Pocket Companion to Robbins Pathologic Basis of Disease

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PREFACE

The expanding volume of medical knowledge has inevitably had its impact on the size of teaching texts including our own *Robbins Pathologic Basis of Disease (RPBD)*, despite our best efforts to control its bulk. In the hope of at least partially alleviating the dilemma of too little time for all the reading that has to be done, assisted by a few selected contributors, we have attempted to extract the essential elements in the parent text for this abbreviated, easy-to-comprehend "Pocket Companion." It is more than a topical outline: rather a concise overview of the more important subjects selected with the following goals in mind:

- To make the more detailed expositions in *RPBD* easier to digest by providing an introductory, quick overview.
- To facilitate the use of the "big book" by cross-referencing with specific page numbers all presentations in the "pocketbook" with their origins in *RPBD*.
- To provide a readily available pocket resource for immediate reference to subjects of interest.
- To serve as a guide for the student who wishes to review the large volume of subject matter learned from the "big book."

We would be remiss if we did not caution that this "Pocket Companion" does not constitute an adequate substitute for its parent. Instead, as the title indicates, it is intended to be a companion to the definitive text. Although it does contain the salient facts, the presentations are brief and devoid of the substance that enriches the facts. We therefore recommend and hope that this Pocket Companion will be used in conjunction with *RPBD*, and that it achieves some of our stated goals. To what extent they have been met, only the users of this abbreviated version can tell, and we invite them to let us know.

Stanley L. Robbins
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PLEASE NOTE

All page references following headings are to *Robbins Pathologic Basis of Disease,* 4th ed. Those within the text refer to other sections of this book.

CONTENTS

ONE

CELL INJURY AND ADAPTATION

INTRODUCTION (p. 1)

Pathology focuses on four aspects of disease:

- Its cause (etiology).
- The mechanisms of its development (pathogenesis).
- The structural alterations induced in cells and tissues (morphology).
- The functional consequences of the morphologic changes, as observed clinically.

DEFINITIONS AND CAUSES OF CELLULAR INJURY AND ADAPTATION (p. 2)

All forms of tissue injury start with molecular or structural alterations in cells. Under normal conditions, cells are in a homeostatic "steady state." Cells react to adverse influences by (1) adapting, (2) sustaining reversible injury, or (3) suffering irreversible injury and dying.

Cellular adaptation occurs when excessive physiologic stresses, or some pathologic stimuli, result in a new but altered state that preserves the viability of the cell. Examples are hypertrophy (increase in mass of the cell) or atrophy (decrease in mass of the cell). *Reversible cell injury* denotes pathologic changes that can be reversed when the stimulus is removed, or if the cause of injury is mild. *Irreversible injury* denotes pathologic changes that are permanent and cause cell death. It occurs with severe or prolonged injury.

CAUSES OF CELLULAR INJURY (p. 2)

1. Hypoxia (decrease of oxygen) occurs as a result of (1) ischemia (loss of blood supply), (2) inadequate oxygenation (e.g., cardiorespiratory failure), or (3) loss of oxygen-carrying capacity of the blood (e.g., anemia, carbon monoxide poisoning).
2. Physical agents, including trauma, heat, cold, radiation, and electric shock.
3. Chemical agents and drugs, including:
   a. Therapeutic drugs (e.g., acetaminophen (Tylenol)).
   b. Nontherapeutic agents (e.g., lead, alcohol).
4. Infectious agents, including viruses, rickettsiae, bacteria, fungi, and parasites.
5. Immunologic reactions.
6. Genetic derangements.
7. Nutritional imbalances.

MECHANISMS OF CELL INJURY

PRINCIPLES

Four intracellular systems are particularly vulnerable to cell injury:
- Maintenance of the integrity of cell membranes.
- Aerobic respiration and production of ATP.
- Synthesis of enzymes and structural proteins.
- Preservation of the integrity of the genetic apparatus.

These systems are closely related, and thus injury at one locus leads to wide-ranging secondary effects.

