UNIT 1
Cell Injury, Cell Death, and Adaptations

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Lecturer
Introduction to Pathology

- Vocabulary
  - Pathology
    - Literally it is the study of suffering
    - What happens to tissues/organs of the body in the presence of disease
  - Disease
    - Literally a “lack of ease”
    - Pathological process of the body organ(s) with its’ own signs and symptoms
    - Dysfunction of significant number of cells in the organ must occur first
– Disorder
  • Organ is normal but malfunction of the organ exists
  • Disease may or may not be present
– Sickness
  • The physical and/or mental state of being “unwell”
  • Can be due to emotions, background, inheritance self image, presence or absence of psychiatric problems, etc.
Introduction to Pathology

• Vocabulary
  – Health
    • Well being state indicating normality of body, mind and spirit
    • Origin in health cells in tissues and organs
  – Sign
    • Observable “objective” or measurable physical manifestations of disease(s) or disorder(s)
Introduction to Pathology

– **Symptom**
  - “Subjective” evidence of a disease or disorder

– **Diagnosis**
  - Attachment of a specific name to a specific disease or disorder
  - Summation of signs, symptoms, tissue changes, chemistry, physiology or function changes unique to that disease or disorder
Introduction to Pathology

- Vocabulary
  - Prognosis
    - Making a prediction of the outcome of a disease or disorder
- Therapy
  - Treatment of a disease or disorder
  - Several components
  - Supportive – lenses
  - Restorative – VT
  - Physical agents – laser
  - Chemical – medications
  - Surgical
Introduction to Pathology

– Etiology
  • The “cause of” a disease or disorder
– Pathogenesis
  • Underlying mechanisms resulting in the signs and symptoms of the patient
– Morphology
  • Gross or microscopic appearance of cells and tissues
  • For a disease or disorder to become manifested clinically, there first must be a dysfunction of a significant number of cells in an organ or tissue
Overview of Cellular Responses to Stimuli

• Cells operate in a very narrow range of physiologic parameters – they maintain homeostasis

• Homeostasis – equilibrium of the microenvironment of the cell
  – Chemical – electrolytes, glucose, pH, etc.
  – Physical – temperature, etc.
Overview of Cellular Responses to Stimuli

• Constantly adjust their structure and function adapting to their altered environment
• Adaptation – adjusting to a new situation to preserve viability and function
• Stress – pathological definition – any demand on the cell requiring it to adapt
Overview of Cellular Responses to Stimuli

- Inability to adapt will compromise the cell and result in injury and possibly death
- Principle adaptive responses
  - Hypertrophy
  - Hyperplasia
  - Atrophy
  - Metaplasia
Overview of Cellular Responses to Stimuli

• If the adaptive capability of the cell is exceeded or the stress inherently harmful, cell injury occurs
  – Reversible – return to baseline
  – Irreversible
  – Cell death – causes include ischemia, infections, toxins, and immune reactions
  – Cell death can be a normal and essential process
Stages in cellular response to stress and injurious stimuli
Cell reaction to stimuli
Overview of Cellular Responses to Stimuli

• Other factors that affect stress on the cell
  – Vulnerability - by location
  – Differentiation – by specific cellular function, i.e., different cells do different things which may predispose to protection or problems
  – Blood supply – better supply, better chance of survival
  – State of nutrition
  – State of cellular health at the time of stress
Overview of Cellular Responses to Stimuli

- Molecular and biochemical levels that stress may affect
  - Maintenance of cellular membrane
    - Cell and its components
    - Trauma, acids, etc.
  - Maintenance of ionic/osmotic balance
    - Water, medications, etc.
  - Energy production by the cell
  - Protein synthesis
    - nutrition
  - Genetic apparatus
    - Viruses, radiation, etc.
Cellular Adaptations to Stress

• Adaptations are reversible changes in the number, size, metabolic activity, and functions of cells

