PTM 4210 CELL INJURY

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DEPARTMENT OF PATHOLOGY AND MICROBIOLOGY

Content

- Pathology explained
- PTM 4210
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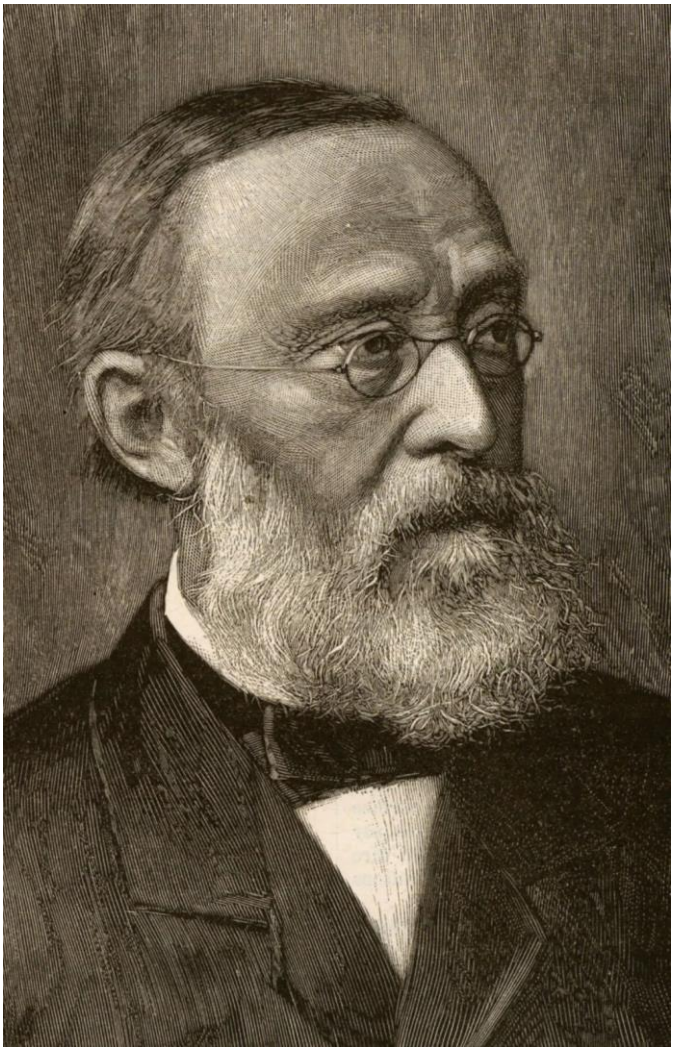
Pathology explained



Patholog y explained

How do we understand disease?

Pathology

Pathos: suffering=disease Logos: study

Pathology is the study of disease

1. Clinical manifestations
2. Underlying mechanisms, biochemical and molecular changes, morphologic and functional changes that underlie disease

We then can find cures, remedies, treatments and methods of prevention

PTM 4210

- Compliments and complimented by other courses like microbiology
- Three components
- Chemical pathology: Diabetes, endocrine disorders etc
- Haematology: Blood: normal and disease
- Red blood cells: *Sickle cell disease*
- White blood cells: *Leukemias* (increase in WBC) and *Lymphomas*
- Platelets
- Clotting factors: Haemophilia
- General and *Systemic* Pathology: *Histopathology*
- *Morphology: How things look=disease*
- *Gross level: naked eye*
- *Microscope: light microscope and electron microscope*

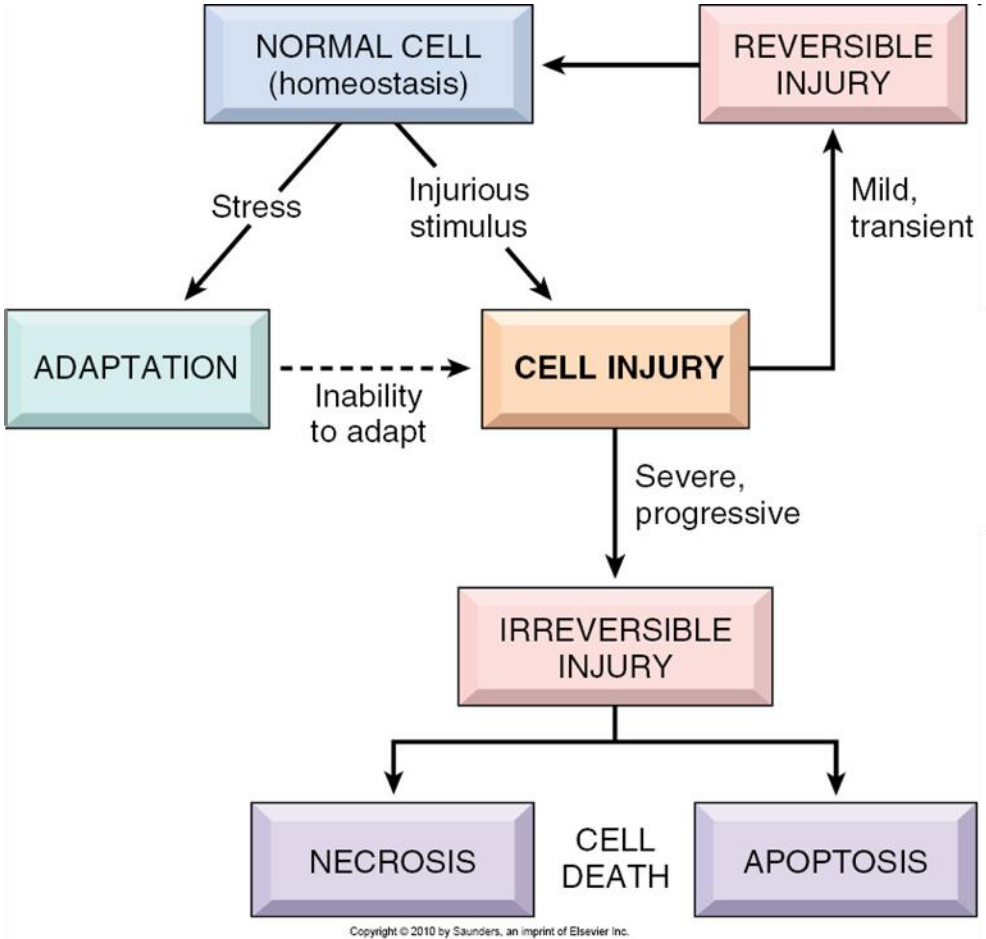
- *Molecular: Breast cancer oestrogen ER, BRCA-1*

Cellular Injury, Necrosis, Apoptosis

ADOPTED: www.life.illinois.edu

Cell injury results when cells are stressed and can no longer adapt

Injury may progress through a reversible stage



Reversible Cell Injury

Reduced oxidative phosphorylation with resultant depletion of energy stores in the form of adenosine triphosphate (ATP)

Cellular swelling caused by changes in ion concentrations and water influx

Cell Death

Necrosis- pathologic

Damage to membranes is severe, lysosomal enzymes enter the cytoplasm and digest the cell, and cellular contents leak out

Apoptosis- normal and pathologic

DNA or proteins are damaged beyond repair, the cell kills itself characterized by nuclear dissolution, fragmentation of the cell without complete loss of membrane integrity

Autophagy- normal and pathologic

Causes of Cell Injury

Oxygen Deprivation

Hypoxia is a deficiency of oxygen that can result in a reduction in aerobic oxidative respiration. Extremely important common cause of cell injury/cell death.

Causes include reduced blood flow (ischemia), inadequate oxygenation of the blood, decreased blood oxygen-carrying capacity.

Physical Agents

Mechanical trauma, extremes of temperature (burns and deep cold), sudden changes in atmospheric pressure, radiation, and electric shock.

Chemical Agents and Drugs

Infectious Agents

Immunologic Reactions

Genetic Derangements

Nutritional Imbalances

Protein-calorie and/or vitamin deficiencies. Nutritional excesses (overnutrition)

Morphology of Cell Injury

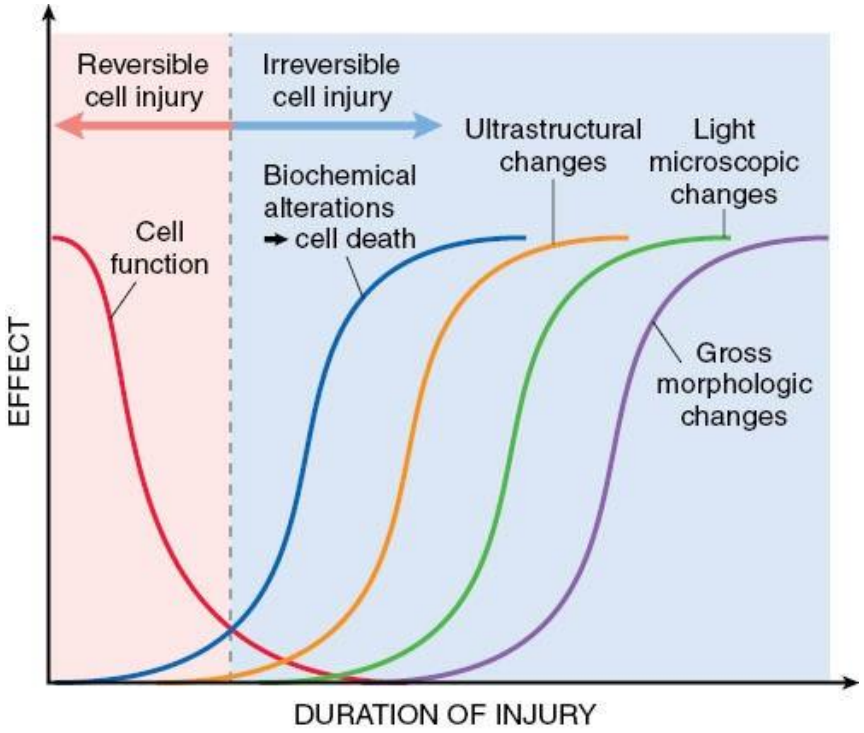


FIGURE 1–7 Sequential development of biochemical and morphologic changes in cell injury. Cells may become rapidly nonfunctional after the onset of injury, although they are still viable, with potentially reversible damage; a longer duration of injury may eventually lead to irreversible injury and cell death. Note that irreversible biochemical alterations may cause cell death, and typically this precedes ultrastructural, light microscopic, and grossly visible morphologic changes.

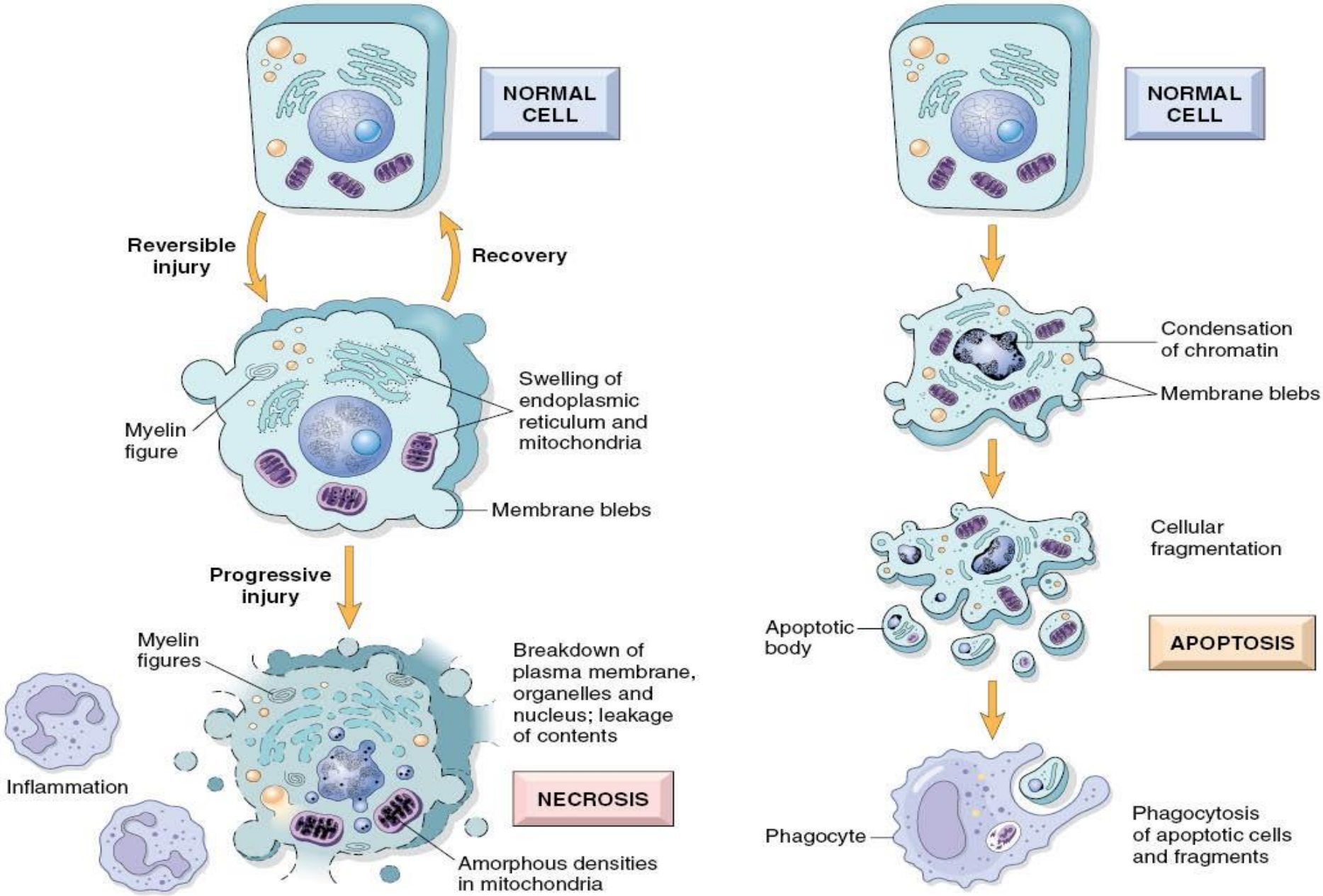
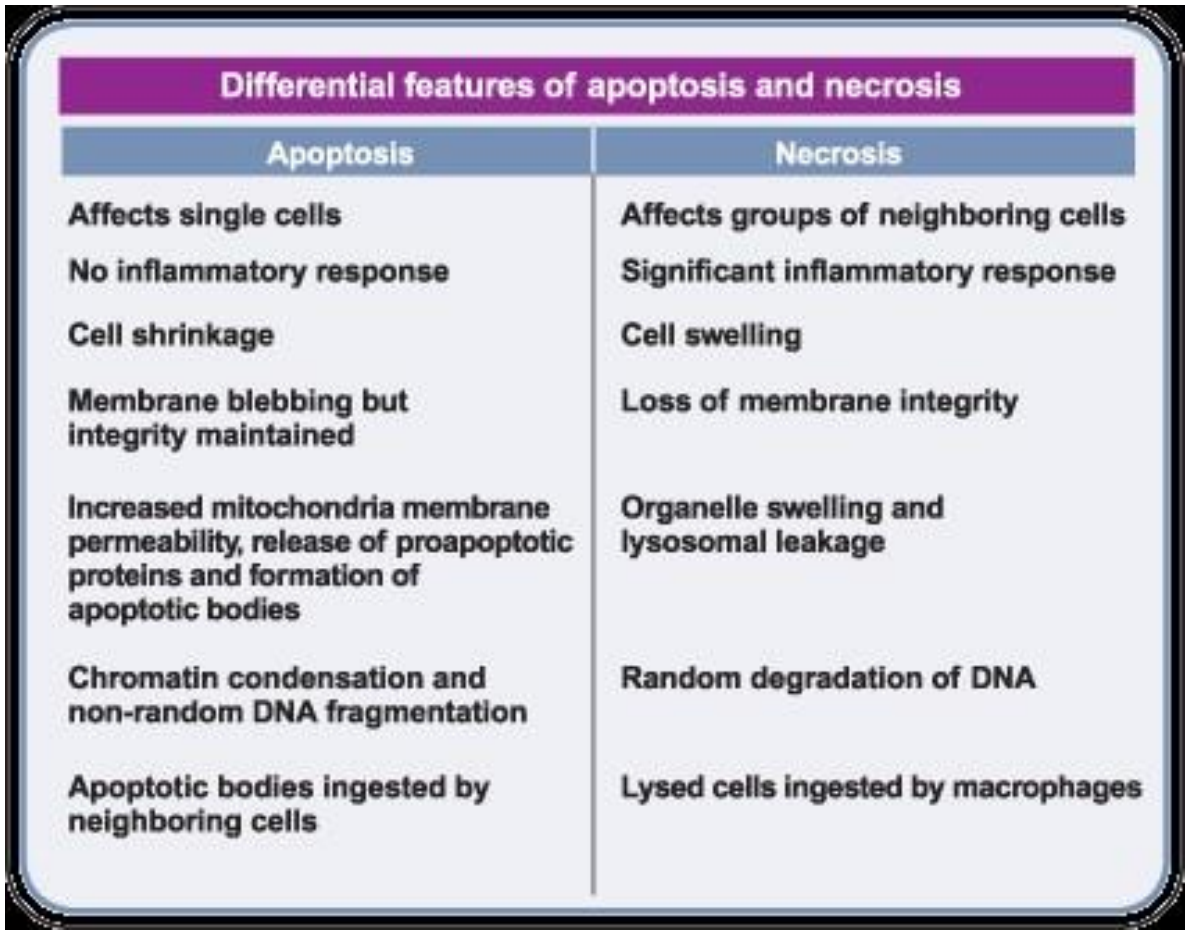


FIGURE 1–8 Schematic illustration of the morphologic changes in cell injury culminating in necrosis or apoptosis.