The morphologic changes of cell injury become apparent only after some critical biochemical system within the cell has been deranged. The consequences of cell injury depend on the type, duration, and severity of injurious agents, and also the type, state, and adaptability of the responding cell.

Three examples of cell injury follow: (1) hypoxic injury, (2) chemical injury, and (3) virus-induced injury, as well as the role of free radicals in cell injury.

HYPOXIC CELL INJURY (p. 4)

(Fig. 1–1)

Hypoxia first causes loss of oxidative phosphorylation and ATP generation by mitochondria. Decreased ATP (and an associated increase in AMP) stimulate fructokinase and phosphorylation, resulting in aerobic *glycolysis*. Glycogen is rapidly depleted, and lactic acid and inorganic phosphate are produced, thus reducing intracellular pH. At this point, there is also clumping of nuclear chromatin.

Reversible Injury

An early and common manifestation of nonlethal hypoxic injury is *acute cellular swelling*. This is caused by
- Failure of ouabain-sensitive Na^+,K^+-ATPase active membrane transport, causing sodium to enter the cell, potassium to diffuse out of the cell, and an isosmotic gain of water.

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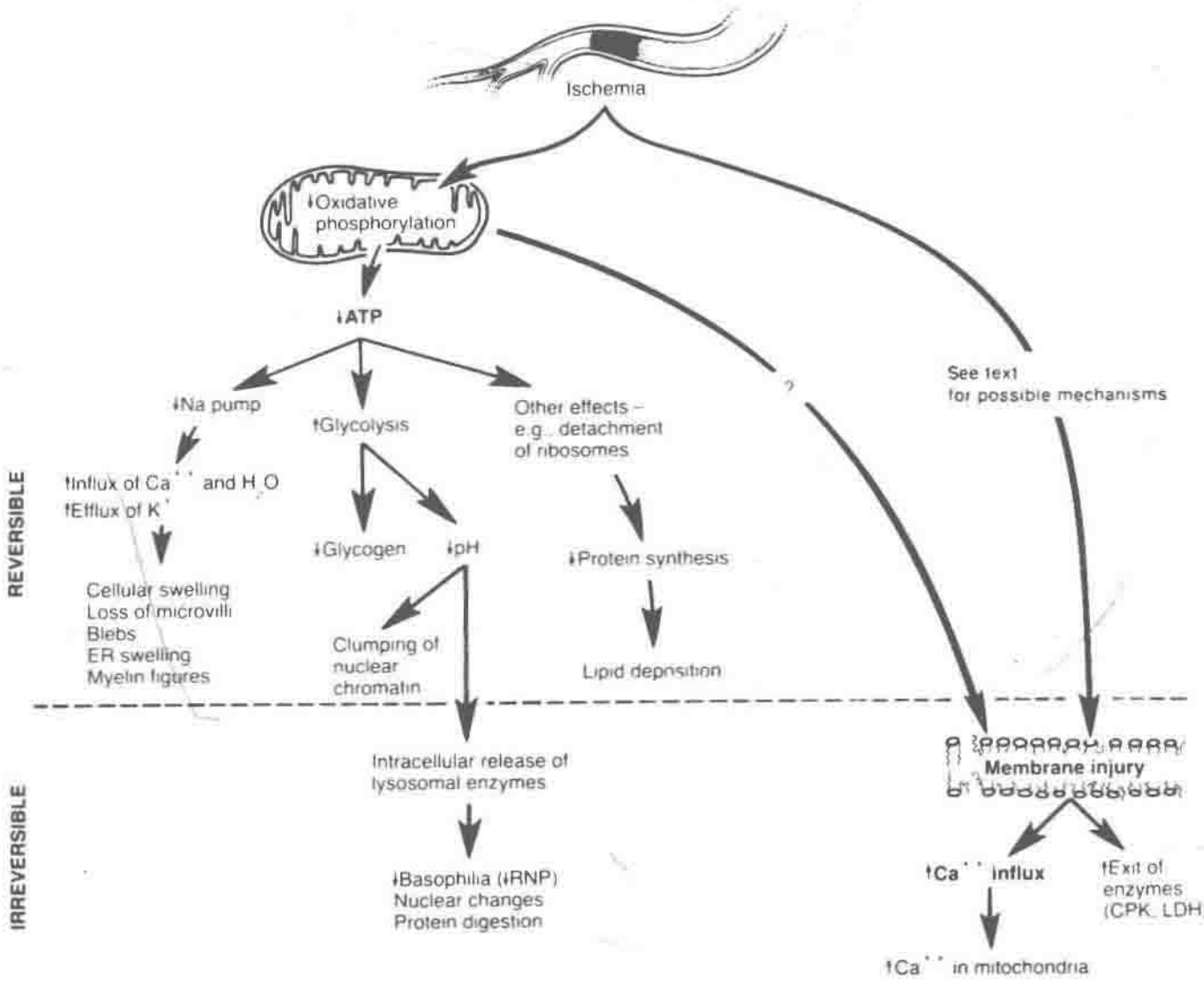

