CELLULER RESPONSES : ADAPTATION, INJURY, DEATH

Dian Yuliartha Lestari

PATHOLOGY

- Suatu ilmu yang mempelajari perubahan struktur, biokimia, serta fungsi sel, jaringan dan organ yang mendasari terjadinya suatu penyakit
- Merupakan jembatan dari ilmu kedokteran dasar (basic sciences) dan ilmu klinis (Clinical medicine)
- Ada 2 macam :
  - *General Pathology : reaksi umum dari sel atau jaringan akibat adanya stimulus, contoh : radang akut*
  - *Systemic Pathology : mempelajari hubungan dan mekanisme dasar yang terjadi pada organ spesifik suatu penyakit tertentu, contoh : ischemic heart disease*
- Inti Pathology :
  - *Etiologi*
  - *Pathogenesis*
  - *Morphologic changes*
  - *Clinical Manifestation*

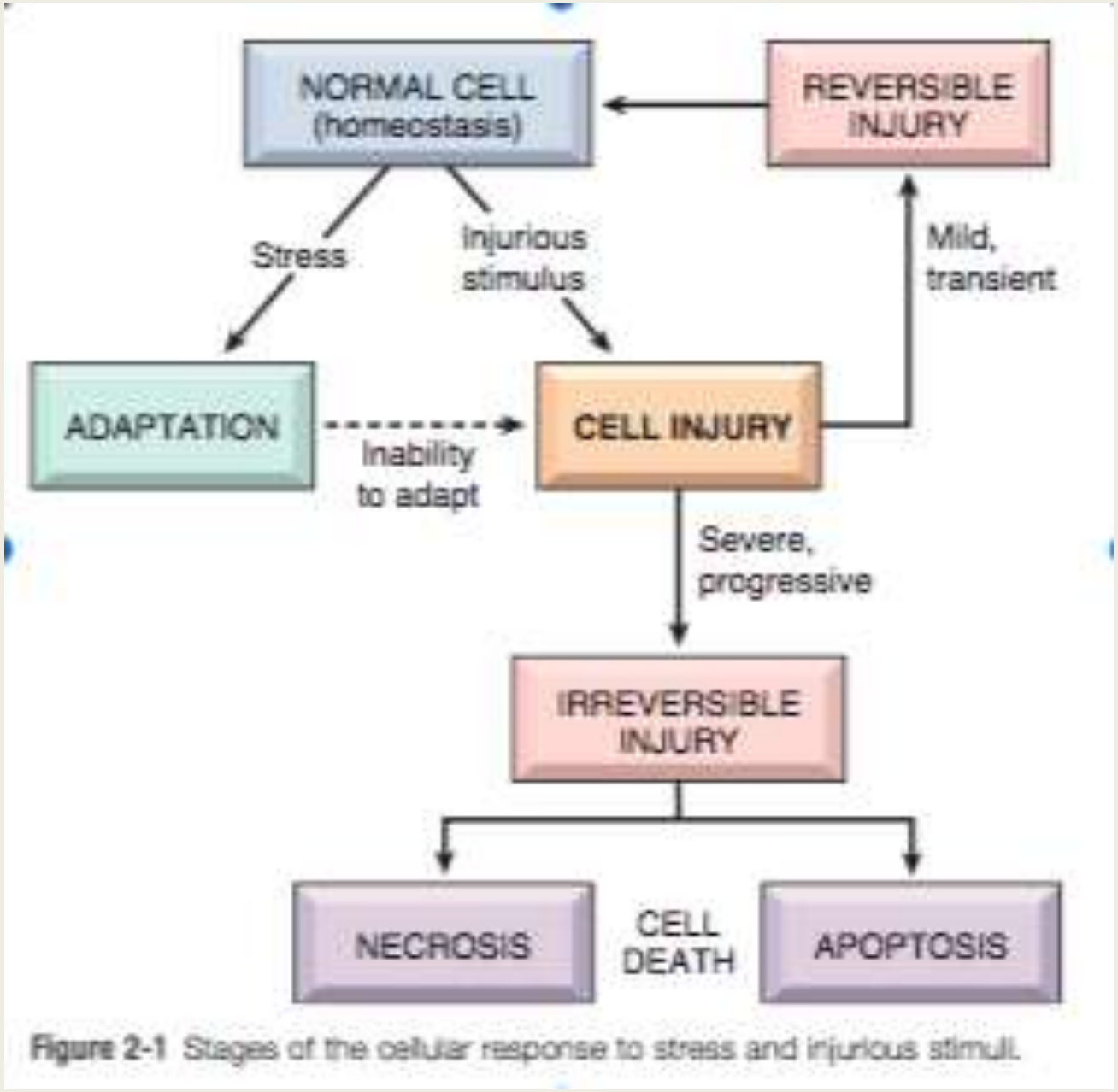
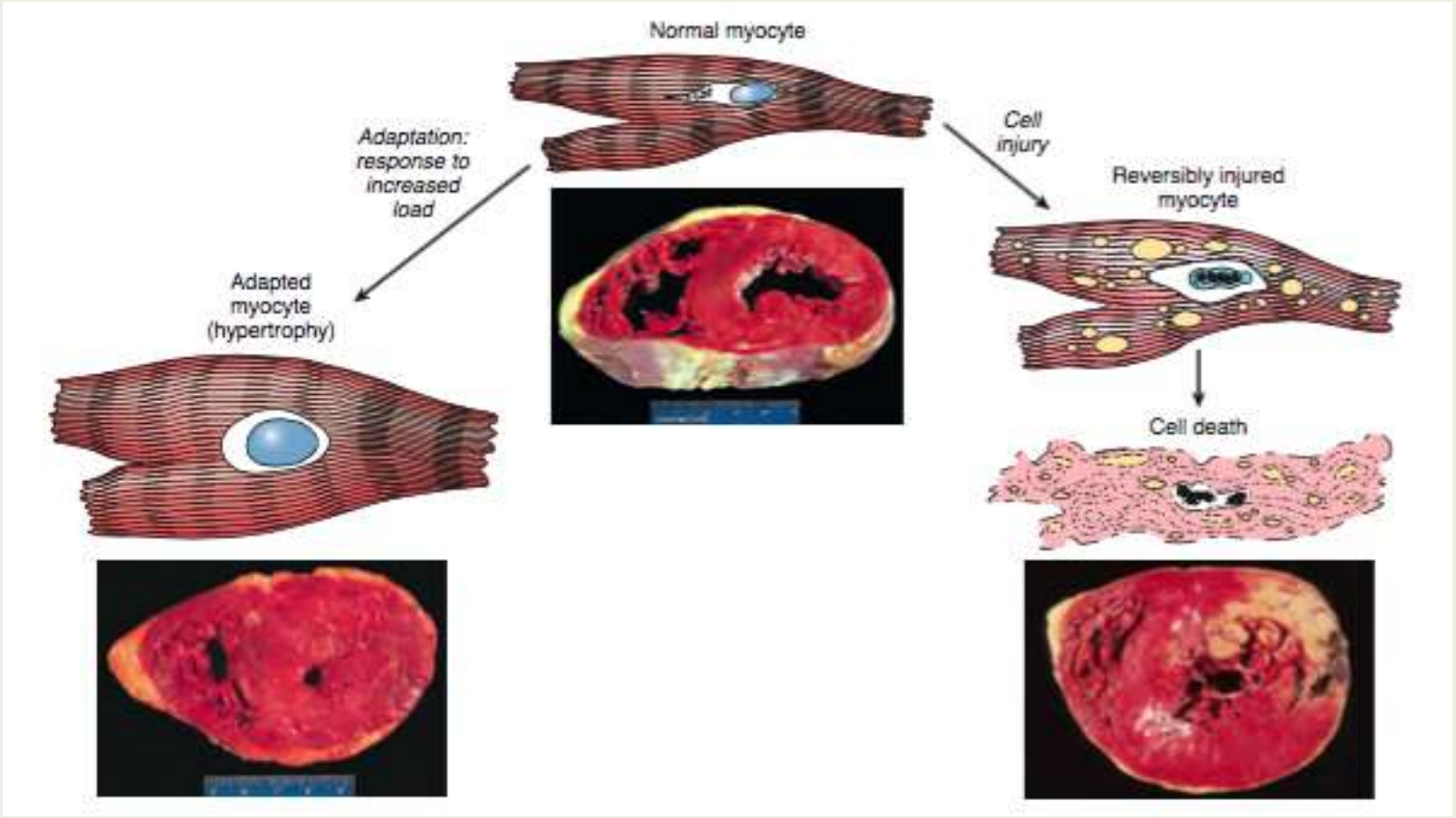
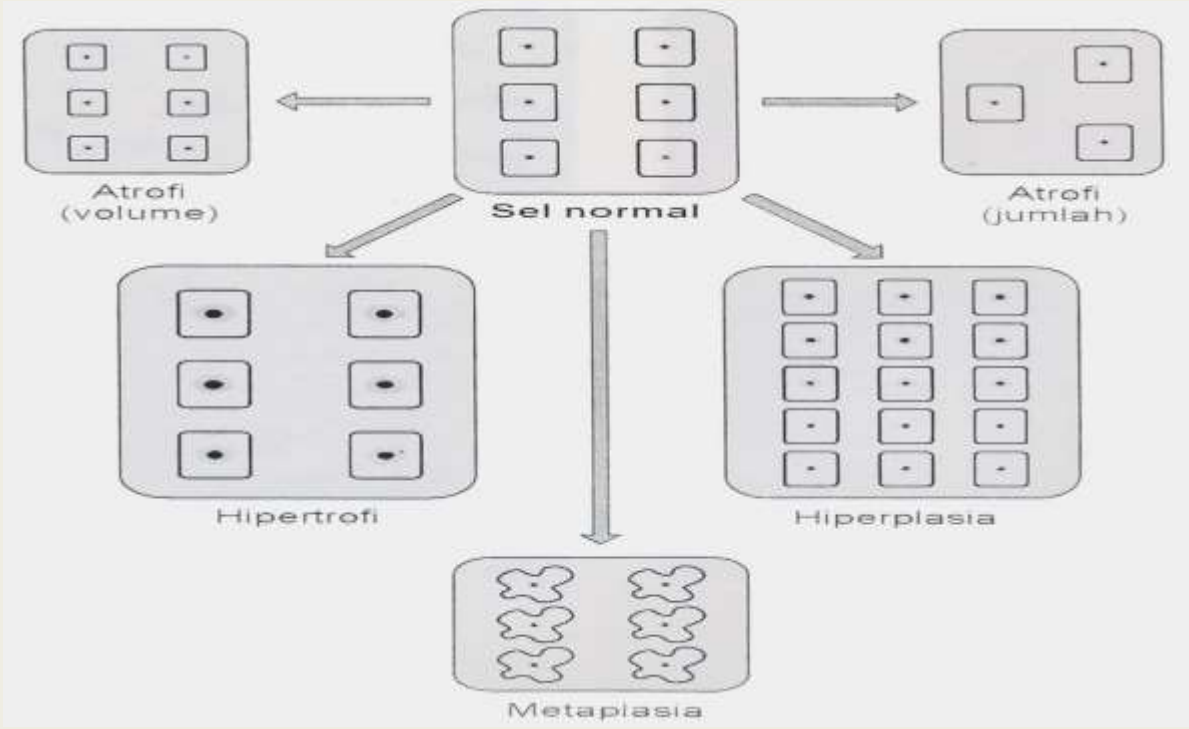


Figure 2-1 Stages of the cellular response to stress and injurious stimuli.


Normal myocyte
Adaptation: response to increased load
Cell injury
Adapted myocyte (hypertrophy)
Reversibly injured myocyte
Cell death

ADAPTASI

- Penyesuaian sel atau jaringan secara reversible akibat adanya rangsangan lingkungan atau jejas sehingga terjadi perubahan morfologi dan fungsi
- Ada 4 macam :
  - *Hipertrofi*
  - *Hiperplasia*
  - *Atrofi*
  - *metaplasia*