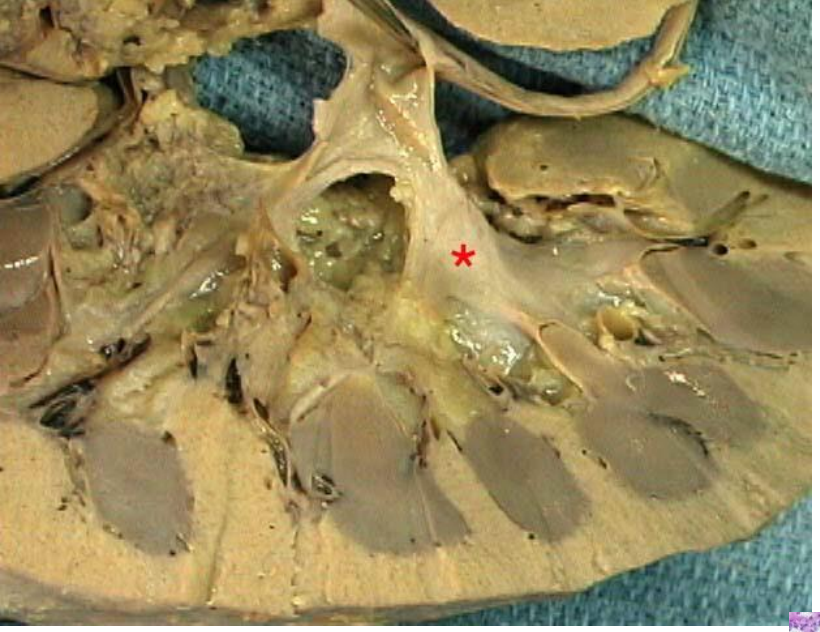
TABLE 1-2 -- Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage



http://www.biooncology.com/research-education/apoptosis/images/critical_table_1_1.gif

Normal Kidney



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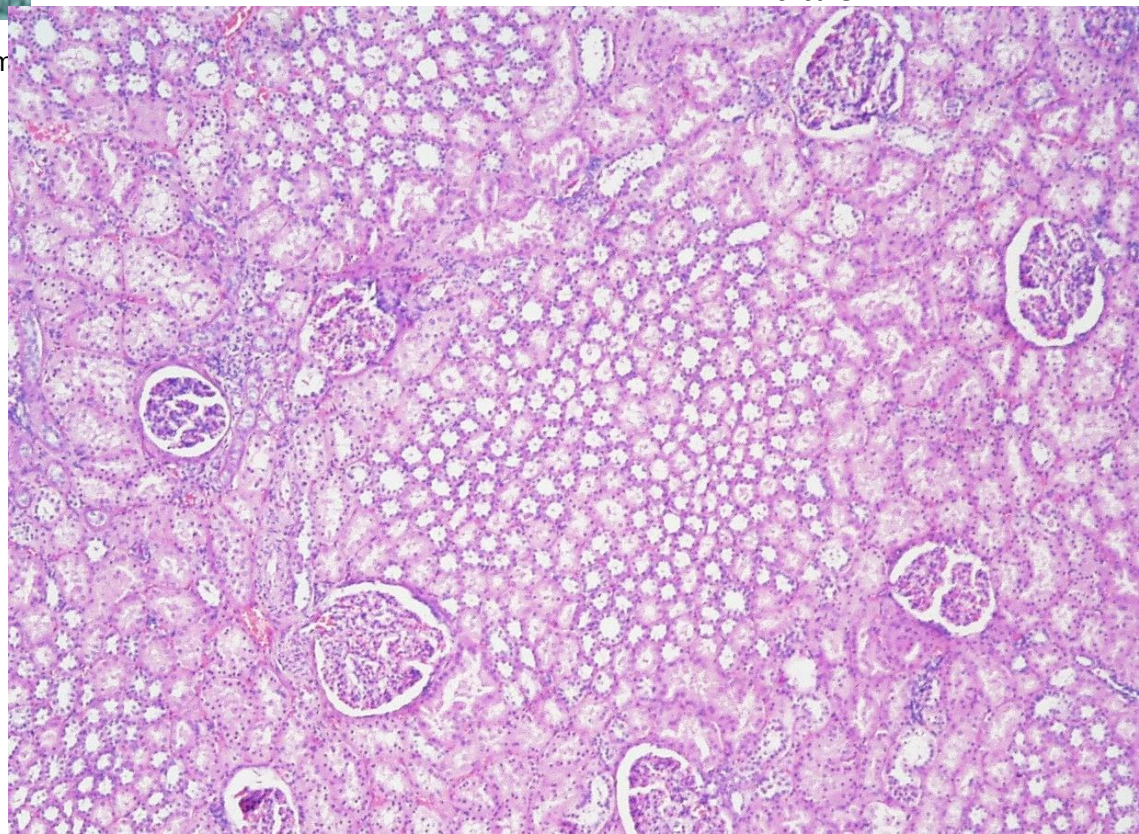
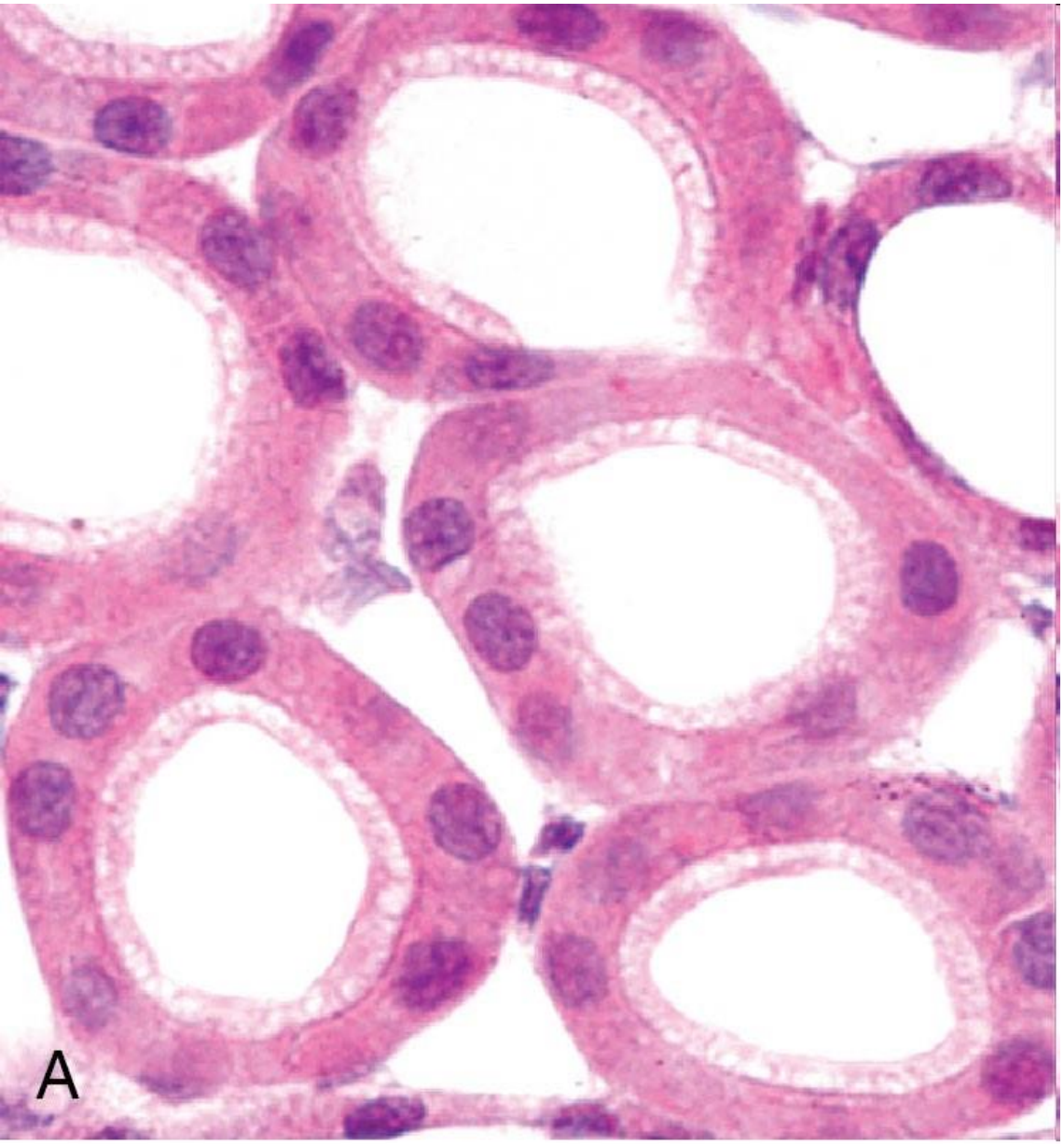


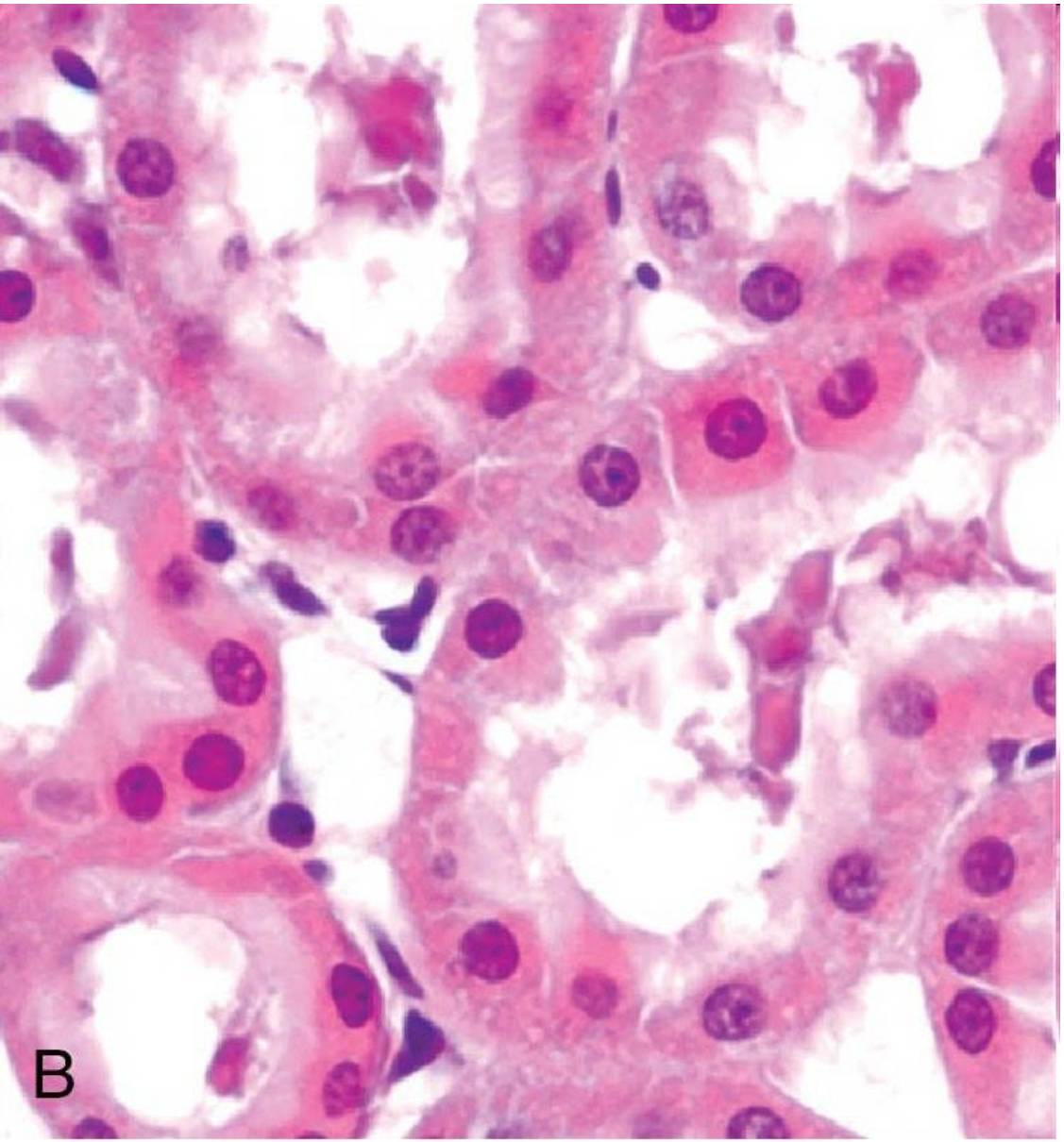
Normal kidney tubules



(Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, TX.)

- Epithelial cells stain evenly pink (eosinophilic) in cytoplasm, with purple, basophilic, nucleic acids confined to the nuclei
- Apical surfaces are ciliated
- Interstitia not infiltrated with immune cells nor congested with proteins

Swollen kidney tubules

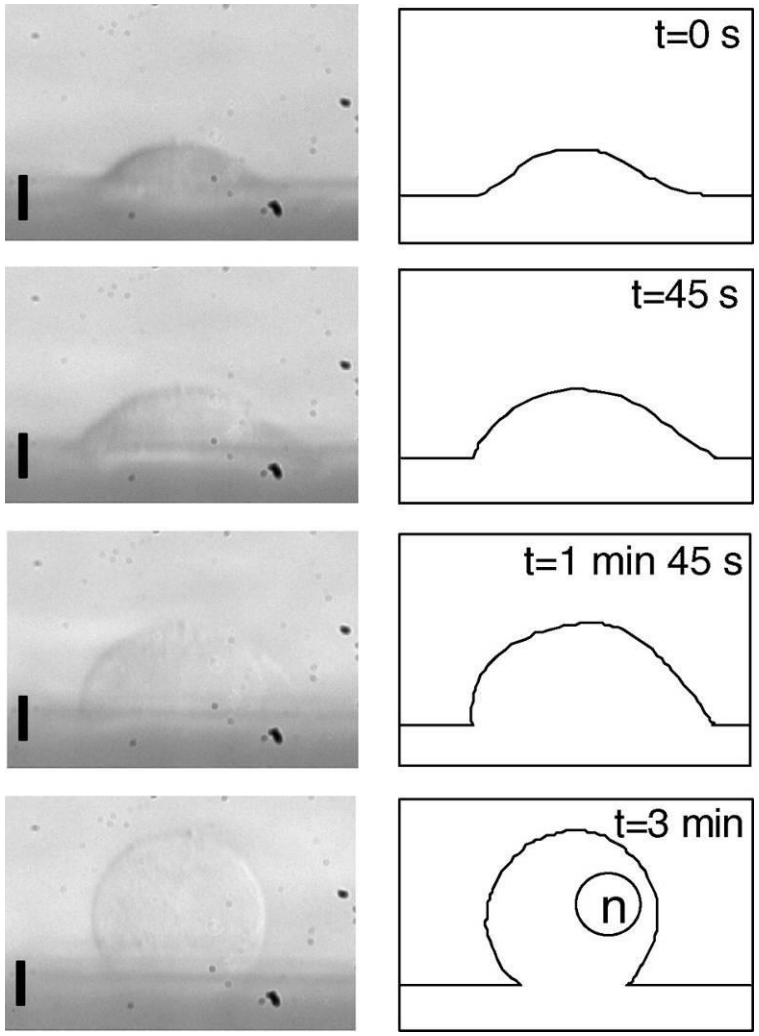


(Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, TX.)

- Increased eosinophilic staining
- Decreased basophilic staining (RNA)
- Plasma membrane rounding, blebbing, loss of cilia, due to loss of connections with cytoskeleton
- Integrity of tubules degrading, but basement membranes i ntact

- Nuclei largely intact, slightly narrowed, pyknotic

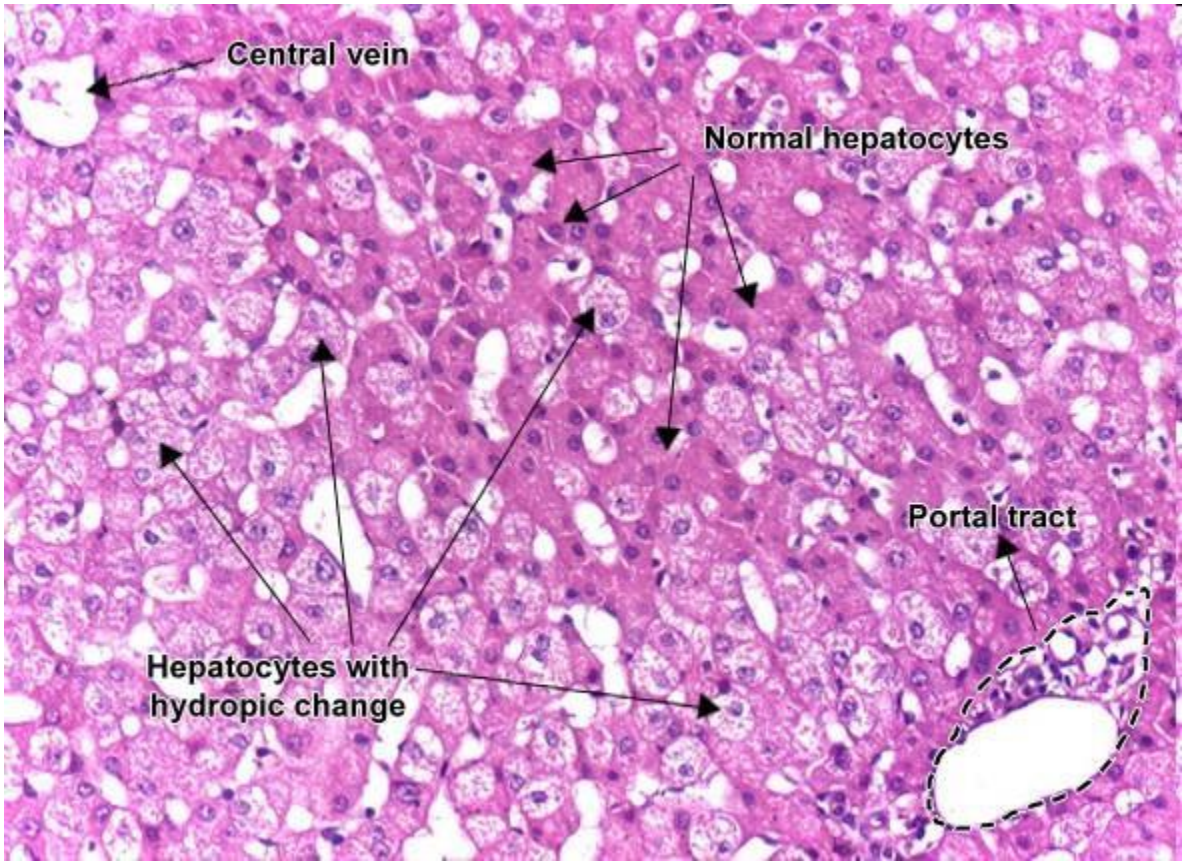
How much can a cell swell?



Boudreault F , Grygorczyk R J Physiol 2004;561:499-513

The Journal of Physiology
A publication of The Physiological Society

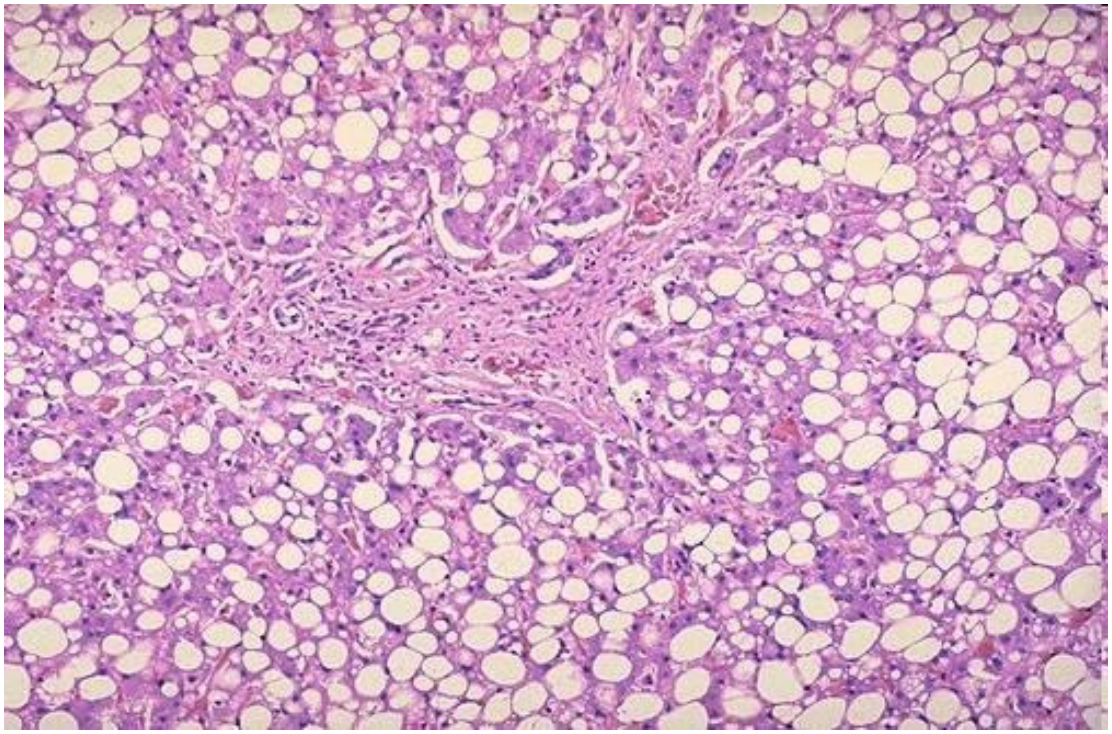
Reversible damage – cellular swelling



Cellular swelling (synonyms: hydropic change, vacuolar degeneration, cellular edema) is an acute reversible change resulting as a response to nonlethal injuries. It is an intracytoplasmic accumulation of water due to incapacity of the cells to maintain the ionic and fluid homeostasis. It is easy to be observed in

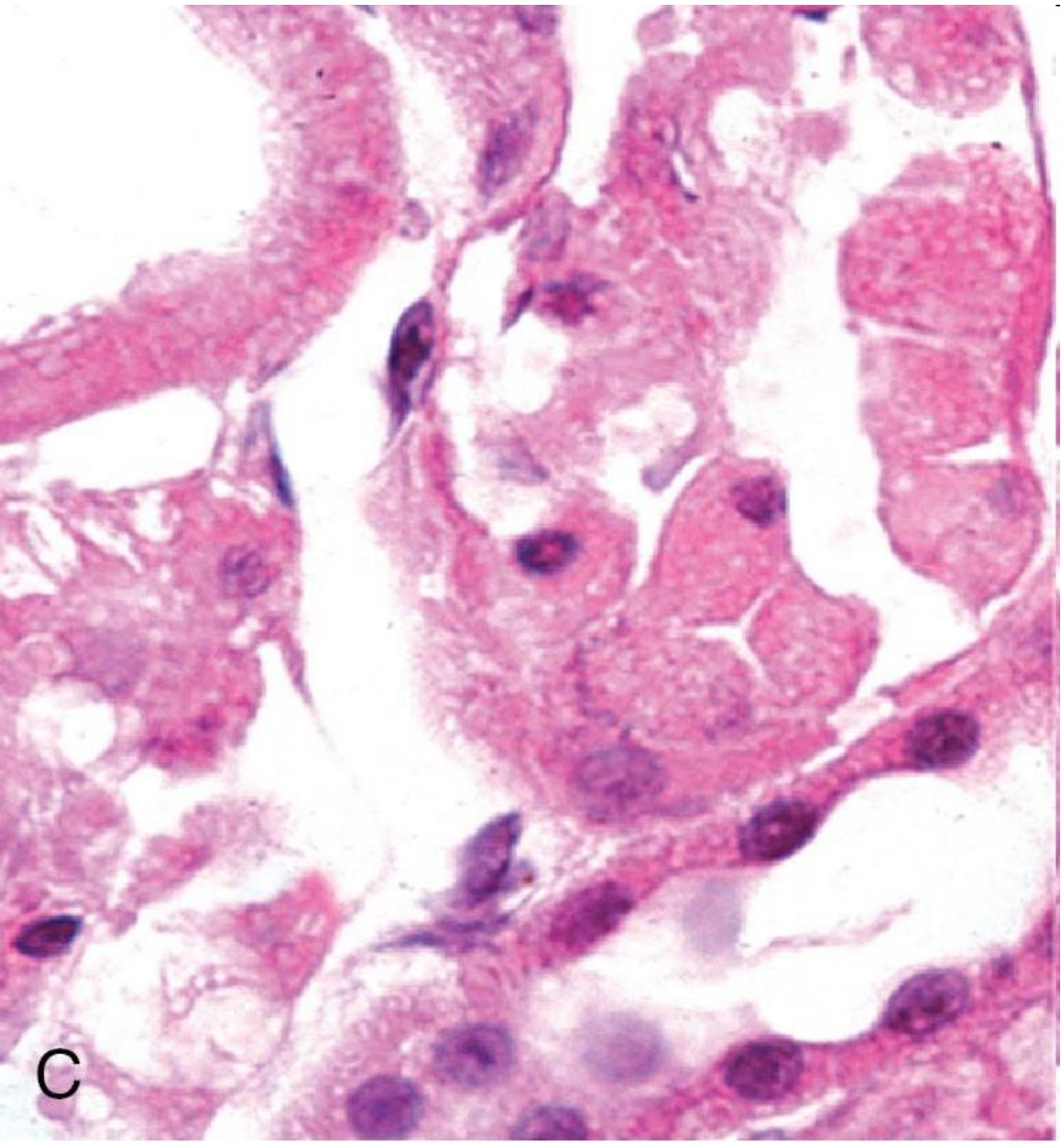
parenchymal organs : liver (hepatitis, hypoxia), kidney (shock), myocardium (hypoxia, phosphate intoxication). It may be local or diffuse, affecting the whole organ.