Figure 1–1. Postulated sequence of events in ischemic injury. Note that although reduced oxidative phosphorylation and ATP levels have a central role, ischemia causes direct membrane damage by mechanisms described in the text. (From Cotran, R. S., Kumar, V., and Robbins, S. L.: Robbins Pathologic Basis of Disease. 4th ed. Philadelphia, W. B. Saunders Co., 1989, p. 5.)

- Increased intracellular osmotic load due to the accumulation of inorganic phosphates, lactate, and purine nucleosides.

Other early findings of hypoxic injury include detachment of ribosomes from the endoplasmic reticulum, formation of membrane blebs, and myelin figures. *All of the above changes are reversible if oxygenation is restored.*

Irreversible Injury

Irreversible injury is marked by severe mitochondrial vacuolization, extensive damage to plasma membranes, swelling of lysosomes, and the appearance of large, amorphous densities in mitochondria. Injury to lysosomal membranes leads to leakage of the enzymes into the cytoplasm, and by their activation, enzymatic digestion of cell and nuclear components, leading to nuclear alterations characteristic of cell death (see below).

Two critical events are involved in irreversible injury: ATP depletion and cell membrane damage.

- *ATP depletion.* An early event in cell injury that contributes to the functional and structural consequences of ischemic hypoxia, and also to cell membrane damage; however, it is

controversial whether it is the immediate or primary cause of irreversibility.

- *Cell membrane damage.* The earliest phase of irreversible injury is associated with functional and structural defects of cell membranes. Several mechanisms may contribute to such membrane damage:
  1. *Progressive loss of phospholipids,* due to either
     - Activation of membrane phospholipases by the increased cytosolic calcium, leading to phospholipid degradation and phospholipid loss; or
     - Decreased phospholipid reacylation and synthesis, possibly related to loss of ATP.
  2. *Cytoskeletal abnormalities.* Activation of intracellular proteases, induced by increased cytosolic calcium, may cause degradation of intermediate cytoskeletal elements, rendering the cell membrane susceptible to stretching and rupture, particularly in the presence of cell swelling.
  3. *Toxic oxygen radicals.* These are involved in *reperfusion injury* occurring after restoration of blood flow to the ischemic organ. The toxic oxygen species are produced largely by infiltrating polymorphonuclear leukocytes.
  4. *Lipid breakdown products.* Free fatty acids and lysophospholipids accumulate in ischemic cells as a result of phospholipid degradation and are directly toxic to membranes.

Loss of membrane integrity causes massive influx of calcium from the extracellular space, resulting in mitochondrial dysfunction, inhibition of cellular enzymes, denaturation of proteins, and the cytologic alterations characteristic of coagulative necrosis (see below).

In summary, hypoxia affects oxidative phosphorylation and hence the synthesis of vital ATP supplies; membrane damage is critical to the development of lethal cell injury; and calcium is an important mediator of the biochemical alterations leading to cell death.

FREE RADICALS AND CELL INJURY (p. 9)

Free radicals are highly reactive, unstable species that interact with proteins, lipids, and carbohydrates and are involved in cell injury induced by a variety of chemical and biologic events.