• Two basic types
  – Physiologic
    • Cellular response to normal stimulation
      – e.g. - hormones
  – Pathologic
    • Modified cellular response to avoid injury
Hypertrophy

- Increase in the size of cells resulting in increase in the size of the organ
- No new cells, just bigger cells
- Occurs in cells that cannot divide
- Physiologic – weight lifter
- Pathologic - cardiac enlargement – hypertension, aortic valve stenosis
- Cardiac failure – adaptation to stress can lead to functionally significant cell injury
Hyperplasia

• Increase in cell number
• Occurs in cells capable of replication
• Can occur with hypertrophy
• Physiologic
  – Hormonal – breast during puberty and pregnancy
  – Compensatory – part of tissue is removed: kidney, liver
Hyperplasia

• Pathologic
  – Caused by excessive hormonal (abnormal menstrual bleeding) or growth factor stimulation (viral infection causing warts)
  – If stimulation abates, hyperplasia disappears. Not so with cancers
Atrophy

- Shrinkage in the size of the cell by loss of cell substance
- Tissue or organ size diminishes in size
- Function diminishes – not death
Atrophy

• Causes
  – Immobilization
  – Loss of innervation
  – Diminished blood supply
  – Inadequate nutrition
  – Loss of endocrine stimulation
  – Aging
• Autophagy can occur
• Physiologic and pathologic
Metaplasia

• Reversible change in which one adult cell type is replaced by another adult cell type
• Cells sensitive to a certain stress are replaced by another cell type capable of better withstanding that stress
Metaplasia

• It is a genetic “reprogramming” of stem cells and not changing of already differentiated cells
  – Function can be reduced
  – Increased chance of malignant transformation

• Examples
  – Cigarette smoking
  – Gastric reflux
Metaplasia of columnar to squamous epithelium
Cell Injury and Death

• Occurs when cells are unable to adapt to stress or when they are exposed to damaging agents or suffer intrinsic abnormalities
• Reversible cell injury
  – Damage reversed when stimulus removed
Cell Injury and Death

• Cell death
  – Injury is irreversible
  – Two types
    • Necrosis – enzymes leak out of lysosomes and cell is digested. Leakage through cell membrane elicits inflammation. Due to ischemia, toxins, infections, trauma
    • Apoptosis – cell kills itself, no membrane leakage
Necrosis vs. Apoptosis

NORMAL

Necrosis

Enzymatic digestion and leakage of cellular contents

Apoptotic body

Phagocyte

Phagocytosis of apoptotic cells and fragments

Apoptosis
Causes of Cell Injury

• Iatrogenic
  – Doctor caused disease or disorder – medication reaction

• Fomite
  – Object capable of transmitting a disease – improperly cleaned instrument

• Stress factors
  – Hypoxia – oxygen deficiency
    • Ischemia – decreased blood supply
    • Inadequate oxygenation of blood – pneumonia
    • Reduction in oxygen-carrying capacity of blood – anemia, CO poisoning
Causes of Cell Injury

– Chemical agents
  • Alter membrane permeability, osmotic homeostasis, enzyme damage
  • Examples – glucose, salt, oxygen
– Infectious agents
  • Viruses, bacteria, fungi, protozoans, etc.
Causes of Cell Injury

• Stress factors
  – Immunologic reactions
    • Defend against pathologic organisms
    • Autoimmune reactions against one’s own tissues
    • Allergic reactions
  – Genetic defects
    • Can cause cell injury by inborn errors of metabolism
    • Accumulation of damaged DNA
Causes of Cell Injury

– Nutritional imbalances
  • Protein-calorie insufficiency
  • Vitamin deficiencies
  • Excesses in nutrition
    – Obesity – diabetes mellitus, atherosclerosis
Causes of Cell Injury

• Stress factors
  – Physical agents
    • Trauma
    • Extremes of temperature
    • Radiation
    • Electrical energy
    • Changes in atmospheric pressure
Causes of Cell Injury

