Univerzita Pavla Jozefa Šafárika v Košiciach
Lekárska fakulta

Introduction to pathophysiology
Pathophysiology of the cell

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16th September 2025

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https://patfyz.medic.upjs.sk

Study literature

The author	**Title**	**year**
Norris T., Lalchandani R.,	**Porth's Pathophysiology: Concepts of Altered Health States 10th Ed., Lippincott Williams & Wilkins, Philadelphia, USA, 1688 p., ISBN-10: 1496377559**	**2018**
Kumar V., Abbas A., Fausto N.	Robbins & Cotran Pathologic Basis of Disease, 9th Ed., Elsevier, Amsterdam, NL 1408 p., ISBN-10: 1455726133	2014
Hammer G., McPhee S.	Pathophysiology of Disease: An Introduction to Clinical Medicine 7/E (Lange Medical Books) 7th Ed., McGraw-Hill Education, New York, USA, ISBN-10: 0071806008	2014
McCance K., Huether S.	Study Guide for Pathophysiology: The Biological Basis for Disease in Adults and Children 8th Ed., Mosby, Maryland Heights, USA, 325 p., ISBN-10: 0323413099	2018
Silbernagl S., Lang F.	Color Atlas of Pathophysiology 3rd Ed., Thieme, Stuttgart, DE, 448 p., ISBN-10: 3131165537	2016
Anatomical Chart Company	Atlas of Pathophysiology, 3rd Ed., Lippincott Williams & Wilkins, Philadelphia, USA, 464 p. ISBN-10: 1605471526	2009
Hall J., Hall M.	Guyton and Hall Textbook of Medical Physiology (Guyton Physiology) 14th Ed., Elsevier, Amsterdam, NL, 1152 p., ISBN-10: 0323597122	2020

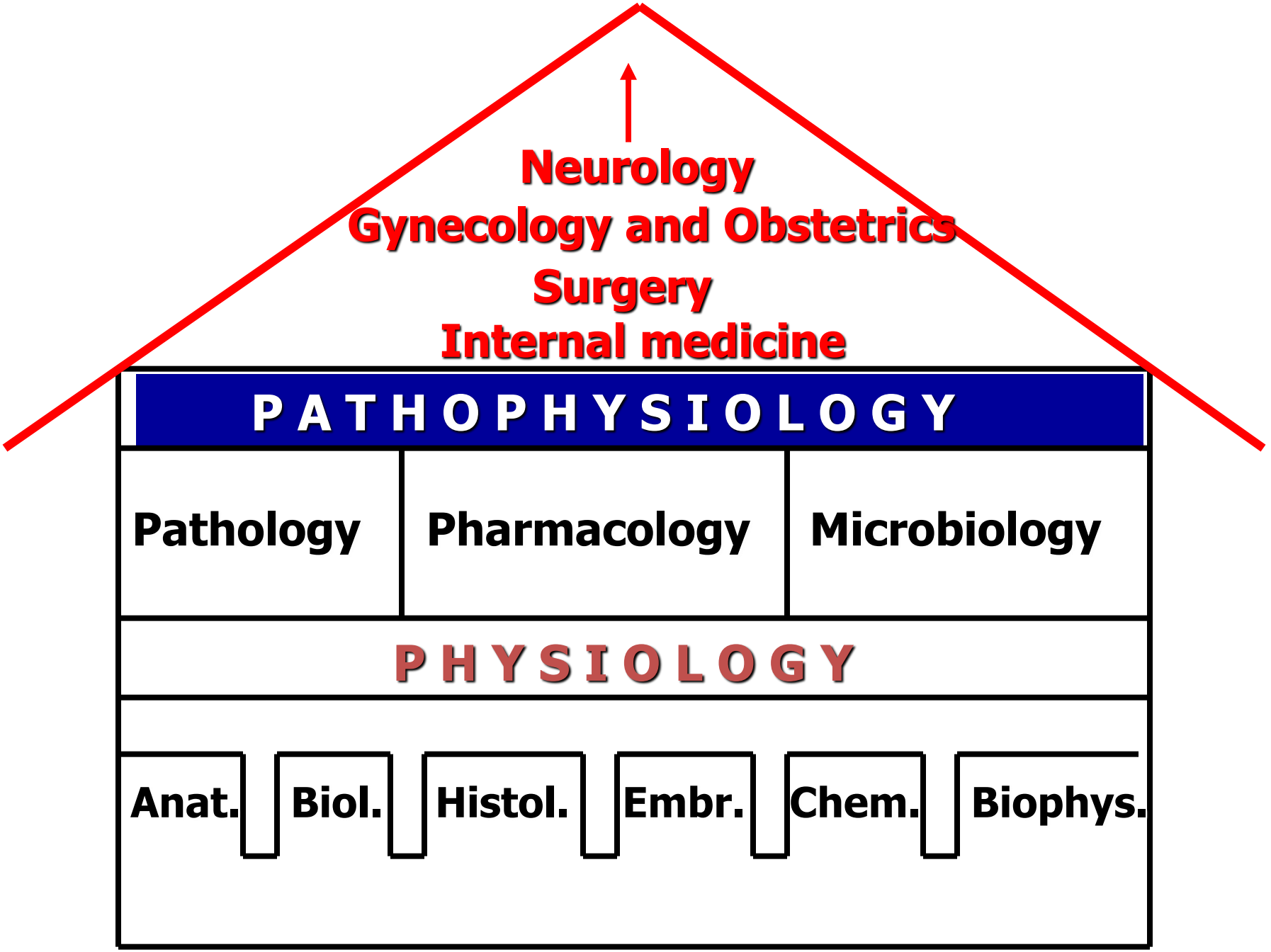
Pathophysiology

- the study of abnormalities in physiologic functioning of living beings
- derives from the intersection of pathology (gr. *pathos,* suffering) and physiology (gr. *physis,* nature)
  - Pathology is the study and diagnosis of *disease* through examination of *organs, tissues, cells,* and *bodily fluids.*
  - Physiology is the study of the mechanical, physical, and biochemical functions of living organisms.
- Pathophysiology seeks to reveal physiologic responses of an organism to disruptions in its internal or external environment.

Pathophysiology

- Pathophysiology examines disturbances of normal mechanical, physical, and biochemical functions, either caused by a disease or resulting from a disease or abnormal syndrome or condition.
- Discovering the responses to abnormalities in physiologic functioning allows a general prediction of clinical progression, identification of possible causes, and selection of interventions that are most likely to be helpful → *causal therapy*

❖ **Pathophysiology is one of the profiling subjects of medical studies. It plays an integrative role in both undergraduate and postgraduate education of doctors.**



adopted from Tatár and Hanáček

Pathophysiology

- Pathophysiological **vertical** (hierarchical levels of organismic organization), **horizontal** (of various organic systems) and **longitudinal** (referral to a time in natural history) **integration** of heterogeneous data and pertinent relations generates a reliable frame of reference for disease appreciation.
- The broad integration adds to upgrading the quality of clinical interpretation. It facilitates the permeation of evidence-based medicine into daily clinical life. It contributes to understanding the etiopathogenetic foundations of pharmacological, surgical and/or technological interventions.

Importance in medicine

- helps to understand the causes of diseases, which is the basis of causal therapy (treatment aimed at the cause, not just the symptoms)
- enables effective diagnosis and prevention
- is essential for the development of new drugs and therapeutic procedures
- serves as a bridge between basic research and clinical practice

Importance in medicine

1. Diagnostics

- It helps to understand the causes and mechanisms of diseases, which allows for more accurate diagnosis.
- It allows for the interpretation of symptoms based on biological processes.
- For example, in the case of fever, it is investigated how inflammatory cytokines affect the thermoregulatory center in the brain.

Importance in medicine

2. Therapy

- Knowledge of pathophysiological processes enables causal treatment - focused on the cause, not just the symptoms.
- It helps in the selection of drugs and therapeutic procedures according to the mechanism of the disease.
- For example, in the case of hypertension, treatment focuses on blocking the renin-angiotensin-aldosterone system.

Importance in medicine

3. Prevention

- It allows the identification of risk factors and pre-morbid conditions.
- It helps to design preventive measures based on knowledge of the pathogenesis of diseases.

4. Research and development

- Pathophysiology is the basis for the development of new drugs, vaccines and therapeutic technologies.
- It is used in clinical trials to assess the efficacy and safety of treatments

Importance in medicine

5. Education of healthcare professionals

- It is crucial in both undergraduate and postgraduate medical education.
- It helps students understand the complexity of diseases and their systemic impacts.

Trends and research in pathophysiology

- Current trends and research in pathophysiology are evolving dynamically due to advances in technology, molecular biology, and personalized medicine.
- Artificial Intelligence in Pathophysiology
- Molecular Neurophysiology
- Personalized Medicine
- Epigenetics and Physical Activity
- Pathophysiology of Cardiovascular Diseases
- Telemedicine and Remote Monitoring

Artificial Intelligence in Pathophysiology

- *Pavol Čekan et al. - **Alpredict project** - AI breast cancer test that can replace the expensive Oncotype DX test with 95% accuracy. The test uses histological images from a biopsy and provides results within seconds, significantly improving the accessibility and speed of diagnosis. It uses deep neural networks to analyze digital images of tumors to accurately predict biological characteristics and clinical course of the disease. This tool significantly expands the possibilities of personalized treatment.*

https://www.startitup.sk/vyznamny-uspech-slovensky-vedec-cekan-oznamil-zrod-prveho-ai-testu-pre-liecbu-rakoviny-prsnika/

Molecular Neurophysiology

- Bonnie Firestein et al. from Rutgers University have discovered a protein called **cypin** that enhances memory and treats Alzheimer's disease by improving communication between neurons.
- Cypin affects synaptic plasticity, which is crucial for learning and memory, and opens the way to new therapies for neurodegenerative diseases.
- Alzheimer's, Parkinson's, brain injuries... - translational research

https://www.startitup.sk/vedci-v-mozgu-odhalili-molekulu-ktora-lieci-pamat-aj-parkinsona-20-rokov-vyskumu-je-na-konci/

Personalized medicine

- Research focuses on individual disease mechanisms, enabling personalized pharmacotherapy – treatment tailored to the individual patient.
- Genetic profiles, biomarkers and AI are used to predict response to treatment.

Epigenetics and Physical Activity

- A study in Slovakia is investigating how exercise affects epigenetic mechanisms in skeletal muscle and the brain.
- Research shows that aerobic strength training can improve cognitive function in obese adolescents and seniors.

Pathophysiology of cardiovascular diseases

- Research focuses on hypertension, heart failure and the effects of modern drugs such as SGLT2 inhibitors or ARNI (angiotensin receptor antagonist/neprilysin inhibitor).
- The mechanisms of cardiac adaptation to pressure and volume overload are investigated.

Telemedicine and remote monitoring

- The use of telemedicine allows patients with chronic diseases to be monitored remotely, reducing the need for hospitalization.
- AI helps predict cardiovascular risks based on ECGs and electronic health records.

Future of pathophysiology

- Integration of AI, molecular biology and personalized medicine
- Expected to expand the availability of diagnostic tools, improve therapeutic accuracy and allow earlier intervention in chronic diseases.

Pathophysiology

Type	Focus	Example Topics
General Pathophysiology	Broad mechanisms of disease	Inflammation, fever, hypoxia, cell injury
Specialized Pathophysiology	Disease-specific processes	Diabetes mellitus, heart failure, renal failure

General pathophysiology

- the branch of medical science that studies the **fundamental mechanisms of disease**
- focuses on **universal processes** - inflammation, cell injury, immune responses, and metabolic disturbances, rather than disease-specific details

Specialized pathophysiology

- refers to the study of disease mechanisms that are specific to individual organs, systems, or particular diseases
- focuses on the **unique functional changes** that occur in the body due to specific illnesses

General pathophysiology

1. It deals with the recognition and description of the **causes** of diseases and the **conditions** under which these causes of diseases give rise to:
   a) Causes of diseases = noxious agents - biological, physical, chemical and social; exogenous, endogenous
   b) Conditions for the development of diseases - a decrease in the level of non-specific or specific resistance of the organism against noxious agents, stress, genetic changes, inadequate nutrition...
2. It deals with the recognition and description of general mechanisms applied in the process of recovery from illness (**sanogenesis**) and in the process of strengthening health (**prevention**).