Free radical initiation occurs by

- Absorption of radiant energy (UV light, x-rays).
- Oxidative metabolic reactions.
- Enzymatic conversion of exogenous chemicals or drugs (CCl_4 to $CCl_3\cdot$).

Oxygen-Derived Radicals

Free radicals derived from oxygen are a particularly important toxic species (see below).

- *Superoxide* is generated directly during auto-oxidation in mitochondria, or enzymatically by oxidases:

$$O_2 \xrightarrow{\text{oxidase}} O_2^{\cdot-}$$

Superoxide is inactivated by superoxide dismutase (SOD):

$$O_2^{\cdot -} + O_2^{\cdot -} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$$

- *Hydrogen peroxide* is produced
  1. By dismutation of superoxide (as above).
  2. Directly by oxidases present in peroxisomes.
- *Hydroxyl radicals* are formed
  1. By hydrolysis of water caused by ionizing radiation

$$H_2O \rightarrow H\cdot + OH\cdot$$

  2. By interaction with transitional metals in the Fenton reaction

$$Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + OH\cdot + OH^-$$

  3. Through the Haber-Weiss reaction:

$$H_2O_2 + O_2^{\cdot -} \rightarrow OH\cdot + OH^- + O_2$$

Free radicals cause cell injury through peroxidation of lipids, cross linking of proteins by the formation of disulfide bonds, inactivation of sulfhydryl enzymes, and induction of mutations in DNA that interfere with cell growth.

Free radical *termination* occurs either by spontaneous decay or by inactivation by several mechanisms:

1. Antioxidants (vitamin E, glutathione, ceruloplasmin, and transferrin). Transferrin in particular binds free iron, which catalyzes free radical formation.
2. Enzymes:
   - Superoxide dismutase
   - Catalase

$$2H_2O_2 \rightarrow O_2 + 2H_2O$$

   - Glutathione peroxidase

$$2OH\cdot + 2GSH \rightarrow 2H_2O + GSSG$$

or

$$H_2O_2 + 2GSH \rightarrow 2H_2O + GSSG$$

In many pathologic processes the final effects of stimulus-induced free radicals depend on the net balance between free radical formation and termination.

CHEMICAL INJURY (p. 12)

Chemicals cause cell injury by two mechanisms:

- Directly; e.g., mercury of mercuric chloride binds to SH groups of cell membrane proteins, causing increased permeability and inhibition of ATPase-dependent transport.
- By conversion to reactive toxic metabolites. Toxic metabolites in turn cause cell injury either by direct covalent binding to membrane protein and lipids, or more commonly by the formation of reactive free radicals, as previously described.

An example of chemical injury follows.

CCl_4-Induced Cell Injury

CCl_4, widely used in the dry-cleaning industry, is converted to CCl_3• in the smooth ER in the liver by P-450. CCl_3• initiates lipid peroxidation and autocatalytic reactions that cause swelling and breakdown of the endoplasmic reticulum, dissociation of ribosomes, and decreased hepatic protein synthesis. Loss of lipid acceptor protein leads to lipid accumulation and fatty change in the liver. This is followed by progressive cellular swelling, plasma membrane damage, and cell death.

VIRUS-INDUCED CELLULAR INJURY

Viruses induce cellular changes of two types:
- Cytolytic-cytopathic viruses cause cell injury and lysis.
- Oncogenic viruses cause tumors (see Chap. 7).

Cytopathic viruses cause cell injury by
- Direct cytopathic effects, or by
- Induction of an immune reaction against viral or virus-altered cell antigens.

Direct cytopathic effects follow attachment of the virus to receptors on host cells; entry of the virus into the cell either by phagocytosis, endocytosis in coated vesicles, or direct fusion; followed by active replication of the virus in the cell.

The cell response to viral replication takes several morphologic forms:
- Cell lysis, due to viral interference with macromolecular synthesis and membrane permeability.
- Cytoskeletal alterations.
- The formation of syncytial or multinucleate giant cells.
- The formation of inclusion bodies, containing virions or viral proteins, in the nucleus or cytoplasm.