– Aging
  • Alterations in replication and repair abilities
  • Long term accumulation of toxins, radiation, injuries, etc.?
Cell and Tissue Injury

- Cellular function may be long lost before cell death occurs
  - Example of myocardial cells
- Reversible injury
  - Cellular swelling
  - Fatty change
    - Liver and heart
- Irreversible injury
  - Inability to reverse mitochondrial dysfunction
  - Profound disturbances in membrane function
Necrosis

- Degradative action of enzymes on lethally injured cells
- Membrane integrity is lost and contents leak out causing inflammation
- Enzymes come from cellular lysosomes or from the lysosomes from recruited leucocytes
- Enzymes given off from a particular organ can indicate damage to that organ
  - Heart – CPK, troponin
  - Liver – alkaline phosphatase, transaminases (ALT, AST)
Necrosis

• Types
  – Coagulative – tissue necrosis in which component cells are dead but basic architecture is preserved for a short while
  – Liquefactive – complete digestion of the cell
  – Caseous - friable yellow-white appearance (cheese-like), architecture completed obliterated. Has an inflammatory border giving the appearance of a granuloma.
Cell injury
Subcellular Responses to Injury

- Certain agents and stresses can affect only subcellular organelles
- Some are seen in lethal injury, some in adaptive responses
Subcellular Responses to Injury

- **Lysosomes** – cytoplasmic bodies that contain hydrolytic enzymes used to breakdown phagocytosed material
  - **Autophagy** – digestion of cell’s own components
    - A survival mechanism in times of nutrient deprivation
  - **Heterophagy** – ingestion of outside material for intracellular destruction
    - Example - macrophage
Subcellular Responses to Injury

- Induction (hypertrophy) of smooth endoplasmic reticulum
  - Involved in metabolism of chemicals
  - Hypertrophy is adaptive response to chemical stimuli
Subcellular Responses to Injury

– Example – barbiturates and cytochrome P-450 system; swelling occurs to better metabolize medication but may better metabolize other medications as well (alcohol)

• Mitochondrial alterations
  – Energy producers in the cell
Subcellular Responses to Injury

- Cytoskeletal abnormalities
  - Consists of actin and myosin filaments, microtubules and various filaments that are altered
  - These structures are responsible for:
    - Intracellular transport of organelles and molecules
    - Maintenance of cell architecture
Subcellular Responses to Injury

- Maintenance of mechanical strength for tissue integrity
- Cell mobility
- phagocytosis
Mechanism of Cell Injury

- Cellular response to injurious stimuli depends on the type of injury, its duration, and its severity
- Consequences of the injurious stimulus depends on the type, status, adaptability, and the genetic make-up of the injured cell
  - Striated versus cardiac muscle
Mechanism of Cell Injury

- Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components
  - Mitochondria
  - Cell membranes
  - Protein synthesis
  - Cytoskeletal
  - Genetic apparatus
Principle Sites of Damage in Cell Injury
Examples of Cell Injury and Necrosis

• Ischemia and hypoxic injury
  – Ischemia
    • Diminished blood flow to a tissue
    • Most common cause of cell injury
    • Compromises delivery of substrates for glycolysis
  – Hypoxia
    • Decreased oxygen delivered
Examples of Cell Injury and Necrosis

• Ischemia-reperfusion injury
  – Restoration of blood flow can cause exacerbated and accelerated injury

• Chemical (toxic) injury
  – Chemical may combine with a component of the cell
  – Inactive chemical is converted to a reactive toxic metabolite
Apoptosis

• Cell destroys its own nuclear DNA and nuclear and cytoplasmic proteins
• Plasma membrane remains intact
• Membrane altered inducing phagocytosis but no leakage
• No inflammation
Apoptosis

- **Physiologic**
  - Death of specific cell types at defined times during development of the organism
  - Involution of hormone-dependent tissues upon hormone deprivation
  - Cell loss in proliferating cell populations
    - Intestinal crypt epithelia
Apoptosis