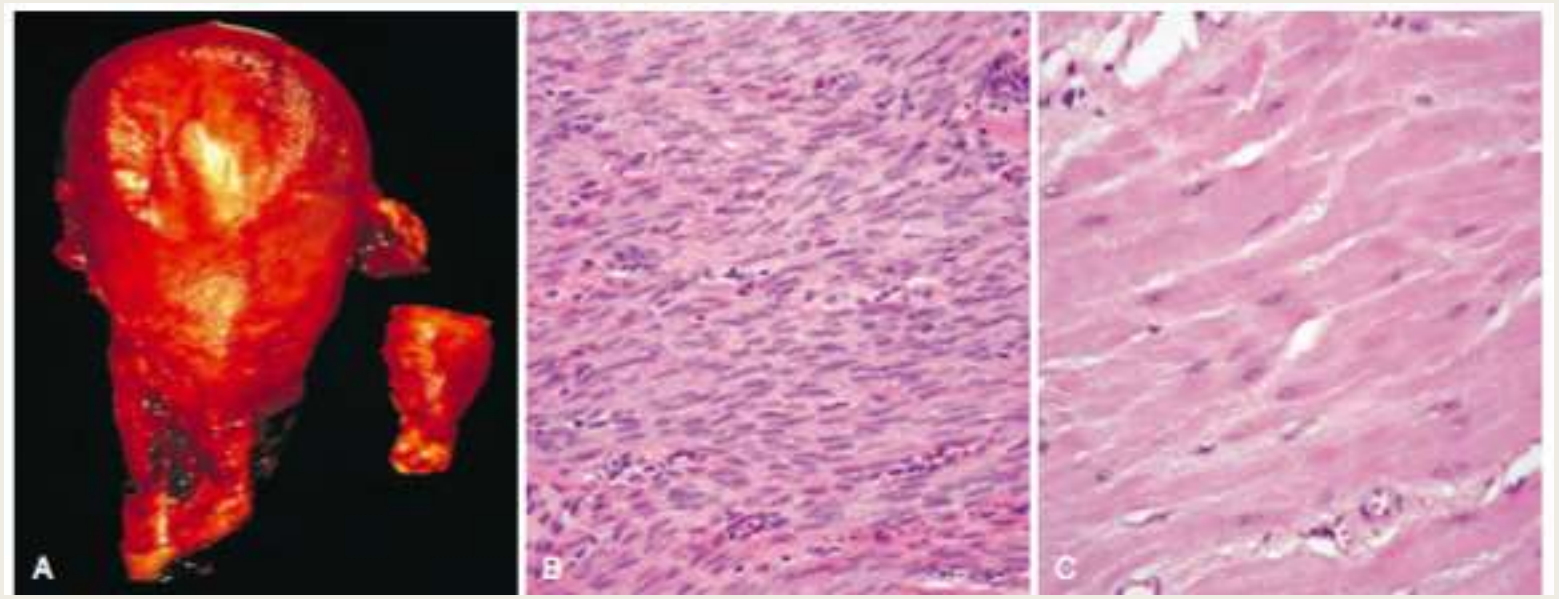


HIPERTROFI

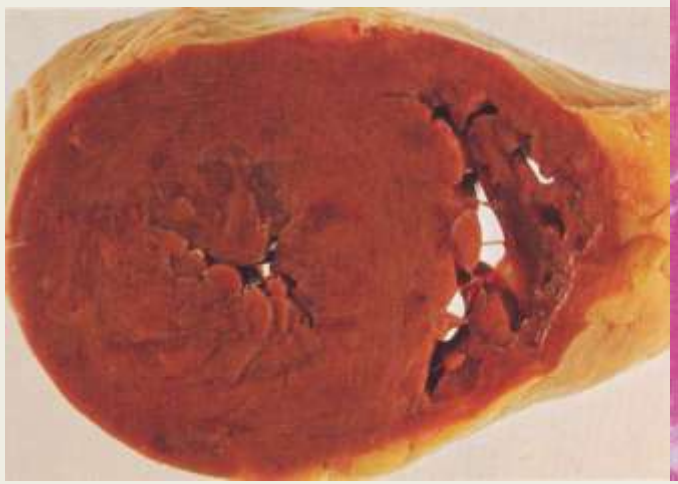
- Bertambah besarnya ukuran sel karena bertambah jumlah ultrastuktur dalam sel, bukan karena penambahan cairan intrasel
- Sering terjadi pada :
  - *Otot jantung*
  - *Otot skelet*

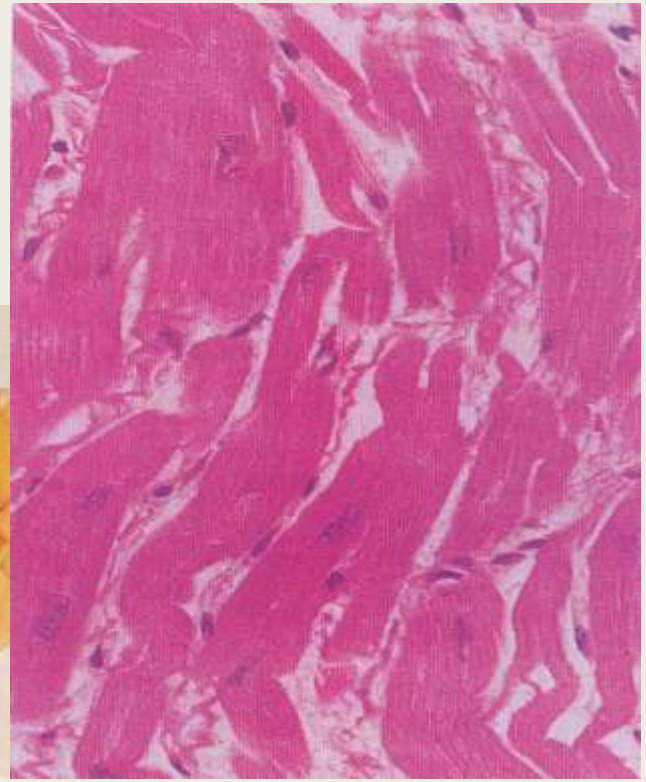
→ Karena kedua otot tersebut tidak mampu meningkatkan metabolisme nya untuk melakukan mitosis

- Dapat merupakan kondisi :
  - *Fisiologis → Myometrium saat kehamilan*
  - *Pathologis → Left ventrikel hypertrophy akibat hipertensi*
- Etiologi
  - *Fungsi sel meningkat karena beban meningkat*
  - *Stimulasi hormonal*



Makroskopis : organ bertambah besar dan berat
Mikroskopis : sel bertambah besar





HUKUM STARLING

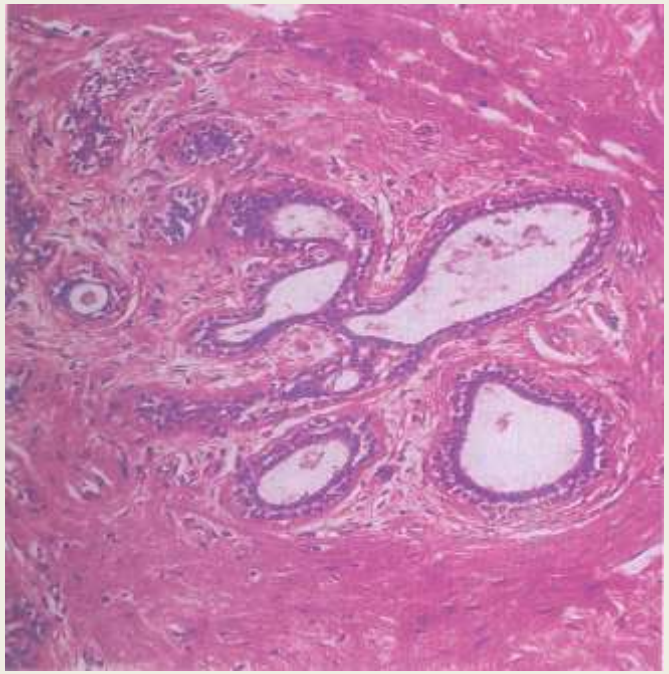
“Apabila suatu otot di regang melebihi batas ambang regangnya maka otot itu akan berhenti meregang dan apabila tetap dipaksa maka otot akan putus”

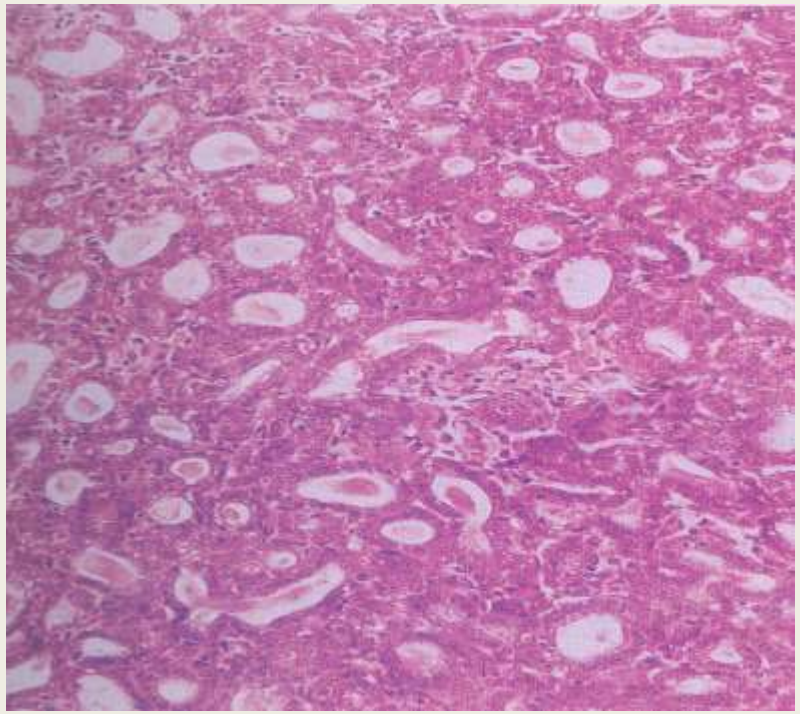
- Contoh : pada LVH akan terjadi lisis dari miosit dan hilangnya miofibrilar contraction agent sehingga terjadi miocyte death, berakibat cardiac failure

HIPERPLASIA

- Bertambahnya jumlah sel akibat rangsang atau stimulus tertentu
- Biasanya diikuti dengan hipertrofi organ
- Didapatkan 2 kondisi :
  - *Fisiologis : Kelenjar endometrium akibat kehamilan. Payudara saat lactasi*
  - *Patologis : Benign Prostat Hyperplasia (BPH), Adenomatous Goiter*
- Tidak semua sel bisa melakukan hiperplasia → yang memiliki kemampuan untuk mitosis

- Daya mitosis tinggi :
  - *Epitel kulit* - *Epitel usus halus*
  - *Hepatosit* - *Sel sumsum tulang*
- Daya mitosis rendah
  - *Tulang rawan, tulang & otot polos*
- Tak memiliki daya mitosis
  - *Sel saraf* - *Otot jantung*
  - *Otot skelet*





ATROFI

- Bertambah kecilnya sel setelah sel tersebut dalam keadaan normal
- Bertambah sedikit jumlah sel setelah sel tersebut dalam keadaan normal
- Etiologi :
  - *Decrease of workload (atrophy of disuse)*
  - *Loss of innervation (denervation atrophy)*
  - *Diminished blood supply*
  - *Inadequate nutrition*
  - *Loss of endocrine stimulation*
  - *Tissue compression*