Reversible damage – fatty change



Intracellular accumulations of a variety of materials can occur in response to cellular injury. Here is fatty metamorphosis (fatty change) of the liver in which deranged lipoprotein transport from injury (most often alcoholism) leads to accumulation of lipid in the cytoplasm of hepatocytes.

Necrotic kidney tubules



(Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, TX.)

- Cellular fragmentation
- Loss and fading of nuclei--karyolysis
- Burst membranes
- Loss of tissue architecture

Necrosis

The morphologic appearance of necrosis is the result of denaturation of

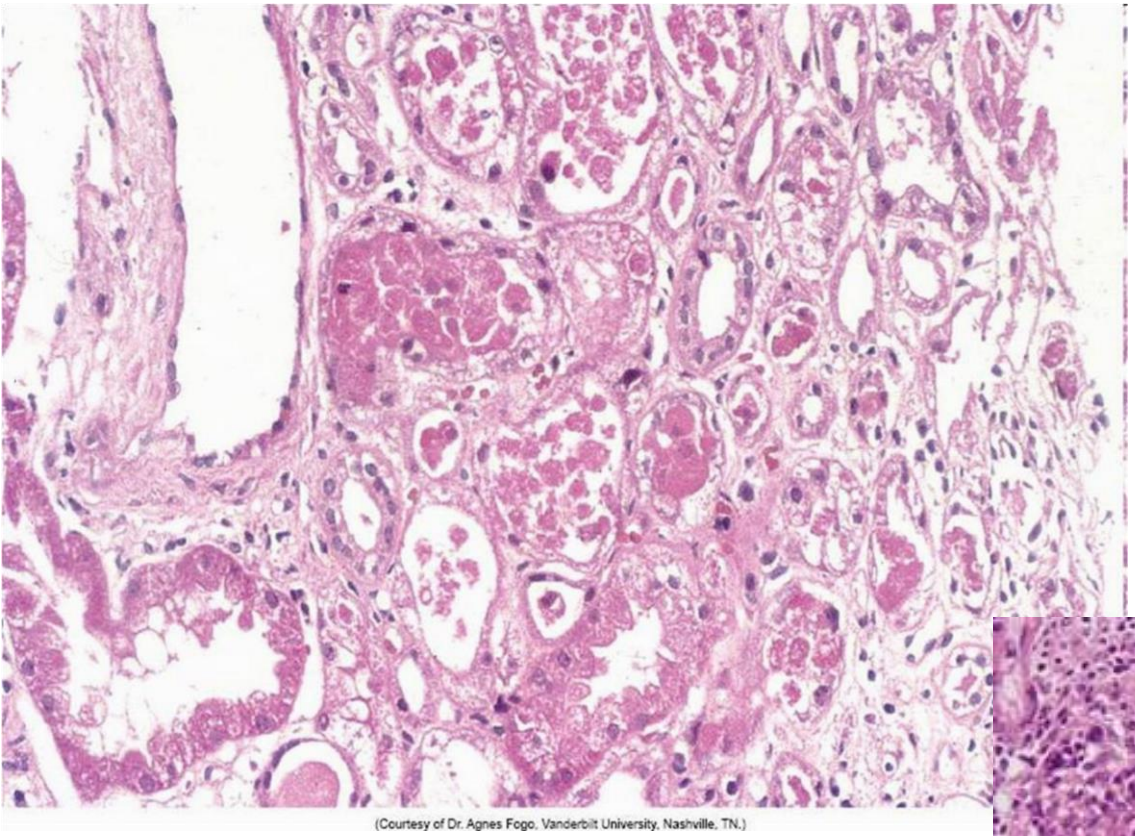
intracellular proteins and enzymatic digestion.

Necrotic cells are unable to maintain membrane integrity and their contents often leak out, a process that may elicit inflammation in the surrounding tissue.

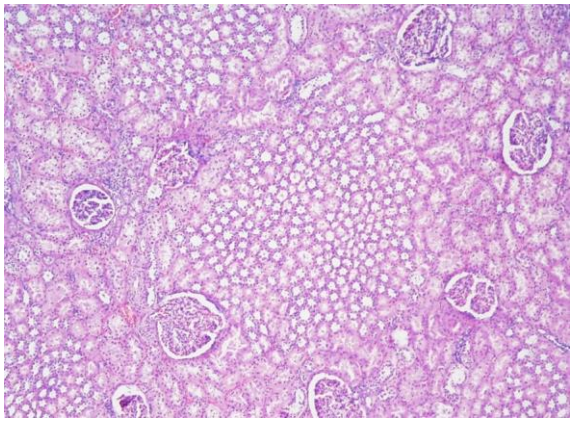
The enzymes that digest the necrotic cell are derived from the lysosomes of the dying cells themselves and from the lysosomes of leukocytes that are called in as part of the inflammatory reaction.

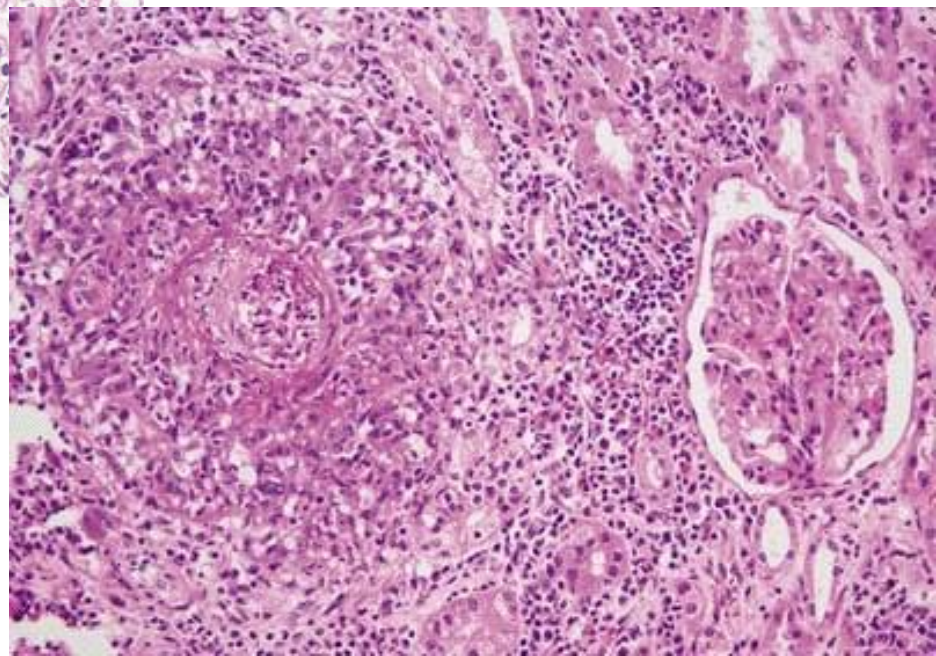
Digestion of cellular contents and the host response may take hours to develop. The earliest histologic evidence of necrosis may not become apparent until 4 to 12 hours.

Necrotic and regenerating tubular epithelia after kidney injury



(Courtesy of Dr. Agnes Fogo, Vanderbilt University, Nashville, TN.)





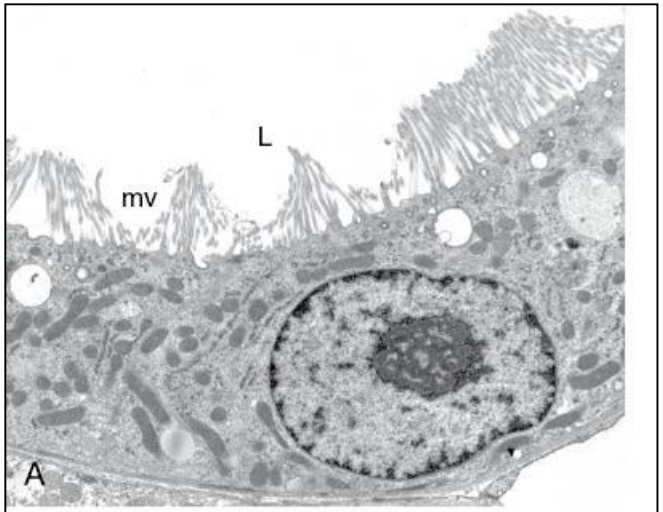


FIGURE 1–10A Ultrastructural features of reversible and irreversible cell injury (necrosis) in a rabbit kidney. **A,** Electron micrograph of a normal epithelial cell of the proximal kidney tubule. Note abundant microvilli (mv) lining the luminal surface (L). **B,** Epithelial cell of the proximal tubule showing early cell injury resulting from reperfusion following ischemia. The microvilli are lost and have been incorporated in apical cytoplasm; blebs have formed and are extruded in the lumen. Mitochondria would have been swollen during ischemia; with reperfusion, they rapidly undergo condensation and become electron-dense. **C,** Proximal tubular cell showing late injury, expected to be irreversible. Note the markedly swollen mitochondria containing electron-dense deposits, expected to contain precipitated calcium and proteins. Higher magnification micrographs of the cell would show disrupted plasma membrane and swelling and fragmentation of organelles.

(Courtesy of Dr. Brigitte Kaisslin, Institute of Anatomy, University of Zurich, Switzerland.)

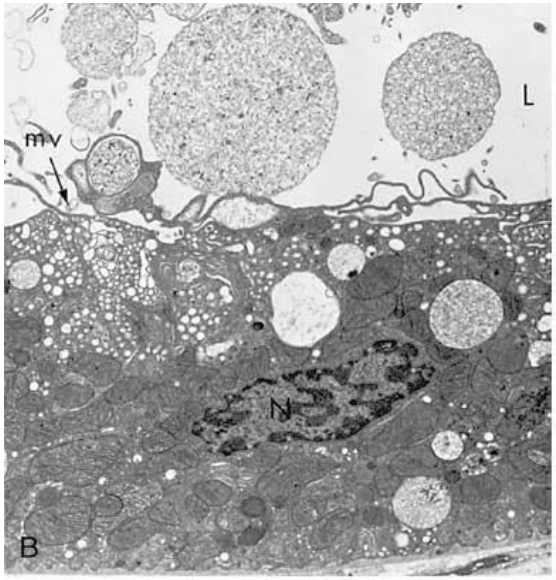


FIGURE 1–10B Ultrastructural features of reversible and irreversible cell injury (necrosis) in a rabbit kidney. **A,** Electron micrograph of a normal epithelial cell of the proximal kidney tubule. Note abundant microvilli (mv) lining the luminal surface (L). **B,** Epithelial cell of the proximal tubule showing early cell injury resulting from reperfusion following ischemia. The microvilli are lost and have been incorporated in apical cytoplasm; blebs have formed and are extruded in the lumen. Mitochondria would have been swollen during ischemia; with reperfusion, they rapidly undergo condensation and become electron-dense. **C,** Proximal tubular cell showing late injury, expected to be irreversible. Note the markedly swollen mitochondria containing electron-dense deposits, expected to contain precipitated calcium and proteins. Higher magnification micrographs of the cell would show disrupted plasma membrane and swelling and fragmentation of organelles.

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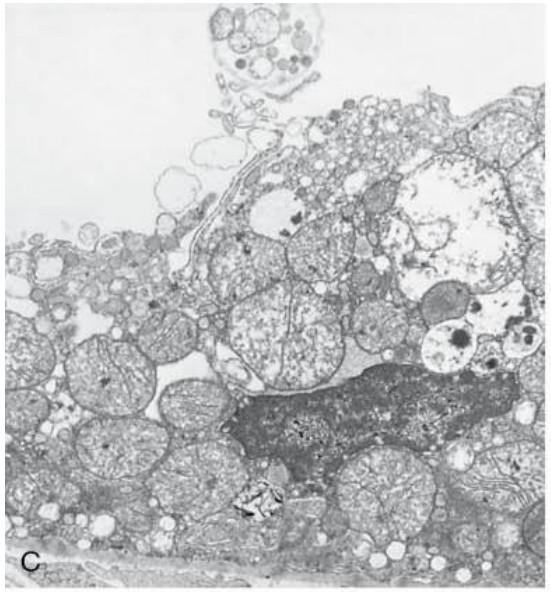


FIGURE 1–10C Ultrastructural features of reversible and irreversible cell injury (necrosis) in a rabbit kidney. **A,** Electron micrograph of a normal epithelial cell of the proximal kidney tubule. Note abundant microvilli (mv) lining the luminal surface (L). **B,** Epithelial cell of the proximal tubule showing early cell injury resulting from reperfusion following ischemia. The microvilli are lost and have been incorporated in apical cytoplasm; blebs have formed and are extruded in the lumen. Mitochondria would have been swollen during ischemia; with reperfusion, they rapidly undergo condensation and become electron-dense. **C,** Proximal tubular cell showing late injury, expected to be irreversible. Note the markedly swollen mitochondria containing electron-dense deposits, expected to contain precipitated calcium and proteins. Higher magnification micrographs of the cell would show disrupted plasma membrane and swelling and fragmentation of organelles.

(Courtesy of Dr. M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, TX.)

Necrosis- cytoplasm

Increased eosinophilia in hematoxylin and eosin (H & E) stains, attributable in part to the loss of cytoplasmic RNA (which binds the blue dye, hematoxylin) and in part to denatured cytoplasmic proteins (which bind the red dye, eosin).

When enzymes have digested the cytoplasmic organelles, the cytoplasm becomes vacuolated and appears moth-eaten.

Dead cells may be replaced by large, whorled phospholipid masses called myelin figures that are derived from damaged cell membranes.

These phospholipid precipitates are then either phagocytosed by other cells or further degraded into fatty acids; calcification of such fatty acid residues results in the generation of calcium soaps. Thus, the dead cells may ultimately become calcified.

Necrosis- nucleus

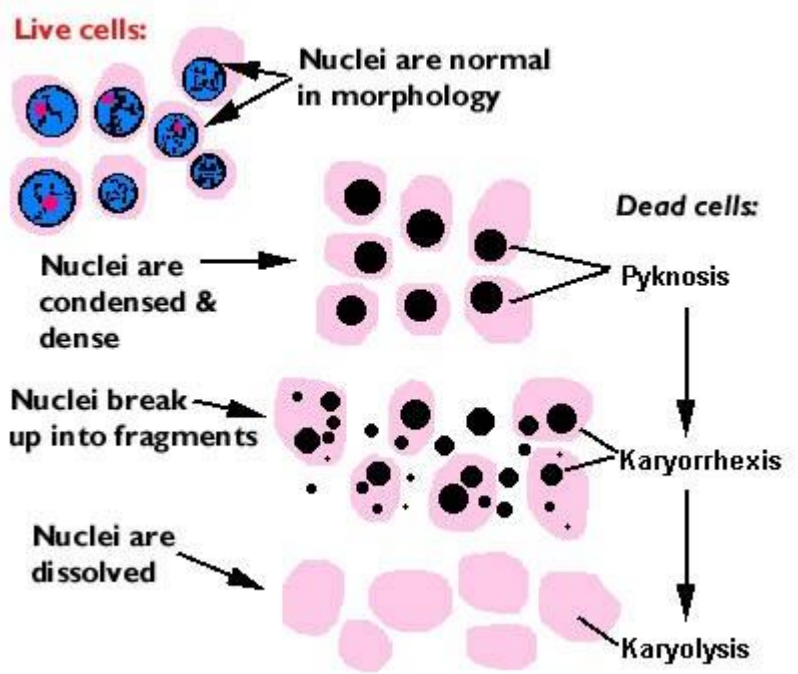
Nuclear changes

Pyknosis, characterized by nuclear shrinkage and increased basophilia.

Karyorrhexis, the pyknotic nucleus undergoes fragmentation. With the passage of time (a day or two), the nucleus in the necrotic cell totally disappears.

Karyolysis, the basophilia of the chromatin fades which appears to reflect loss of DNA because of enzymatic degradation by due to endonucleases.

http://www.vetmed.vt.edu/education/Curriculum/VM8304/vet%20pathology/CASES/CELLINJURY2/karyorrhexdiag%20copy.JPG



Patterns of Tissue Necrosis

When large numbers of cells die the tissue or organ is said to be necrotic

Necrosis of tissues has several morphologically distinct patterns, which are important to recognize because they may provide clues about the underlying cause.

The terms that describe these patterns are somewhat outmoded, they are used often and their implications are understood by pathologists and clinicians.

"Types" of Tissue necrosis

- Coagulative

- Liquefactive
- Gangrenous
- Caseous
- Fat
- Fibrinoid

Coagulative Necrosis

Architecture of dead tissues is preserved for a span of at least some days.

