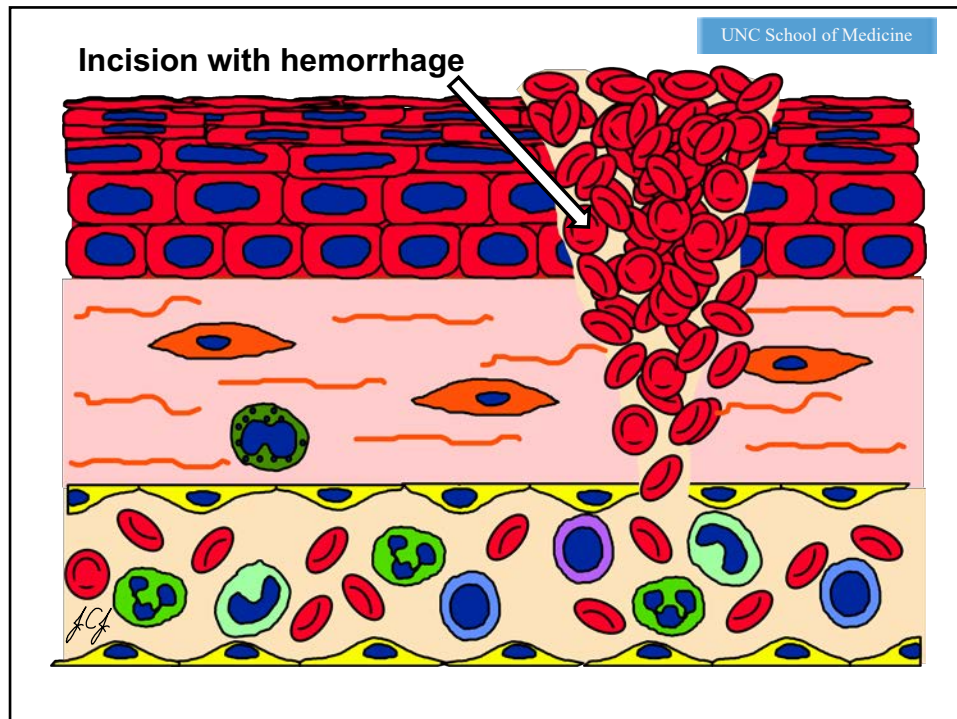
Chronic inflammation has predominantly mononuclear leukocytes including lymphocytes, monocytes, and macrophages.

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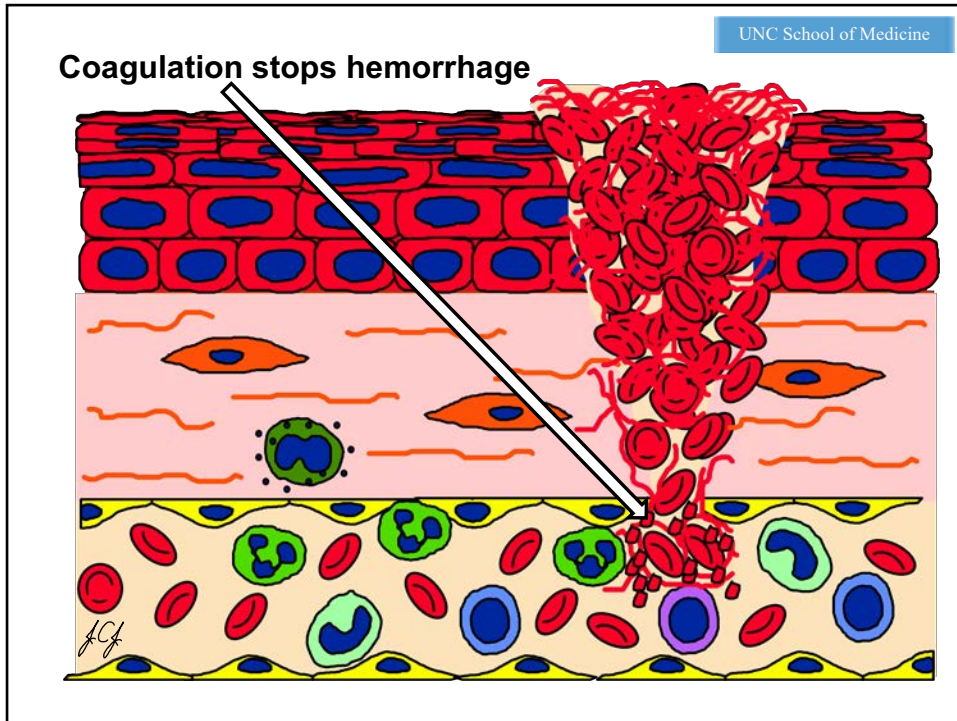
Response to injury is biologically similar in all tissues, and in response to injury caused by many etiologies. Knowing one example informs all examples.