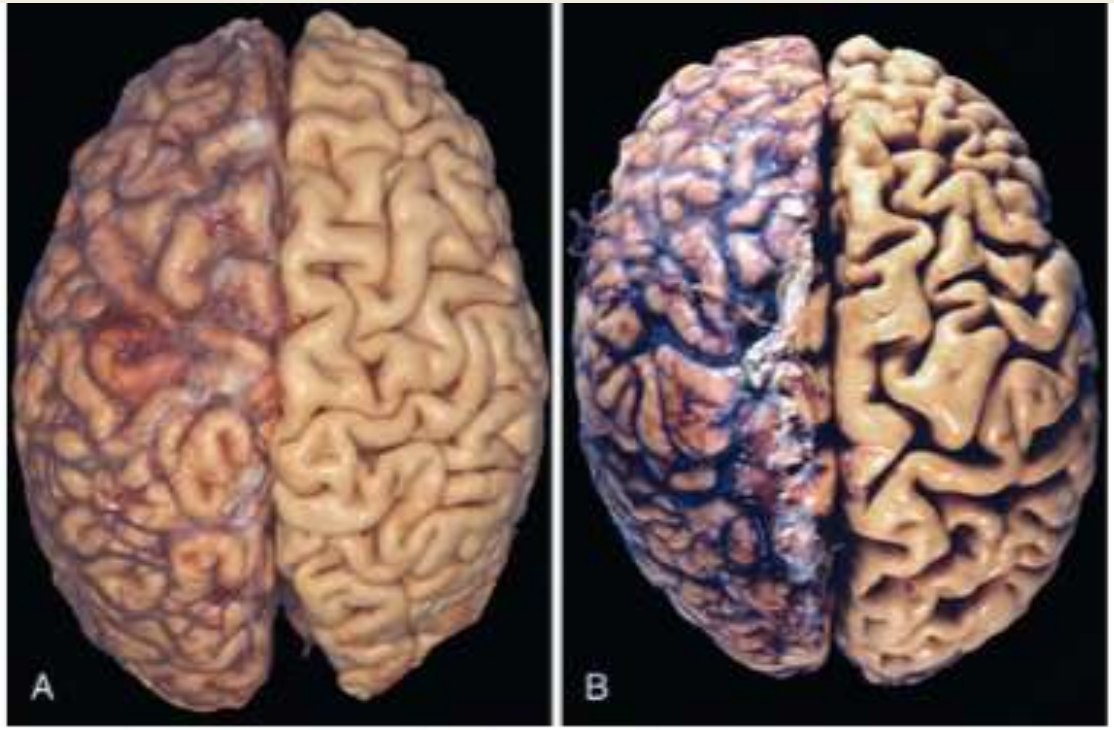
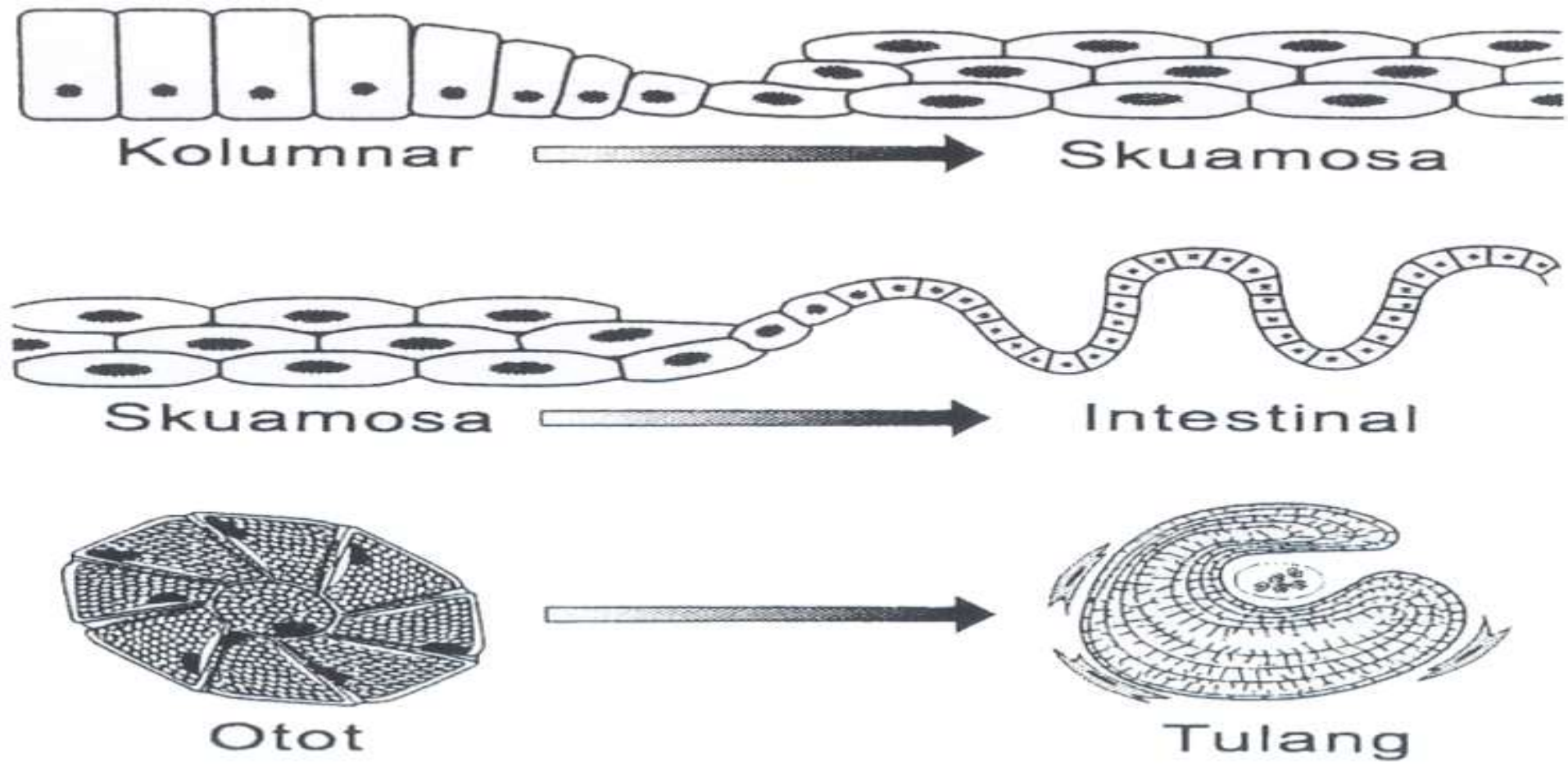
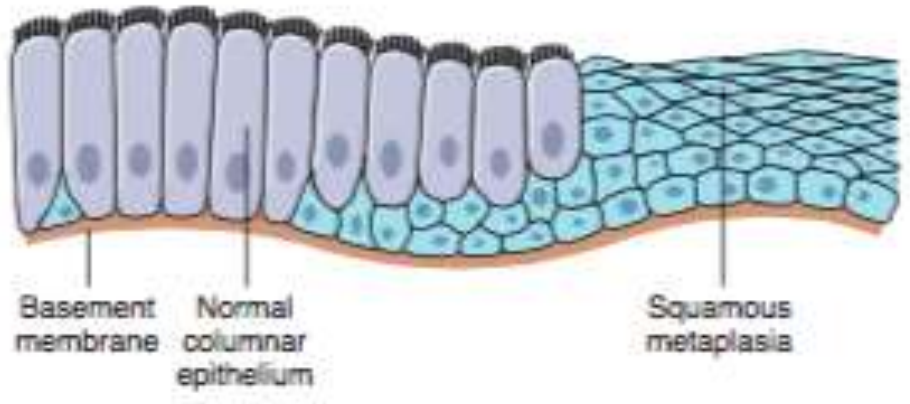


Figure 2-5 Atrophy. **A,** Normal brain of a young adult. **B,** Atrophy of the brain in an 82-year-old man with atherosclerotic cerebrovascular disease, resulting in reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges have been stripped from the right half of each specimen to reveal the surface of the brain.

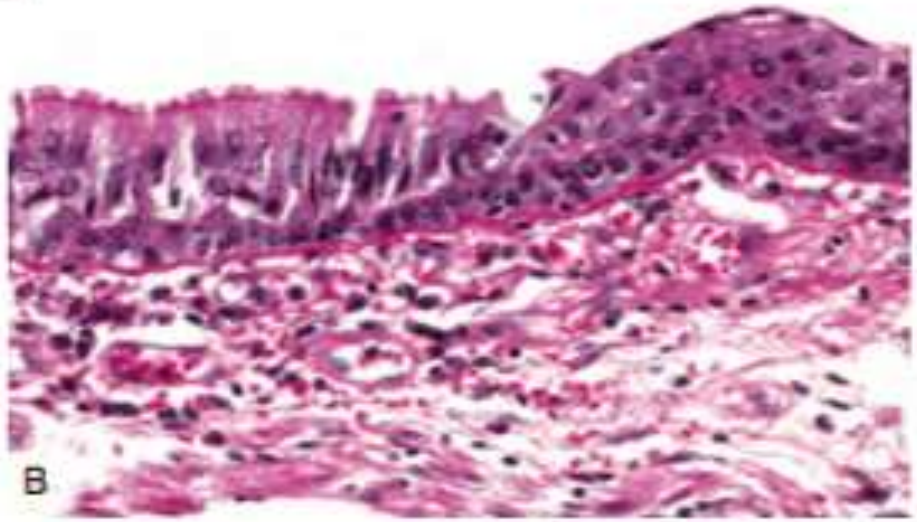
METAPLASIA

- Berubahnya suatu sel dewasa (epitel atau mesenchimal) menjadi tipe sel dewasa lain





A



B

Figure 2-6 Metaplasia of columnar to squamous epithelium. **A,** Schematic diagram. **B,** Metaplasia of columnar epithelium *(left)* to squamous epithelium *(right)* in a bronchus.

DISPLASIA

“Berubahnya sel yang meliputi bentuk, ukuran dan susunannya” bukan termasuk reaksi adaptasi

Disebut juga : ***Borderline to Neoplasm***

Epitel yng mengalami displasi mempunyai sifat :

1. Kehilngan orientasi thd sel sekitarnya
2. Berubah dlm bentuk dan ukuran sel
3. Berubah reaksinya thd pengecatan

Morfologi :

-Epitel melebar
-Maturasi sel tak normal
-Inti basofil

-Proliferasi stratum basale
- Mitosis tdk hanya di basal
- Mitosis normal

HIPOPLASIA – APLASIA - AGENESIS

HIPOPLASIA

Kegagalan untuk mencapai perkembangan yang sempurna, sehingga menjadi organ yang lebih kecil daripada normal, fx < normal kadang msh bisa mencukupi kebutuhan

APLASIA

Organ terbentuk tapi sangat tak sempurna, kecil dan fx tak mencukupi kebutuhan

AGENESIS

Organ tidak terbentuk sama sekali

CELL INJURY

- REVERSIBLE INJURY → Apabila rangsangan/jejas dihilangkan, maka sel akan kembali seperti semula
- Hallmark :
  - *Penurunan fosforilasi oksidative dengan hasil deplesi ATP*
  - *Intracellular swelling akibat kegagalan pompa natrium sehingga air masuk ke intrasel*
- CELL DEATH → irreversible injury
  - *Nekrosis*
  - *Apoptosis*

Penyebab Cell Injury

- Oxygen deprivation (hypoxia)
- Physical agent (temperatur, mechanical, radiation, etc)
- Infectious agents
- Immunologic reaction
- Genetic dearrangement
- Nutritional imbalance

Mechanism cell injury

- Tingkat kerusakan bergantung dari jenis trauma, jumlah, dan durasi
- Tingkat konsekuensi kerusakan sel bergantung dari tipe, status dan kemampuan sel beradaptasi
- Kerusakan sel merupakan hasil dari beberapa mekanisme seluler

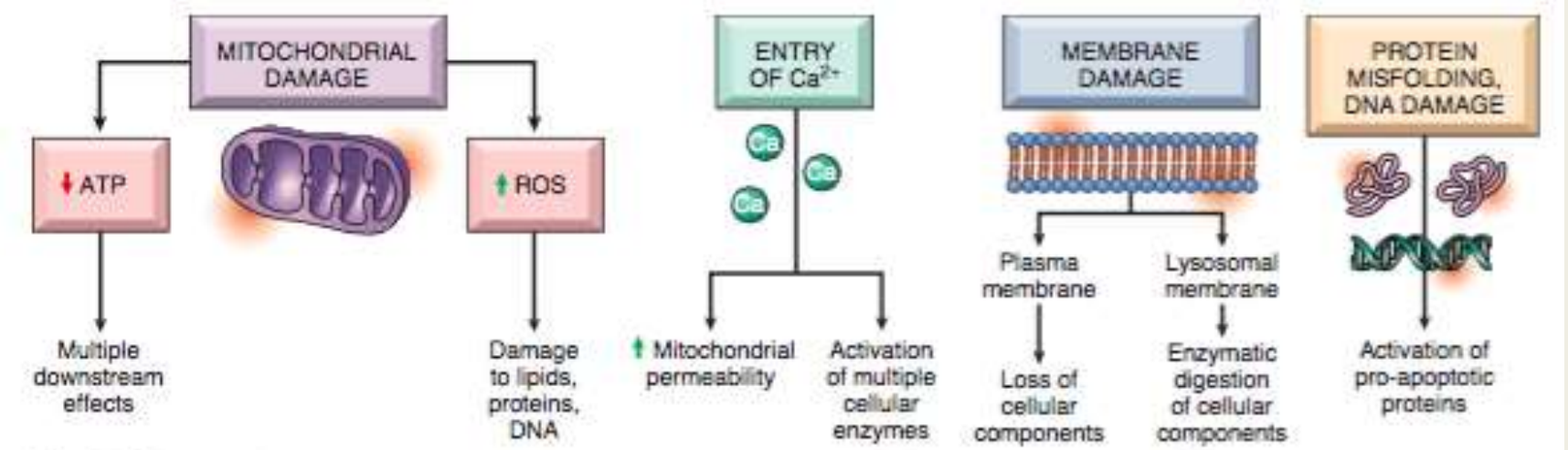
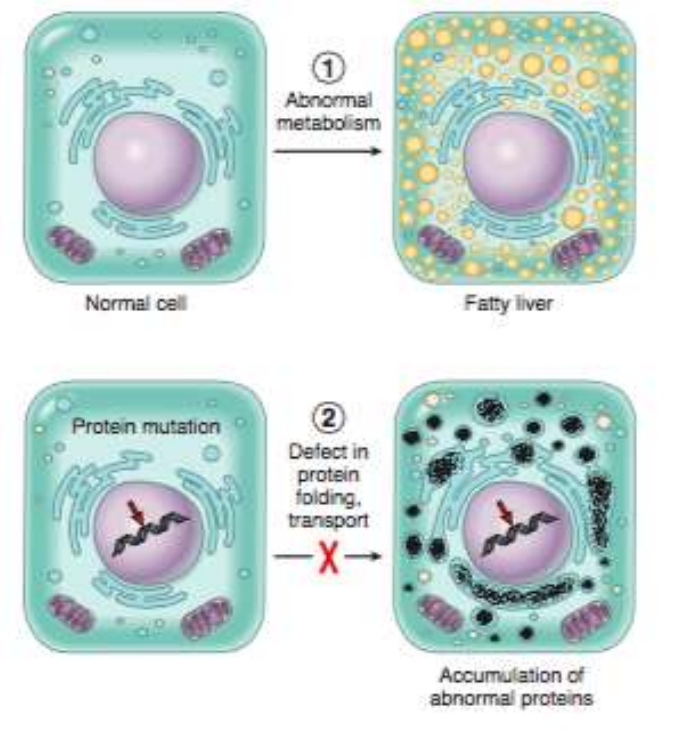


Figure 2-16 The principal biochemical mechanisms and sites of damage in cell injury. ATP, Adenosine triphosphate; ROS, reactive oxygen species.

Reversible injury

- Ada 2 keadaan yang dapat dilihat :
- *Cellular swelling → terjadi jika sel tidak mampu untuk mempertahankan homeostasis ion dan cairan akibat kegagalan pompa pada membran sel*
- *Fatty change → terjadi akibat hipoksia atau bahan toksik, ditandai dengan adanya lipid vacuole pada sitoplasma. Biasa terjadi pada hepatosit dan myocardial cell*



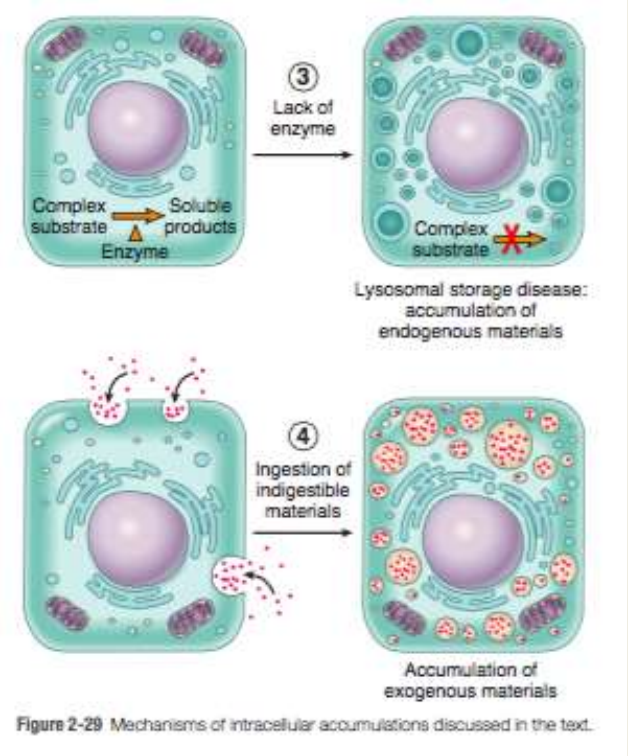


Figure 2-29 Mechanisms of intracellular accumulations discussed in the text.