Tissues exhibit a firm texture

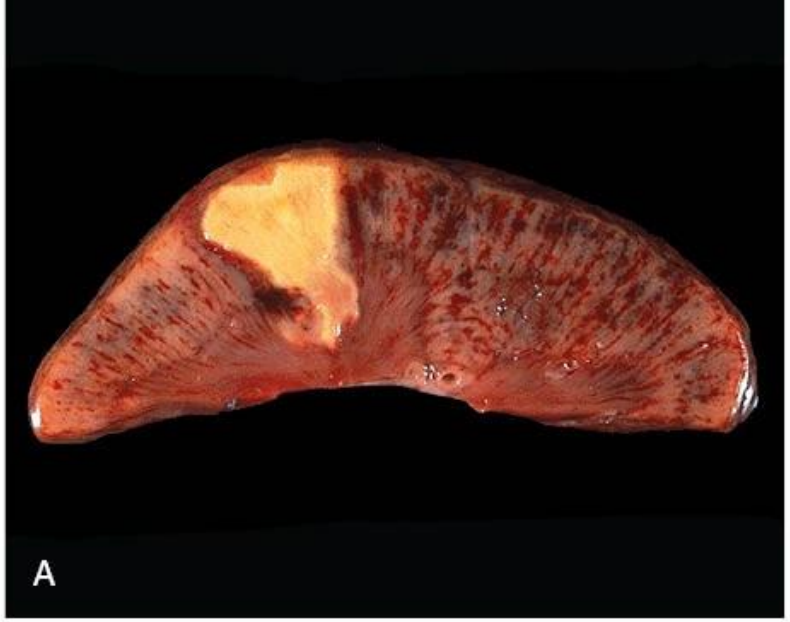


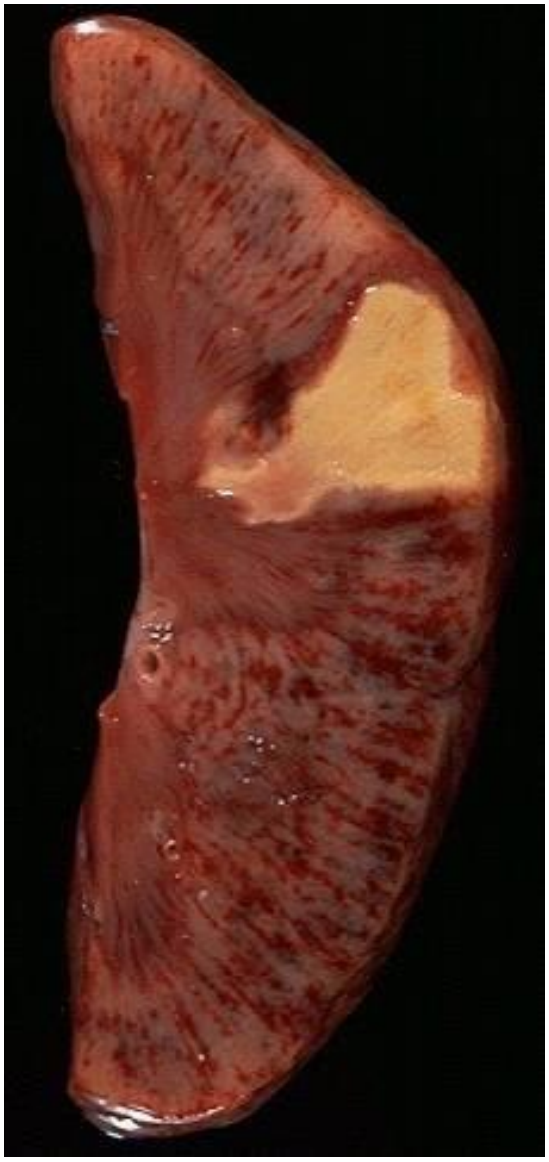
FIGURE 1–11A Coagulative necrosis. **A,** A wedge-shaped kidney infarct (yellow). **B,** Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I) showing preserved cellular outlines with loss of nuclei and an inflammatory infiltrate (which is difficult to discern at this magnification).

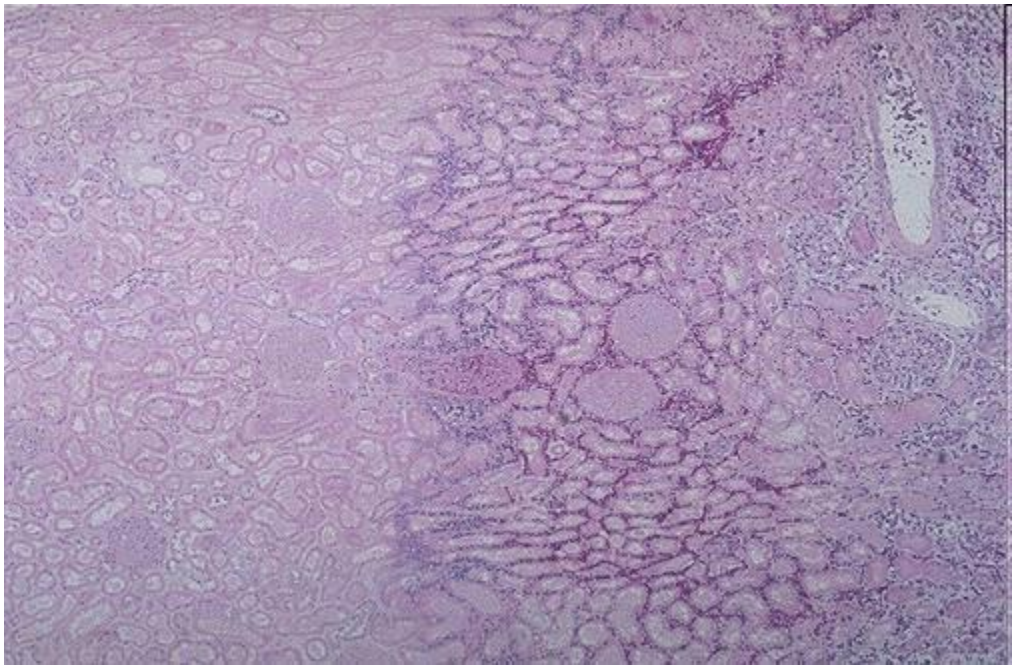
Injury denatures proteins and enzymes blocking proteolysis of the dead cells;

Eosinophilic, anucleate cells may persist for days or weeks.

Ultimately the necrotic cells are removed by phagocytosis of the cellular debris by infiltrating leukocytes.

Coagulative necrosis—kidney infarction





This is the typical pattern with ischemia and infarction (loss of blood supply and resultant tissue anoxia). Here, there is a wedge-shaped pale area of coagulative necrosis (infarction) in the renal cortex of the kidney. Microscopically, the renal cortex has undergone anoxic injury at the left so that the cells appear pale and ghost-like. There is a hemorrhagic zone in the middle where the cells are dying or have not quite died, and then normal renal parenchyma at the far right.

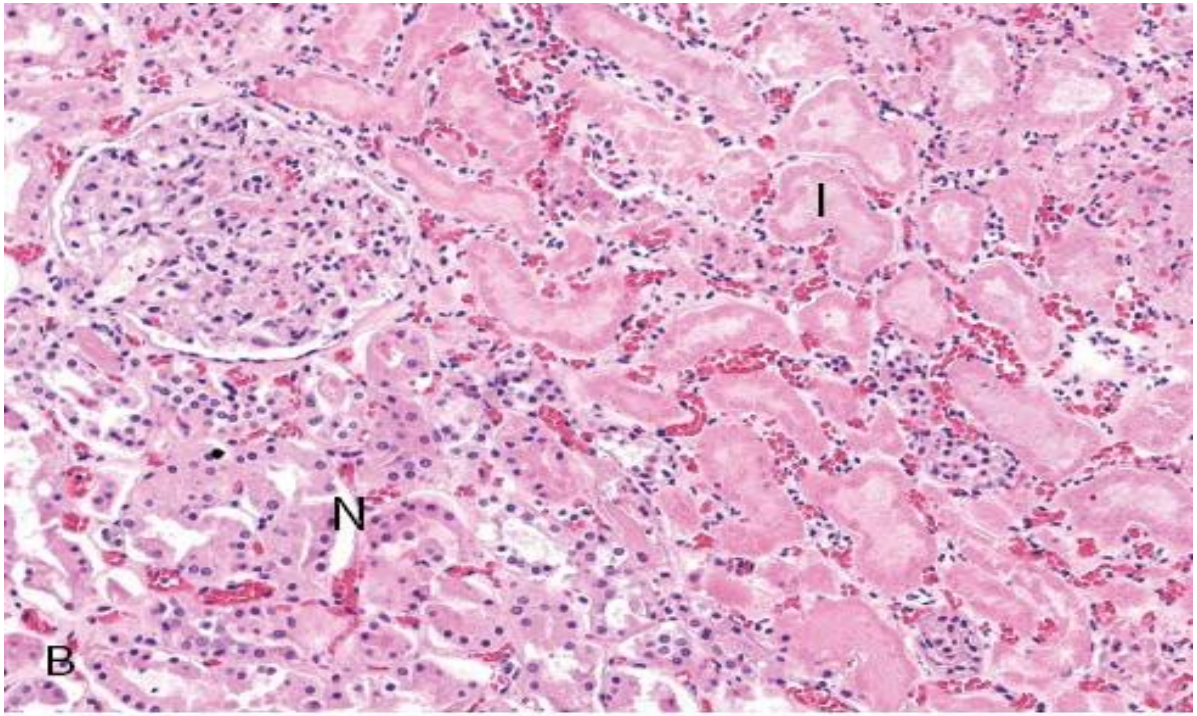
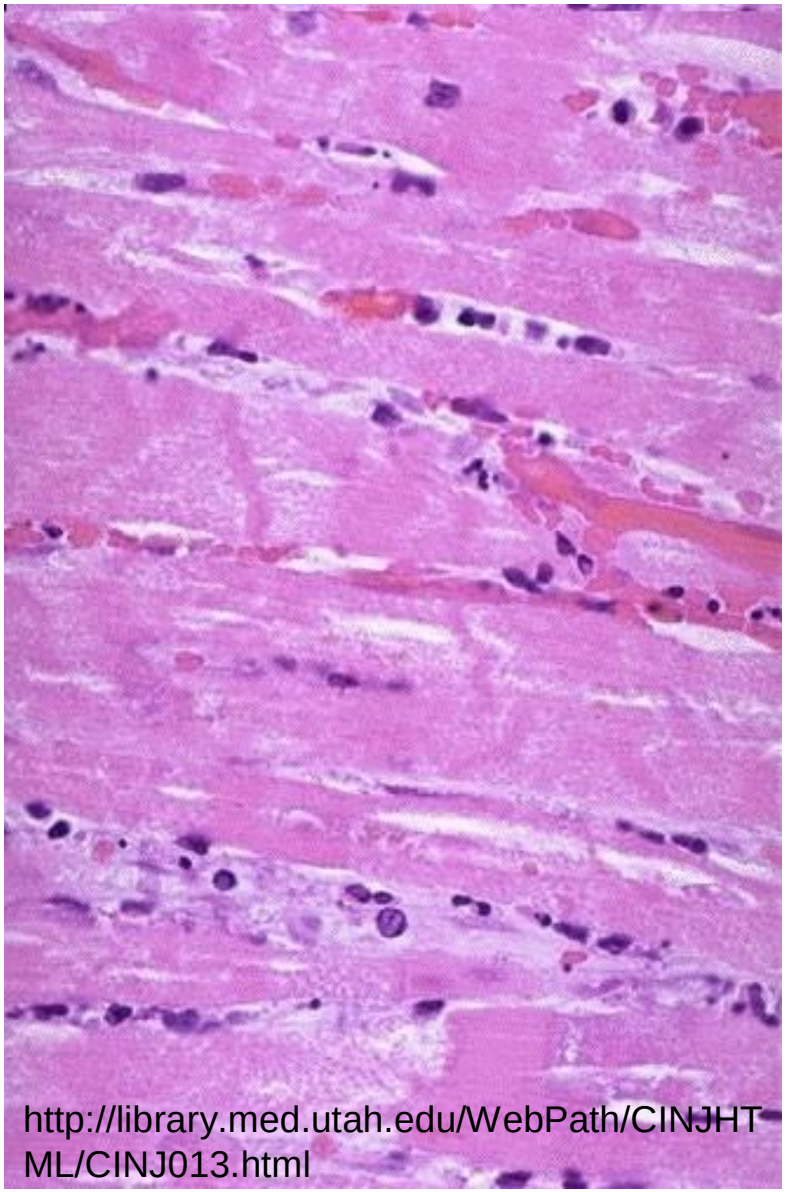


FIGURE 1–11B Coagulative necrosis. **A,** A wedge-shaped kidney infarct (yellow). **B,** Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I) showing preserved cellular outlines with loss of nuclei and an inflammatory infiltrate (which is difficult to discern at this magnification).

Coagulative necrosis—myocardial infarction



http://library.med.utah.edu/WebPath/CINJHTML/CINJ013.html

Here is myocardium in which the cells are dying as a result of ischemic injury from coronary artery occlusion. This is early in the

http://bcrc.bio.umass.edu/histology/files/images/SZR1.preview.jpg

process of necrosis. The nuclei of the myocardial fibers are being lost. The cytoplasm is losing its structure, because no well-defined cross-striations are seen.

Liquefactive Necrosis

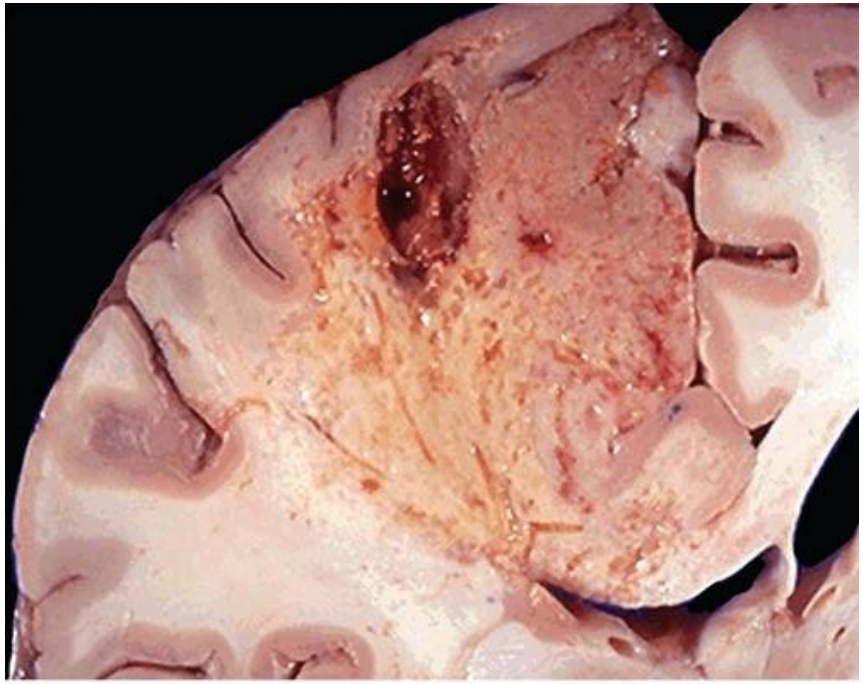
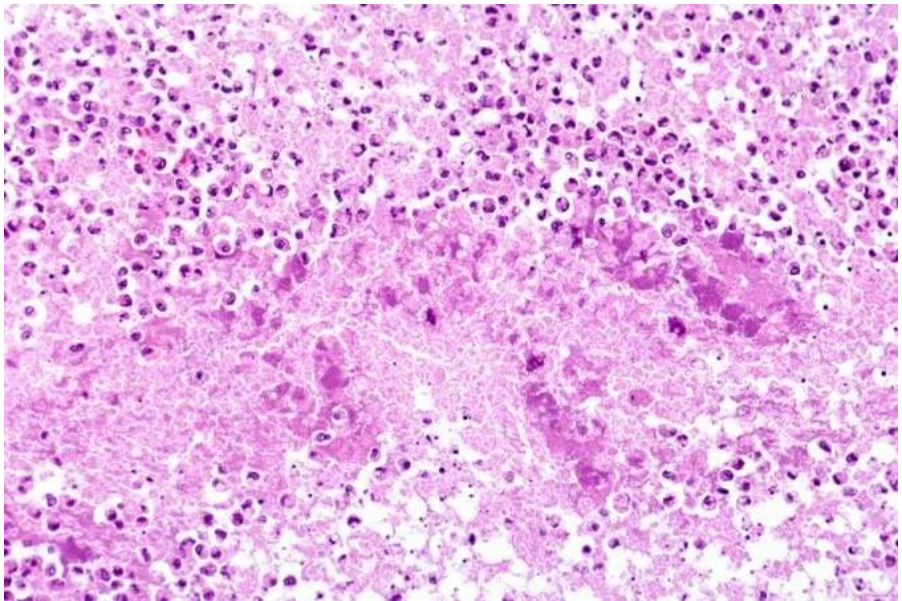


FIGURE 1–12 Liquefactive necrosis. An infarct in the brain, showing dissolution of the tissue.

Digestion of the dead

Transformation of the tissue into a liquid viscous mass.

The necrotic material is frequently creamy yellow because of the presence of dead leukocytes and is called **pus**.



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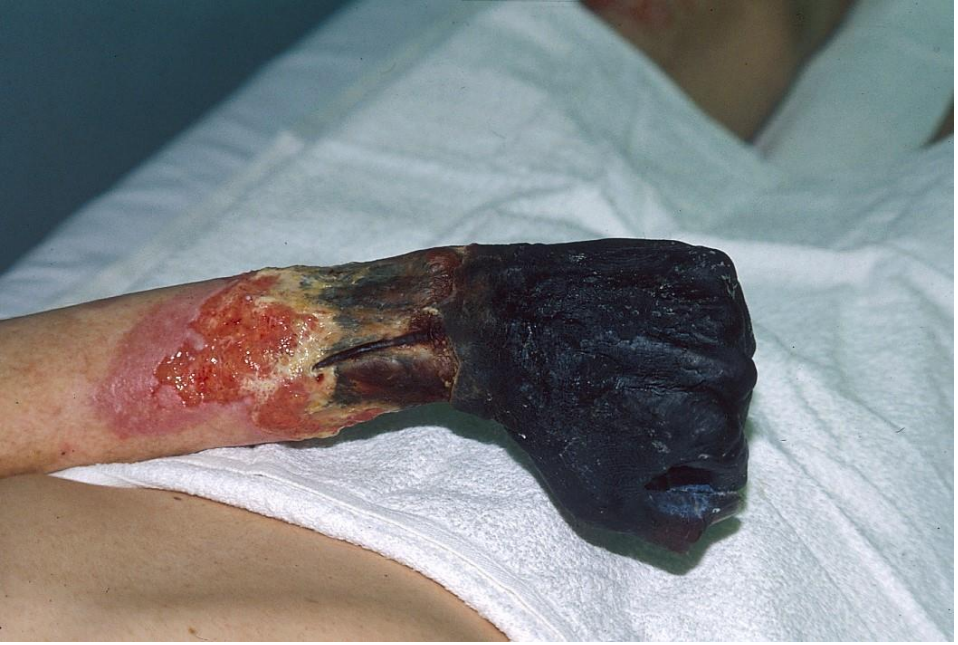


Gangrenous Necrosis

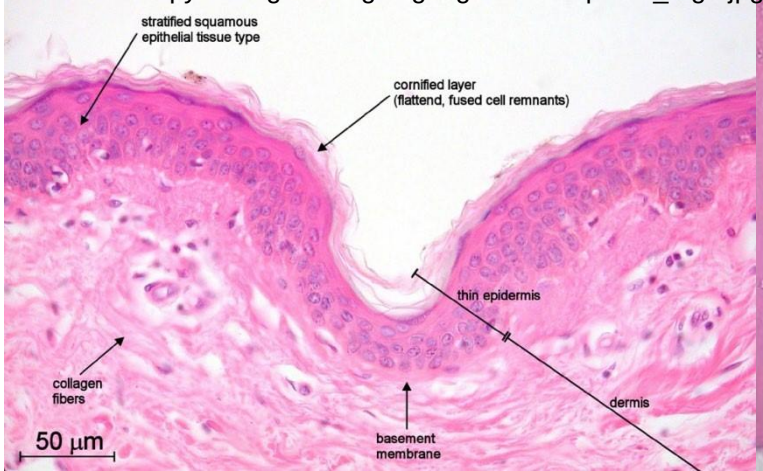
Not a specific pattern.

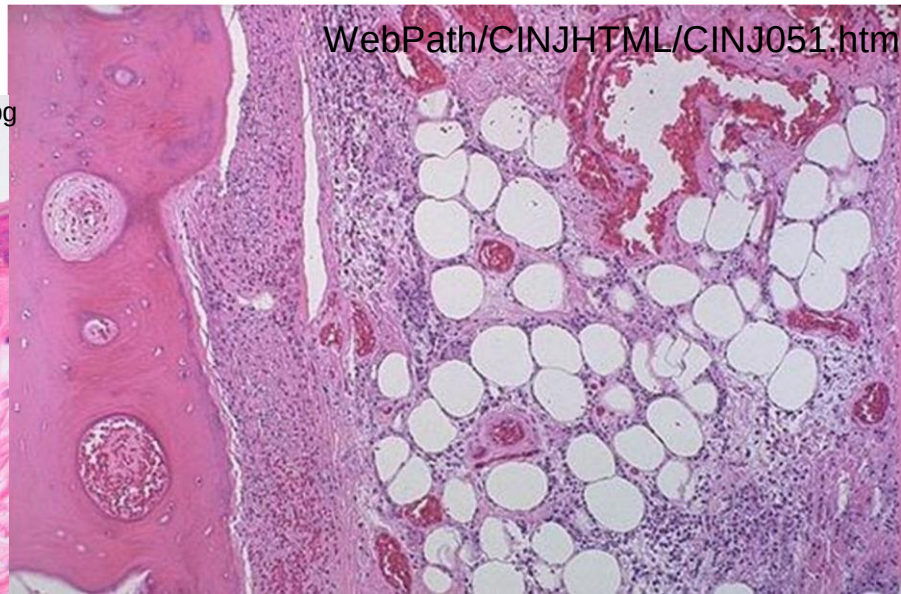
Term is commonly used in clinical practice.