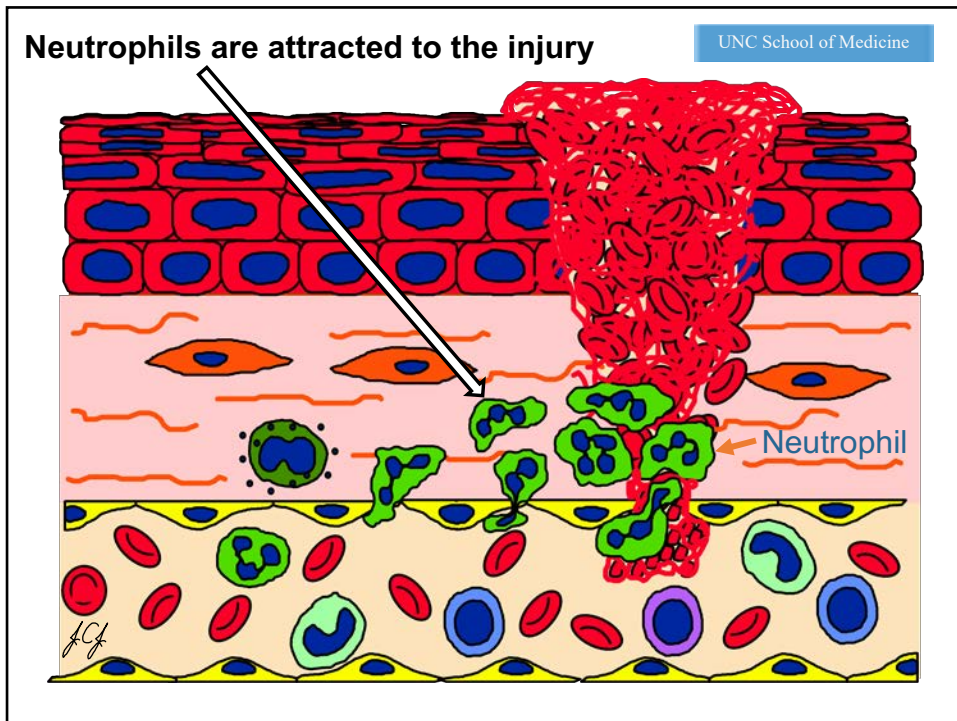
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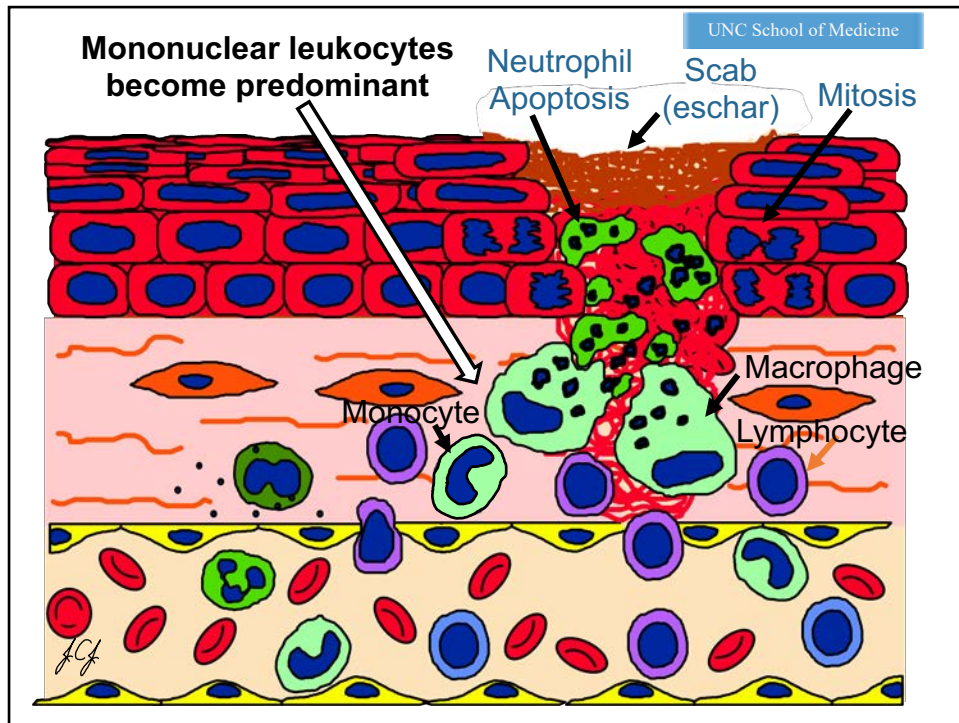
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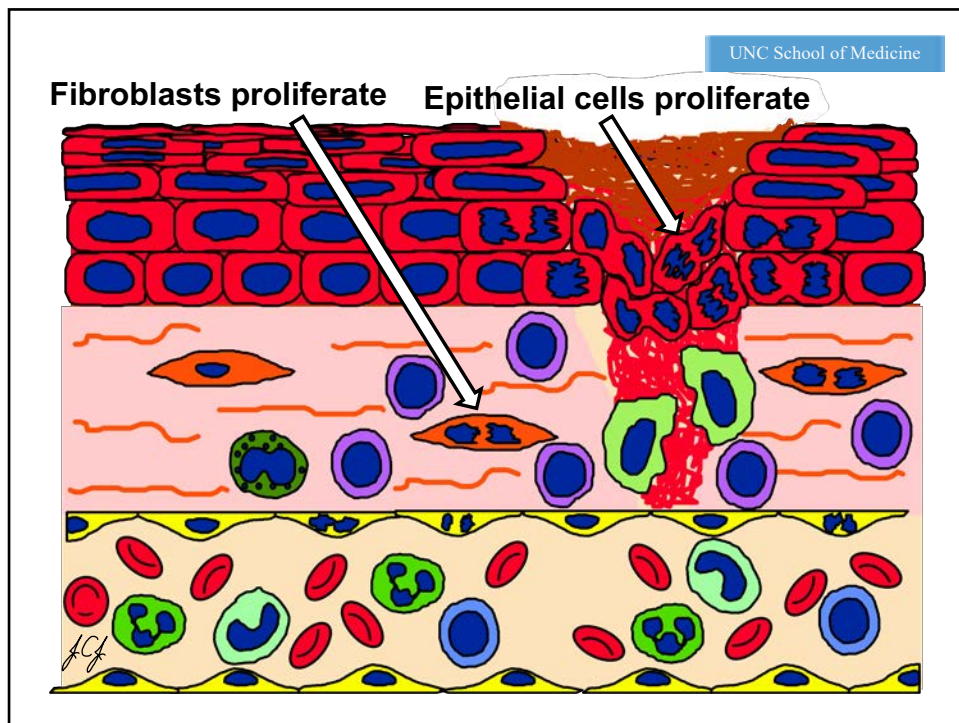