General pathophysiology

- **General pathological processes** - inflammation, fever, shock, stress, hypoxia, edema, dystrophy, disorders of regulatory processes (positive feedback, apoptosis, damage to genetic information….)
- **Defense- and adaptive processes** - nonspecific and specific immunity, hypertrophy, atrophy, hyperfunction, hypofunction, homeostasis
- **Increased predisposition to disease (diathesis)** - genetically determined or influenced by environmental conditions

Pathophysiology - terminology

- **Nosology (gr. nosos = disease; logos = science)** - the branch of medical science dealing with the classification of diseases
- **Etiology (gr. aitiá = cause)** - the cause, set of causes, or manner of causation of a disease or condition
- **Pathogenesis (gr. pathos = pain, suffering; genesis - onset)** - the manner of development of a disease
  - general pathogenesis → understanding the general pathomechanisms
  - special pathogenesis → understanding the pathomechanisms leading to the development of a specific type of disease
- **Sanogenesis (gr. sanos = health)** - deals with mechanisms involved in recovery from disease to health.

Pathophysiology - terminology

- **Semiology (gr. sémeion = sign, symptom)** - deals with symptoms and signs of diseases
- **Thanatogenesis (gr. thanatos = death)** - deals with processes leading to death

Specialized pathophysiology

- covers:

Etiology: Specific causes of a disease (e.g. autoimmune triggers in T1DM)

Pathogenesis: How the disease develops & progresses in a particular organ/system

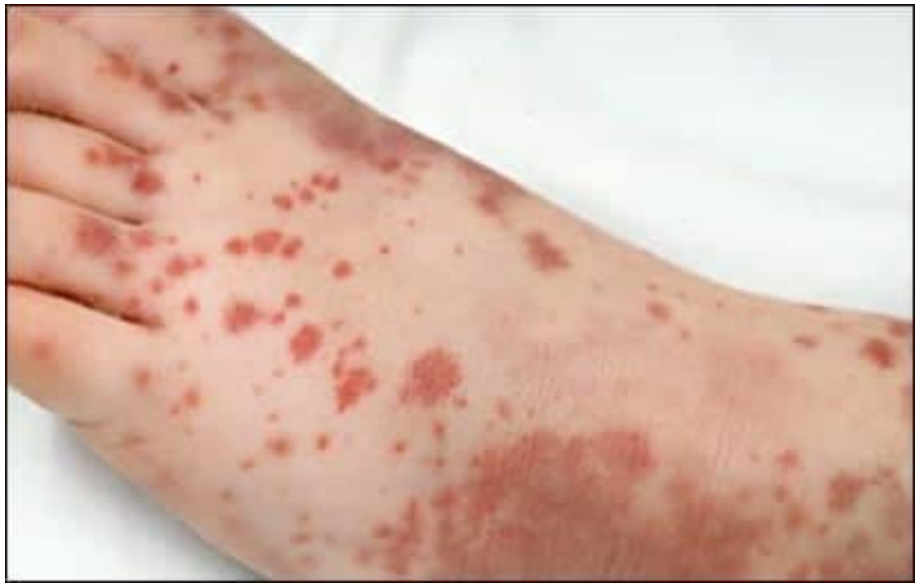
Clinical Manifestations: Signs and symptoms unique to the disease

Complications: Organ-specific consequences (e.g. neuropathy in diabetes)

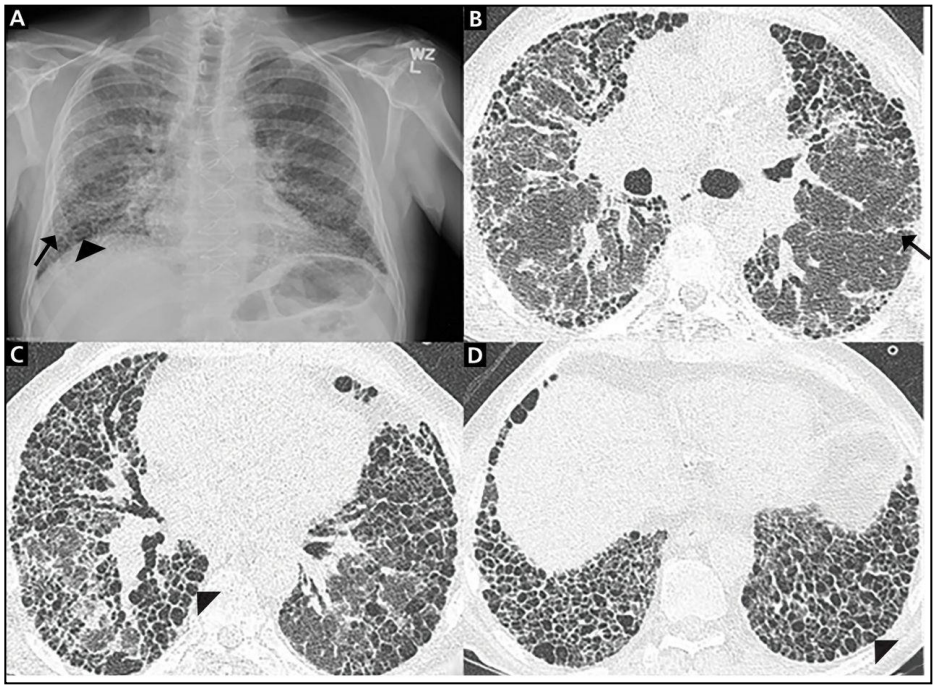
Therapeutic Targets: Mechanisms that can be influenced by treatment

Etiology

- **the study of the causes or reasons for phenomena**
- the identification of causal factors that provoke a particular disease or injury
- *idiopathic condition* - when the cause is unknown
- *iatrogenic condition* - if the cause is the result of an unintended or unwanted medical intervention
- Most disorders are *multifactorial*, having several different etiologic factors that contribute to their development.

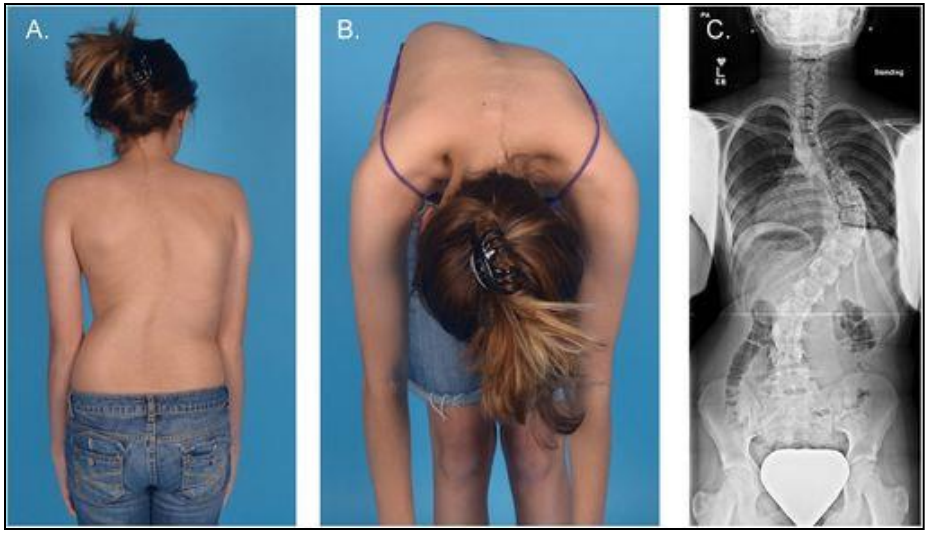


Idiopathic Thrombocytopenic Purpura

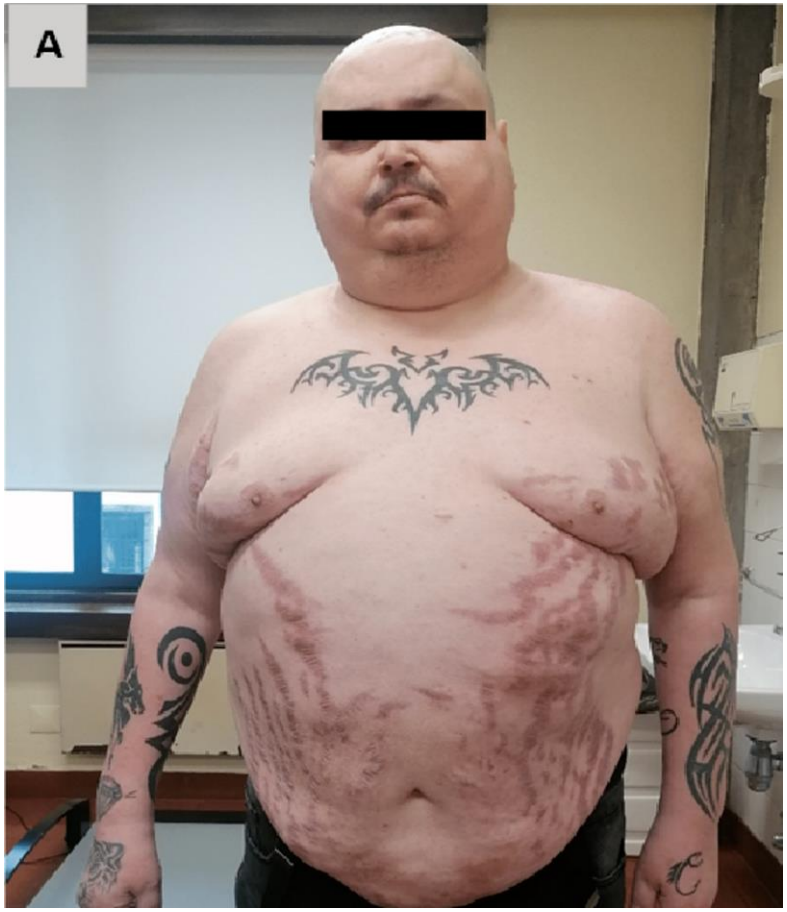


Idiopathic pulmonary fibrosis

Idiopathic Intracranial Hypertension



Adolescent Idiopathic Scoliosis



Cobicistat, used as a pharmacokinetic booster in therapeutic combination with human immunodeficiency virus (HIV) protease inhibitors and integrase inhibitors, is a strong inhibitor of cytochrome P450 3A4 (CYP3A4). Since most glucocorticoids are metabolized by the isoenzyme of the cytochrome P450 pathway, their plasma concentrations can be highly increased in the presence of cobicistat-boosted darunavir, with subsequent risk of iatrogenic Cushing's syndrome and secondary adrenal insufficiency.

Iatrogenic Cushing's Syndrome: The Result of Cobicistat and Glucocorticoid Interaction in an HIV Patient After Bariatric Surgery

https://www.cureus.com/articles/134896-iatrogenic-cushings-syndrome-the-result-of-cobicistat-and-glucocorticoid-interaction-in-an-hiv-patient-after-bariatric-surgery#!/

Etiologic Classification of Diseases

Congenital (inborn) diseases or birth defects
Degenerative diseases
Iatrogenic diseases
Idiopathic diseases
Immunologic diseases
Infectious diseases
Inherited diseases
Metabolic diseases
Neoplastic diseases
Nutritional deficiency diseases
Physical agent–induced diseases
Psychogenic diseases

Pathophysiology by Jacquelyn L Banasik, 2019

Pathogenesis

- the development or evolution of a disease, from the initial stimulus to the ultimate expression of the manifestations of the disease
- the sequence of physiologic events that occurs in response to an etiologic agent - a dynamic interplay of changes in cell, tissue, organ, and systemic function

Clinical Manifestations

- ***signs of disease*** – objectively observed manifestations of diseases gathered by clinical examination or by biochemical analysis, diagnostic imaging, and other laboratory tests
- ***symptoms –*** the subjective feelings of an abnormality in the body (can only be reported by the affected individual to an observer)
- ***a syndrome*** – the disorder with the etiology of a particular set of signs and symptoms that has not yet been determined

Clinical presentation - stages

- *a latent period* - the interval between exposure of a tissue to an injurious agent and the first appearance of signs and symptoms (an *incubation period* in the case of infectious diseases)
- *the prodromal period/prodrome* - the appearance of the first signs and symptoms indicating the onset of a disease (e.g., headache, malaise, anorexia, nauzea)
- *the acute phase* - the stage of manifest illness, the disease reaches its full intensity, and signs and symptoms attain their greatest severity
- *termination of the disease* by recovery (complete/incomplete cure) or failure to recover (transition to chronicity/death).

Clinical presentation – clinical course

- *a subclinical stage* - the patient functions normally, although the disease processes are well established
- *Peracute conditions* - the onset and development of a pathological condition is rapid (minutes, hours) (e.g. aspiration with suffocation, anaphylactic reaction and suffocation, acute myocardial infarction, sudden cardiac death, CO or cyanide poisoning, etc.).
- *Acute diseases* - the condition arises and develops over several days to 2 weeks. For example, acute infectious diseases - respiratory (e.g. nasopharyngitis, bronchitis), gastrointestinal (e.g. gastritis, enteritis, acute pancreatitis), urogenital (cystitis, pyelonephritis), skin (furunculus), non-infectious (stroke, injuries)

Clinical presentation – clinical course

- *Subacute diseases* - the disease/pathological process develops gradually and lasts 2-8 weeks (e.g. subacute bacterial endocarditis)
- *Chronic diseases* - persist for more than 6-8 weeks, or exacerbations (e.g. CHD, COPD, DM, obesity)

Clinical presentation – clinical course

- *an exacerbation* - a relatively sudden increase in the severity of a disease or any of its signs and symptoms
- *a remission* - an abatement or decline in severity of the signs and symptoms of a disease. If a remission is permanent (sometimes defined as longer than 5 years), the person is said to be cured.
- *convalescence* - the stage of recovery after a disease, injury, or surgical operation
- *a sequela* (plural: sequelae) – a subsequent pathologic condition caused by a disease (an inflammatory process → scarring; acute rheumatic inflammation of the heart → scarring and deformation of cardiac valves)

Treatment Implications

- An understanding of the etiology, pathogenesis, and clinical consequences of a particular disorder may suggest, or “imply,” that certain treatments could be helpful.