MORPHOLOGY OF INJURED CELLS (p. 15)

The ultrastructural changes described earlier are shown in Figure 1–2.

REVERSIBLE INJURY

Cellular swelling is a near-universal manifestation of reversible injury by light microscopy. In cells involved in fat metabolism, *fatty change* (*see p. 8*) can also denote reversible injury.

NECROSIS (IRREVERSIBLE INJURY)

Necrosis is the sum of the morphologic changes that follow cell death in living tissue or organs. Two processes cause the basic morphologic changes of necrosis:
- Denaturation of proteins.
- Enzymatic digestion of organelles and cytosol.

Autolysis indicates enzymatic digestion by lysosomes of the dead cells themselves. *Heterolysis* is digestion by lysosomes of immigrant leukocytes.
- The necrotic cell is eosinophilic and glassy and may be

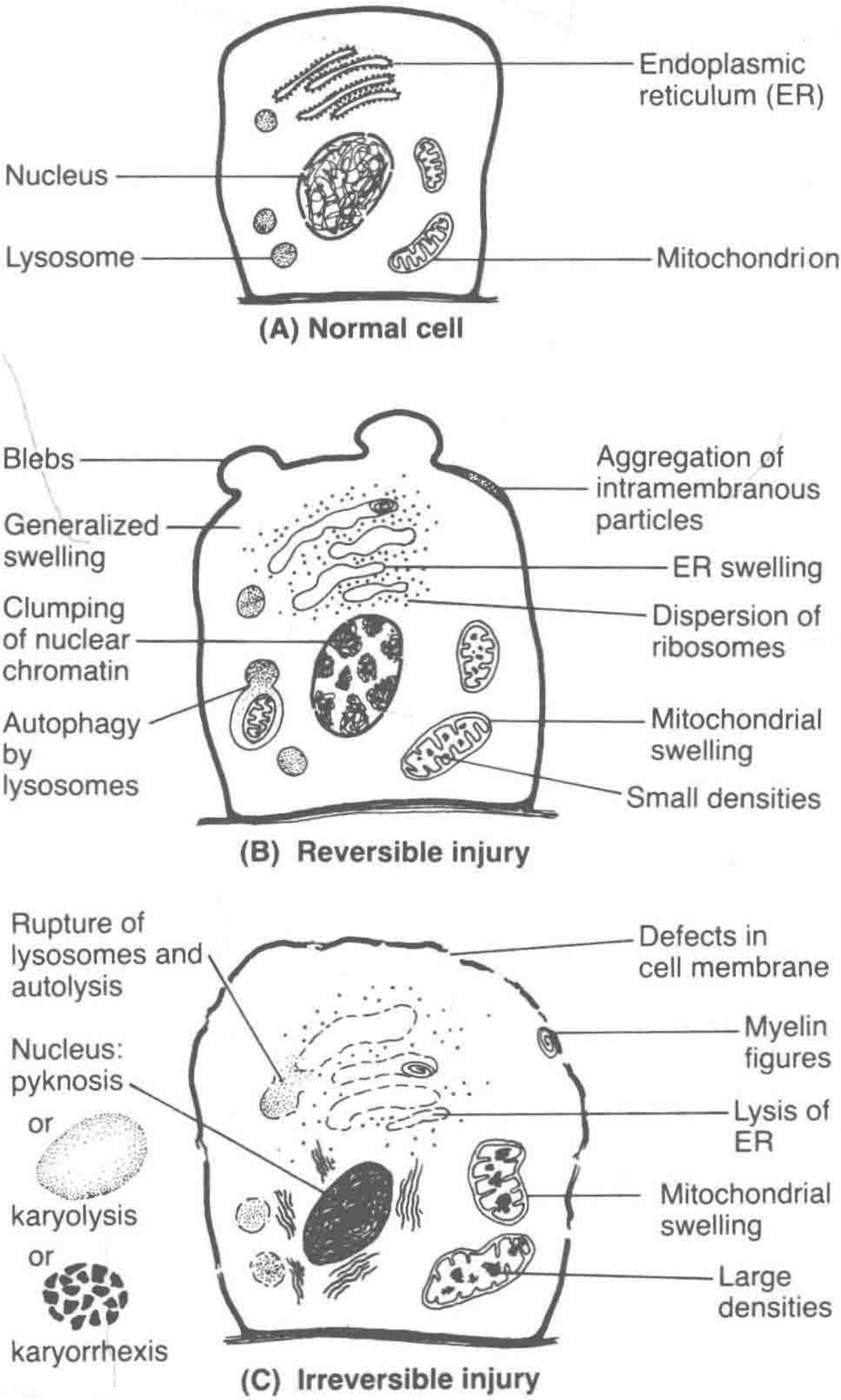

Figure 1–2. Schematic representation of a normal cell (A) and the ultrastructural changes in reversible (B) and irreversible (C) cell injury. (From Cotran, R. S., Kumar, V., and Robbins, S. L.: Robbins Pathologic Basis of Disease. 4th ed. Philadelphia, W. B. Saunders Co., 1989, p. 6.)

vacuolated. The cell membranes are fragmented. Nuclear changes in necrotic cells include *pyknosis* (small, dense nucleus); *karyolysis* (faint, dissolved nucleus); and *karyorrhexis* (nucleus broken up into many clumps).

Apoptosis is a morphologic pattern of cell death that occurs during embryogenesis, in hormone-dependent evolution of tissues, in cytotoxicity induced by T lymphocytes, and in some pathologic conditions (e.g., Councilman bodies in viral hepatitis). Apoptosis involves rapid DNA damage, possibly due to

activation of endogenous endonucleases and early condensation and fragmentation of chromatin, followed by cell lysis. The fragmented "apoptotic bodies" may be phagocytosed by adjacent macrophages.

Types of Necrosis

These depend on the balance of denaturation versus digestion.
- *Coagulation necrosis.* The most common pattern of necrosis occurs in the myocardium, kidney, liver, and other organs.