- Death of cells that served their purpose
  - Neutrophils in an acute inflammatory response
- Elimination of potential harmful self-reactive lymphocytes
  - Prevents reaction against one’s own tissue
Apoptosis

• Pathologic
  – Eliminates cells that are genetically altered or injured
  • DNA damage
  • Cell injury in certain infections – viruses
Apoptosis

- Examples
  - Growth factor deprivation
    - Hormone-sensitive cells deprived of the hormone
    - Lymphocytes not stimulated by antigens
    - Neurons deprived of nerve growth factor
Apoptosis

– DNA damage
  • Exposure to radiation or chemotherapeutic agents

– Self-reactive lymphocytes
  • Lymphocytes that encounter self antigens
  • Failure of apoptosis here causes autoimmune diseases
Cellular Aging

• Result of a progressive decline in the proliferative capacity and life span of cells and the effects of continuous exposure to exogenous factors that cause accumulation of cellular and molecular damage

• Responsible mechanisms
  – DNA damage
    • Occurs during normal replication
    • Defects in DNA repair mechanisms
      – DNA repair mechanisms can be activated by caloric restriction
Cellular Aging

– Decreased cellular replication
  • All normal cells have a limited capacity for replication
– Reduced regenerative capacity of stem cells
– Accumulation of metabolic damage
  • Cellular life span is a balance between damage from metabolic events and molecular response that repair the damage
GENERAL PATHOLOGY AND SLIDE DEMONSTRATION
Table 1-1. CELLULAR RESPONSES TO INJURY

Cellular Adaptations
- Atrophy, hypertrophy, hyperplasia, metaplasia (Chapter 2)