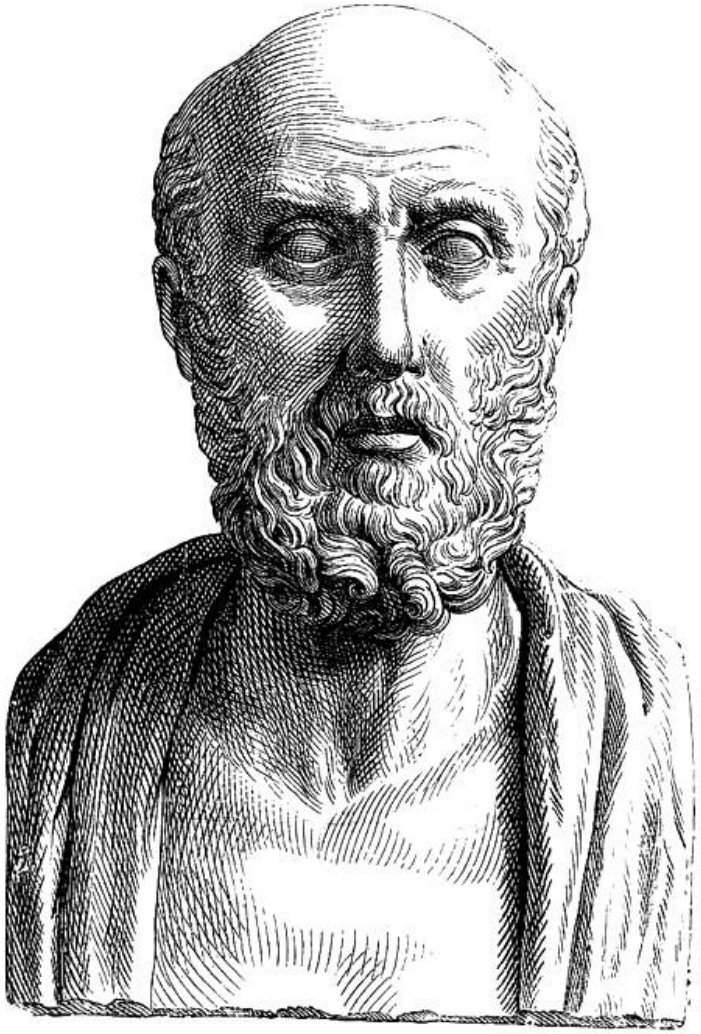
Interim Summary

- Pathophysiology includes four interrelated topics: etiology, pathogenesis, clinical manifestations, and treatment implications.
- Etiology refers to study of the proposed cause or causes of a particular disease process. Etiology is a complex notion because most diseases are multifactorial, resulting from interplay between genetic constitution and environmental influences.
- Pathogenesis refers to the proposed mechanisms whereby an etiologic stimulus leads to typically observed clinical manifestations. Pathogenesis describes the direct effects of the initiating event, as well as the usual physiologic responses and compensatory mechanisms.
- Clinical manifestations describe the signs and symptoms that typically accompany a particular pathophysiologic process. Manifestations may vary depending on the stage of the disorder, individual variation, and acuity or chronicity.
- An understanding of the etiology, pathogenesis, and clinical consequences of a particular disorder implies that certain treatments may be helpful.

Methods in pathophysiological research

- observation
- experiment
- formulation of hypotheses
- clinical-pathophysiological studies

History of pathophysiology



History of pathophysiology

- **Hippocrates** (460-370 BC)- the father of Western medicine, was the first to construct theories of the causes of disease based on observations in his patients. His pathophysiology focused on understanding the body as a complex system with inherent healing capabilities, influenced by internal and external factors. His emphasis on observation, reasoning, and holistic care laid the foundation for modern medicine.
- **Claude Bernard** (1813 - 1878) - introduced the term "experimental pathology“

History of pathophysiology

- **Rudolf Wirchov** (1821 – 1902), founder of cellular pathology - emphasized the key role of the dysregulation of physiological processes as the basic mechanism of disease - used the term: pathological physiology
- **J. E. Purkyně** (1787 - 1869) - predicted the emergence of pathophysiology as a new discipline with this quote: "Many processes, although they belong to physiology by their mechanism, extend beyond its borders into the field of pathology, because it often happens that what was a simple transient phenomenon turns into a disease. Such reasoning leads to the establishment of a special doctrine of pathological physiology."

History of pathophysiology

- **A.F. Hecker** (1790) – author of the „Textbook in pathophysiology”
- **L. Gallo/Galliot** (1819) - published a medical textbook "General pathology and pathological physiology".
- other excellent pathophysiologist: Prof. Pashutin, Prof. Pavlov, Prof. Hans Selye (Canada 1907-1982) - Stress theory; ...

Cellular injury, adaptation, aging, and death

Cellular injury, adaptation, aging, and death

- **Reversible Cell Injury**
  - Hydropic Swelling
  - Intracellular Accumulations
- **Cellular Adaptation**
  - Atrophy
  - Hypertrophy
  - Hyperplasia
  - Metaplasia
  - Dysplasia
- **Irreversible Cell Injury**
  - Necrosis
  - Apoptosis

Cellular injury, adaptation, aging, and death

- **Etiology of Cellular Injury**
  - Ischemia and Hypoxic Injury
  - Nutritional Injury
  - Infectious and Immunologic Injury
  - Chemical Injury
  - Physical and Mechanical Injury
- **Cellular Aging**
  - Cellular Basis of Aging
  - Physiologic Changes of Aging
- **Somatic Death**

Cells‘ response to injury

- *(1) a reversible cell injury:* When the change is mild or short lived, the cell may withstand the assault and completely return to normal.
- *(2) cellular adaptation (reversible):* The cell may adapt to a persistent but sublethal injury by changing its structure or function.
- (3) *an irreversible cell injury:* Cell death may occur by *necrosis* and *apoptosis* if the injury is too severe or prolonged.

Reversible cell injury

- often results in cellular swelling and the accumulation of excess substances within the cell
- the cell's inability to perform normal metabolic functions because of insufficient cellular energy in the form of ATP or dysfunction of associated metabolic enzymes
- Once the acute stress or injury has been removed, the cell returns to its preinjury state.

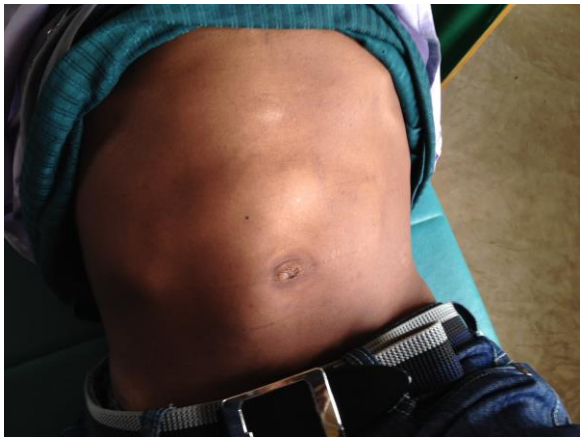
- hydropic swelling/oncosis
- intracellular accummulations

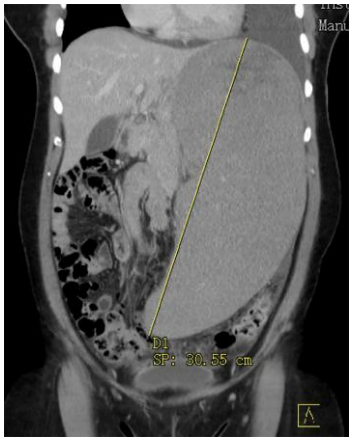
Hydropic Swelling (oncosis)

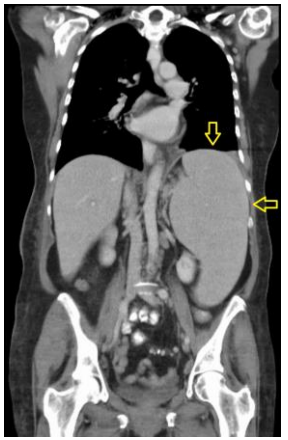
- cellular swelling attributable to accumulation of water
- the first manifestation of most forms of reversible cell injury
- results from malfunction of the Na+/K+ pumps that leads to accumulation of Na+ within the cell, creating an osmotic gradient for water entry
- any injury that causes insufficient energy (ATP) production will result in hydropic swelling

Hydropic Swelling (oncosis)

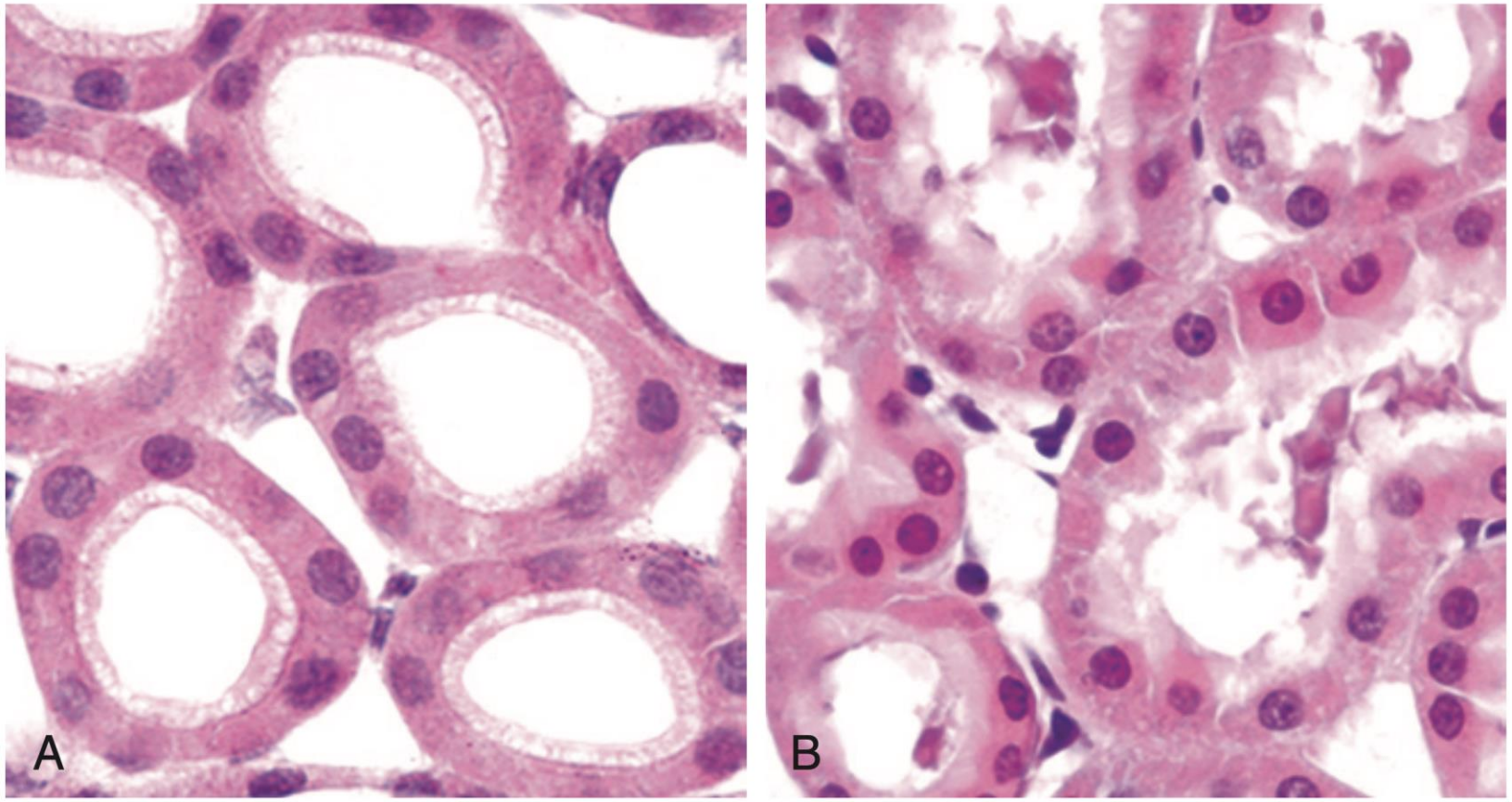
- is characterized by a large, pale cytoplasm; dilated ER; and swollen mitochondria
- ER may rupture and form large water-filled vacuoles
- Generalized swelling in the cells of a particular organ may cause the organ to increase in size and weight. Organ enlargement is indicated by the suffix *-megaly* (e.g., *splenomegaly* denotes an enlarged spleen, *hepatomegaly* denotes an enlarged liver).