Degenerasi Albuminous

- Etiologi : terganggunya metabolisme protein dan air ok kekerasan/jejas yang ringan → cairan masuk > keluar
- Gangguan pada :
  - *Respirasi sel*
  - *Sintesis ATP*
  - *Pompa Na*
- Makros : organ lbh pucat, berat, tegang, turgor ↑
- Mikros : sel edema didesak oleh ruang kapiler
- Prognosa : baik (tdk menyebabkan ggn fungsi) → ttp mrpk tanda penting ok dpt mjd lebih berat

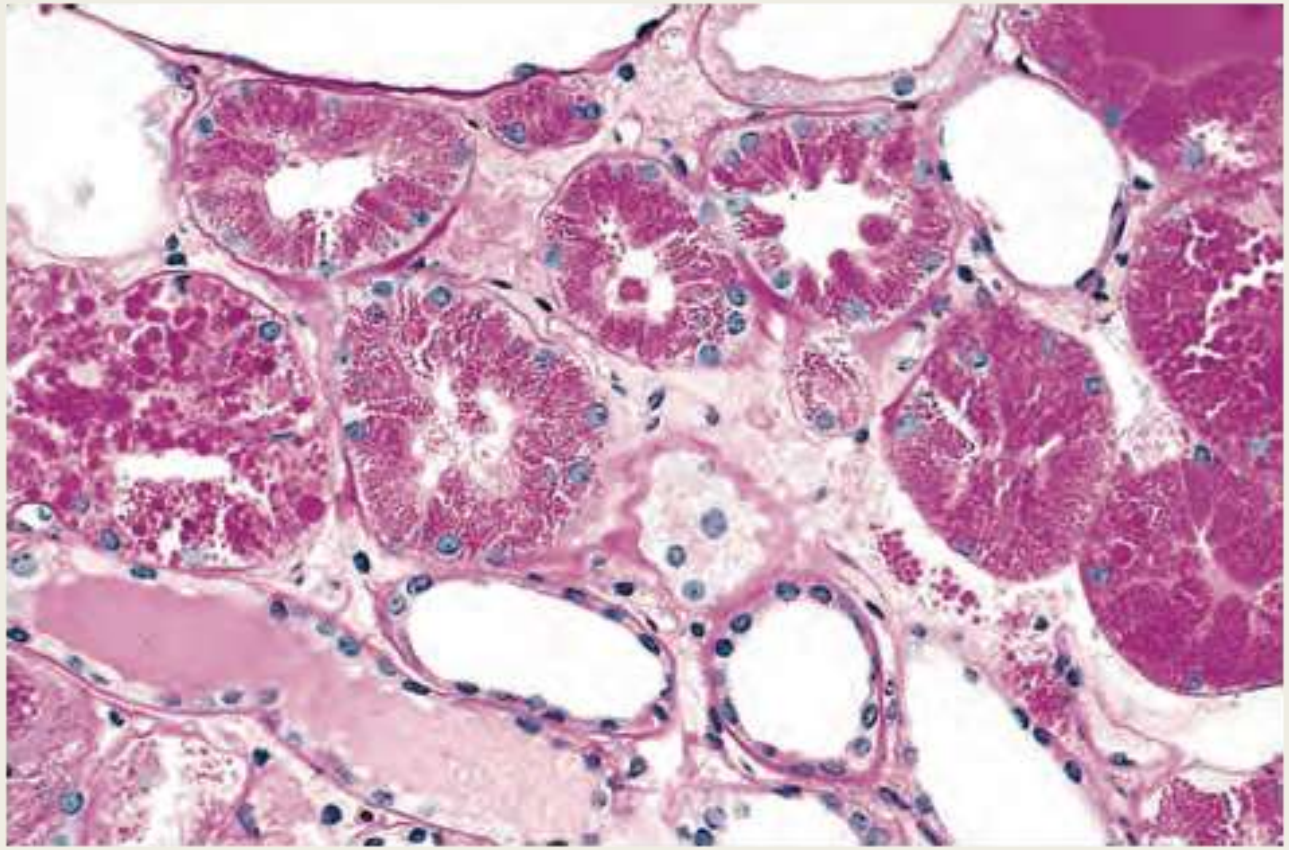


Figure 2-32 Protein reabsorption droplets in the renal tubular epithelium. (Courtesy Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)

Degenerasi Hidrofik

- Merupakan kelanjutan dari degenerasi albuminous
- Disebut juga: ‘Hydrophic change’ / ‘Vacuolar degeneration’
- Air terus masuk ke dalam sel → vakuola dlm sitoplasma yang dapat membesar & mendesak organel dalam sel
- Sering mengenai :
  - *tubulus proksimalis ginjal,*
  - *sel hati*
  - *sel otot jantung*
  - *Hipokalemia*

** Keracunan CCL4*
** Suhu tinggi*
** penyakit infeksi*

Degenerasi Hidrofik

- Makros: organ menjadi agak keras dan kepucatan serta bertambah besar
- Mikros : - terlihat rongga jernih dalam sitoplasma

  - sukar dibedakan dgn lemak tnp pengecatan khusus
- Prognosa : baik, tidak ada gangguan fungsi

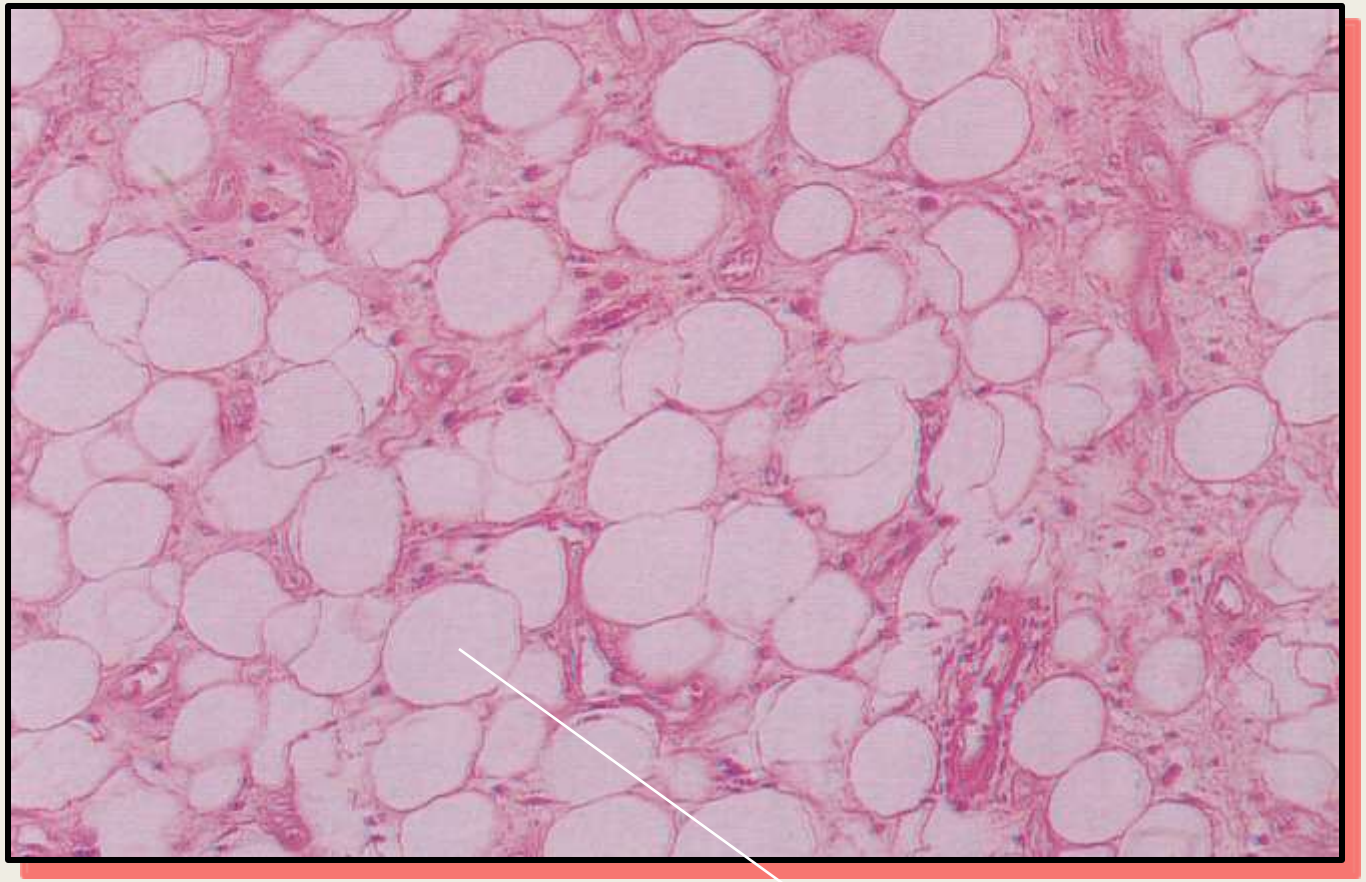
Degenerasi Lemak

- Penimbunan lemak dalam sel yang bersifat reversibel yang menyebabkan gangguan fungsi
- Disebut juga: *'FATTY CHANGE'*
- Sering pada hati, ginjal, jantung
- Indikator akan terjadinya nekrosis
- Etiologi :
  - *Bahan kimia : alkohol, CCl4, fosfor, ethionine*
  - *Jejas biologik : bakteri/ virus*
  - *Jejas nutrlsi : ekses / defisiensi*

Perlemakan Hepar (Fatty Liver)

- Makros: Hati membesar (berat mencapai 5-6 kg), warna kuning, konsistensi lunak, tepi rata dan tumpul
- Mikros: vakuola-vakuola lemak dlm sitoplasma shg inti terdesak, shg sel seolah-olah hanya membran sel dgn inti ditepi, sedang sitoplasma kosong, ok lemak larut dlm proses pembuatan sediaan

Degenerasi Lemak



Vakuol lemak dlm sitoplasma

Irreversible injury → Cell Death

- Ada 2 macam :
  - *Nekrosis → kematian sel yang bersifat irreversible akibat jejas yang melebihi batas sel untuk beradaptasi*
  - *Apoptosis → kematian sel yang terprogram*
- Nekroptosis → kematian sel dimana dua mekanisme berjalan bersamaan yaitu nekrosis dan apoptosis
- Autofagia → proses sel mencerna atau memakan kandungan sel itu sendiri

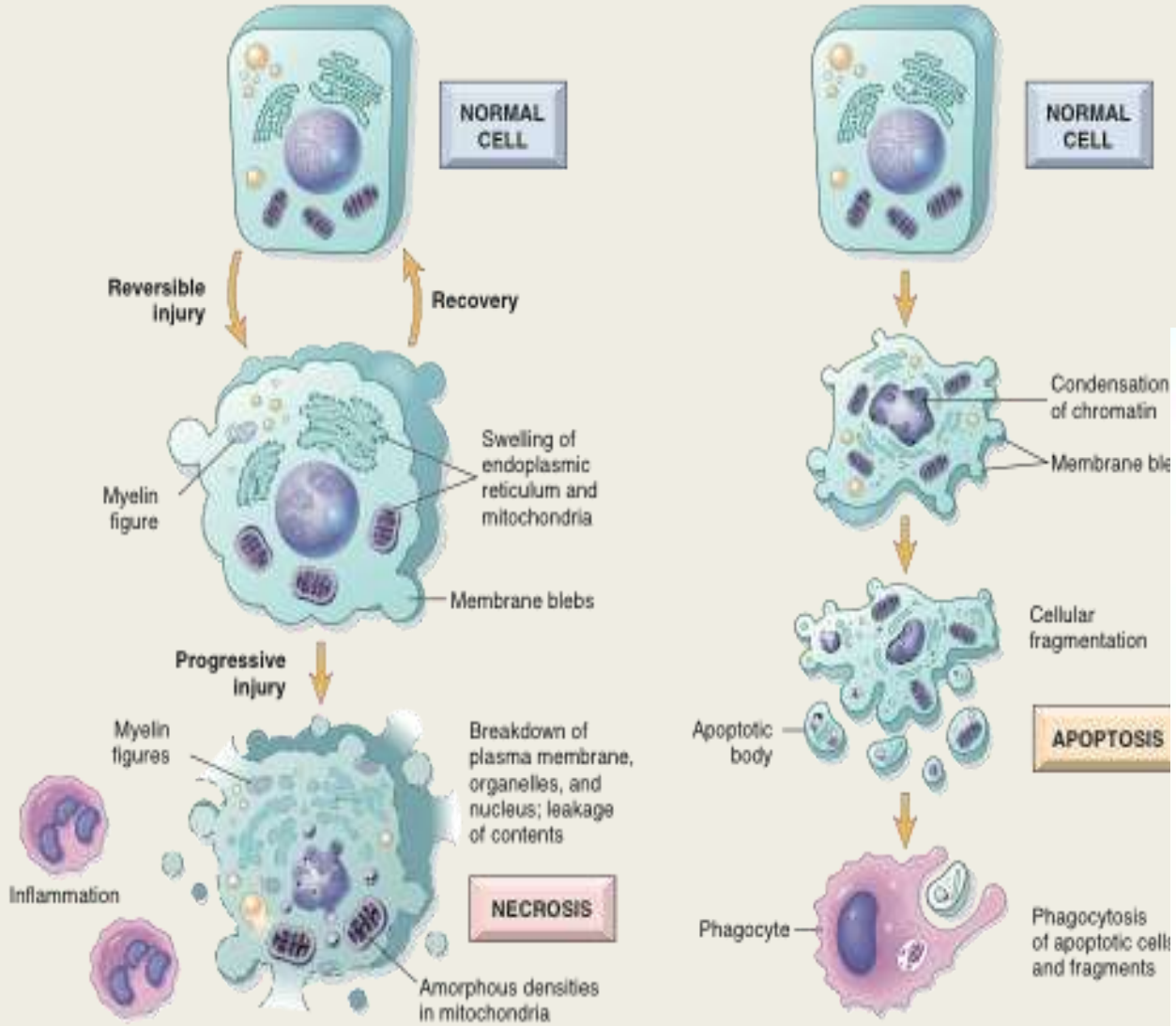


Figure 2-8 Schematic illustration of the morphologic changes in cell injury culminating in necrosis or apoptosis.