- *Liquefaction necrosis.* Occurs when autolysis and heterolysis prevail over protein denaturation. Occurs in the brain and localized bacterial infections (abscesses).
- *Fat necrosis.* Induced by the action of lipases that catalyze decomposition of triglycerides to fatty acids, which then complex with calcium to create calcium soaps.
- *Caseous necrosis.* Characteristic of tuberculous lesions, this appears grossly as soft, friable, cheesy material and microscopically as amorphous debris.

INTRACELLULAR ACCUMULATIONS (p. 20)

Proteins, carbohydrates, and lipids can accumulate in cells and sometimes cause cellular injury. They may be
- A *normal* cellular constituent accumulating in excess.
- An *abnormal* substance, usually a product of abnormal metabolism.
- A *pigment.*

Processes that result in abnormal intracellular accumulations include
- *Abnormal* metabolism of a *normal* endogenous substance (e.g., fatty liver).
- *Lack of an enzyme* necessary for the metabolism of a normal or abnormal endogenous substance (e.g., lysosomal storage disease).
- *Deposition of abnormal exogenous substances* (e.g., carbon-laden macrophages).

FATTY CHANGE

This represents a normal constituent accumulating in excess and leading to an absolute increase in intracellular lipids. It results in the formation of intracellular fat vacuoles. It occurs occasionally in almost all organs but is most common in the liver; when excessive it may lead to cirrhosis.

PATHOGENESIS OF FATTY LIVER. Causes of fatty liver include alcohol abuse, protein malnutrition, diabetes mellitus, obesity, hepatotoxins, and drugs. Fatty livers are enlarged, yellow, and greasy and the fat is seen microscopically as small, fatty, cytoplasmic droplets or as large vacuoles. The condition is caused by one of the following mechanisms, as illustrated in Figure 1–3:
- Excessive entry of free fatty acids into the liver (e.g., starvation, corticosteroid therapy).
- Enhanced fatty acid synthesis.
- Decreased fatty acid oxidation.

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