Usually applied to a limb, generally the lower leg, that has lost its blood supply Sepsis induced DIC has led to extensive arterial and has undergone, typically, thrombosis, resulting in profound tissue death.

coagulative necrosis

http://www.microscopy-uk.org.uk/mag/imgaug02/HistPaper01_Fig2.jpg





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http://meded.ucsd.edu/clinicalimg/skin_gangrene_dic.jpg

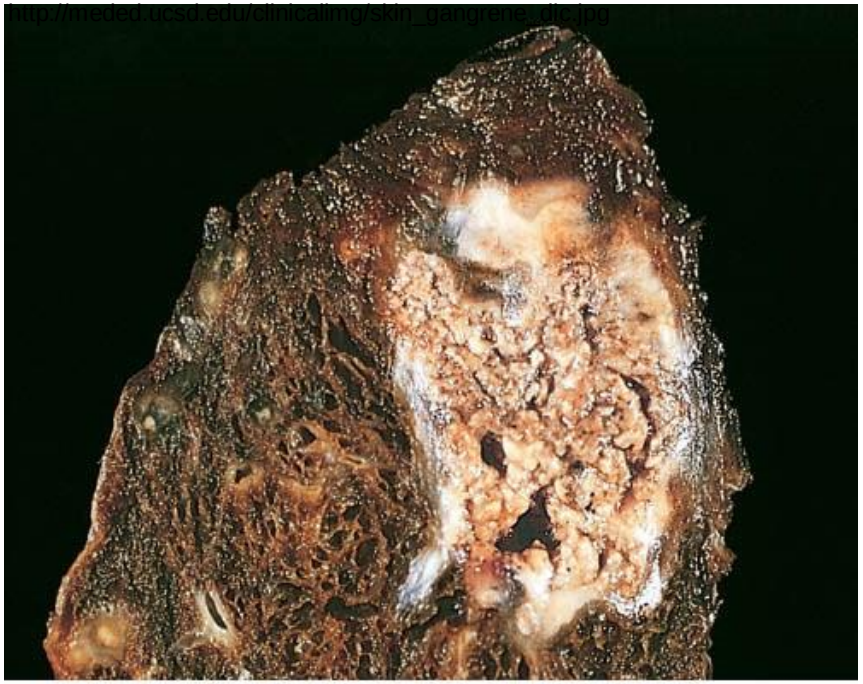


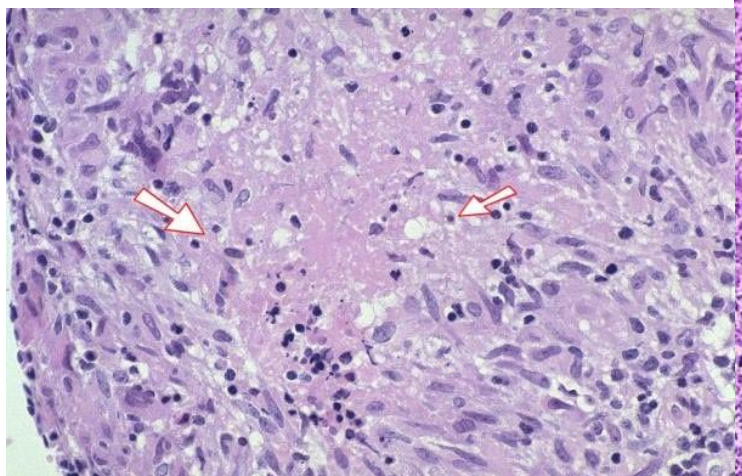
FIGURE 1–13 Caseous necrosis. Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white and cheesy debris.

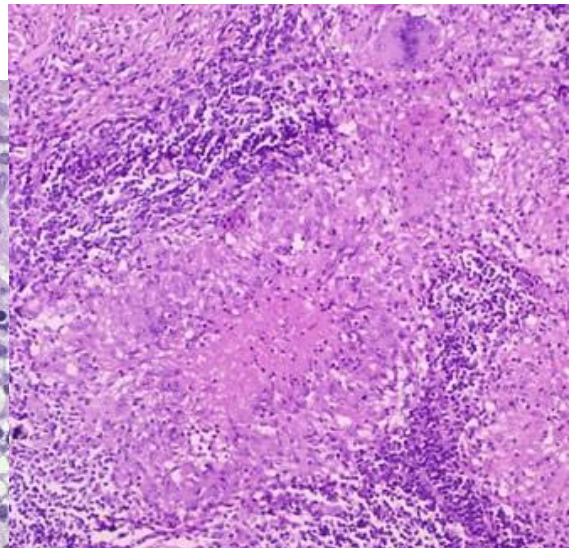
Caseous Necrosis

"Caseous" (cheeselike) is derived from the friable white appearance of the area of necrosis

Necrotic area appears as a collection of fragmented or lysed cells and amorphous granular debris enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a granuloma.

http://www.med.nus.edu.sg/path/images/t b-myco.jpg





http://granuloma.homestead.com/files/granuloma_apoptotic2.jpg

Fat Necrosis

Not a specific pattern

Focal areas of fat destruction, typically resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity.

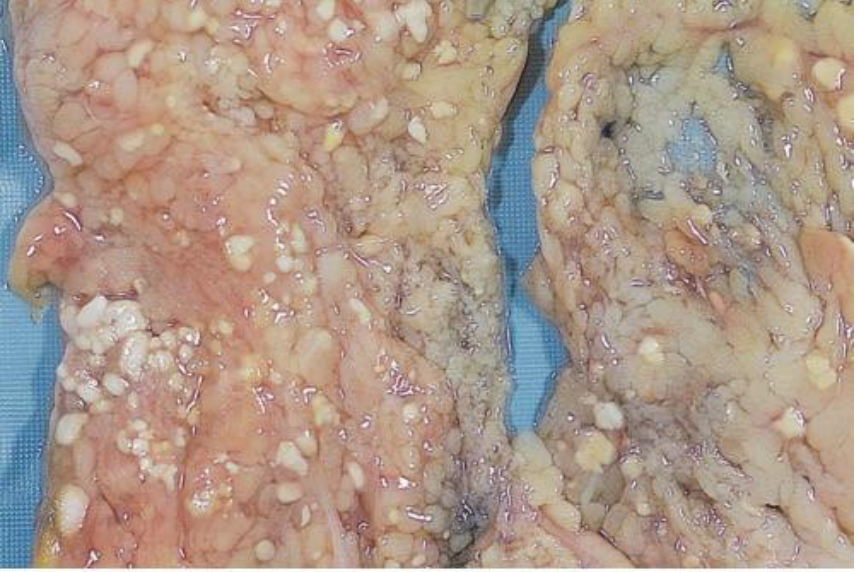
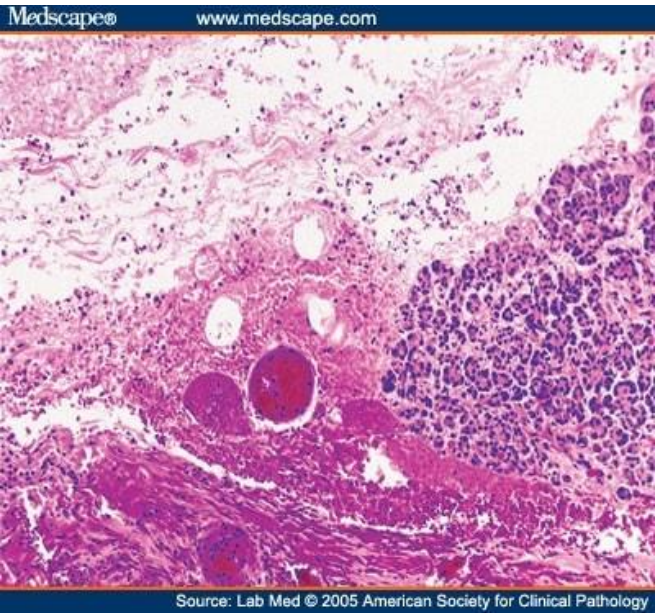


FIGURE 1–14 Fat necrosis. The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.

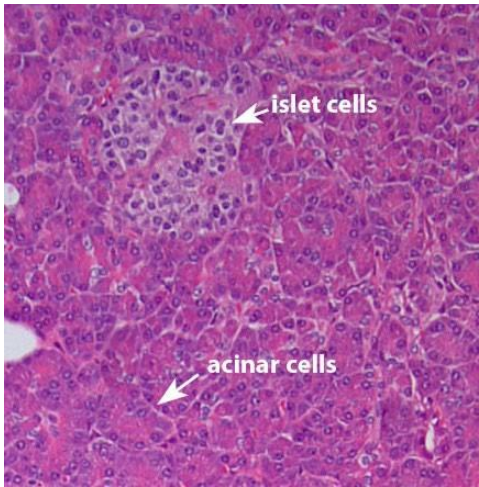
Lipases split the triglyceride esters contained within fat cells. Free fatty acids can combine with calcium to produce grossly visible chalky-white areas (fat saponification).

http://pancreas.org/wpcontent/uploads/nl-pancreas-cells.jpg



Fibrinoid Nec

Usually seen in immune reactions involving blood vessels.



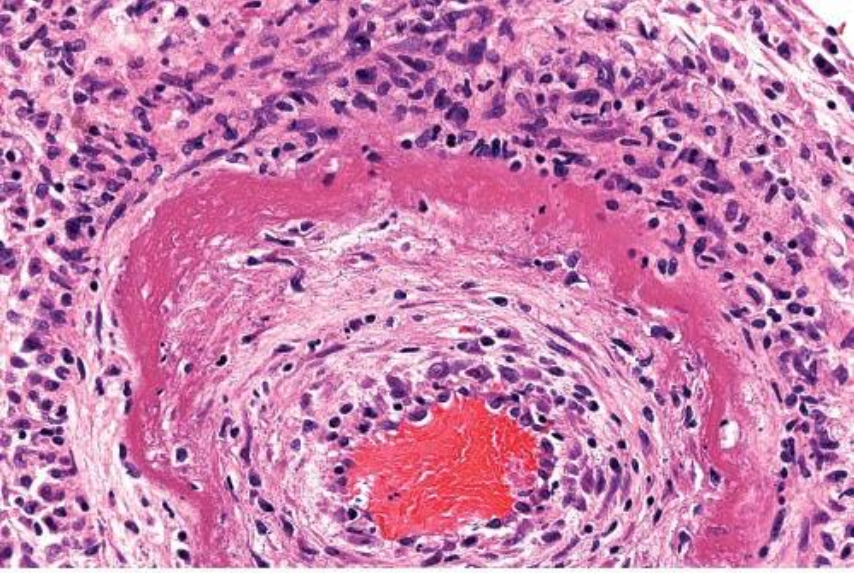
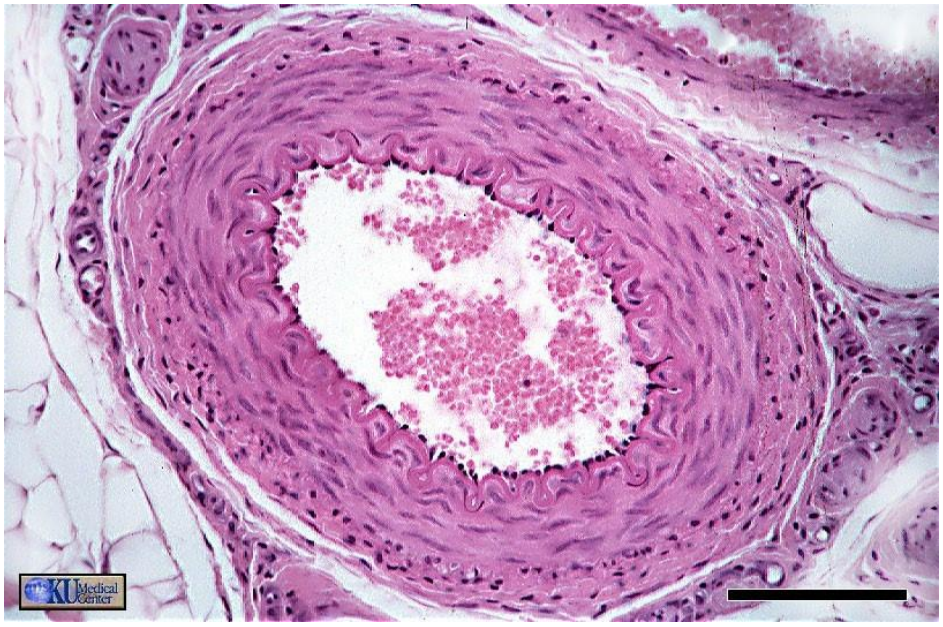


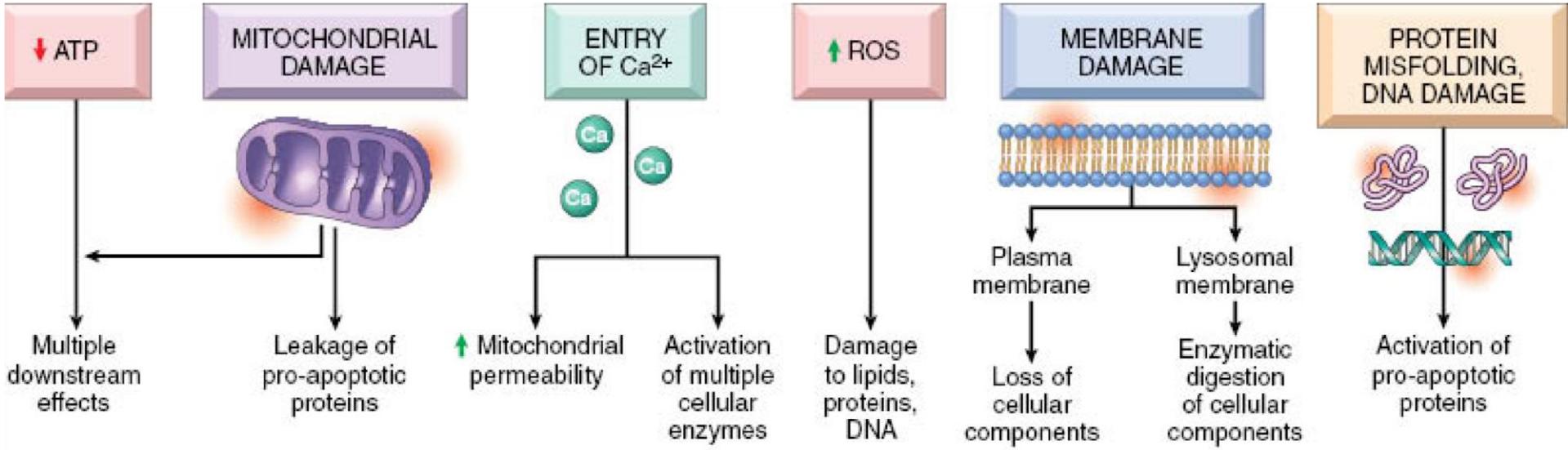
FIGURE 1–15 Fibrinoid necrosis in an artery. The wall of the artery shows a circumferential bright pink area of necrosis with inflammation (neutrophils with dark nuclei).

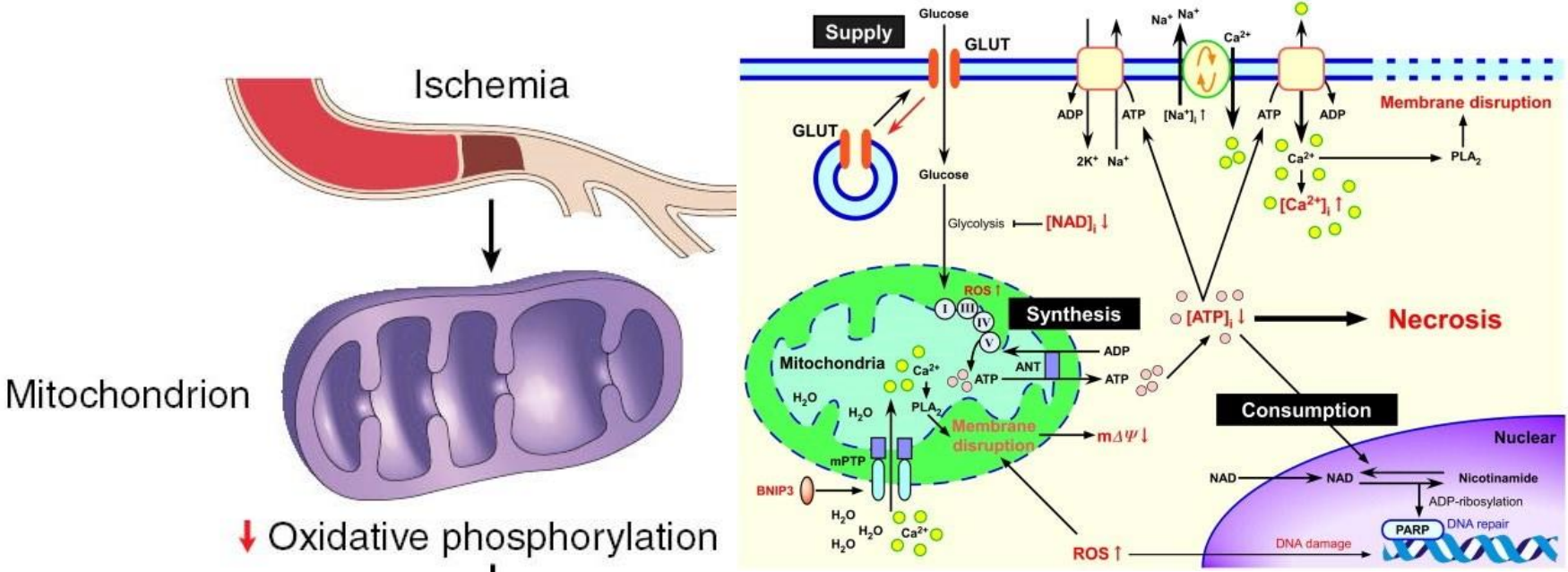
Deposits of “immune complexes,” together with fibrin that has leaked out of vessels.

Bright pink and amorphous appearance in H&E stains, called “fibrinoid” (fibrin-like) by pathologists.



Mechanisms leading to necrotic cells





http://ars.els-cdn.com/content/image/1-s2.0-S0163725809001120-gr2.jpg

Calcium Flux

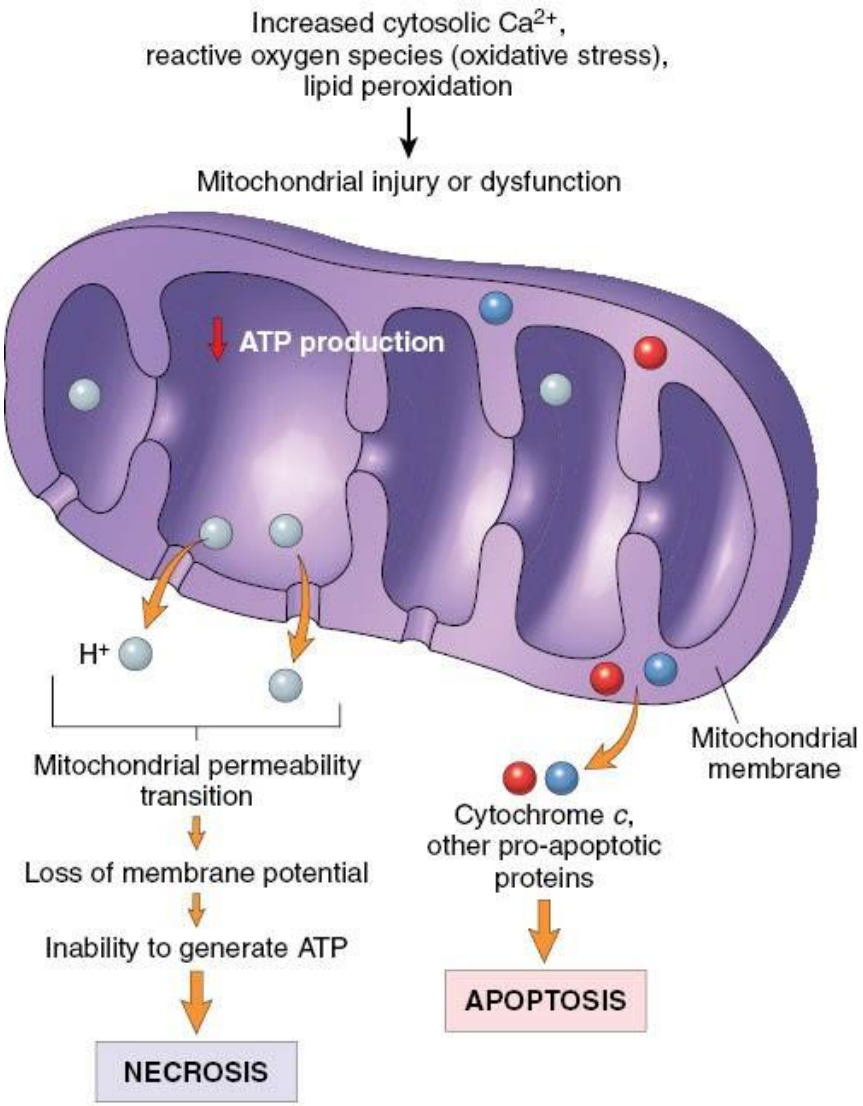


FIGURE 1–18 Consequences of mitochondrial dysfunction, culminating in cell death by necrosis or apoptosis.