Table 2-2 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

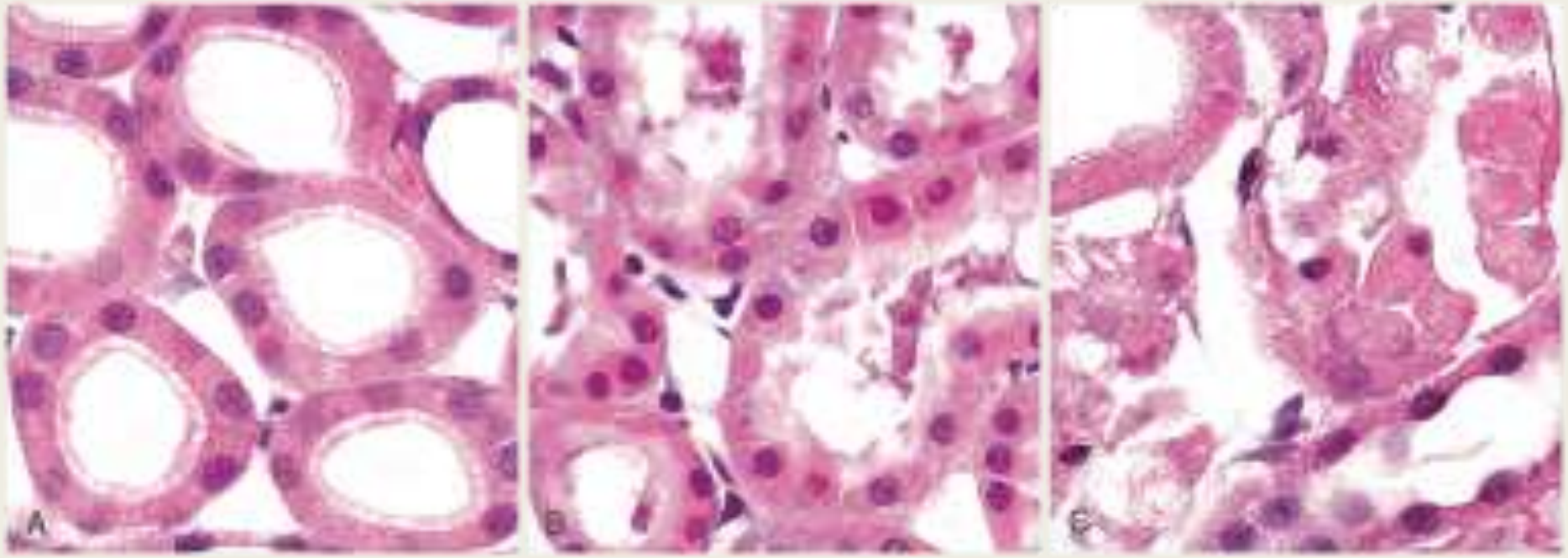


Figure 2-9 Morphologic changes in reversible cell injury and necrosis. **A,** Normal kidney tubules with viable epithelial cells. **B,** Early (reversible) ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. **C,** Necrosis (irreversible injury) of epithelial cells, with loss of nuclei, fragmentation of cells, and leakage of contents. The ultrastructural features of these stages of cell injury are shown in Fig. 2-10. (Courtesy Drs. Neal Pinckard and M. A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, Texas.)

Terdapat perubahan inti sel sebagai berikut :

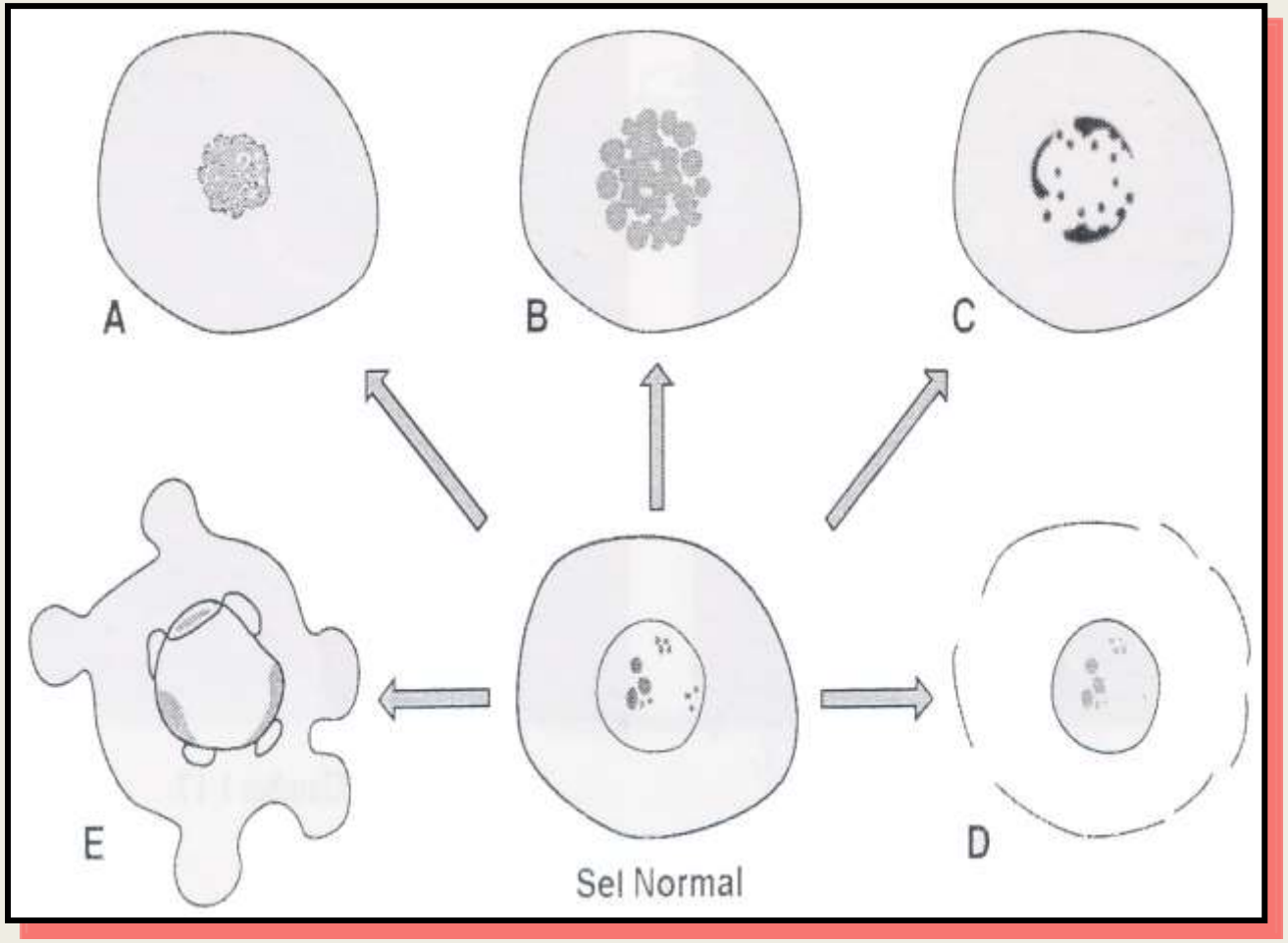
A. Piknotik

B. Kariorexis

C. Kariolisis

D. Ruptur membran sel

E. Apoptosis



MACAM NEKROSIS

1. ***Nekrosis LIQUEFAKSI (Nekrosis Perlunakan)***

   Sel yang mati dihancurkan oleh enzim proteolitik dengan cepat sehingga terjadi protein cair (sel mencair / hilang)

   Contoh : Jaringan otak yang mengalami anoksia

   Etiologi: infeksi bakteri (tu piogenik) → timbul jar. nekrotik yg banyak mgd cairan kaya akan protein dan sisa-sisa leukosit → PUS (nanah)

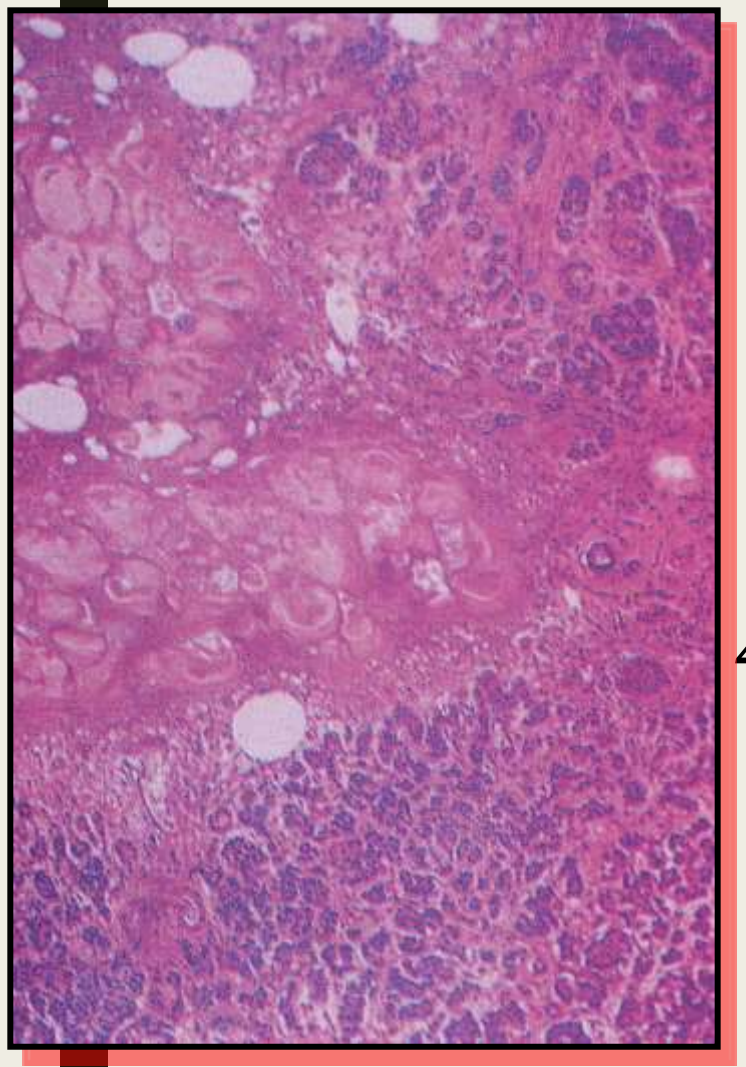
2. Nekrosis KOAGULASI

Bentuk sel (kerangka sel) masuk utuh, inti sel hilang dengan sitoplasma sangat eosinofilik

Contoh : keracunan fenol, formaldehid dan Hg

Tidak pernah terjadi pada Otak

3. Nekrosis KASEOSA



- disebut juga Nekrosis Pengejuan (putih seperti keju)
- merupakan gabungan antara nekrosis liquefaksi dgn nekrosis koagulasi
- Contoh : Infeksi TBC → mycobacterium tbc mengeluarkan enzym yg mgd lipopolisakarida dan mendenaturasi protein pecahan ikatan lemak → sel-sel mati akan berubah menjadi material seperti keju → disebut ***NEKROSIS PENGEJUAN***

4. Nekrosis ENZIMATIK

- Nekrosis yang disebabkan oleh reaksi enzimatik akut.
- Yang sering adalah enzim lipase pada jaringan lemak → lemak jadi hancur
- Contoh : Pankreatitis Akut