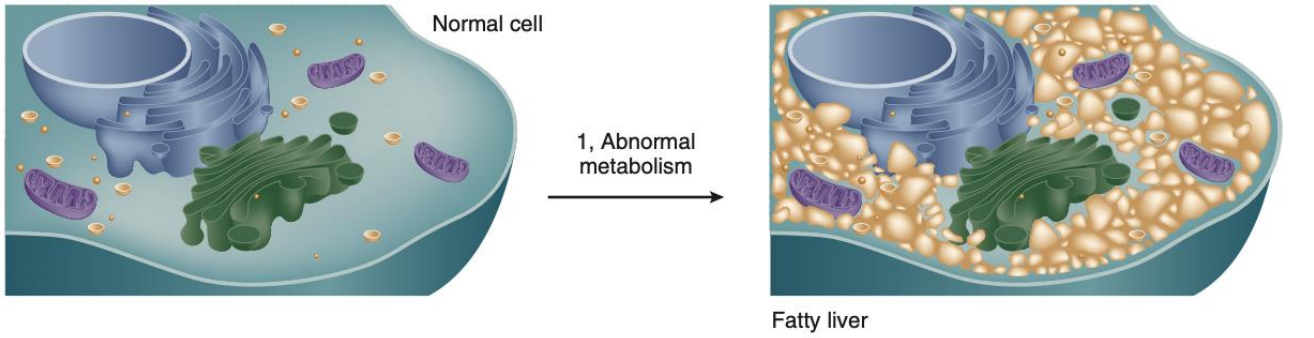


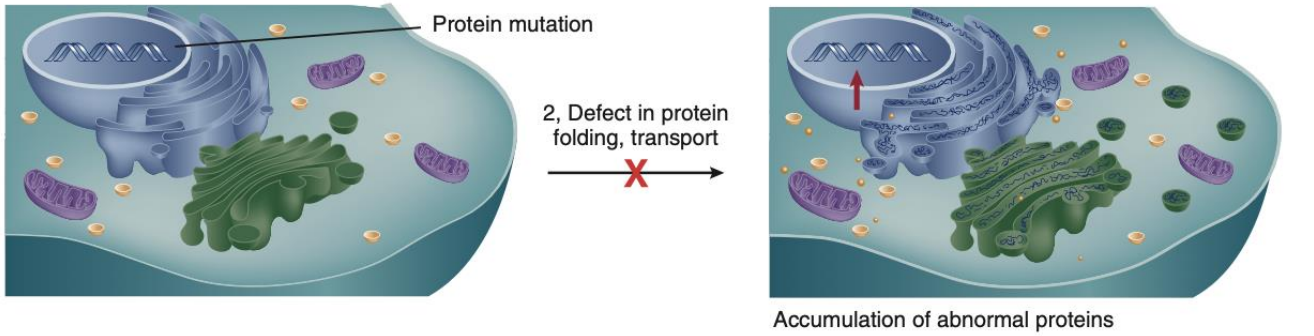
Cellular swelling in kidney tubule epithelial cells. **A,** Normal kidney tubule with cuboidal cells. **B,** Early ischemic changes showing surface blebs and swelling of cells. (From Kumar V et al: *Robbins and Cotran Pathologic basis of disease*, ed 9, Philadelphia, 2015, Saunders, p 42.)

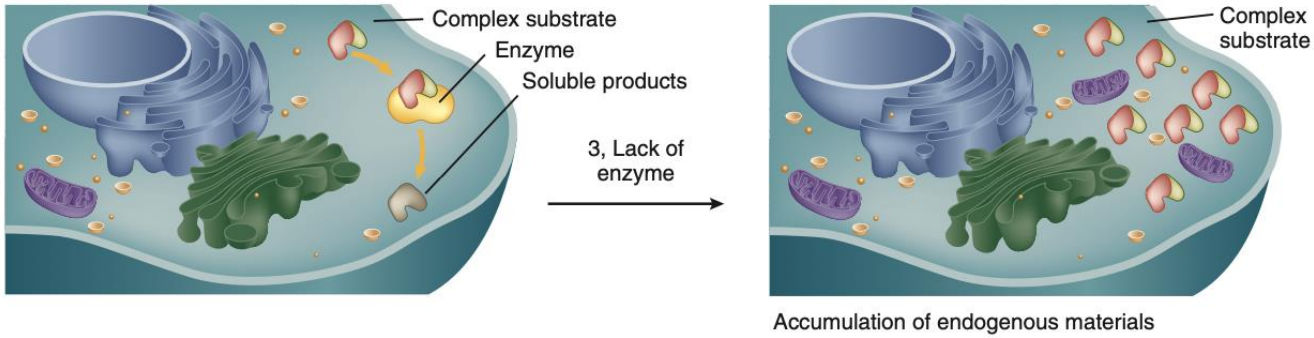


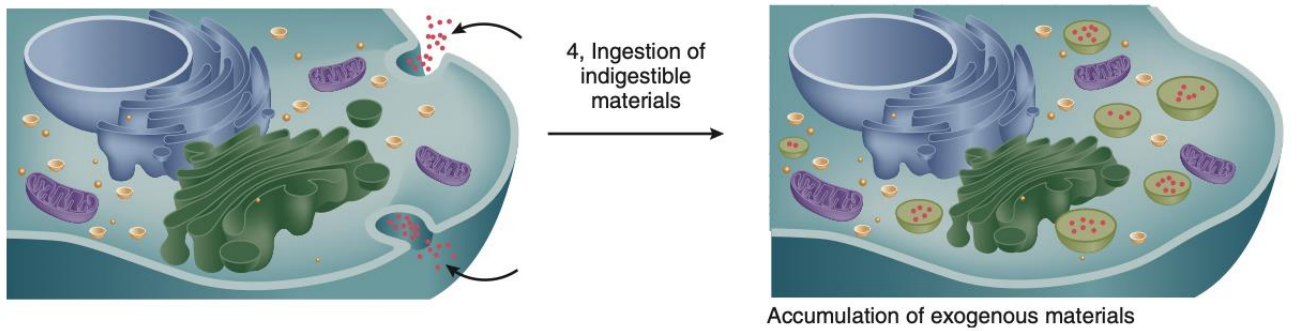
Intracellular Accumulations

- Excess accumulations of substances in cells may result in cellular injury because the substances are toxic or provoke an immune response, or merely because they occupy space needed for cellular functions.
- Intracellular accumulations may be categorized as:
  - (1) excessive amounts of normal intracellular substances such as fat, carbohydrates, glycogen, and proteins
  - (2) accumulation of abnormal substances produced by the cell because of faulty metabolism or synthesis,
  - (3) accumulation of pigments and particles that the cell is unable to degrade







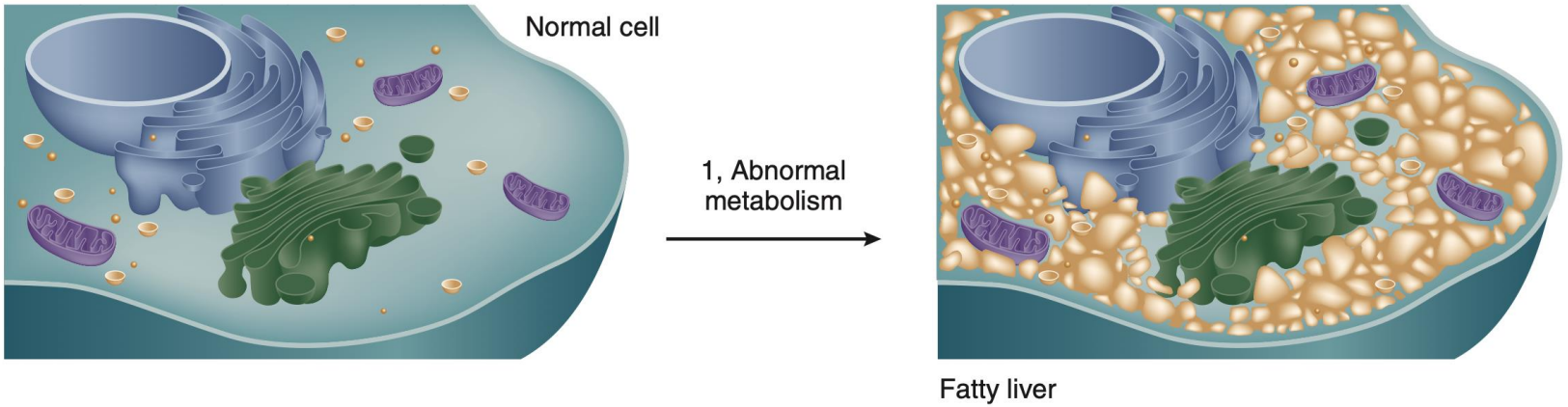


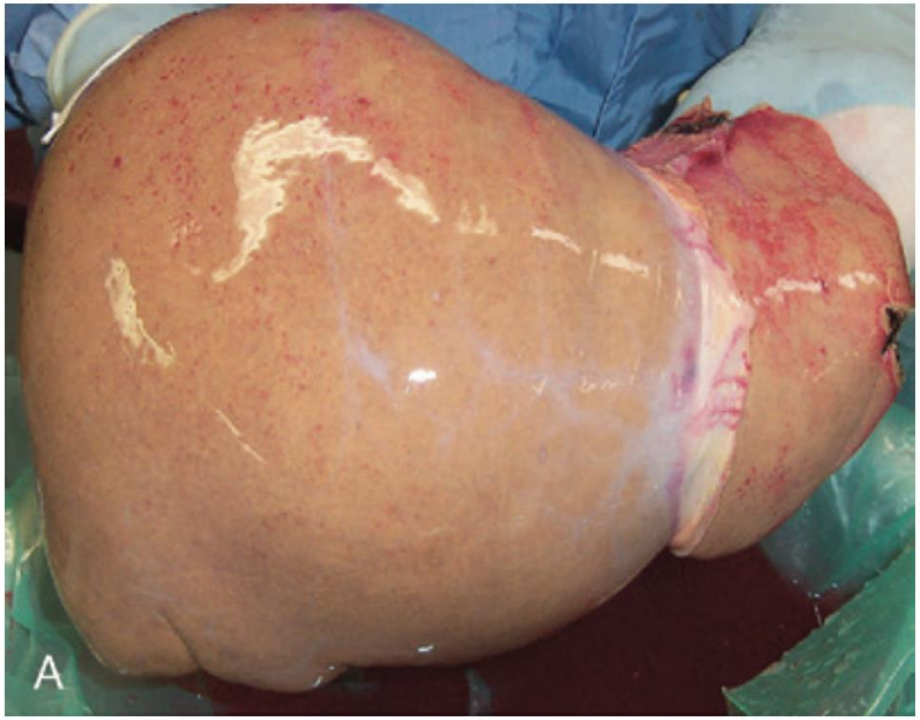
General mechanisms of intracellular accumulation:

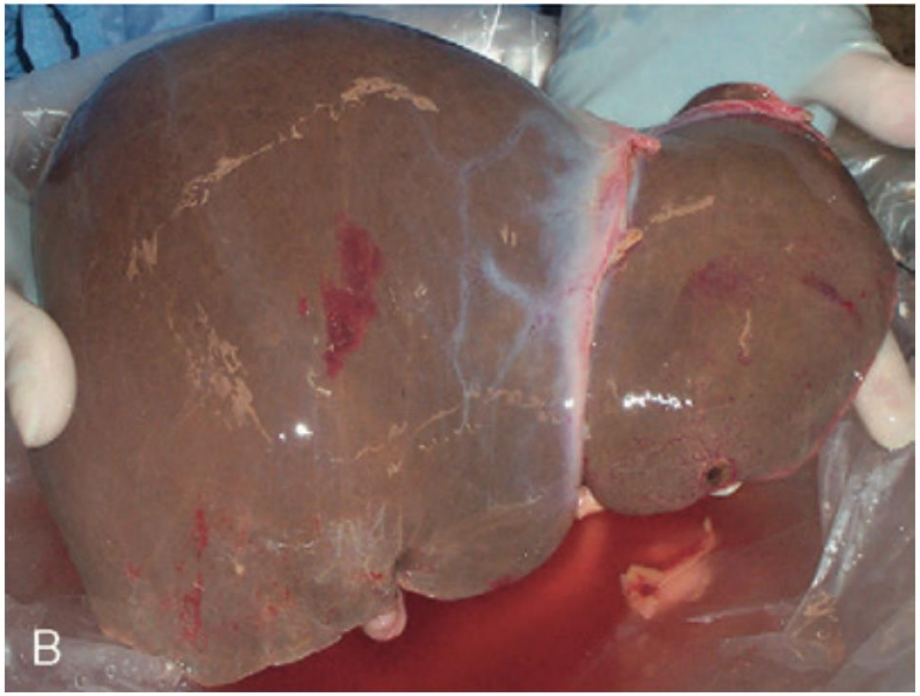
- (1) abnormal metabolism as in fatty change in the liver,
- (2) mutations causing alterations in protein folding and transport so that defective proteins accumulate,
- (3) deficiency of critical enzyme responsible for lysosomal degradation,
- (4) an inability to degrade phago-cytosed particles such as coal dust.