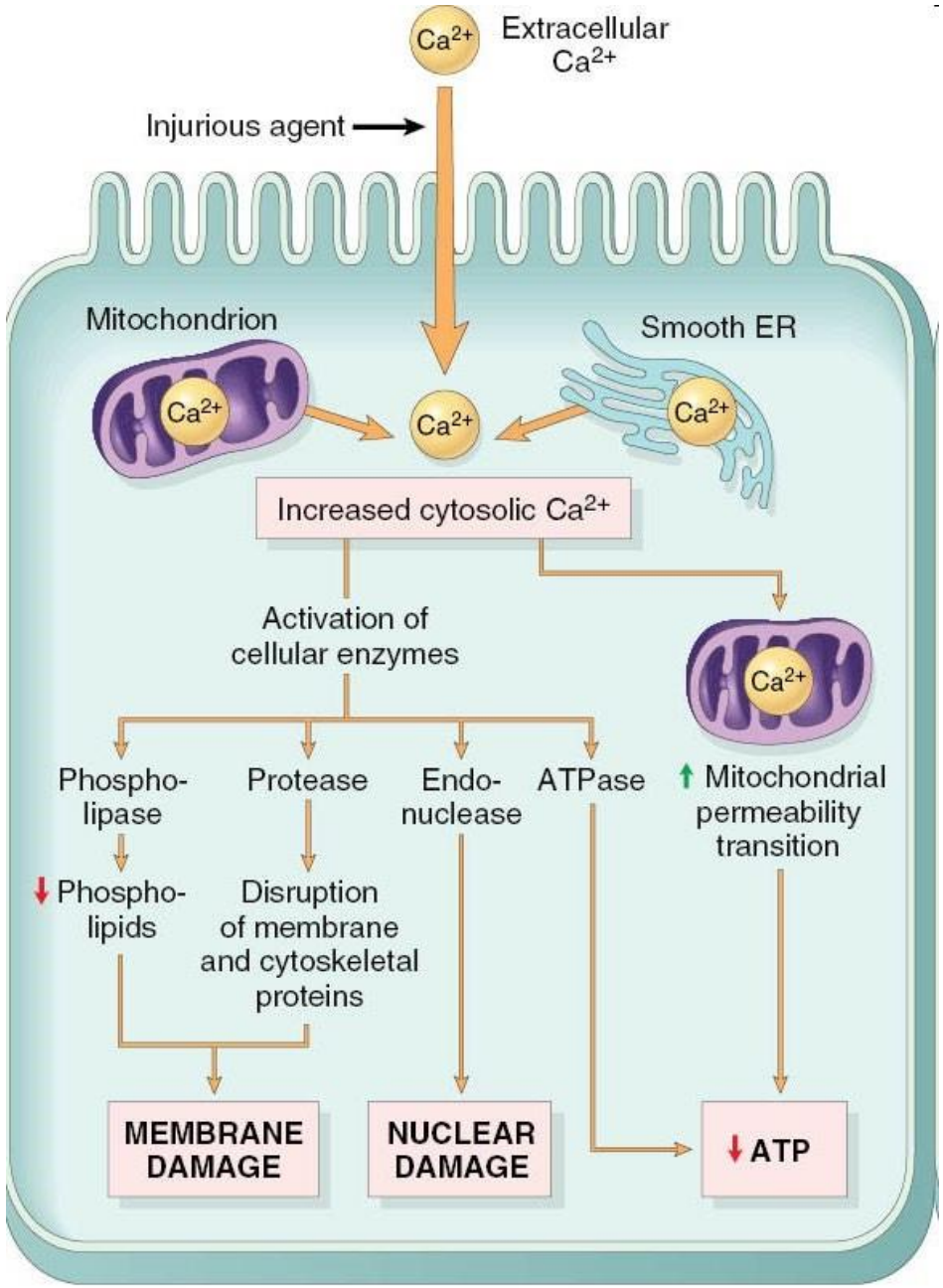
Intracellular, cytosolic [Ca++] as many as 4 orders of magnitude lower than extracellular or organellar (ER, SR, Mt)

Mitochondrial damage and ER swelling releases Ca++ to cytosol

Hydrolytic enzymes activated

Apoptosis may be activated

Necrosis occurs

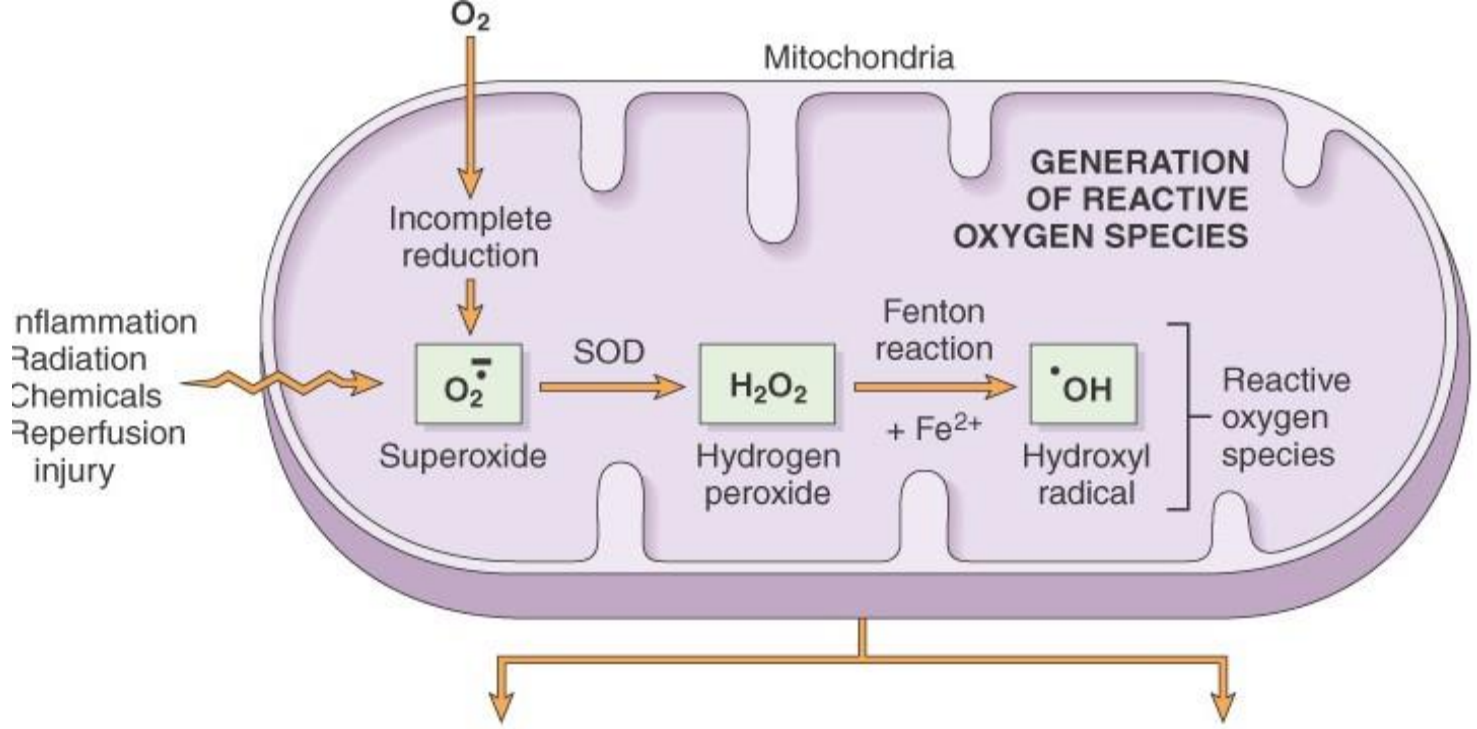


ROS and free radicals

- Hydroxyl radicals and hydrogen may be split from water by ionizing radiation
- Superoxide radicals, hydrogen peroxide, lipid peroxides normally present in small amounts
  - Neutralized by catalase or glutathione peroxidase
- ROS created and released by neutrophils in response to microbial infection
- Toxic chemicals natively, or after activation by P450 redox in liver or kidney, may result in free radicals

- ROS initiate chain reaction of lipid peroxidation in membranes

Inflammation
Radiation
Chemicals
Reperfusion Injury



PATHOLOGIC EFFECTS OF ROS: CELL INJURY AND DEATH

ROS react with:

- Fatty acids → oxidation → generation of lipid peroxidases → disruption of plasma membrane, organelles
- Proteins → oxidation → loss of enzymatic activity, abnormal folding
- DNA → oxidation → mutations, breaks

REMOVAL OF FREE RADICALS

Antioxidant mechanisms:

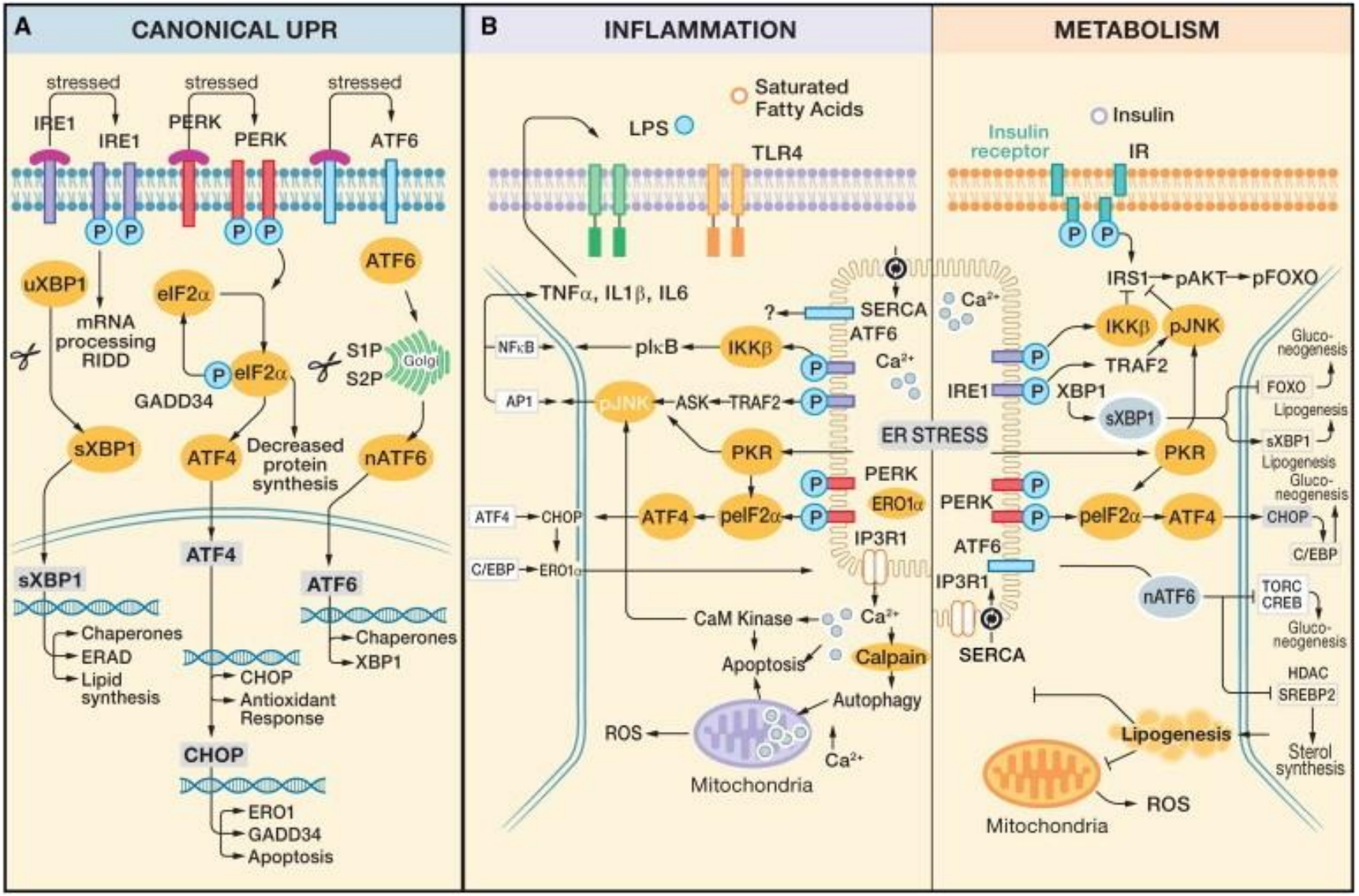
- SOD (in mitochondria) converts $O_2^{\bullet-}$ → H_2O_2
- Glutathione peroxidase (in mitochondria) converts $^{\bullet}OH$ → H_2O_2 → $H_2O + O_2$
- Catalase (in peroxisomes) converts H_2O_2 → $H_2O + O_2$

TABLE 1-3 -- **Properties of the Principal Free Radicals Involved in Cell Injury**

Properties	$O_2^{\cdot-}$	H_2O_2	$^{\cdot}OH$	$ONOO^-$
MECHANISMS OF PRODUCTION	Incomplete reduction of O_2 during oxidative phosphorylation; by phagocyte oxidase in leukocytes	Generated by SOD from O_2^- and by oxidases in peroxisomes	Generated from H_2O by hydrolysis, e.g., by radiation; from H_2O_2 by Fenton reaction; from $O_2^{\cdot-}$	Produced by interaction of $O_2^{\cdot-}$ and NO generated by NO synthase in many cell types (endothelial cells, leukocytes, neurons, others)
MECHANISMS OF INACTIVATION	Conversion to H_2O_2 and O_2 by SOD	Conversion to H_2O and O_2 by catalase (peroxisomes), glutathione peroxidase (cytosol, mitochondria)	Conversion to H_2O by glutathione peroxidase	Conversion to HNO_2 by peroxiredoxins (cytosol, mitochondria)
PATHOLOGIC EFFECTS	Stimulates production of degradative enzymes in leukocytes and other cells; may directly damage lipids, proteins, DNA; acts close to site of production	Can be converted to $^{\cdot}OH$ and OCl^-, which destroy microbes and cells; can act distant from site of production	Most reactive oxygen-derived free radical; principal ROS responsible for damaging lipids, proteins, and DNA	Damages lipids, proteins, DNA

HNO_2, nitrite; H_2O_2, hydrogen peroxide; NO, nitric oxide; $O_2^{\cdot-}$, superoxide anion; OCl^-, hypochlorite; $^{\cdot}OH$, hydroxyl radical; $ONOO^-$, peroxynitrite; ROS, reactive oxygen species; SOD, superoxide dismutase.

Loss of ER Homeostasis


A
CANONICAL UPR
stressed
IRE1
IRE1
PERK
PERK
ATF6
uXBP1
mRNA processing RIDD
sXBP1
eIF2α
GADD34
eIF2α
ATF4
Decreased protein synthesis
ATF6
S1P
S2P
Golgi
nATF6
sXBP1
Chaperones
ERAD
Lipid synthesis
ATF4
CHOP
Antioxidant Response
CHOP
ERO1
GADD34
Apoptosis
ATF6
Chaperones
XBP1
B
INFLAMMATION
Saturated Fatty Acids
LPS
TLR4
TNFα, IL1β, IL6
NFκB
AP1
pIκB
IKKβ
pJNK
ASK
TRAF2
SERCA
ATF6
Ca2+
PKR
PERK
ERO1α
ATF4
CHOP
peIF2α
ATF4
C/EBP
ERO1α
IP3R1
CaM Kinase
Ca2+
Apoptosis
Calpain
Autophagy
ROS
Ca2+
Mitochondria
METABOLISM
Insulin
Insulin receptor
IR
IRS1
pAKT
pFOXO
IKKβ
pJNK
TRAF2
IRE1
XBP1
sXBP1
ER STRESS
PKR
PERK
peIF2α
ATF4
ATF6
IP3R1
SERCA
nATF6
Ca2+
Gluco-neogenesis
FOXO
Lipogenesis
sXBP1
Lipogenesis
Gluco-neogenesis
CHOP
C/EBP
TORC
CREB
Gluco-neogenesis
HDAC
SREBP2
Sterol synthesis
Lipogenesis
ROS
Mitochondria

http://www.sciencedirect.com/science/article/pii/S1550413112001027

A. NORMAL PROTEIN PRODUCTION AND ASSEMBLY

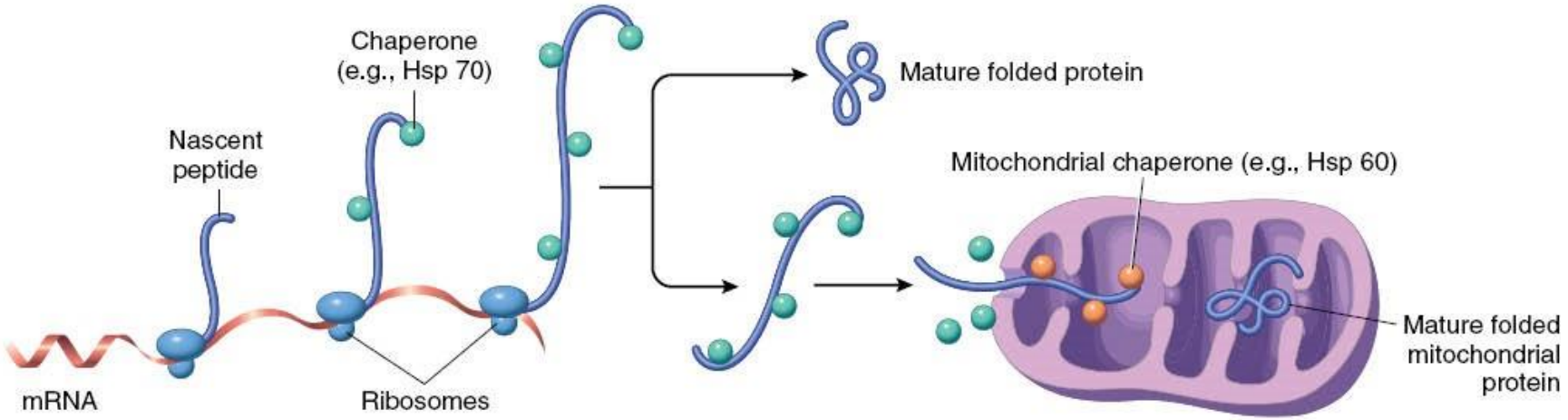


FIGURE 1–27A Mechanisms of protein folding and the unfolded protein response. **A,** Chaperones, such as heat shock proteins (Hsp), protect unfolded or partially folded proteins from degradation and guide proteins into organelles. **B,** Misfolded proteins trigger a protective unfolded protein response (UPR). If this response is inadequate to cope with the level of misfolded proteins, it induces apoptosis.