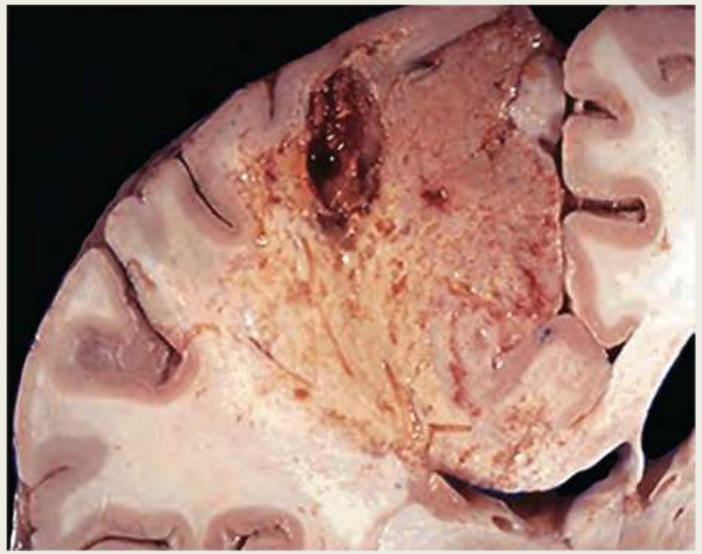
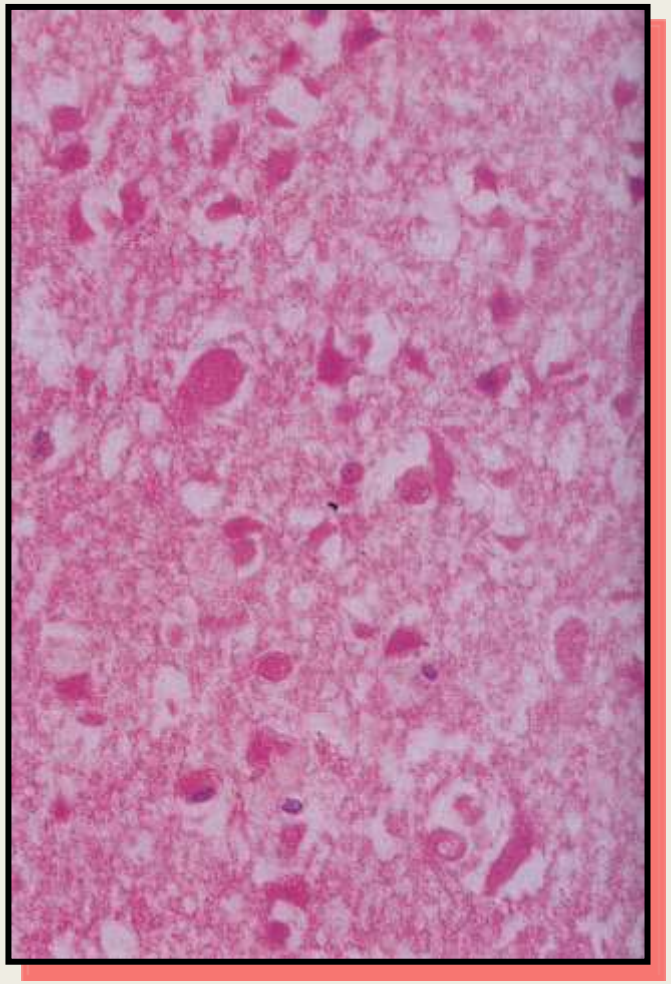


Figure 2-12 Liquefactive necrosis. An infarct in the brain, showing dissolution of the tissue.



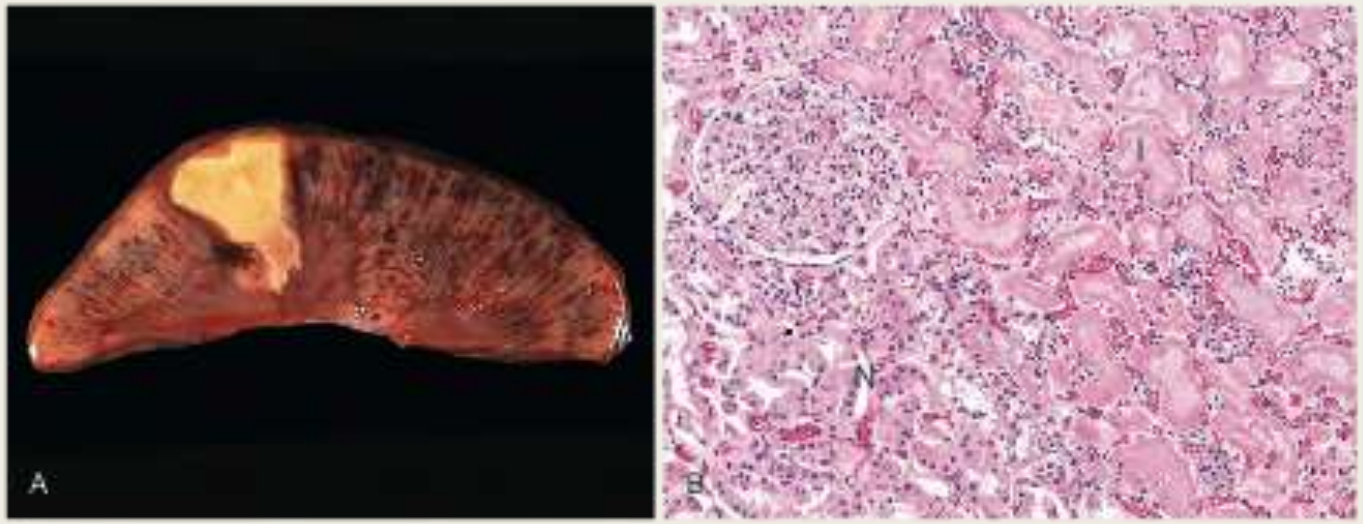
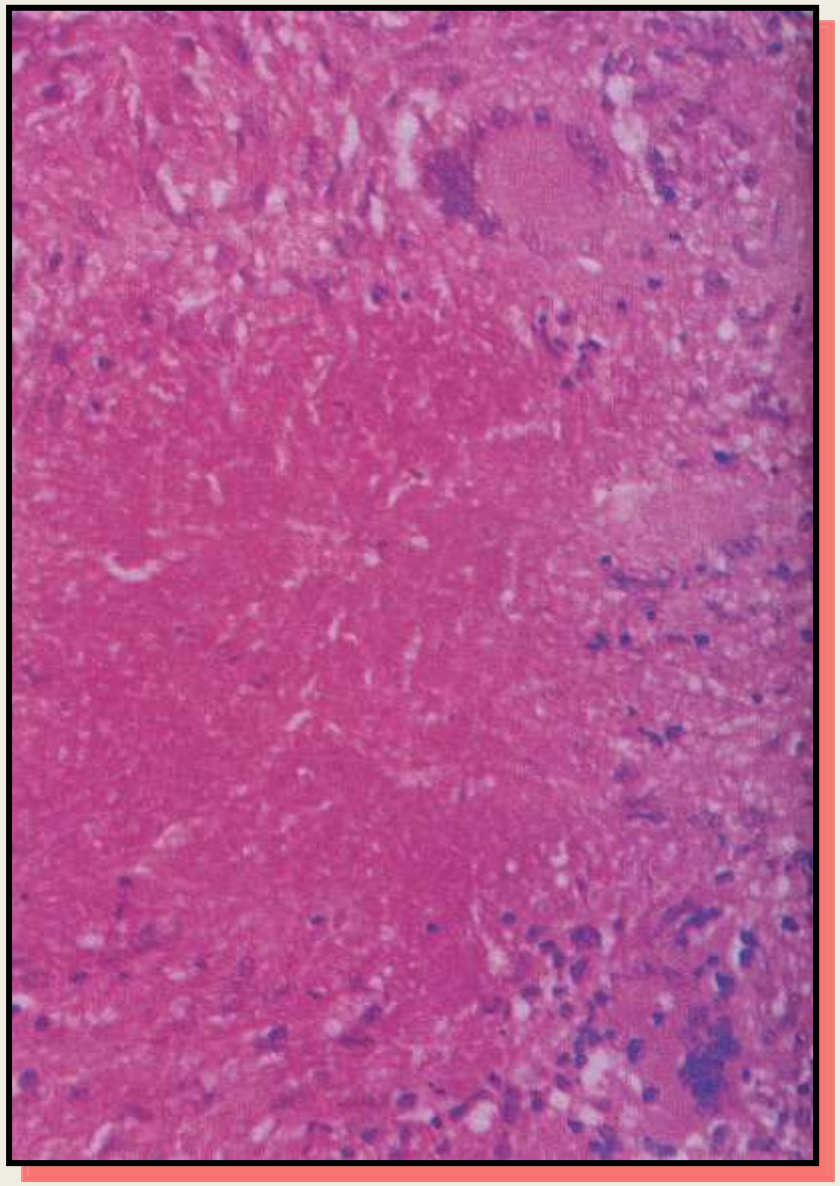


Figure 2-11 Coagulative necrosis. **A,** A wedge-shaped kidney infarct (yellow). **B,** Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I) showing preserved cellular outlines with loss of nuclei and an inflammatory infiltrate (seen as nuclei of inflammatory cells in between necrotic tubules).



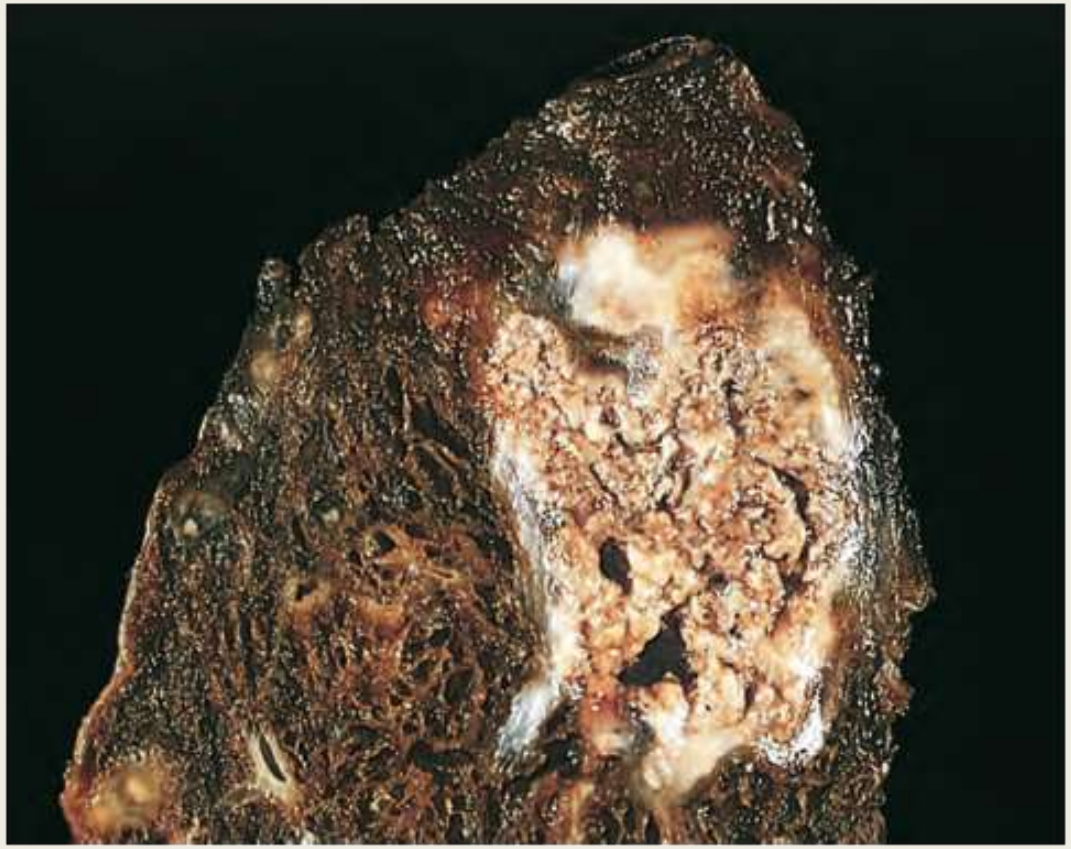


Figure 2-13 Caseous necrosis. Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white and cheesy debris.

Gangrenous necrosis is not a specific pattern of cell death, but the term is commonly used in clinical practice. It is usually applied to a limb, generally the lower leg, that has lost its blood supply and has undergone necrosis (typically coagulative necrosis) involving multiple tissue planes. When bacterial infection is superimposed there is more liquefactive necrosis because of the actions of degradative enzymes in the bacteria and the attracted leukocytes (giving rise to so-called **wet gangrene**).

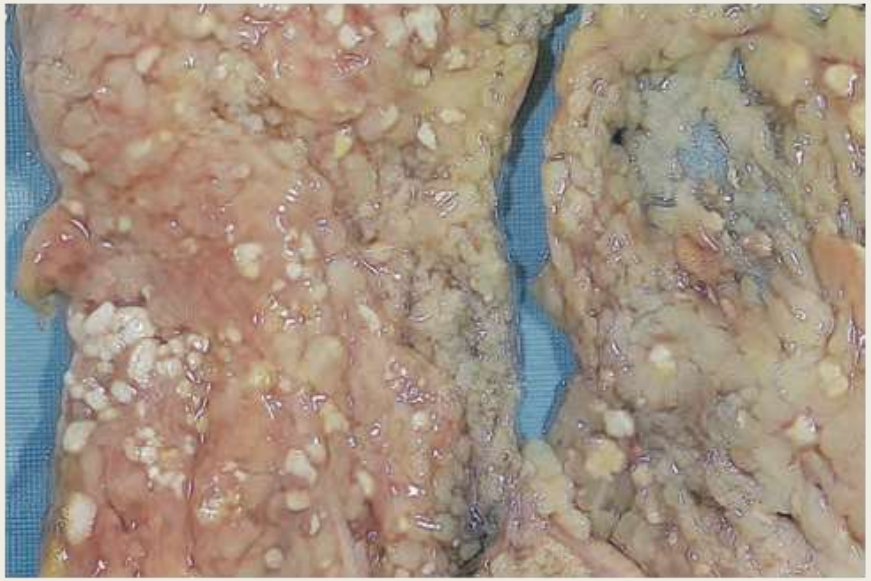


Figure 2-14 Fat necrosis. The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.

Fat necrosis is a term that is entrenched in medical parlance but does not in reality denote a specific pattern of necrosis. Rather, it refers to focal areas of fat destruction, typically resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. This occurs in the calamitous abdominal emergency known as acute pancreatitis (Chapter 19). In this disorder pancreatic enzymes leak out of acinar cells and liquefy the membranes of fat cells in the peritoneum. The released lipases split the triglyceride esters contained within fat cells. The fatty acids, so derived, combine with calcium to produce grossly visible chalky-white areas (fat saponification), which enable the surgeon and the pathologist to identify the lesions (Fig. 2-14). On histologic examination the necrosis takes the form of foci of shadowy outlines of necrotic fat cells, with basophilic calcium deposits, surrounded by an inflammatory reaction.