Intracellular Accumulations

- fatty liver, excessive alcohol intake (direct toxic effects, the preferential metabolism of alcohol instead of lipid)
- atherosclerotic diseases – accumulation of lipids in blood vessels, kidney, heart, and other organs
- genetic disorders - the enzymes needed to metabolize lipids are impaired; e.g., Tay-Sachs disease, Gaucher disease → lipids accumulate in neurologic tissue







Gross appearance of a fatty donor liver **(A)** compared with a normal nonfatty donor liver **(B).**

(From Odze RD, Goldblum JR. *Surgical pathology of the GI tract, liver, biliary tract, and pancreas*, ed 2, St Louis, 2009, Elsevier.)

Intracellular Accumulations

- *mucopolysaccharidoses* - a group of genetic diseases in which the enzymatic degradation of glycosaminoglycans (mucopolysaccharides) is impaired and they collect within the cell. Mental disabilities and connective tissue disorders are common findings.

	Morquio	Hurler	San Filippo	Hunter
Pathophysiology	Type A (galactosamine-6-sulfate-sulphatase deficiency). Type B (beta-galactosidase deficiency)	Caused by alpha-L iduronidase deficiency	Multiple enzyme deficiencies	Sulpho-iduronate-sulphatase deficiency
Genetics	AR	AR	AR	X-linked
Proportionate dwarfism	Yes	Yes	Yes	Yes
Mental Retardation	No	Yes	Yes	Yes
Studies	Keratan sulfate in urine	Dermatan sulfate in the urine	Heparan sulfate in the urine	Dermatan/heparan sulfate in urine
Prognosis	Type A is more severe Type A and B survive into adulthood	Death in first decade of life	Death in second decade of life	Death in second decade of life

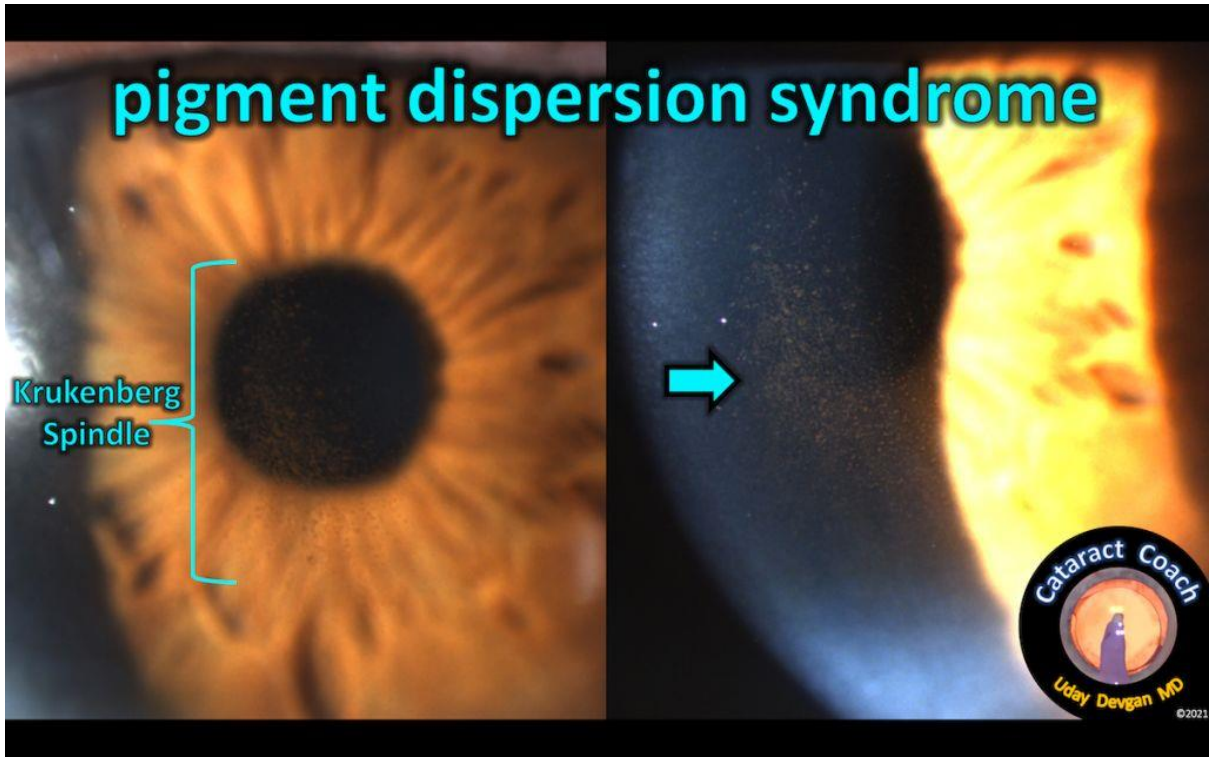
Intracellular Accumulations

- *excessive glycogen storage* – in inborn errors of metabolism, in diabetes mellitus
- Cellular stress may lead to accumulation and aggregation of denatured proteins.
- A family of stress proteins (*chaperone or heat-shock proteins*) is responsible for binding and refolding aberrant proteins back into their correct 3D forms. If the chaperones are unsuccessful in correcting the defect, the abnormal proteins form complexes with another protein called *ubiquitin.* Ubiquitin targets the abnormal proteins to enter a proteosome complex, where they are digested into fragments that are less injurious to cells.

Intracellular Accumulations

- *endogenous and exogenous pigment accumulations* - melanin, hemosiderin, bilirubin; calcium, tar, mineral dusts coal, silica, iron, lead, silver.
- Deposits of calcium salts occur in conditions of altered calcium intake, excretion, or metabolism. Calcium phosphate salts are deposited in the tissues of the eye, heart, and blood vessels.
- With the exception of inorganic particles, the intracellular accumulations generally are reversible if the causative factors are removed.

Intracellular Accumulations



A Krukenberg spindle = a vertical, spindle-shaped pattern of pigment granules seen on the inner surface of the cornea, caused by pigment released from the iris that accumulates on the back of the cornea due to high eye pressure. It is a key sign of pigment dispersion syndrome, a condition where pigment flakes off the iris, which can lead to pigmentary glaucoma.

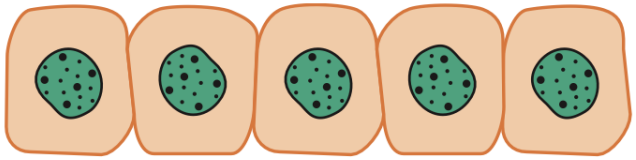
https://cataractcoach.com/2021/07/21/1171-pigment-dispersion-syndrome/

KEY POINTS

- Hydropic swelling is an early indicator of cell injury. It results from Na+–K+ pump dysfunction at the cell membrane.
- Intracellular accumulations of abnormal endogenous or exogenous particles indicate a disorder of cellular metabolism.
- Damage from accumulation of abnormal intracellular protein is limited by chaperone proteins that attempt to refold the protein into its correct shape and by the ubiquitin–proteosome system that digests targeted proteins into fragments.

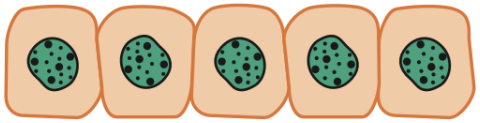
Cellular Adaptation

- **Adaptive cellular responses indicate cellular sublethal stress caused by altered functional demand or chronic sublethal (reversible cellular) injury.**
- The common adaptive responses are:
  - atrophy (decreased cell size),
  - hypertrophy (increased cell size),
  - hyperplasia (increased cell number),
  - metaplasia (conversion of one cell type to another),
  - dysplasia (disorderly growth).

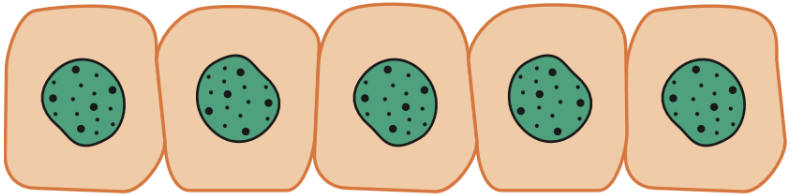


Normal

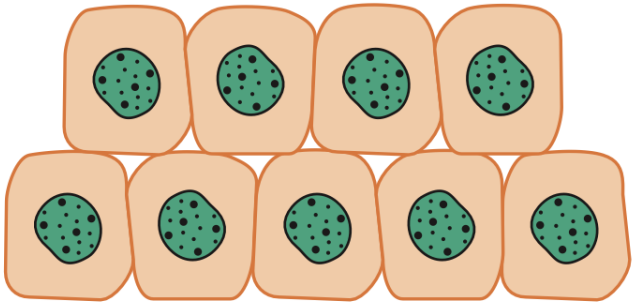
Cells are able to adapt to increased work demands or threats to survival by changing their size (atrophy and hypertrophy), number (hyperplasia), and form (metaplasia).



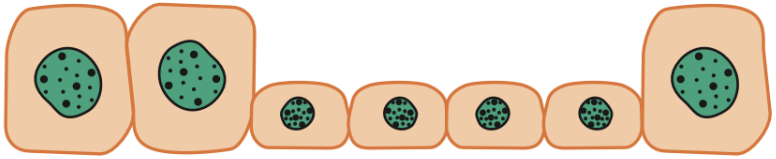
Atrophy
(decreased cell size)



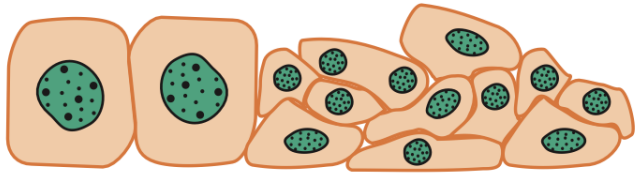
Hypertrophy
(increased cell size)



Hyperplasia
(increased cell number)



Metaplasia
(conversion of one cell type to another)

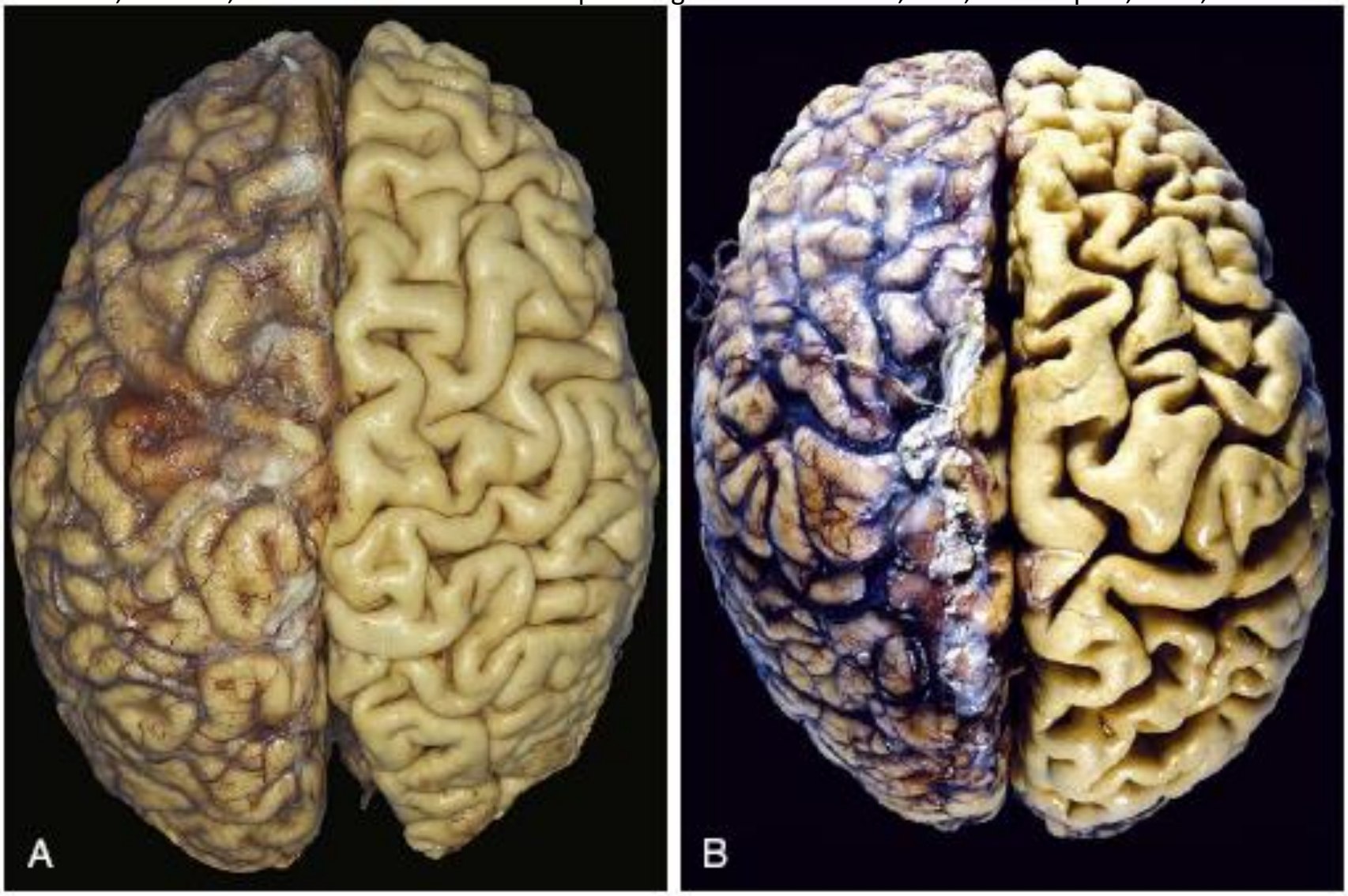


Dysplasia
(disorderly growth)