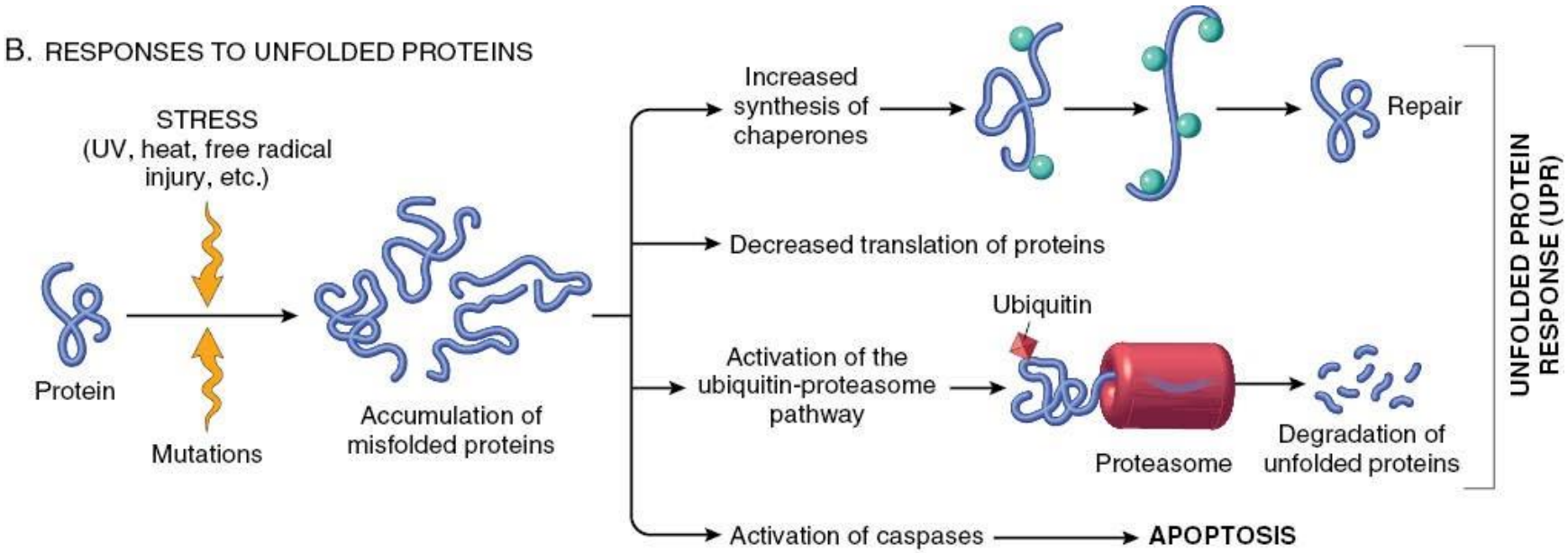


FIGURE 1–27B Mechanisms of protein folding and the unfolded protein response. **A,** Chaperones, such as heat shock proteins (Hsp), protect unfolded or partially folded proteins from degradation and guide proteins into organelles. **B,** Misfolded proteins trigger a protective unfolded protein response (UPR). If this response is inadequate to cope with the level of misfolded proteins, it induces apoptosis.

Apoptosis

- Programmed cell death
  - Especially during fetal development
  - In response to hormonal cycles (e.g. endometrium)
  - Normal turnover in proliferating tissues (e.g. intestinal epithelium)
- Cells shrink, not swell

- Nuclei condense and DNA fragments
- Cells fragment into membrane-bound bits
- Bits are phagocytosed by macrophages

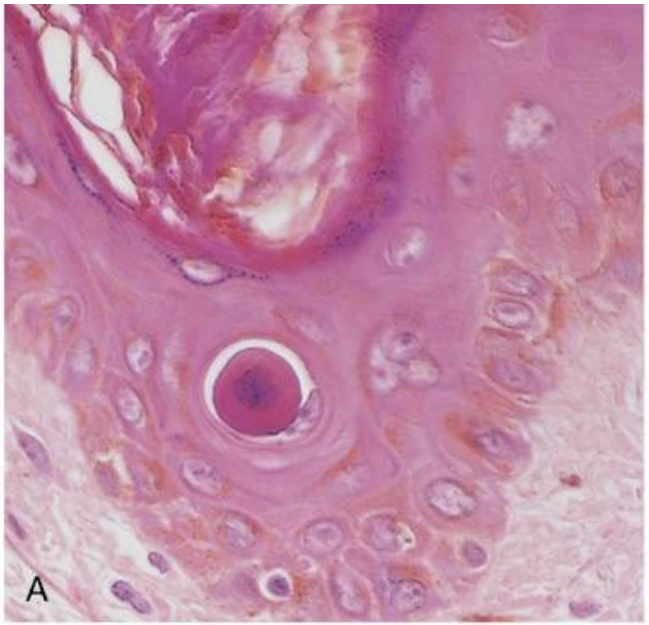
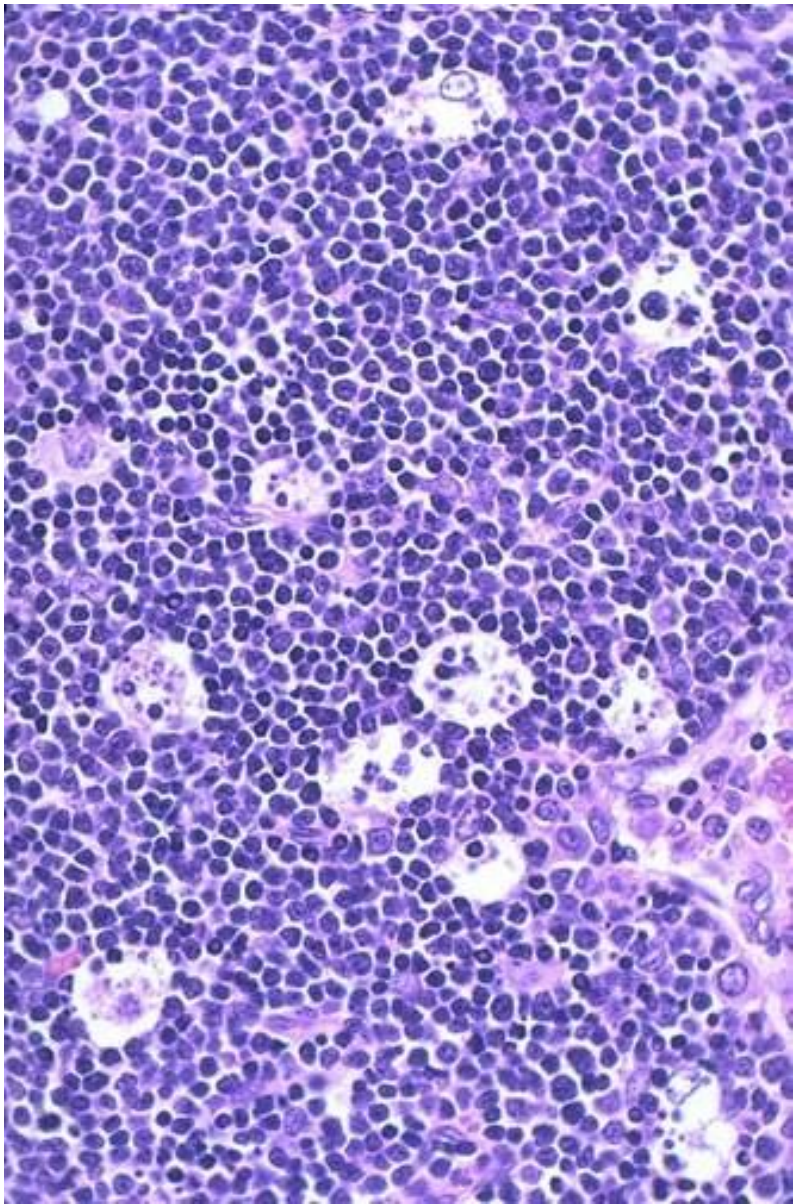


FIGURE 1–22A Morphologic features of apoptosis. **A,** Apoptosis of an epidermal cell in an immune reaction. The cell is reduced in size and contains brightly eosinophilic cytoplasm and a condensed nucleus. **B,** This electron micrograph of cultured cells undergoing apoptosis shows some nuclei with peripheral crescents of compacted chromatin, and others that are uniformly dense or fragmented. **C,** These images of cultured cells undergoing apoptosis show blebbing and formation of apoptotic bodies (*left panel,* phase contrast micrograph), a stain for DNA showing nuclear fragmentation *(middle panel),* and activation of caspase-3 (*right panel,* immunofluorescence stain with an antibody specific for the active form of caspase-3, revealed as red color).



Apoptotic fetal thymus

In this fetal thymus there is involution of thymic lymphocytes by the mechanism of apoptosis. In this case, it is an orderly process and part of normal immune system maturation. Individual cells fragment and are consumed by phagocytes to give the appearance of clear spaces filled with cellular debris. Apoptosis is controlled by many mechanisms. Genes such as BCL-2 are turned off and Bax genes turned on. Intracellular proteolytic enzymes called

caspases produce much cellular breakdown.

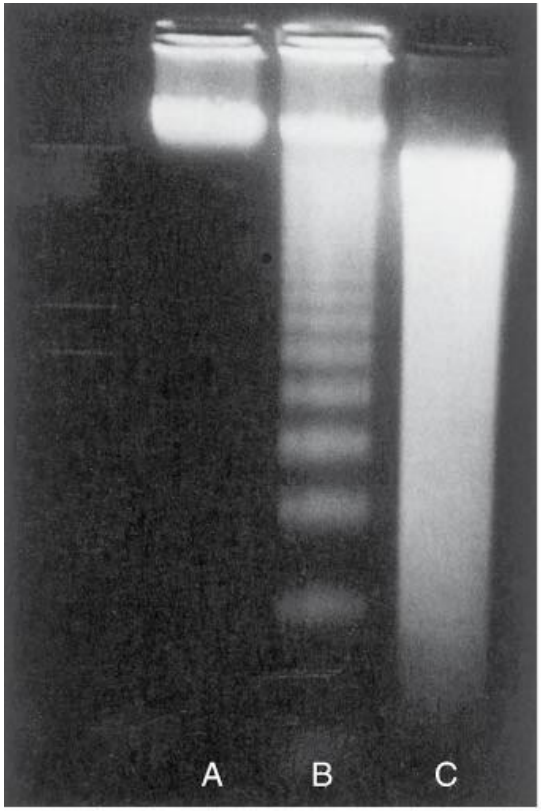


FIGURE 1–23 Agarose gel electrophoresis of DNA extracted from culture cells. Ethidium bromide stain; photographed under ultraviolet illumination. **Lane A,** Viable cells in culture. **Lane B,** Culture of cells exposed to heat showing extensive apoptosis; note ladder pattern of DNA fragments, which represent multiples of oligonucleosomes. **Lane C,** Culture showing cell necrosis; note diffuse smearing of DNA.

(From Kerr JFR, Harmon BV: Definition and incidence of apoptosis: a historical perspective. In Tomei LD, Cope FO: Apoptosis: The Molecular Basis of Cell Death. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1991, p 13.)

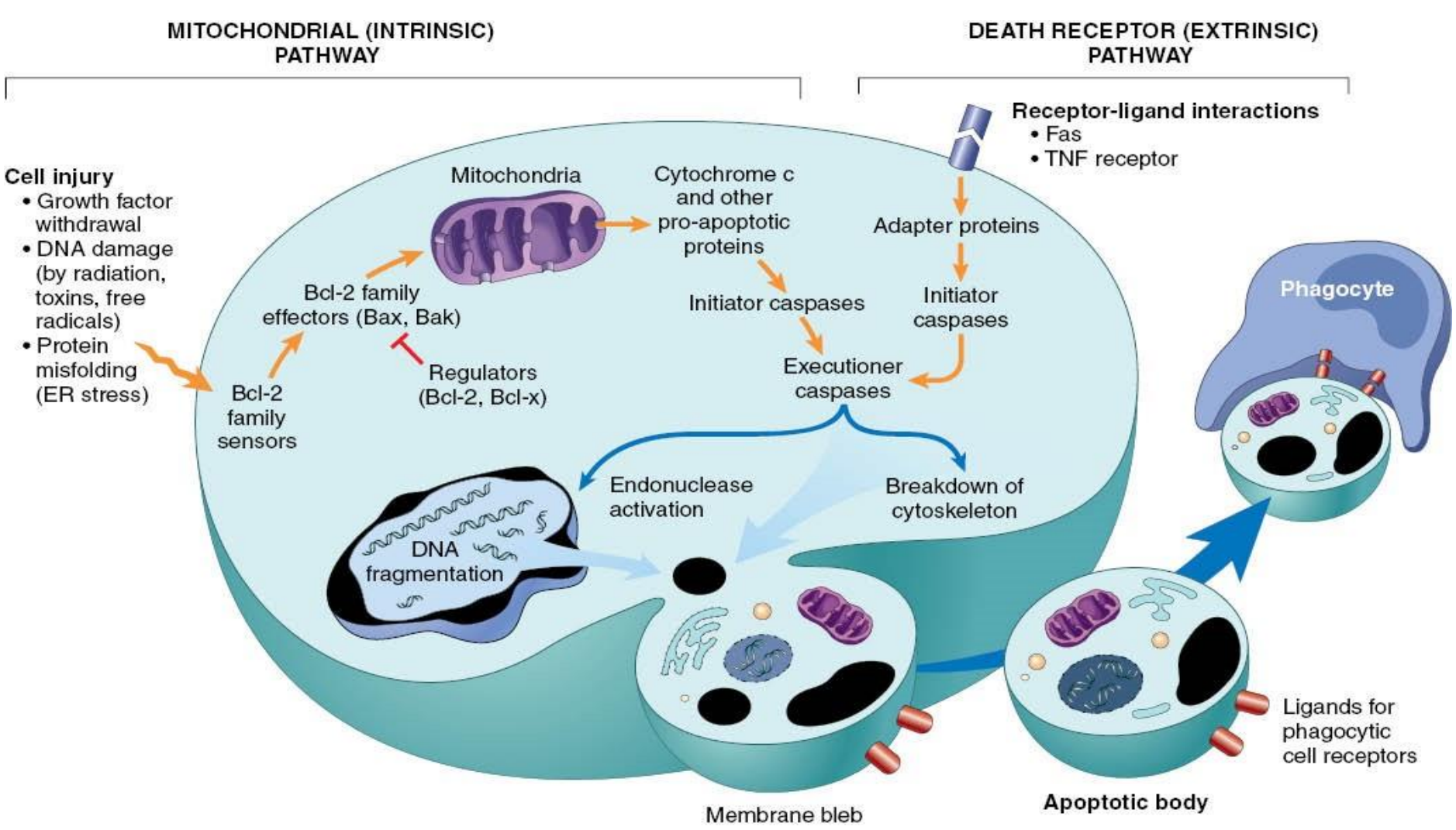
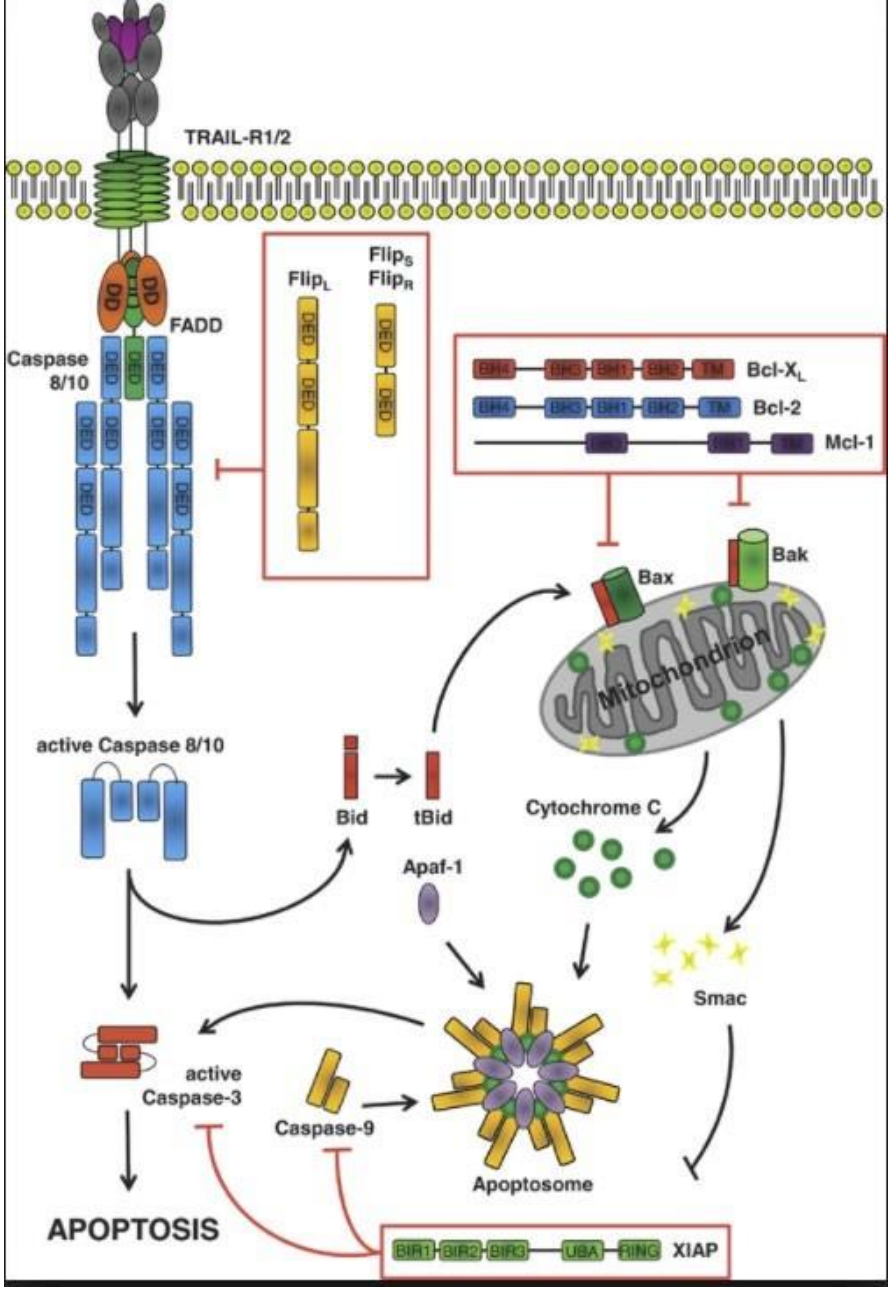


FIGURE 1–24 Mechanisms of apoptosis. The two pathways of apoptosis differ in their induction and regulation, and both culminate in the activation of "executioner" caspases. The induction of apoptosis by the mitochondrial pathway involves the action of sensors and effectors of the Bcl-2 family, which induce leakage of mitochondrial proteins. Also shown are some of the anti-apoptotic proteins ("regulators") that inhibit mitochondrial leakiness and cytochrome *c*–dependent caspase activation in the mitochondrial pathway. In the death receptor pathway engagement of death receptors leads directly to caspase activation. The regulators of death receptor–mediated caspase activation are not shown. ER, endoplasmic reticulum; TNF, tumor necrosis factor.

Getting TRAIL back on track for cancer therapy **Article · Literature Review (PDF Available)** *in* Cell Death and Differentiation 21(9) · June 2014 *with* 301 ReadsDOI: 10.1038/cdd.2014.81 · Source: PubMed



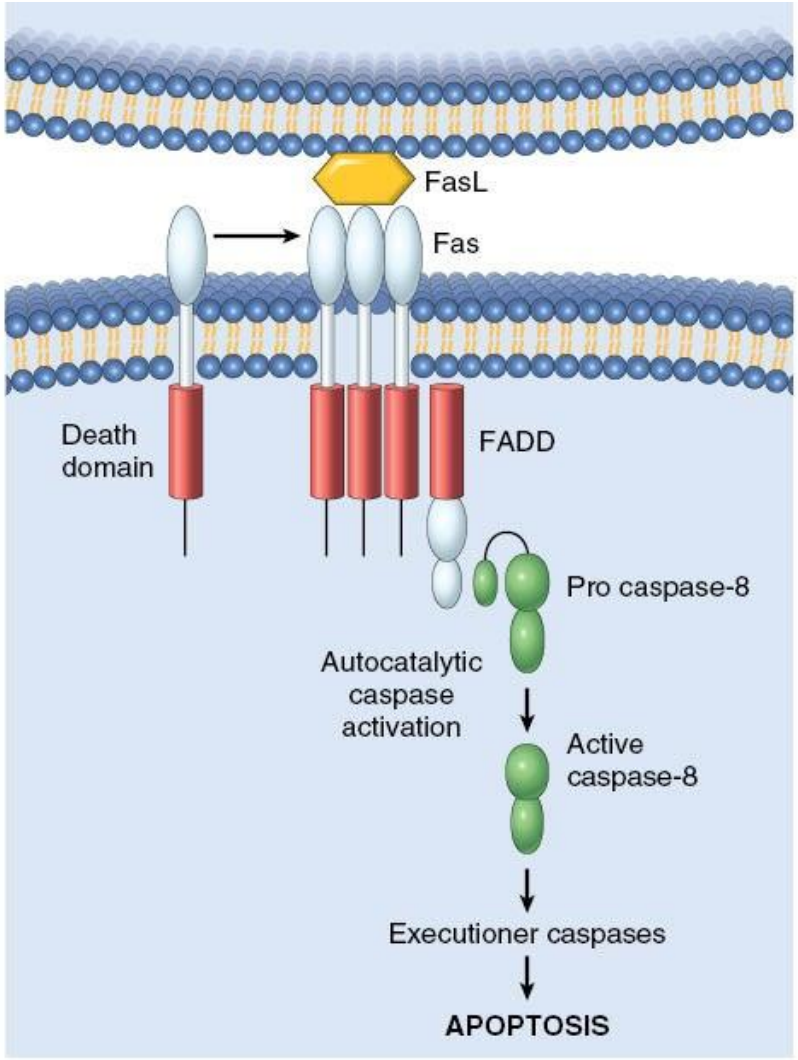


FIGURE 1–26 The extrinsic (death receptor–initiated) pathway of apoptosis, illustrated by the events following Fas engagement. FAAD, *F*as-*a*ssociated *d*eath *d*omain; FasL, Fas ligand.