Acute Cell Injury
- Reversible Injury
- Cell death

Subcellular Alterations and Cell Inclusions

Intracellular Accumulations

Pathologic Calcification

Cellular Adaptations = Growth Disturbances
- Reversible and irreversible cell injury leading to necrosis or apoptosis—are morphologic patterns of acute cell injury induced by various stimuli.
- subcellular alterations, which occur largely as a response to more chronic or persistent injurious stimuli;
- intracellular accumulations of a number of substances—lipids, carbohydrates, and proteins—which occur as a result of derangements in cell metabolism or excessive storage;
- and pathologic calcification, a common consequence of cell and tissue injury.
<table>
<thead>
<tr>
<th>Lesion groups</th>
<th>Concept</th>
<th>Principles of classification into groups</th>
<th>Principles of classification into types</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Degeneration</td>
<td>Non-pigmented cytoplasmic changes</td>
<td>Abnormalities located in the cytoplasm with accumulation of non-pigmented endogenous substances</td>
<td>Based on the type of SUBSTANCE accumulated &amp; on the TYPE of cell</td>
</tr>
<tr>
<td>2 Necrosis</td>
<td>Cytoplasmic, nuclear and membrane changes</td>
<td>Abnormalities located in the nucleus, cytoplasm &amp; cell membrane</td>
<td>Based on GROSS APPEARANCE of the tissue &amp; the STRUCTURE of the cell</td>
</tr>
<tr>
<td>3 Inflammation</td>
<td>A complex sets of tissue response to injury involving neural, vascular, humoral &amp; cellular reaction within the site of injury</td>
<td>Complex abnormalities involving degeneration, necrosis, growth disturbances, circulatory disturbances and increase of inflammatory cells in tissues</td>
<td>Based on EXUDATES &amp; type of LESIONS</td>
</tr>
<tr>
<td>4 Growth Disturbances</td>
<td>Abnormal cell growth but still under control of the body</td>
<td>Abnormalities of cell growth affecting the whole cell in terms of size, number, type and arrangement of cells in tissues</td>
<td>Based on the SIZE, NUMBER, TYPE &amp; ARRANGEMENT of cells</td>
</tr>
<tr>
<td>Circulatory disturbances</td>
<td>Abnormalities in the cardiovascular system (CVS)</td>
<td>Abnormalities located in the CVS i.e. in the blood, heart &amp; vessels (which can effect on other tissue (e.g. liver, lung)</td>
<td>Based on the ORGAN, TISSUE &amp; VESSEL</td>
</tr>
<tr>
<td>6 Trauma</td>
<td>Physical &amp; chemical injury to organs</td>
<td>Abnormalities located in organs that have undergone anatomical displacements due to physical injury</td>
<td>Based on the ORGAN &amp; LOCATION</td>
</tr>
<tr>
<td>7 Pigmentation</td>
<td>A condition where there is accumulation of excess pigments in the cells</td>
<td>Abnormalities located in the cytoplasm with accumulation of pigmented substances of endogenous or exogenous origin</td>
<td>Based on the type of EXOGENOUS &amp; ENDOGENOUS PIGMENTS, HEPATOGENOUS or HAEMATOGENOUS</td>
</tr>
<tr>
<td>8 Neoplasia</td>
<td>Growth disturbance without control of the body</td>
<td>Abnormalities of cell growth affecting the whole cell in terms of size, number, type and arrangement of cells in tissues, but with anaplastic features</td>
<td>Based on HISTOGENESIS (where the tumor come from) &amp; its BEHAVIOUR (benign or malignant)</td>
</tr>
<tr>
<td>9 Congenital anomalies</td>
<td>Abnormalities during the development of the embryo or foetus</td>
<td>Abnormalities of cell growth affecting the whole cell, in terms of size, number, type and arrangement of cells in tissues, but occurring during the development of the embryo or foetus</td>
<td>Based on the FAILURE OF THE DEVELOPMENTAL PROCESS (e.g. failure of organ to close, separate, persisting structures, abnormal location &amp; enzyme defects)</td>
</tr>
<tr>
<td>10 Miscellaneous</td>
<td>Miscellaneous conditions not in the other groups</td>
<td>Abnormalities that are excluded from the other groups</td>
<td>Based mainly on location</td>
</tr>
</tbody>
</table>
Cellular Injury

- cellular injury as reversible or irreversible conditions which occur after the limits of adaptive response to a stimulus are exceeded
- Include degeneration and necrosis
- Degeneration = reversible cell injury
- Necrosis = irreversible cell injury
A basic cell is bounded by a cell membrane. Within the cell is a nucleus containing chromatin, often condensed at the periphery, along with larger clumps called chromocenters, and in some cells a nucleolus into which RNA is concentrated. The cytoplasm contains the cytosol and a variety of organelles, including mitochondria that power the cell via production of ATP, endoplasmic reticulum and ribosomes that synthesize new materials, a Golgi apparatus, and lysosomes.
Degeneration

- A lesion group involving cytoplasmic changes when non-pigmented substances accumulate in the cytoplasm
- 10 types of degeneration
- Based on the type of substance which accumulate in the cytoplasm
- These substances are normal substances including $\text{H}_2\text{O}$, CHO, Protein and Fat
FATTY CHANGE

• One type of degeneration
• Presence of fat in parenchymal cell especially liver
• Appear as vacuoles in hepatocytes
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.
NECROSIS