Cellular Adaptation

- **Hypertrophy** and **hyperplasia** generally result from increased functional demand.
- **Atrophy** results from decreased functional demand or chronic ischemia.
- **Metaplasia** and **dysplasia** result from persistent injury.

Kumar V, Abbas A, Fausto N: Robbins & Cotran pathologic basis of disease, ed 8, Philadelphia, 2007, Saunders



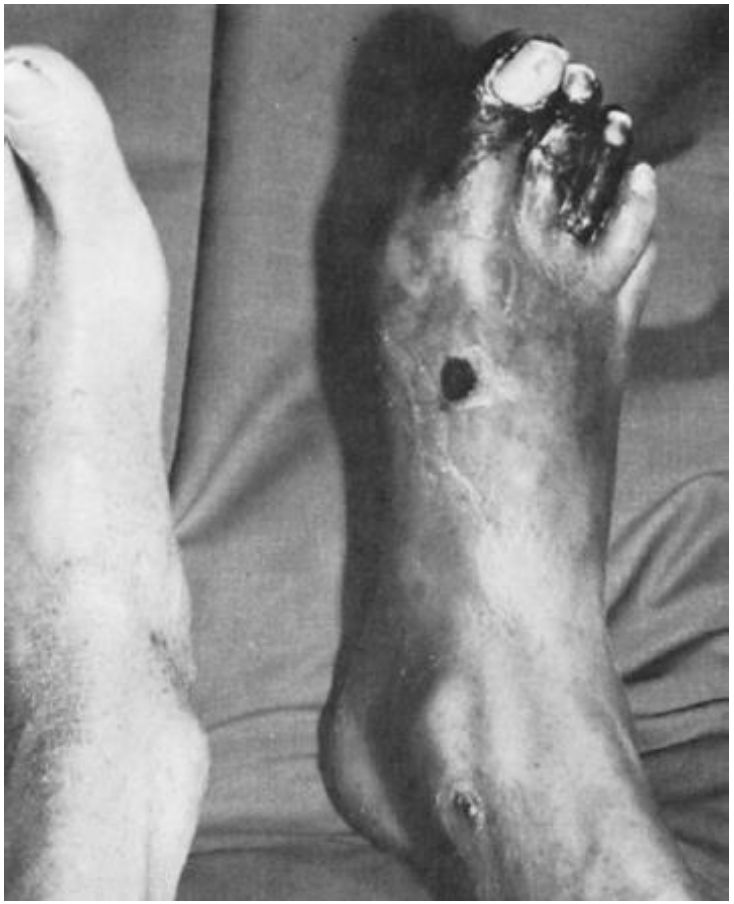
(B): Atrophy of the brain in an 82-year-old male with atherosclerotic disease. Atrophy of the brain is a result of aging and reduced blood supply. Loss of brain substance narrows the gyri and widens the sulci.

Irreversible cell injury

- Pathologic cellular death occurs when an injury is too severe or too prolonged.
  - **necrosis**
  - **apoptosis** (from a Greek word meaning falling off)

Necrosis

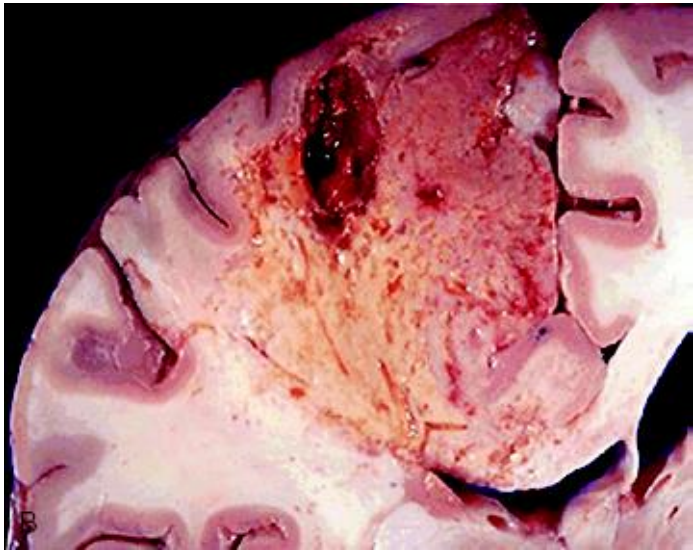
- occurs when the injury is too severe or prolonged to allow adaptation
- a consequence of disrupted blood supply/ischemia or toxic injury
- is characterized by cell rupture, spilling of contents into the extracellular fluid, and inflammation
- local and systemic indicators of necrotic cell death include: pain, elevated serum enzyme levels, inflammation (fever, elevated WBC count, malaise), and loss of function
- different tissues exhibit necrosis of different types: heart (coagulative), brain (liquefactive), lung (caseous), and pancreas (fat). Special cases of coagulative necrosis are hemorrhagic necrosis, caseous necrosis, and Zenker's muscle necrosis.



Coagulative necrosis

- the most common type
- the steps leading to coagulative necrosis: (1) ischemic cellular injury, leading to (2) loss of the plasma membrane's ability to maintain electrochemical gradients, which results in (3) an influx of calcium ions and mitochondrial dysfunction, and (4) degradation of plasma membranes and nuclear structures
- The area of coagulative necrosis is composed of denatured proteins and is relatively solid. The coagulated area is then slowly dissolved by proteolytic enzymes.

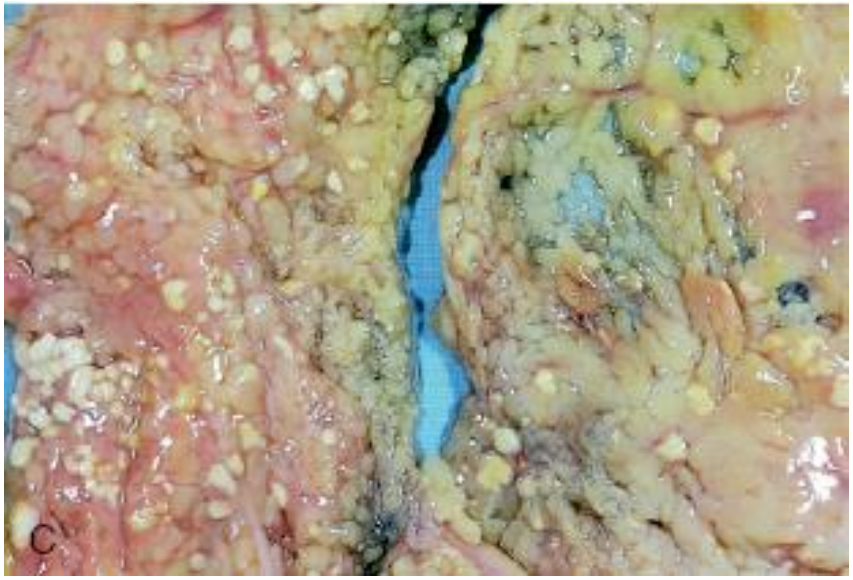
From Kumar V et al: Robbins and Cotran pathologic basis of disease, ed 9, Philadelphia, 2015, Saunders, pp 43–44.)



Liquefactive necrosis

- when the dissolution of dead cells occurs very quickly, a liquefied area of lysosomal enzymes and dissolved tissue may result and form an abscess or cyst
- may be seen in the brain (rich in degradative enzymes and contains little supportive connective tissue)
- Liquefaction may also result from a bacterial infection that triggers a localized collection of phagocytic WBCs (degradative enzymes may completely digest dead cells → liquid debris)

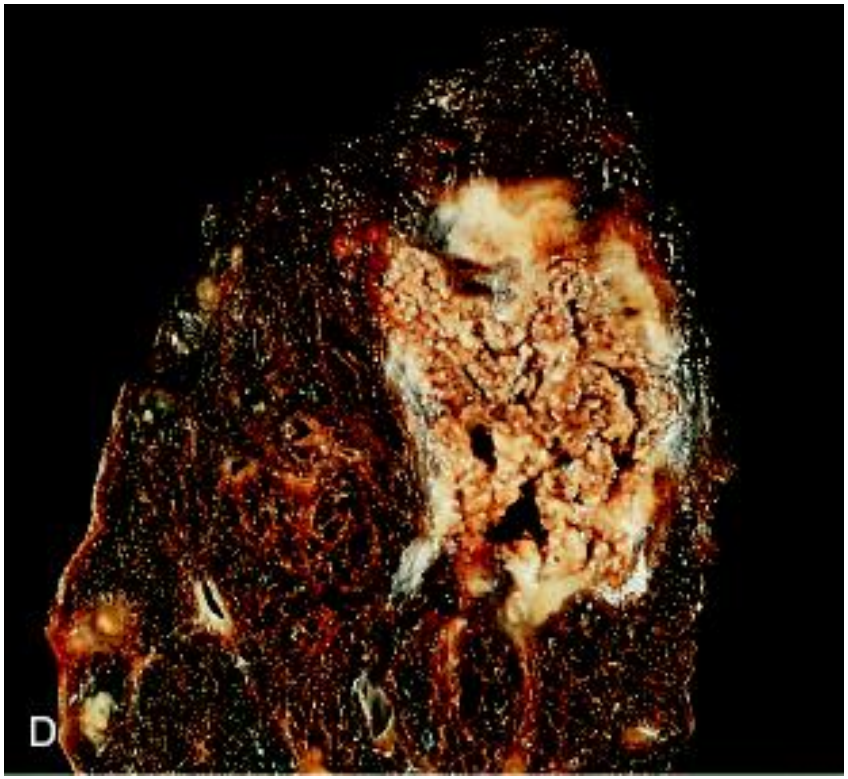
From Kumar V et al: Robbins and Cotran pathologic basis of disease, ed 9, Philadelphia, 2015, Saunders, pp 43–44.)



Fat necrosis

- death of adipose tissue
- usually results from trauma or pancreatitis
- The released activated digestive enzymes from the pancreas or injured tissue attack the cell membranes of fat cells, causing release of their TAG stores. Pancreatic lipase can then hydrolyze the TAG to free fatty acids and glycerol, which precipitate as calcium soaps (saponification).
- Fat necrosis appears as a chalky white area of tissue.

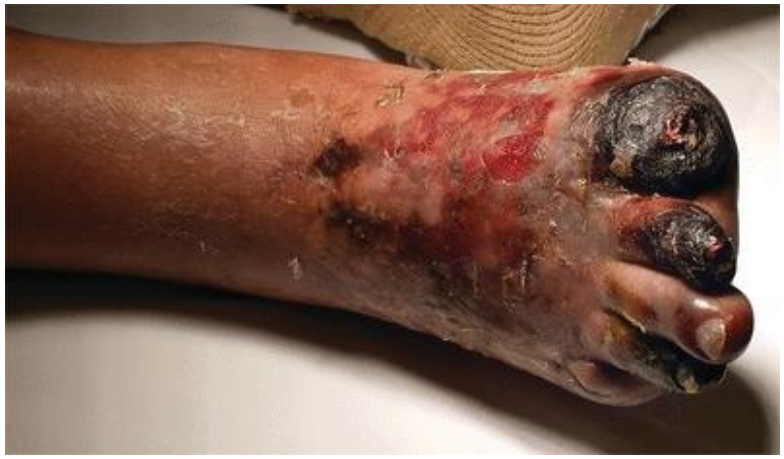
From Kumar V et al: Robbins and Cotran pathologic basis of disease, ed 9, Philadelphia, 2015, Saunders, pp 43–44.)