Fibrinoid necrosis is a special form of necrosis usually seen in immune reactions involving blood vessels. This pattern of necrosis typically occurs when complexes of antigens and antibodies are deposited in the walls of arteries. Deposits of these "immune complexes," together with fibrin that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains, called "fibrinoid" (fibrin-like) by pathologists (Fig. 2-15). The immunologically mediated vasculitis syndromes in which this type of necrosis is seen are described in Chapter 11.

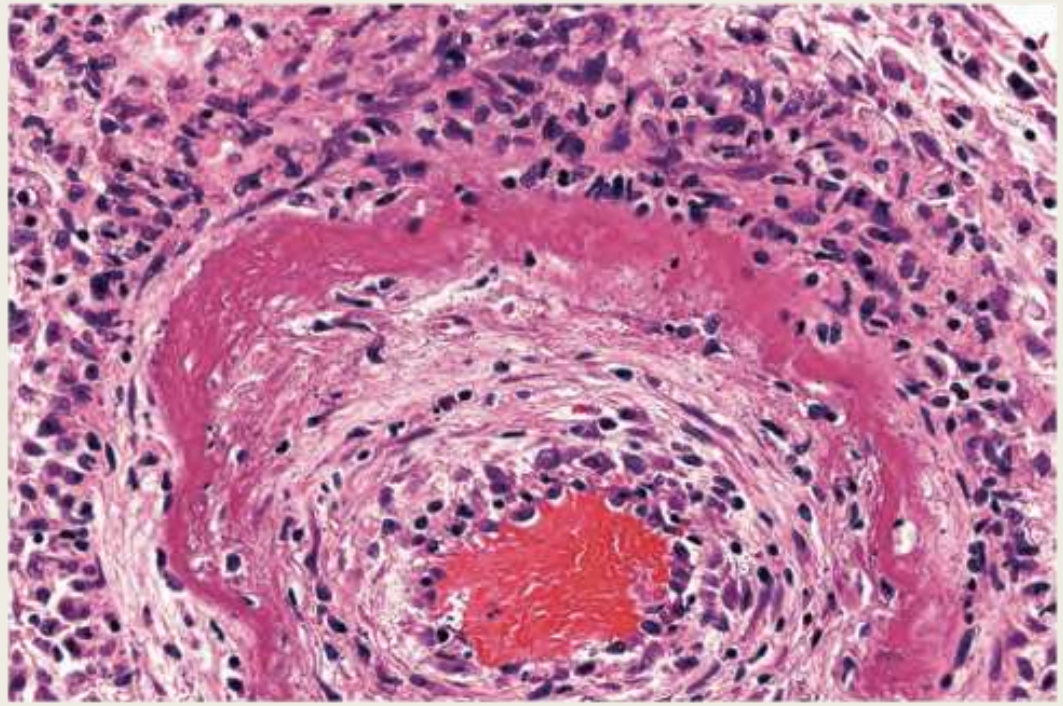


Figure 2-15 Fibrinoid necrosis in an artery. The wall of the artery shows a circumferential bright pink area of necrosis with inflammation (neutrophils with dark nuclei).

APOPTOSIS

- Adalah suatu jalur kematian sel yang dicetuskan oleh program bunuh diri dimana terjadi aktivasi intrinsik enzimatik yang berfungsi mendegradasi sel itu sendiri
- Penyebab apoptosis :
  - *Kondisi fisiologis : embriogenesis, involution of hormone-dependent tissue, cell loss in profilating population (imatur sel B dan sel T), elimination potentially harmful self reactive lymphocyte, death of host cell (neutrofil)*
  - *Kondisi pathologis : kerusakan DNA, akumulasi misfolded protein, kematian sel akibat infeksi, pathologic atrophy ec duct obstruction*

MORPHOLOGY

The following morphologic features, some best seen with the electron microscope, characterize cells undergoing apoptosis (Fig. 2-22, and see Fig. 2-8).

Cell shrinkage. The cell is smaller in size, the cytoplasm is dense (Fig. 2-22A), and the organelles, although relatively normal, are more tightly packed. (Recall that in other forms of cell injury, an early feature is cell swelling, not shrinkage.)

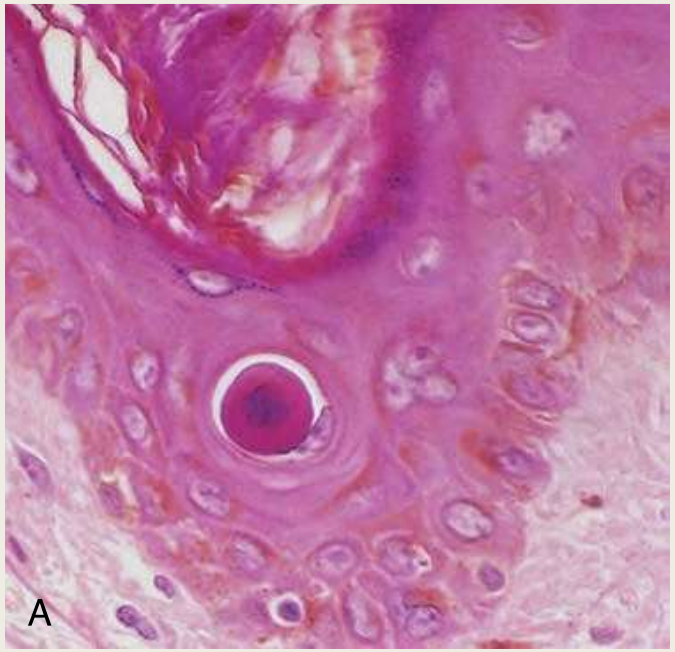
Chromatin condensation. This is the most characteristic feature of apoptosis. The chromatin aggregates peripherally, under the nuclear membrane, into dense masses of various shapes and sizes (Fig. 2-22B). The nucleus itself may break up, producing two or more fragments.

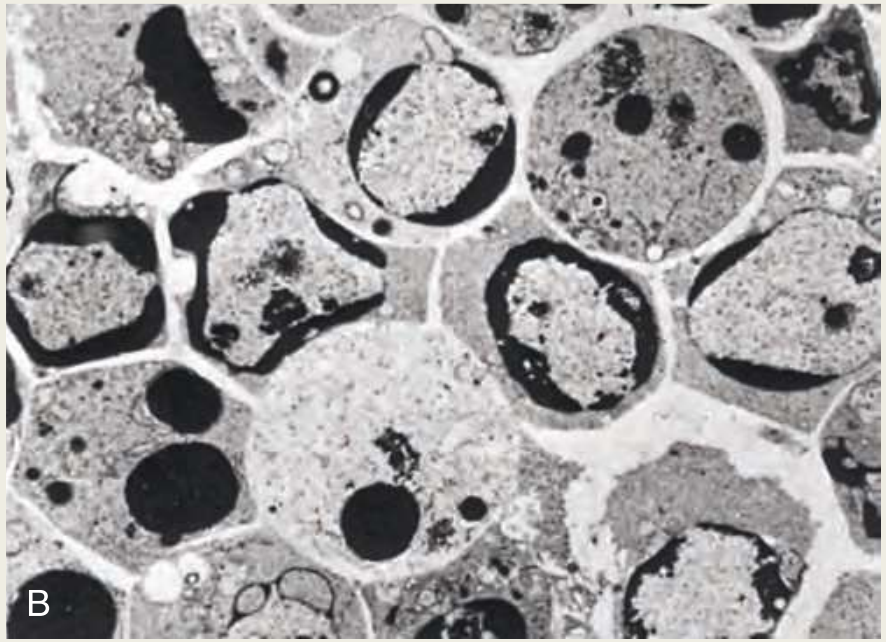
Formation of cytoplasmic blebs and apoptotic bodies. The apoptotic cell first shows extensive surface blebbing, then undergoes fragmentation into membrane-bound apoptotic bodies composed of cytoplasm and tightly packed organelles, with or without nuclear fragments (Fig. 2-22C).

Phagocytosis of apoptotic cells or cell bodies, usually by macrophages. The apoptotic bodies are rapidly ingested by phagocytes and degraded by the phagocyte's lysosomal enzymes.

Plasma membranes are thought to remain intact during apoptosis, until the last stages, when they become permeable to normally retained solutes.

On histologic examination, in tissues stained with hematoxylin and eosin, the apoptotic cell appears as a round or oval mass of intensely eosinophilic cytoplasm with fragments of dense nuclear chromatin (Fig. 2-22A). Because the cell shrinkage and formation of apoptotic bodies are rapid and the pieces are quickly phagocytosed, considerable apoptosis may occur in tissues before it becomes apparent in histologic sections. In addition, apoptosis—in contrast to necrosis—does not elicit inflammation, making it more difficult to detect histologically.





Mechanism apoptosis

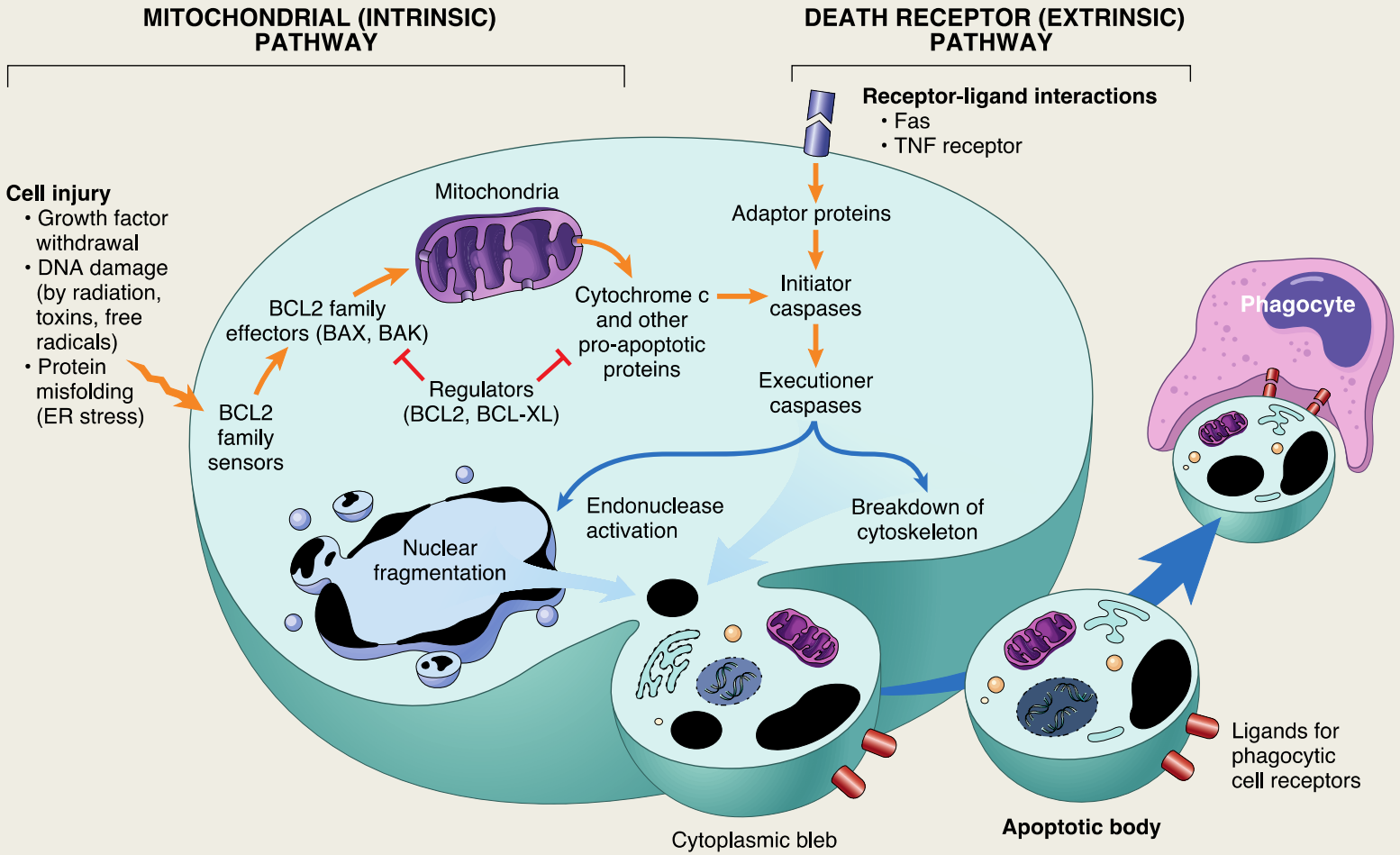


Figure 2-23 Mechanisms of apoptosis. The two pathways of apoptosis differ in their induction and regulation, and both culminate in the activation of caspases. In the mitochondrial pathway, proteins of the BCL2 family, which regulate mitochondrial permeability, become imbalanced and leakage of various substances from mitochondria leads to caspase activation. In death receptor pathway, signals from plasma membrane receptors lead to the assembly of adaptor proteins into a "death-including signaling complex," which activates caspases, and the end result is the same.