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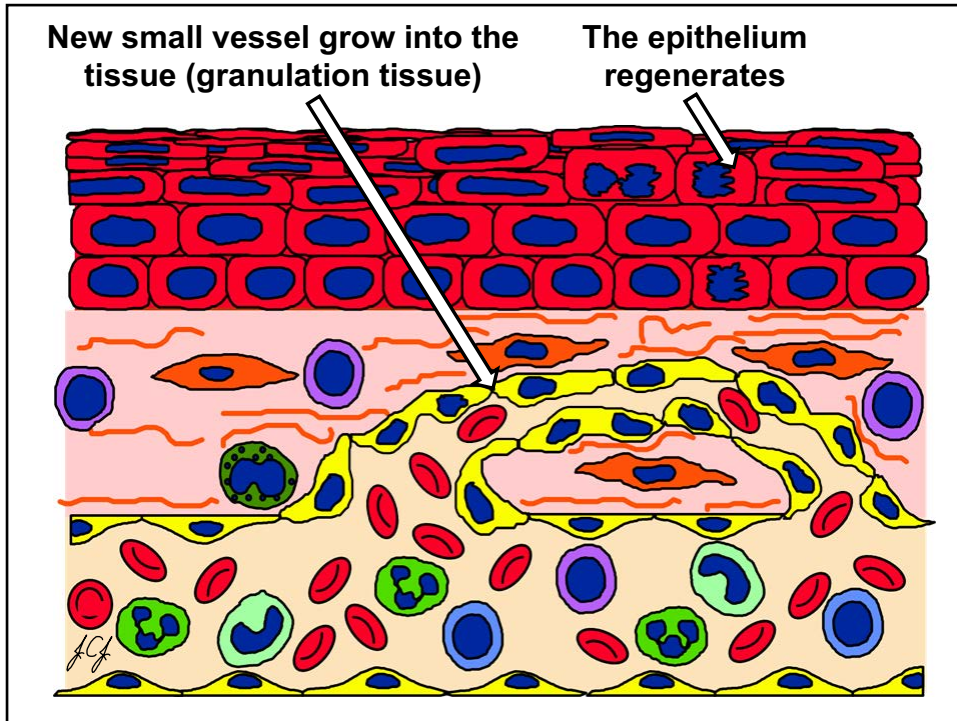
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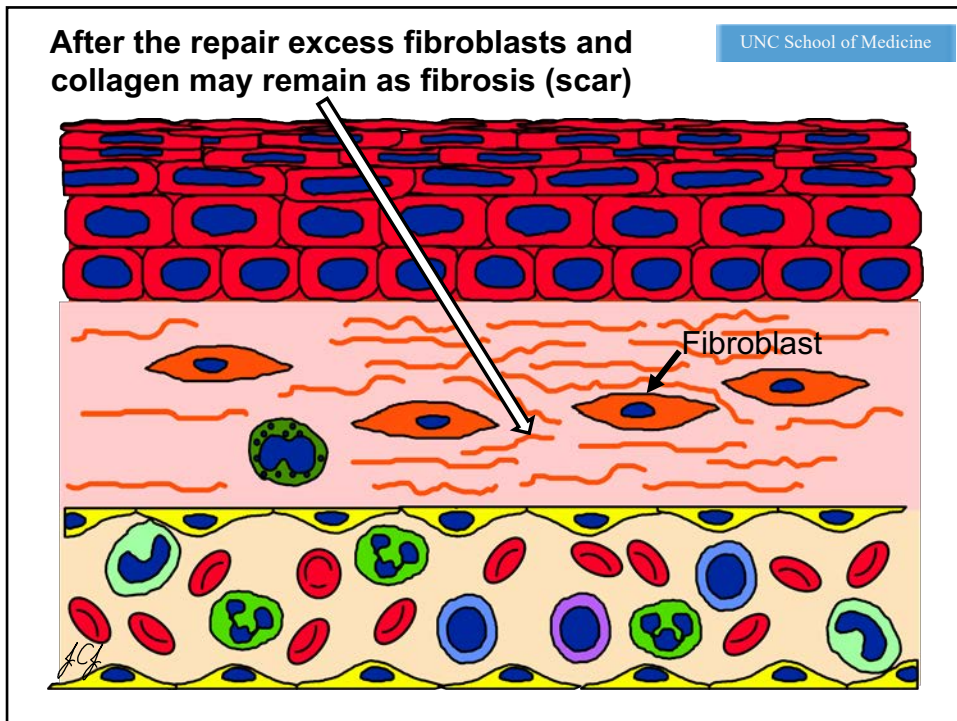
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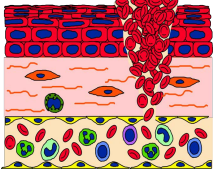
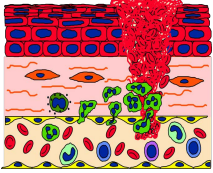
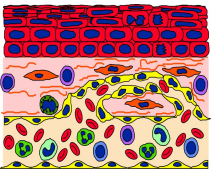
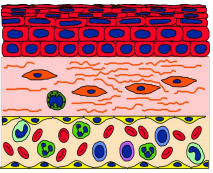