Caseous necrosis

- is characteristic of lung tissue damaged by tuberculosis
- The areas of dead lung tissue are white, soft, and fragile, resembling clumpy cheese.
- Dead cells are walled off from the rest of the lung tissue by inflammatory WBCs. In the center, the dead cells lose their cellular structure but are not totally degraded.
- Necrotic debris may persist indefinitely.

From Kumar V et al: Robbins and Cotran pathologic basis of disease, ed 9, Philadelphia, 2015, Saunders, pp 43–44.)



Gangrene

- cellular death/necrosis involving a large area of tissue
- may be described as dry, wet, or gas gangrene
- usually results from interruption of the major blood supply to a particular body part, such as the toes, leg, or bowel

Dry gangrene *- a form of coagulative necrosis characterized by blackened, dry, wrinkled tissue separated from adjacent healthy tissue by an obvious line of demarcation (on the extremities)*

Wet gangrene *- typically found in internal organs, appears cold and black, and may be foul smelling because of the invasion of bacteria.*

Gas gangrene *- characterized by the formation of bubbles of gas in damaged tissue. It is the result of infection of necrotic tissue by anaerobic bacteria of the genus Clostridium.*

https://thoracickey.com/wet-gangrene/

Apoptosis

- (from a Greek word „falling off“)
- is cell death resulting from activation of intracellular signaling cascades that activate a cellular suicide response
- requires adequate amounts of ATP be present in the cell
- Apoptotic cells generally do not rupture and are ingested by neighboring cells with minimal disruption of the tissue and without inflammation.
- Apoptosis is not always a pathologic process and occurs as a necessity of development and tissue remodeling.

Apoptosis

Normal physiologic processes that regulate normal system function:

- large numbers of cells are continually undergoing programmed cell death as tissues remodel
- during fetal development, more than half of the nerve cells that form undergo apoptosis
- more than 95% of the T lymphocytes that are generated in the bone marrow are induced to undergo apoptosis after reaching the thymus

Apoptosis

Apoptosis implicated in pathologic cell death and disease:

- the area of tissue death after a myocardial infarction is about 20% necrotic and 80% apoptotic
- death of cancer cells in response to radiation or chemotherapy is believed to be primarily caused by apoptotic mechanisms
- a primary factor in heart failure and dementia
- environmental or extrinsic signals may induce apoptosis
- apoptosis may be triggered by withdrawal of “survival” signals that normally suppress the apoptotic pathways

Apoptosis

- Apoptosis can be triggered by extracellular signals, such as the *Fas* ligand, that bind to the cell and trigger the death cascade through activation of “death receptors.”
- Apoptosis can be triggered by internal pathways. Mitochondrial damage with leakage of cytochrome *c* into the cytoplasm is a critical activator of the intrinsic apoptotic pathway (governed in part by a protein *p53).*
- Apoptosis involves numerous IC signals and enzymes

➢ *Caspases* - a family of enzymes (proenzymes activated in a cascade), the main component of the proteolytic cascade that degrades key IC structures leading to cell death (ATP needed)

Etiology of cellular injury

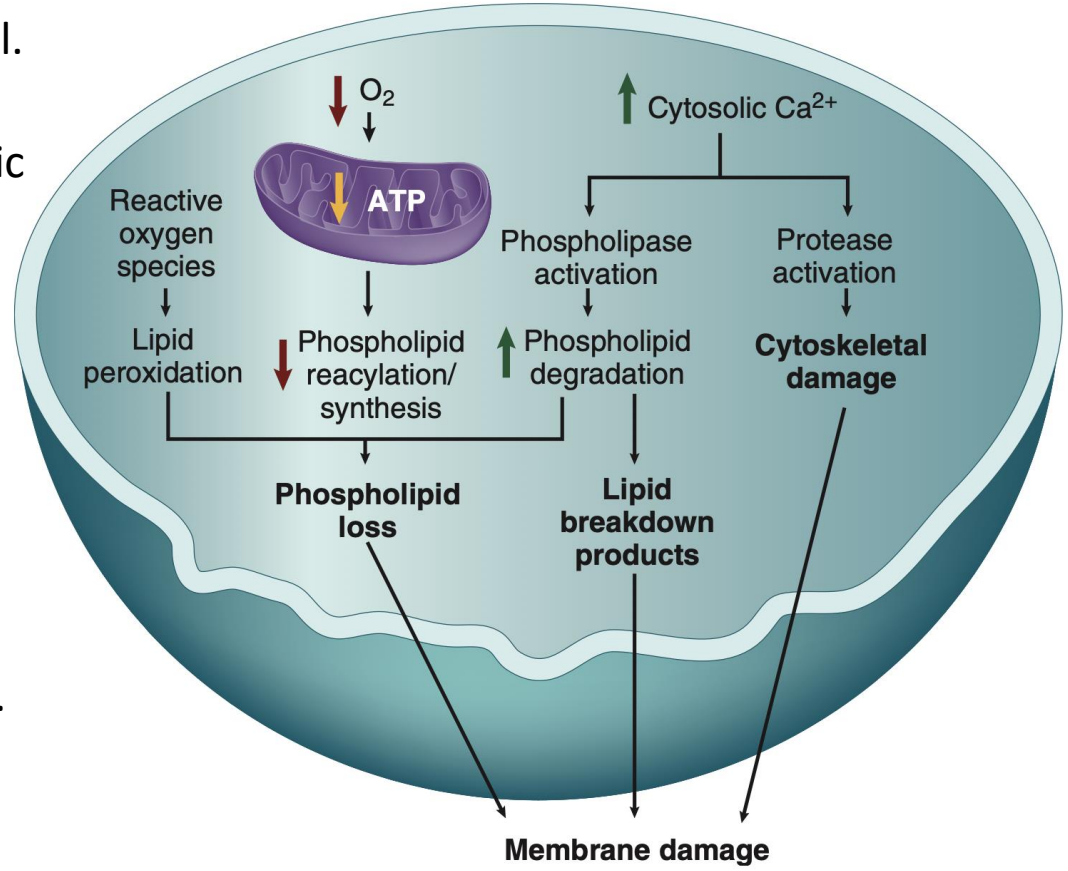
- Ischemia and Hypoxic Injury
- Nutritional Injury
- Infectious and Immunologic Injury
- Chemical Injury
- Physical and Mechanical Injury

Etiology of cellular injury

- **Hypoxia** is an important cause of cell injury that usually results from poor oxygenation of the blood (**hypoxemia**) or inadequate delivery of blood to the cells (**ischemia**).
- **Reperfusion injury** to cells may occur when circulation is restored as a result of the production of partially reduced oxygen molecules that damage cell membranes and trigger immune-mediated injury.

Mechanisms of ischemia-induced cell injury and membrane damage

- Decreased O2 delivery to the mitochondria causes ATP production in the cell to stall and ATP-dependent pumps (Na+–K+ and Ca2+ pumps) to fail.
- Na accumulation within the cell creates an osmotic gradient resulting in hydropic swelling.
- Excess IC Ca collects in the mitochondria, further interfering with mitochondrial function.
- The pyruvate end products of glycolysis accumulate and are converted to lactate, causing cellular acidification. Lactate can escape into the bloodstream, resulting in lactic acidosis. Cellular proteins and enzymes become progressively more dysfunctional as the pH falls.
- When the plasma, mitochondrial, and lysosomal membranes are critically damaged, cell death ensues.



Loss of cell membrane integrity is a critical event in necrosis.

Etiology of cellular injury

- **Nutritional injury** is a common cause of dysfunction and disease. Malnutrition is rampant in many poor countries, whereas industrialized nations are facing an epidemic of obesity-related disorders, including heart disease and diabetes.
- Nutritional deficiencies - result from poor intake, altered absorption, impaired distribution by the circulatory system, or inefficient cellular uptake.
- Common causes of malnutrition include:

  poverty, chronic alcoholism, acute and chronic illness, self-imposed dietary restrictions, malabsorption syndromes.
- Vitamin deficiencies, deficiencies of minerals - common

Vitamins: Major Functions and Deficiency Syndromes

Vitamin	Functions	Deficiency Syndromes
Fat Soluble		
Vitamin A	A component of visual pigment	Night blindness, xerophthalmia, blindness
	Maintenance of specialized epithelia	Squamous metaplasia
	Maintenance of resistance to infection	Vulnerability to infection, particularly measles
Vitamin D	Facilitates intestinal absorption of calcium and phosphorus and mineralization of bone	Rickets in children Osteomalacia in adults
Vitamin E	Major antioxidant; scavenges free radicals	Spinocerebellar degeneration
Vitamin K	Cofactor in hepatic carboxylation of procoagulants—factors II (prothrombin), VII, IX, and X; and protein C and protein S	Bleeding diathesis
Water-Soluble		
Vitamin B_1 (thiamine)	As pyrophosphate, is coenzyme in decarboxylation reactions	Dry and wet beriberi, Wernicke syndrome, Korsakoff syndrome
Vitamin B_2 (riboflavin)	Converted to coenzymes flavin mononucleotide and flavin adenine dinucleotide, cofactors for many enzymes in intermediary metabolism	Ariboflavinosis, cheilosis, stomatitis, glossitis, dermatitis, corneal vascularization
Niacin	Incorporated into NAD and NAD phosphate; involved in a variety of redox reactions	Pellagra—"three D's": dementia, dermatitis, diarrhea
Vitamin B_6 (pyridoxine)	Derivatives serve as coenzymes in many intermediary reactions	Cheilosis, glossitis, dermatitis, peripheral neuropathy
Vitamin B_{12}	Required for normal folate metabolism and DNA synthesis	Megaloblastic pernicious anemia and degeneration of posterolateral spinal cord tracts
	Maintenance of myelinization of spinal cord tracts	
Vitamin C	Serves in many oxidation-reduction (redox) reactions and hydroxylation of collagen	Scurvy
Folate	Essential for transfer and use of 1-carbon units in DNA synthesis	Megaloblastic anemia, neural tube defects
Pantothenic acid	Incorporated in coenzyme A	No nonexperimental syndrome recognized
Biotin	Cofactor in carboxylation reactions	No clearly defined clinical syndrome

Selected Trace Elements and Deficiency Syndromes

Element	Function	Basis of Deficiency	Clinical Features
Zinc	Component of enzymes, principally oxidases	Inadequate supplementation in artificial diets Interference with absorption by other dietary constituents Inborn error of metabolism	Rash around eyes, mouth, nose, and anus called acrodermatitis enteropathica Anorexia and diarrhea Growth retardation in children Depressed mental function Depressed wound healing and immune response Impaired night vision Infertility
Iron	Essential component of hemoglobin as well as a number of iron-containing metalloenzymes	Inadequate diet Chronic blood loss	Hypochromic microcytic anemia
Iodine	Component of thyroid hormone	Inadequate supply in food and water	Goiter and hypothyroidism
Copper	Component of cytochrome *c* oxidase, dopamine β-hydroxylase, tyrosinase, lysyl oxidase, and unknown enzymes involved in cross-linking collagen	Inadequate supplementation in artificial diet Interference with absorption	Muscle weakness Neurologic defects Abnormal collagen cross-linking
Fluoride	Mechanism unknown	Inadequate supply in soil and water Inadequate supplementation	Dental caries
Selenium	Component of glutathione peroxidase Antioxidant with vitamin E	Inadequate amounts in soil and water	Myopathy Cardiomyopathy (Keshan disease)

