CELL INJURY AND DEATH
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Introduction
The conditions to which cells are exposed are constantly subject to change. These changes may be induced by physiological or pathological mechanisms.
Responses include
• Adaptive responses if the changes in condition are not excessive
  • Metabolic: e.g. following changes in diet
  • Structural
    • Changes in cell size and/or number
    • Changes in cellular differentiation
• Cell injury: if the limits of adaptive responses are exceeded or if adaptation is not possible

Causes of cell injury
There are many causes of cell injury including hypoxia, extremes of temperature, trauma, chemical agents, radiation, infection. Different injurious agents tend to effect different parts of a cell.

Mechanisms of cell injury
Cell injury occurs via several mechanisms
• ATP depletion and failure of membrane pumps. Oxygen is necessary for ATP production. The capacity for anaerobic production of ATP is limited and the process results in generation of lactic acid and ultimately reduction in cellular pH. This and the lack of ATP result in failure of many enzymes and cellular processes. ATP depleted cells swell as sodium is not pumped from the cell and water osmotically accumulates in the cytoplasm
• Loss of calcium homeostasis and activation of destructive enzymes. Most of the calcium in a cell is contained in the mitochondria and endoplasmic reticulum. Levels in the cytoplasm are low. ATP is important in maintaining the balance. With damage to mitochondria and endoplasmic reticulum and loss of ATP, cytoplasmic calcium increases and uncontrolled activation of potentially damaging enzymes takes place.
• Oxygen derived free radicals. Harmful reactive oxygen species are constantly generated in normal cells but they are normally degraded before doing harm. The protective systems of a cell depend on an adequate nutrient supply. Certain potentially damaging agents also increase the formation of reactive oxygen species.
• Alteration of one leads to alteration of others
Ultimately damage to
• Cell membranes
• Mitochondria
• Enzymatic and structural protein synthesis
• DNA
If damage is mild, the cell can recover, however, cell death occurs once a threshold of accumulated damage has been reached. Cell death may occur acutely or chronically depending on the cause.

Morphology of injured cells
Injury can initially only be detected ultrastructurally, then later histologically
Reversible changes vary depending on the injury but may include
• Swelling of organelles
• Swelling of entire cell
• Accumulation of additional material in the cytoplasm in certain situations e.g. lipids (especially in the liver), lipofuscin (a pigment seen in cells resulting from the lysosomal breakdown of cytoplasmic organelles)
Irreversible changes/cell death. Changes include
• Cell swelling or shrinkage
• Increase in cytoplasmic eosinophilia from denaturation of proteins
• Nuclear changes
  • Reduced basophilia (fading) of the nucleus (karyolysis)
  • Shrinkage with increased basophilia of the nucleus (pyknosis)
  • Fragmentation of a pyknotic nucleus (karyorrhexis)
Cell death
Cell death may occur via
- Necrosis: severe damaging stimuli, always pathological
- Apoptosis: specific pattern of cell death occurring in single cells due to activation of an internally controlled “suicide” program/programmed cell death. May be physiological or pathological.
  - Physiological e.g. in certain tissues in embryogenesis, elimination of potentially self reactive lymphocytes
  - Pathological e.g. in cells with damaged DNA, cell death induced by cytotoxic T cells
  - Regulated by a set of genes that are involved in normal cell growth and differentiation
  - Factors associated with mitochondria and a family of proteins called caspases are important in mediating apoptosis
  - Histologically see shrunken eosinophilic cell with pyknotic nucleus
Ultimately dead cells disappear by a combined process of enzymic digestion and phagocytosis by macrophages
Necrotic cells may leak cellular components into the extracellular space -> blood and their detection can be used for diagnostic purposes.
When cells are removed from the body (e.g. biopsy) or following death of the body, they undergo a process called autolysis in which the enzymes derived from the lysosomes breakdown the cell. Autolysis results in loss of cell and tissue structure. Thus specimens sent for histopathological assessment are generally placed in a fixative (formalin is generally used) to prevent autolysis from occurring. Cooling of tissues (e.g. in a refrigerator) slows autolysis.

Types of necrosis
There are many different types of necrosis. Some you may come across are:
- Coagulative
  - Generally seen with infarction in solid organs and burns
  - Tissue architecture and cellular outlines are retained
  - Dead cells appear very eosinophilic (due to coagulated cytoplasmic proteins staining more intensely with eosin) and nuclei undergo karyolysis
- Liquefactive or colliquative
  - Tissue semisolid due to dissolution by lysosomal enzymes
  - Seen following infarction in the brain and in necrosis associated with suppurative/purulent acute inflammation
- Caseous
  - Macroscopic description
  - Dead tissue is soft and pale resembling cream cheese
  - Histologically see an amorphous mass of eosinophilic proteinaceous material and nuclear debris
  - Classically associated with tuberculosis
- Fat necrosis
  - After trauma to fat (e.g. breast) or liberation of pancreatic enzymes in acute pancreatitis
- Fibrinoid necrosis
  - Characteristic of damage to blood vessel walls in vasculitis or malignant/accelerated hypertension
  - Deeply eosinophilic change seen histologically due to deposition of fibrin
In some cases degenerate and necrotic tissues are not completely removed and calcium deposits within them. This is referred to as dystrophic calcification e.g. in the necrotic tissue in tuberculosis, in atherosclerotic plaques, in some aged aortic valves and blood vessels (Monckeberg’s medial calcific sclerosis) and in the necrotic or degenerate epithelial tissue associated with many pathologies of the breast. The term metastatic calcification is used when calcification occurs in association with hypercalcaemia.

Cell aging
From gradual accumulation of metabolic and DNA damage. Old cells, particularly in heart and liver, may contain lipofuscin pigment derived from breakdown of intracellular organelles.
Cells may atrophy.

Resources used include:
Robbins and Cotran Pathologic Basis of Disease (7th ed.) by Kumar, Abbas and Fausto (Elsevier Saunders).
Rubin’s Pathology, Clinicopathologic Foundations of Medicine (5th ed., 2008) by Rubin and Strayer (Lippincott Williams and Wilkins)