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Tissue Response to Injury

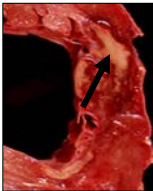
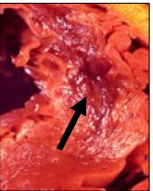
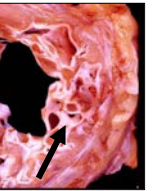


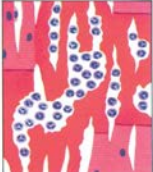
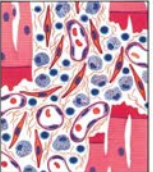
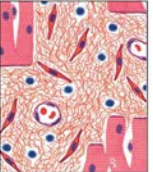
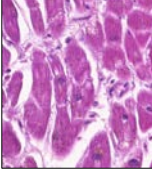
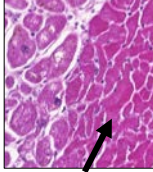
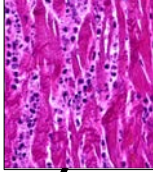
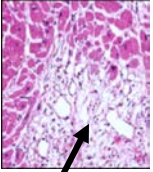
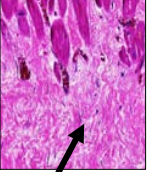
Response to injury is biologically similar in all tissues, and in injury caused by many etiologies. **Knowing one example informs all examples.**

Incised wound	Erythema and eschar	Re-epithelialized granulation tissue	Scar
			
			

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Acute Myocardial Infarction

		24 hours	3 weeks	3 months
				
Normal	12 hours			
				
				
Normal	Coagulative necrosis	Acute inflammation	Granulation tissue	Fibrous tissue (scar)
	Acute response to injury →			Repair →

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Thrombosis and Hemostasis

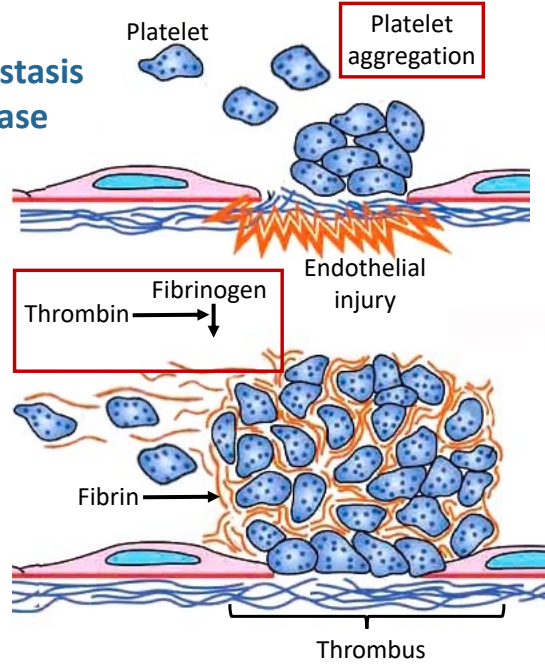
- **Thrombosis involves activation of circulating platelets and coagulation factors.**
- Thrombosis occurs when endothelial function is altered, endothelial continuity is lost, or blood flow is reduced.

The diagram illustrates the process of thrombosis. It shows a cross-section of a blood vessel with an endothelial injury. Platelets are shown aggregating at the site of injury. Thrombin is shown converting fibrinogen to fibrin, which then traps the platelets to form a thrombus.