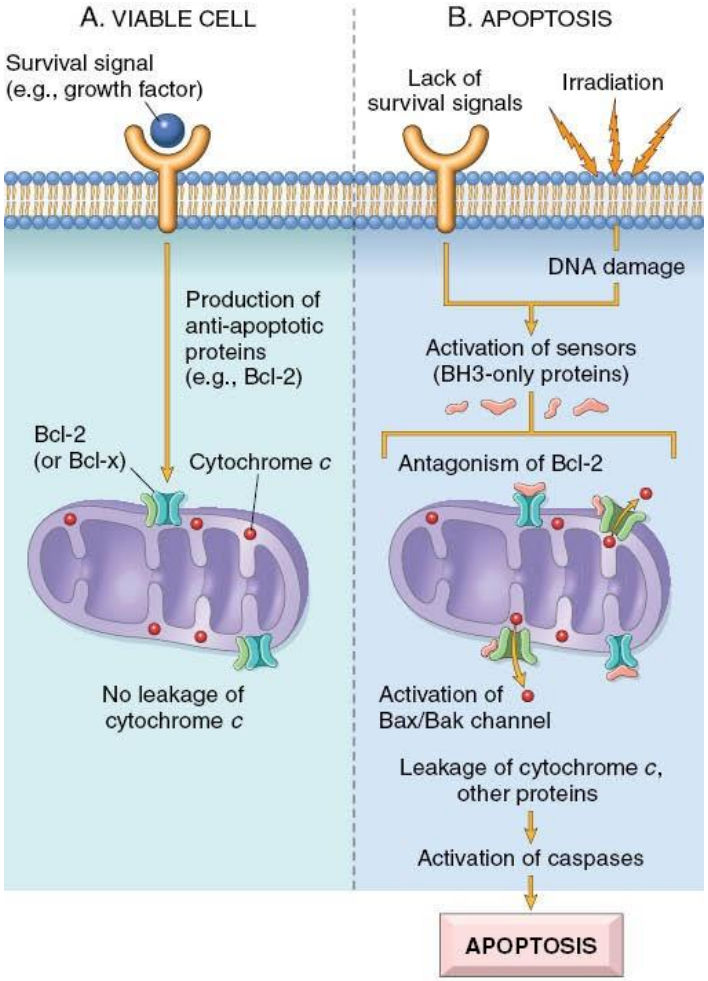
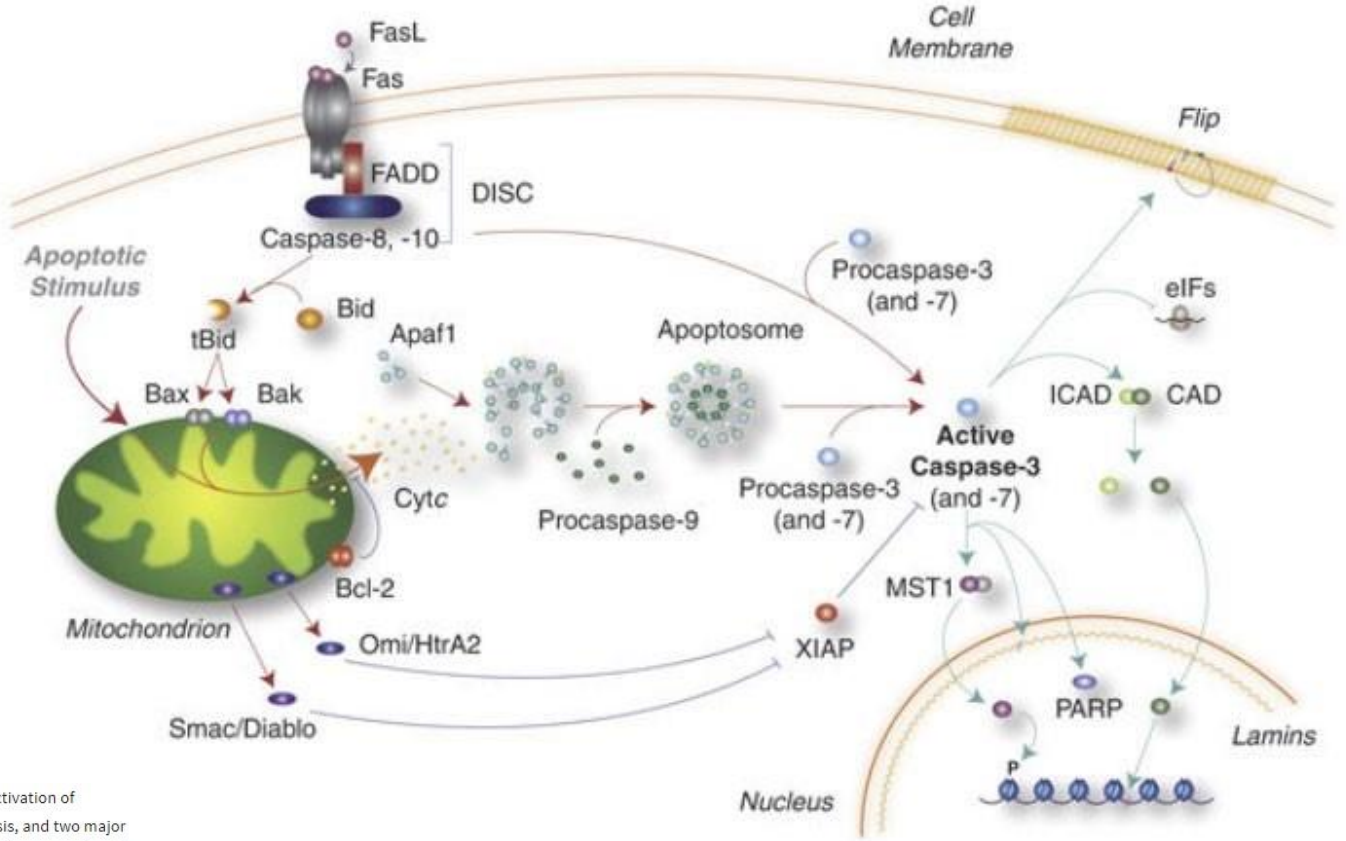


FIGURE 1–25 The intrinsic (mitochondrial) pathway of apoptosis. **A,** Cell viability is maintained by the induction of anti-apoptotic proteins such as Bcl-2 by survival signals. These proteins maintain the integrity of mitochondrial membranes and prevent leakage of mitochondrial proteins. **B,** Loss of survival signals, DNA damage, and other insults activate sensors that antagonize the anti-apoptotic proteins and activate the pro-apoptotic proteins Bax and Bak, which form channels in the mitochondrial membrane. The subsequent leakage of cytochrome *c* (and other proteins, not shown) leads to caspase activation and apoptosis.

Figure 1



Intrinsic and extrinsic pathways of caspase activation in mammals. Activation of executioner caspases-3 and -7 is the key event in mammalian apoptosis, and two major mechanisms exist to carry out this task (see also text). The intrinsic pathway involves the mitochondrion, which acts as an intracellular death receptor receiving a variety of proapoptotic signals that trigger oligomerization of proapoptotic proteins (Bcl-2-associated protein, Bax, and Bcl-2-antagonist killer, Bak, to produce mitochondrial outer membrane permeabilization, MOMP). This leads to the release of cytochrome *c*, which activates Apaf1, induction of apoptosome formation, procaspase-9 recruitment/activation and direct processing and activation of procaspase-3 and -7. In the extrinsic pathway, Fas receptor ligand (FasL) triggers the membrane-bound Death-Inducing Signaling Complex (DISC), which recruits procasapase-8 and activates caspase-3 directly. In some cell types, caspase-8 can also cleave Bid to form tBid, which interacts with Bax/Bak to trigger MOMP, cytochrome *c* release and apoptosome formation. The activation of caspase-3 and -7 is antagonized by IAPs, which in turn can be inhibited by Smac/Diablo and Omi/HtrA2. Activation of caspase-3 and -7 orchestrates the demolition of the cell by cleavage of specific substrates, such as ICAD,[82] Rho effector ROCK1,[83] kinase MST1,[84] PARP,[85] transcription and translation initiation factors[86]

Neuronal caspase-3 signaling: not only cell death
M D'Amelio, V Cavallucci & F Cecconi
Cell Death and Differentiation 17, 1104–1114 (2010)
doi:10.1038/cdd.2009.180
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CELL INJURY
-CELLULAR ADAPTATIONS-

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Cell adaptations=definition

Reversible **CHANGES** in the size, number, structure and function of cells in response to changes in their environment that result in the acquisition of a new steady states

Types of Cellular Adaptations:

- Metaplasia
- Hyperplasia
- Hypertrophy
- Atrophy

Key Questions:

- Why?
- Cause?*
- How?#

Metaplasia

- Change from one mature epithelial type to another mature epithelial type

- Barrett's oesophagus: squamous to columnar: *GERD**
- Respiratory epithelium: Pseudostratified columnar epithelium to squamous epithelium: *Cigarette smoking**
- Uterine cervix: Columnar to squamous: *HPV**
- Not a pre-malignant lesion but serves as a fertile ground for malignant change
- #: Does not result from change of already differentiated cells to another differentiated cell but arises from reprogramming of stem cells/basal cells

Hyperplasia

- **Increase in the number of cells in an organ or tissue in response to a stimulus**
- Physiologic and pathologic*
- Physiologic: *Growth factors/ hormones*
- To increase functional capacity or as a compensatory mechanism
- Uterine endometrial hyperplasia in menstrual cycle
- Breast enlargement at puberty/ in pregnancy
- Bone marrow
- Liver

Hyperplasia

- Pathologic
- Excessive or inappropriate actions of hormones or growth factors acting on target cells
- Endometrial hyperplasia due to ovarian tumour secreting oestrogen which activates the ER#
- Benign prostatic hyperplasia: androgens
- Goitre: No negative feedback#, TSH#

- *While hyperplasia is distinct from cancer, pathologic hyperplasia constitutes a fertile soil in which cancerous proliferations may eventually arise.*

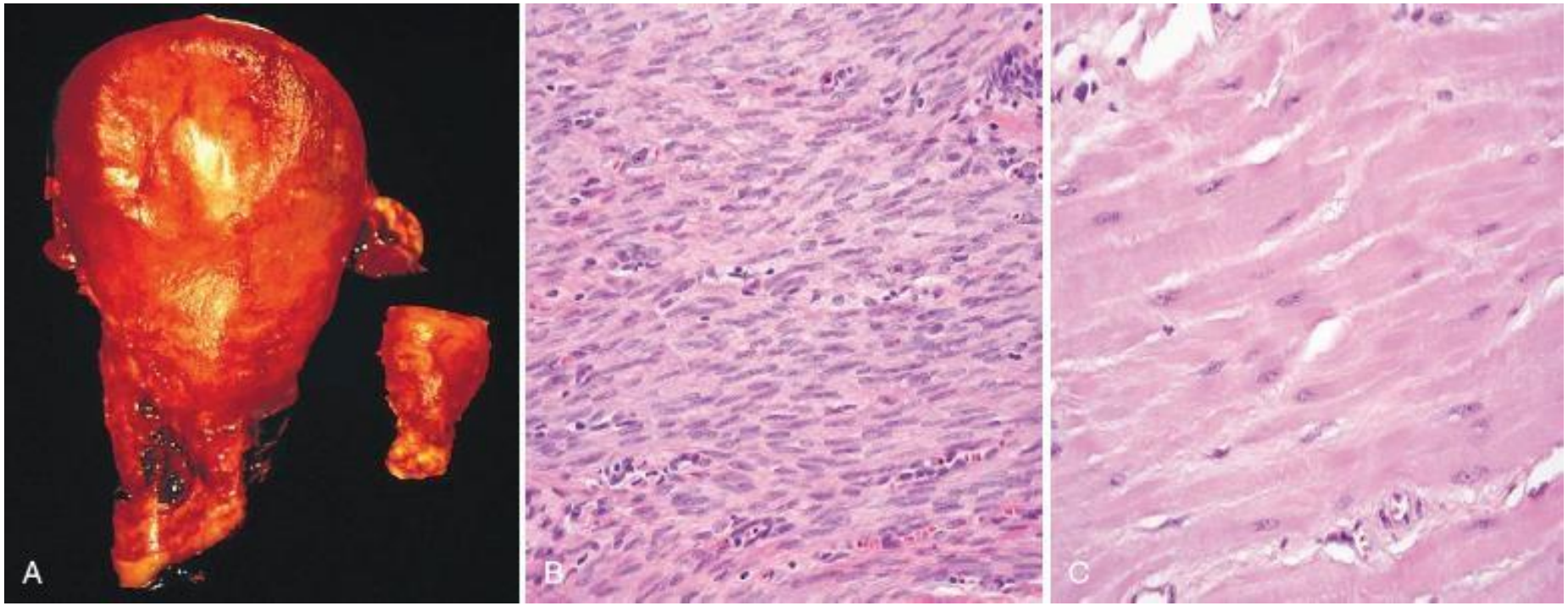
Hyperplasia-How#

- Growth factor-driven proliferation of mature cells
- by increased output of new cells from tissue stem cells

Hypertrophy

- Increase in the size of an organ due to an increase in the size of cells
- Physiologic and pathologic
- Physiologic
- Uterus in pregnancy

Hypertrophy

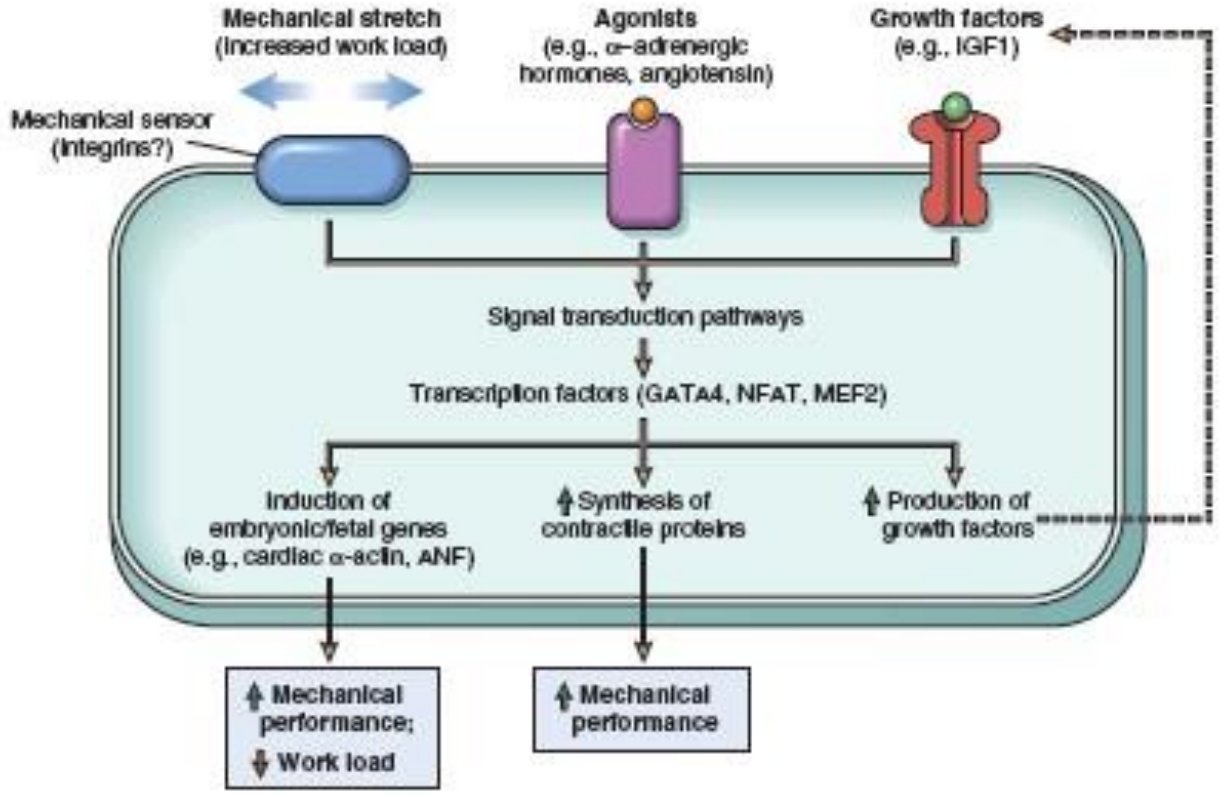


Hypertrophy

Hypertrophy is the result of increased production of cellular proteins

Atrophy: Pathologic

- Atrophy is defined as a reduction in the size of



an organ or tissue due to a decrease in cell size and number. • Physiologic and pathologic

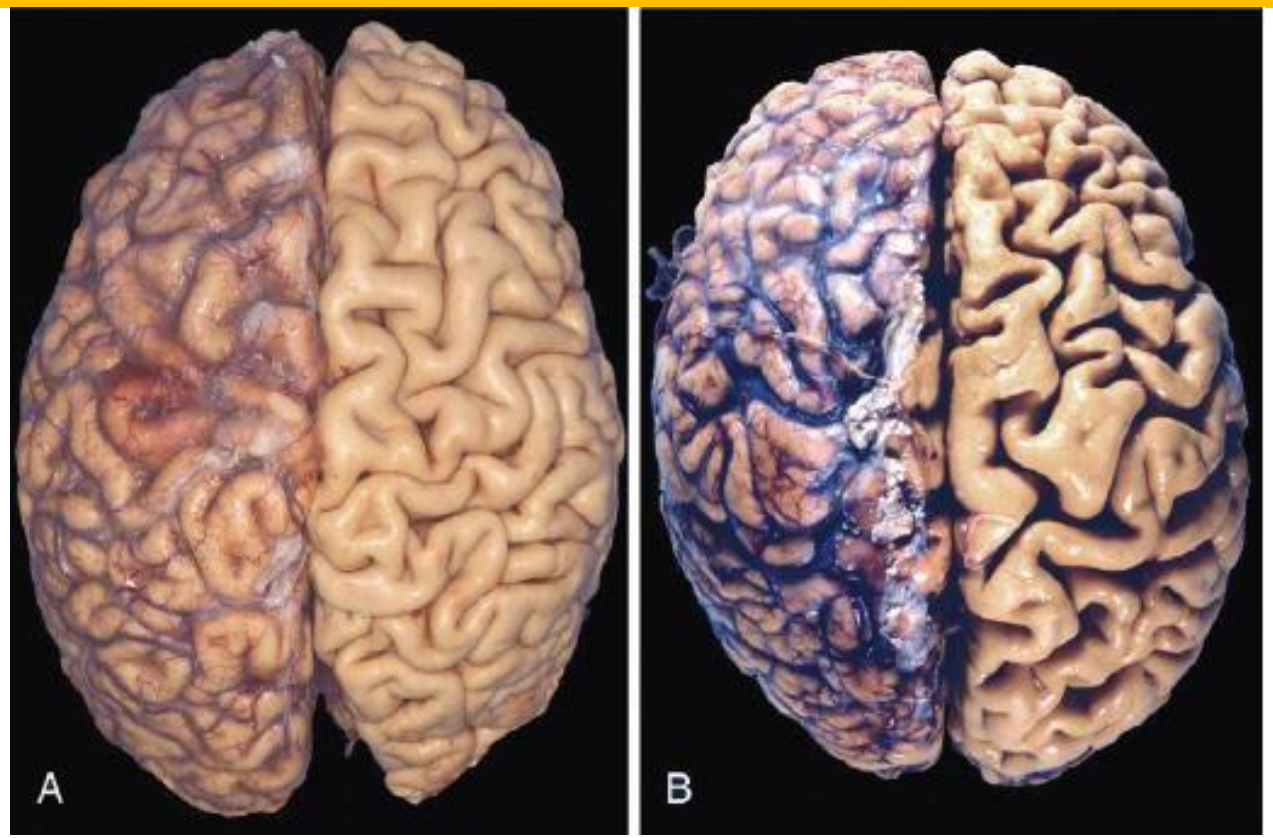
- Physiologic:
- Embryology: Notochord and thyroglossal duct
- Uterus after delivery of the baby
- Pathologic: Local or generalized

Atrophy

- Decreased workload (atrophy of disuse).
- Loss of innervation (denervation atrophy).

- Diminished blood supply.
- Inadequate nutrition.
- Loss of endocrine stimulation
- Pressure

Atrophy



Atrophy

- Atrophy results from decreased protein synthesis and increased protein degradation in cells.