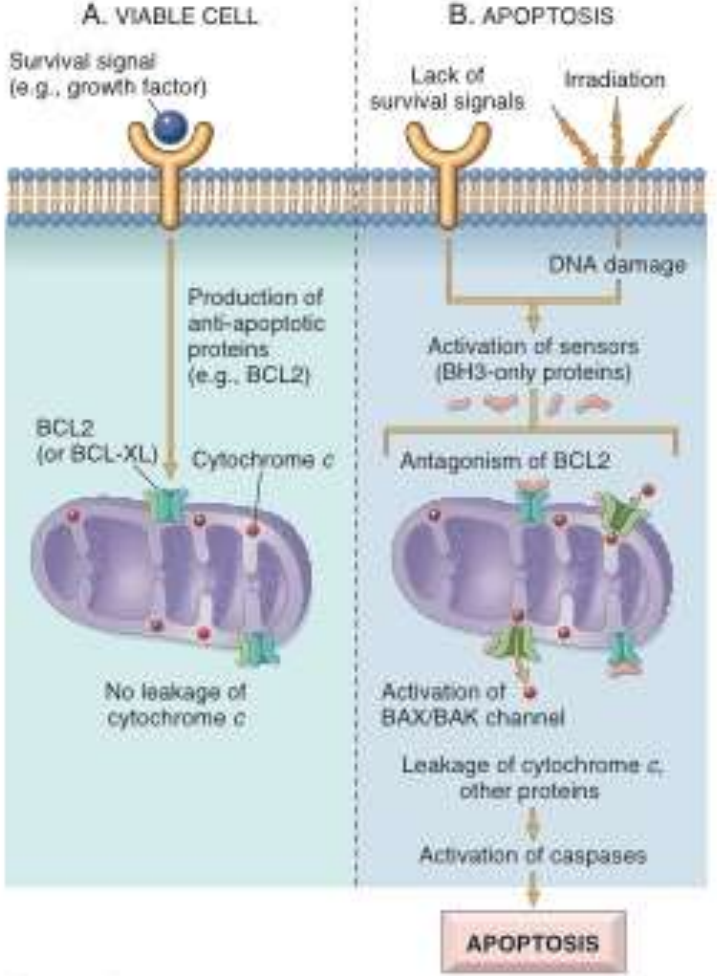


Figure 2-24 The intrinsic (mitochondrial) pathway of apoptosis. **A,** Cell viability is maintained by the induction of anti-apoptotic proteins such as BCL2 by survival signals. These proteins maintain the integrity of mitochondrial membranes and prevent leakage of mitochondrial proteins. **B,** Loss 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.

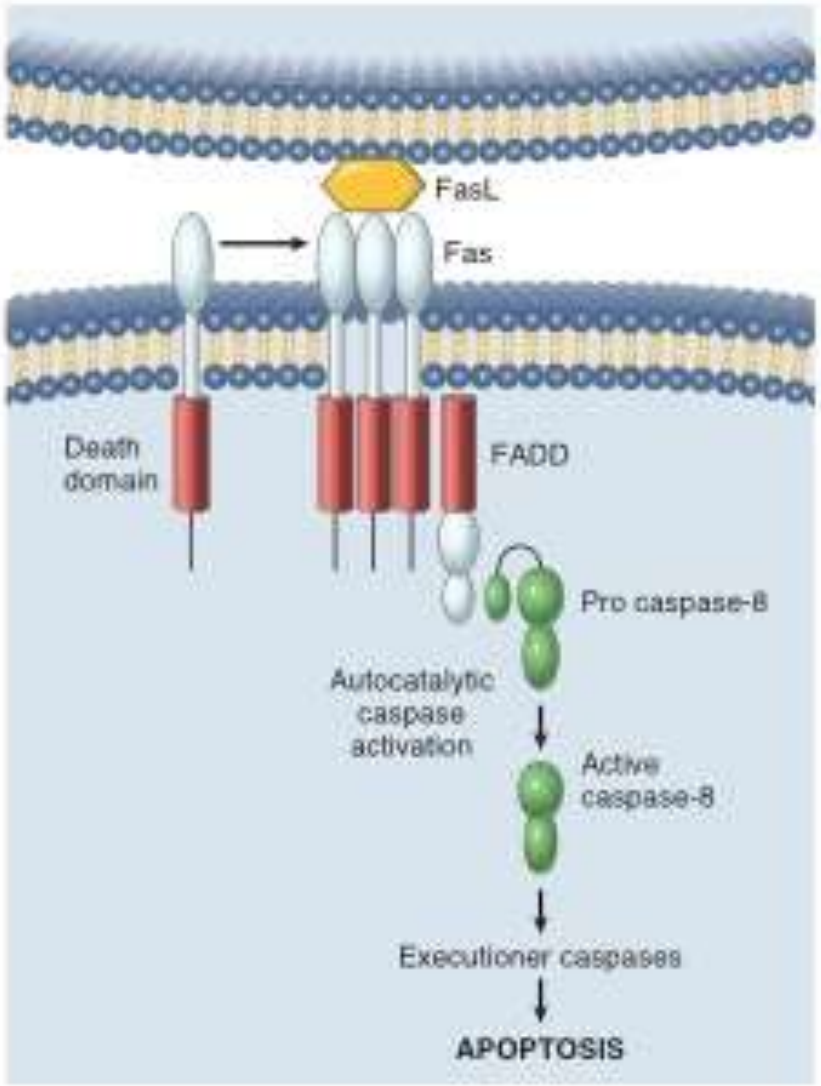


Figure 2-25 The extrinsic (death receptor initiated) pathway of apoptosis, illustrated by the events following Fas engagement. FAAD, Fas-associated death domain; FasL, Fas ligand.

NECROPTOSIS

- Kematian sel yang meliputi kedua aspek : nekrosis dan apoptosis
- Secara morfologi : mirip nekrosis → loss of ATP, cellular swelling, ROS, release lysosomal enzime, ruptur membran
- Secara mekanisme : melalui program kematian sel (apoptosis)
- Contoh necroptosis:
  - *Parkinson disease*
  - *Infeksi CMV*
  - *Steatohepatitis*
  - *Acute pancreatitis*

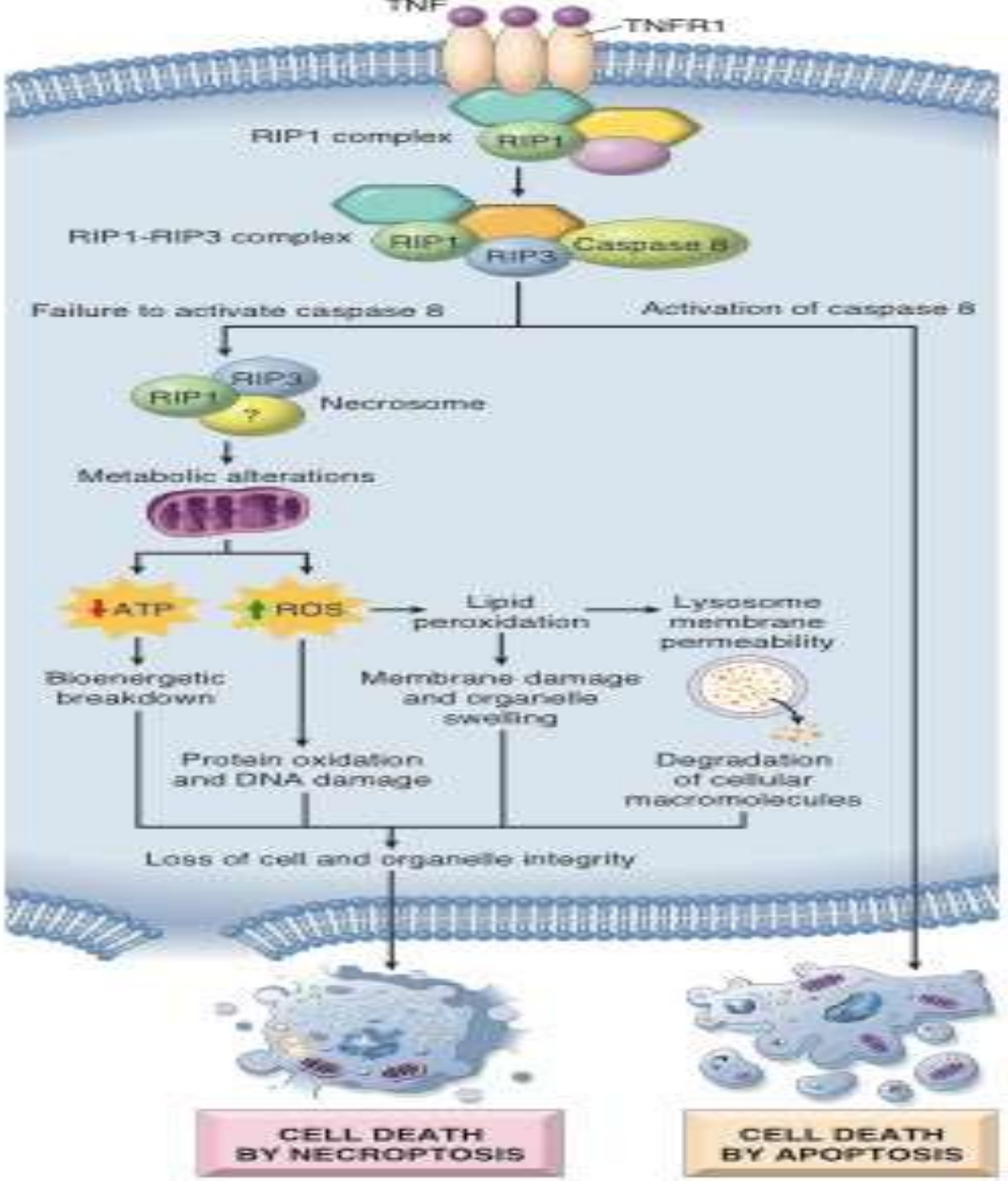


Figure 2-27 Molecular mechanism of TNF-mediated necroptosis. Cross-linking of TNFR1 by TNF causes recruitment of RIP1 and RIP3 along with caspase 8. Activation of the caspase leads to apoptosis as described in the text. Inhibition of caspase 8, as may occur in some viral infections, allows RIP1 and RIP3 to initiate signals that affect mitochondrial generation of ATP and ROS. This is followed by events typical of necrosis. (Adapted from Galluzzi L, et al: Programmed necrosis from molecules to health and disease. Int Rev Cell Molec Biol 289:1, 2011.)

AUTOFAGI

- Proses dimana sel memakan dirinya sendiri (auto = self; phagy = eating)
- Mekanisme :
  - *Pembentukan isolate membran (phagosphore)*
  - *Elongation of vesicle*
  - *Maturation of autophagosome*

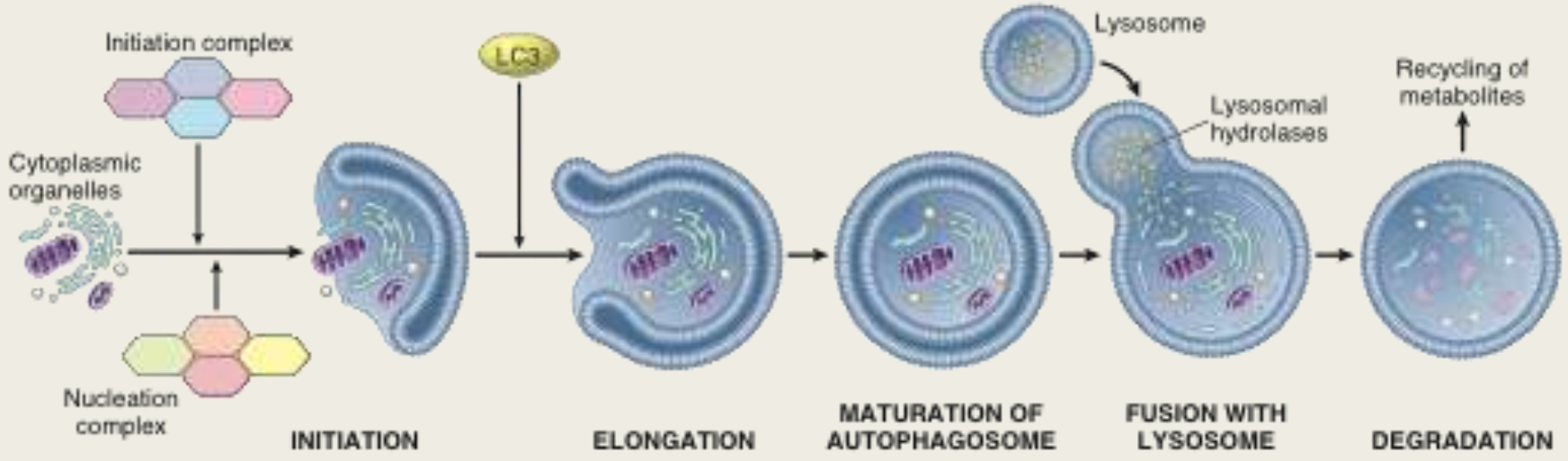


Figure 2-28 Autophagy. Cellular stresses, such as nutrient deprivation, activate an autophagy pathway that proceeds through several phases (initiation, nucleation, and elongation of isolation membrane) and eventually creates double-membrane-bound vacuoles (autophagosome) in which cytoplasmic materials including organelles are sequestered and then degraded following fusion of the vesicles with lysosomes. In the final stage, the digested materials are released for recycling of metabolites. See text for details. (Modified from Choi, AMK, Ryter S, Levine B: Autophagy in human health and disease. N Engl J Med 368:651, 2013.)

- Peningkatan autofagi dapat ditemukan pada kondisi :
  - *Kanker*
  - *Penyakit neurodegenerative*
  - *Infeksi*
  - *Inflammatory bowel disease*

Referensi :

- Robbins and Cotran Pathologic Basis of Disease, 9th edition
- Robbins Basic Pathology, 10th edition
- Text book of Pathology, 7th edition, Ivan Damjanov

- Materi kuliah, materi praktikum dan pedoman praktikum :