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Thrombosis and Hemostasis Mechanisms of Disease

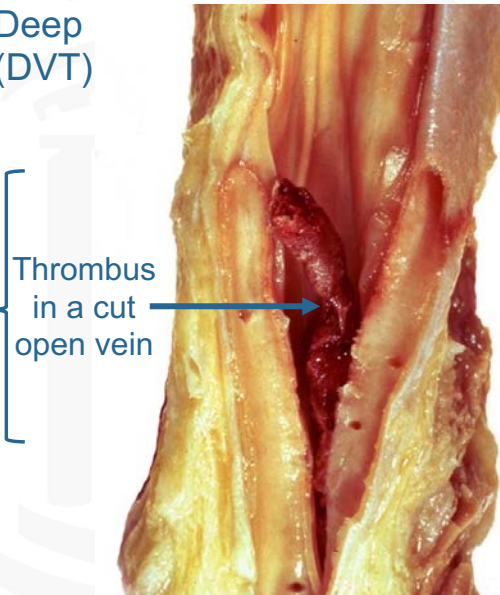
- Inadequate thrombosis causes **hemorrhagic diseases**.
- Thrombosis that obstructs adequate flow causes **ischemic diseases**
- Embolization causes **thromboembolic disease**.



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Lower Extremity Deep Vein Thrombosis (DVT)

A fragment (embolus) could break away from the thrombus and move through veins (embolize) to reach the lungs and occlude a renal artery causing localized ischemia and pulmonary infarction



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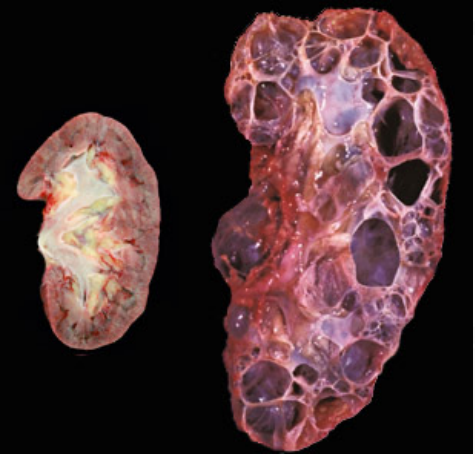
Mechanisms of Disease

- Cellular responses to injury**
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- Biochemical disorder**
 - Genetic
 - Acquired

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Genetic Abnormal Morphogenesis



Normal Kidney

Autosomal dominant polycystic kidney disease

ADPKD is caused by genetic mutations that disrupt kidney structure and function.

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Abnormal Morphogenesis

Agenesis: complete **absence** of an organ or component of an organ

Aplasia: persistence of an **undeveloped** organ anlage without the mature organ

Hypoplasia: **reduced size** caused by incomplete development

Dysplasia: **abnormal tissue differentiation** during development (**distinct from dysplasia developing in a previously normally developed tissue**)


Ectopia: normally formed organ that is outside its normal anatomic location

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Teratogenic Abnormal Morphogenesis

Teratogen: a factor (e.g., chemical, drug, infection) that causes malformation of an embryo or fetus.




Microcephaly (hypoplasia)

Pathogenesis: Zika virus infection of fetal neural stem cells causes defective neurogenesis

(Cell Stem Cell. 2016, S1934-5909(16)30214-4).

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Mechanisms of Disease
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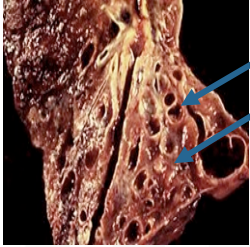

Cystic Fibrosis
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Cystic fibrosis (CF) is an autosomal recessive genetic disease that results from a defective chloride channel, that results in thick mucus in lungs and other tissues.