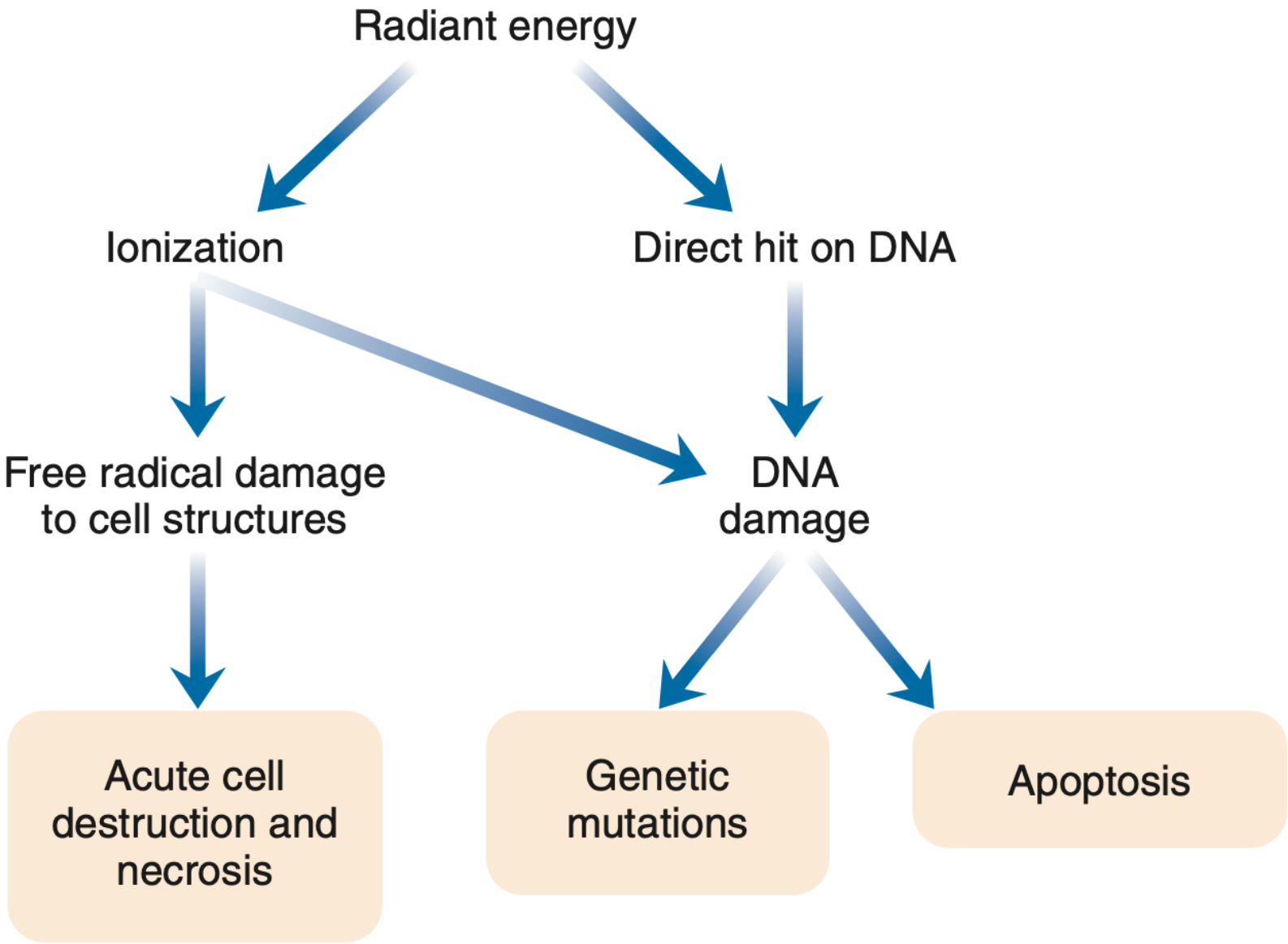
Etiology of cellular injury

- Cellular damage attributable to **infection** and **immunologic responses** is common. Some bacteria and viruses damage cells directly, whereas others stimulate the host's immune system to destroy the host's cells.
- **Chemical, physical, and mechanical factors** cause cell injury in various ways.
- **Chemicals** may interfere with normal metabolic processes in the cell. Some toxic chemicals cause cellular injury directly, whereas others become injurious only when metabolized into reactive chemicals by the body.
- Injury resulting from **physical factors**, such as **burns** and **frostbite**, causes direct destruction of tissues.
- **Radiation-induced** cell death is primarily a result of radiolysis of water, with resulting free radical damage to the cell membrane.

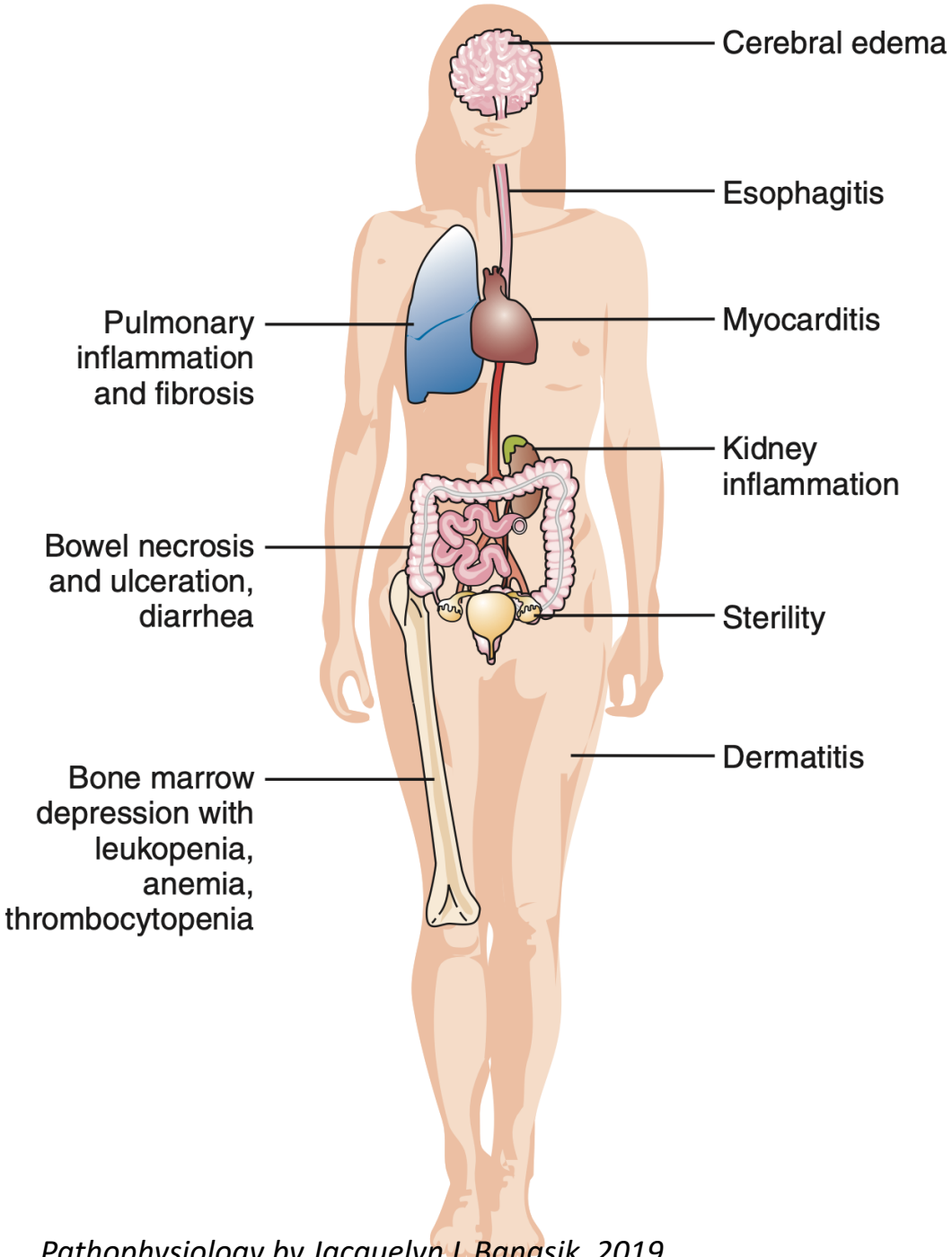
Health Effects of Outdoor Air Pollutants

Pollutant	Populations at Risk	Effects*
Ozone	Healthy adults and children Athletes, outdoor workers Asthmatics	Decreased lung function Increased airway reactivity Lung inflammation Decreased exercise capacity Increased hospitalizations
Nitrogen dioxide	Healthy adults Asthmatics Children	Increased airway reactivity Decreased lung function Increased respiratory infections
Sulfur dioxide	Healthy adults Patients with chronic lung disease Asthmatics	Increased respiratory symptoms Increased mortality Increased hospitalization Decreased lung function
Acid aerosols	Healthy adults Children Asthmatics	Altered mucociliary clearance Increased respiratory infections Decreased lung function Increased hospitalizations
Particulates	Children Individuals with chronic lung or heart disease Asthmatics	Increased respiratory infections Decreased lung function Excess mortality Increased attacks

The mechanism of radiation-induced genetic and cell injury



Pathophysiology by Jacquelyn L Banasik, 2019



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Acute radiation sickness

- Whole-body exposure to sufficiently high levels of radiation (300 rad) results in acute radiation sickness with hematopoietic failure, destruction of the epithelial layer of the gastrointestinal tract, and neurologic dysfunction.
- The high levels of irradiation that cause acute radiation sickness are associated with events such as nuclear accidents and bombings.

Cellular Aging

- Aging is theoretically distinct from disease. The maximal lifespan is limited by the aging process itself rather than by the ravages of disease.
- Aging is thought to be the result of accumulated DNA damage, decreased proliferative capacity of stem cells, and accumulated metabolic damage. Cells may age more quickly when DNA repair mechanisms are faulty and when metabolic damage is excessive because of reduced antioxidant activity.
- Age-related changes in body systems can generally be described as a decrease in functional reserve and a reduced ability to adapt to environmental demands.

Overview of the Physiologic Changes of Aging

System	Physiologic Changes
Cardiovascular	↓ Vessel elasticity caused by calcification of connective tissue (↑ pulmonary vascular resistance)
	↓ Number of heart muscle fibers with ↑ size of individual fibers (hypertrophy)
	↓ Filling capacity
	↓ Stroke volume
	↓ Sensitivity of baroreceptors
	Degeneration of vein valves
Respiratory	↓ Chest wall compliance resulting from calcification of costal cartilage
	↓ Alveolar ventilation
	↓ Respiratory muscle strength
	Air trapping and ↓ ventilation due to degeneration of lung tissue (↓ elasticity)
Renal/urinary	↓ Glomerular filtration rate due to nephron degeneration (↓ one third to one half by age 70)
	↓ Ability to concentrate urine
	↓ Ability to regulate H+ concentration
Gastrointestinal	↓ Muscular contraction
	↓ Esophageal emptying
	↓ Bowel motility
	↓ Production of HCl, enzymes, and intrinsic factor
	↓ Hepatic enzyme production and metabolic capacity
	Thinning of stomach mucosa

System	Physiologic Changes
Neurologic/sensory	Nerve cells degenerate and atrophy
	↓ Of 25%–45% of neurons
	↓ Number of neurotransmitters
	↓ Rate of conduction of nerve impulses
	Loss of taste buds
	Loss of auditory hair cells and sclerosis of eardrum
Musculoskeletal	↓ Muscle mass
	↑ Bone demineralization
	↑ Joint degeneration, erosion, and calcification
Immune	↓ Inflammatory response
	↓ In T cell function due to involution of thymus gland
Integumentary	↓ Subcutaneous fat
	↓ Elastin
	Atrophy of sweat glands
	Atrophy of epidermal arterioles causing altered temperature regulation

Pathophysiology by Jacquelyn L Banasik, 2019

Somatic Death

- Somatic death is characterized by the absence of respirations and heartbeat. Definitions of brain death have been established to describe death in instances in which heartbeat and respiration are maintained mechanically.
- After death, body temperature falls, blood and body fluids collect in dependent areas, and rigor mortis ensues. Within 24 to 48 hours the tissues begin to deteriorate and rigor mortis gives way to flaccidity.
- Criteria for determining brain death as proof of somatic death include: unresponsiveness, flaccidity, absence of brainstem reflexes (e.g., swallowing, gagging, pupil and eye movements), absence of respiratory effort, absence of electrical brain waves, and lack of cerebral blood flow.

Summary

- Cells and tissues face many challenges to survival, including injury from lack of oxygen and nutrients, infection and immune responses, chemicals, and physical and mechanical factors.
- Cells respond to environmental changes or injury in three general ways:
  - (1) If the change is mild or short lived, the cell may withstand the assault and return to its preinjury status.
  - (2) The cell may adapt to a persistent but sublethal injury by changing its structure or function.
  - (3) Cell death by apoptosis or necrosis may occur if the injury is too severe or prolonged.
- Characteristics of reversible cell injury include hydropic swelling and the accumulation of abnormal substances.

Summary (cont.)

- Cell necrosis is characterized by irreversible loss of function, release of internal cellular components into the bloodstream, and an inflammatory response. The disruption of the permeability barrier of the plasma membrane is a critical event in necrotic cellular death.
- Apoptosis is characterized by a tidy, noninflammatory autodigestion of the cell.
- Aging is a normal physiologic process characterized by a progressive decline in functional capacity and adaptive ability. Several theories have been proposed to explain certain aspects of the aging process. At present, most sources differentiate between the biological alterations of aging and the alterations consequent to disease processes.

Evidence-based medicine

- **evidence-based practice** - the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

Levels of Evidence