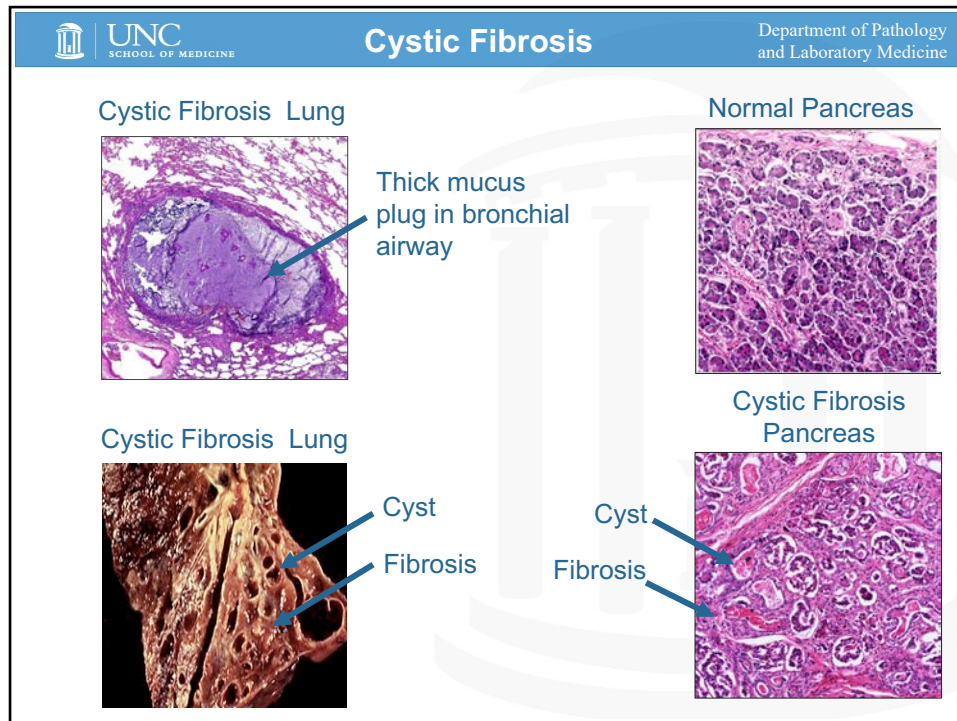
Characterized by chronic pulmonary disease caused by thick mucus and infections.

Thick mucus causes disease in multiple other organs, including small intestine, liver, pancreas and reproductive tract.

Cystic Fibrosis Lung



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Case Study

Department of Pathology and Laboratory Medicine

A 67-year-old man presented to the emergency department with acute abdominal pain and chest pain. On physical examination he had tenderness in the upper-left-quadrant of his abdomen. His medical history was remarkable for a myocardial infarction one month earlier.

Laboratory studies revealed elevated circulating fibrin fragments (D-dimers) indicating thrombosis, and elevated lactate-dehydrogenase (intracellular enzyme) indicating tissue necrosis.

Abdominal CT scan revealed multiple wedged-shaped areas of decreased density in the spleen, consistent with multiple infarcts. Echocardiogram demonstrated a large thrombus in the left ventricle of the heart.

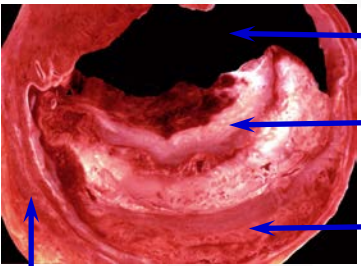
- **Symptoms:** abdominal pain and chest pain
- **Signs:** abdominal tenderness, elevated blood fibrin fragments and intracellular enzymes, and intracardiac thrombus by imaging
- **Diagnosis:** cardiac thrombus and splenic infarcts secondary to thromboembolism

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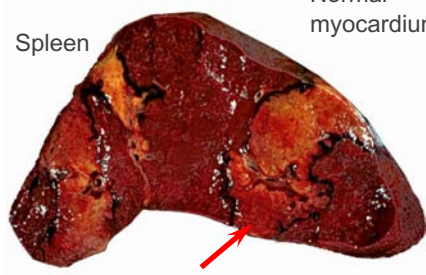
Department of Pathology and Laboratory Medicine

Case Study

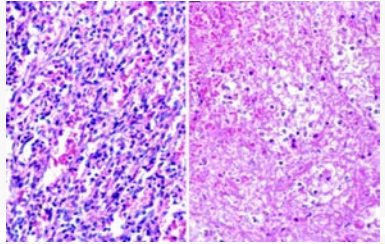
Pathogenesis: thrombosis in the heart overlying a myocardial infarct scar released emboli that lodged in splenic arteries resulting in ischemic necrosis (infarction).



Left ventricular lumen
Acute thrombus
Atrophic and fibrotic myocardium caused by repair of infarct



Spleen
Normal myocardium
Ischemic infarct with necrosis



Normal spleen with normal staining of nuclei
Necrotic spleen with loss of nuclear staining

Not an actual patient case

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Department of Pathology and Laboratory Medicine

Module 1: The Basics of Pathology

Introduction to Mechanisms of Disease

Learning and understanding pathology terminology helps learn and understand mechanisms of disease.

This was the goal of this presentation

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