• A Lesion group involving cytoplasmic, nuclear and membrane changes

• 8 types of necrosis based on 2 criteria:
  – Based on the gross appearance of the necrotic tissue
  – Based on the type of tissue affected
COAGULATIVE NECROSIS
When many cells undergo necrosis at once, then definable patterns of necrosis are produced, depending upon the nature of the injury, the type of tissue, and the length of time. This is an example of coagulative necrosis. 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 (Arrow).
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. This is an example of coagulative necrosis.
Two large infarctions (areas of coagulative necrosis) are seen in this sectioned spleen. Since the etiology of coagulative necrosis is usually vascular with loss of blood supply, the infarct occurs in a vascular distribution. Thus, infarcts are often wedge-shaped with a base on the organ capsule.
When there is marked cellular injury, there is cell death. This microscopic appearance of myocardium is a mess because so many cells have died that the tissue is not recognizable. Many nuclei have become pyknotic (shrunken and dark) and have then undergone karorrhexis (fragmentation) and karyolysis (dissolution). The cytoplasm and cell borders are not recognizable.
Here is myocardium in which the cells are dying. The nuclei of the myocardial fibers are being lost. The cytoplasm is losing its structure, because no well-defined cross-striations are seen.
The small intestine is infarcted. The dark red to grey infarcted bowel contrasts with the pale pink normal bowel at the bottom. Some organs such as bowel with anastomosing blood supplies, or liver with a dual blood supply, are hard to infarct. This bowel was caught in a hernia and the mesenteric blood supply was constricted by the small opening to the hernia sac.
This is gangrene, or necrosis of many tissues in a body part. In this case, the toes were involved in a frostbite injury. This is an example of "dry" gangrene in which there is mainly coagulative necrosis from the anoxic injury.
This is gangrene of the lower extremity. In this case the term "wet" gangrene is more applicable because of the liquefactive component from superimposed infection in addition to the coagulative necrosis from loss of blood supply. This patient had diabetes mellitus.
LIQUEFACTIVE NECROSIS
The two lung abscesses seen here are examples of liquefactive necrosis in which there is a liquid center in an area of tissue injury. One abscess appears in the upper lobe (Short Arrow) and one in the lower lobe (Long Arrow). Liquefactive necrosis is typical of organs in which the tissues have a lot of lipid (such as brain) or when there is an abscess with lots of acute inflammatory cells whose release of proteolytic enzymes destroys the surrounding tissues.
The liver shows a small abscess here filled with many neutrophils. This abscess is an example of localized liquefactive necrosis.
Grossly, the cerebral infarction at the upper left here demonstrates liquefactive necrosis. Eventually, the removal of the dead tissue leaves behind a cavity.
At high magnification, liquefactive necrosis of the brain demonstrates many macrophages at the right which are cleaning up the necrotic cellular debris. The job description of a macrophage includes janitorial services such as this, particularly when there is lipid.
CASEOUS NECROSIS
This is more extensive caseous necrosis, with confluent cheesy tan granulomas in the upper portion of this lung in a patient with tuberculosis. The tissue destruction is so extensive that there are areas of cavitation (cystic spaces) being formed as the necrotic (mainly liquefied) debris drains out via the bronchi (Arrow).
FAT NECROSIS
This is fat necrosis of the pancreas. Cellular injury to the pancreatic acini leads to release of powerful enzymes which damage fat by the production of soaps, and these appear grossly as the soft, chalky white areas (Arrow) seen here on the cut surfaces.
Microscopically, fat necrosis adjacent to pancreas is seen here. There are some remaining steatocytes at the left (S) which are not necrotic. The necrotic fat cells at the right (Arrow) have vague cellular outlines, have lost their peripheral nuclei, and their cytoplasm has become a pink amorphous mass of necrotic material.
Growth Disturbances

- Cellular adaptations
- Changes in 4 aspects of cells:
  - Size
  - Number
  - Type
  - Arrangement
The testis at the right has undergone atrophy and is much smaller than the normal testis at the left.
This is cerebral atrophy in a patient with Alzheimer disease. The gyri are narrowed and the intervening sulci widened, particularly pronounced toward the frontal lobe region.
HYPERTROPHY
Any increase in tissue size is not necessarily neoplasia. Here is an example of left ventricular cardiac hypertrophy in which there has been an increase in the size of the myocardial fibers in response to an increased pressure load from hypertension. With hypertrophy, the cells increase in size, but the cells do not increase in number. Except for being larger, the cells are normal in appearance.

Alterations in cell growth can be physiologic (normal responses to stimuli) or pathologic. These alterations of cell growth are potentially reversible and include:

**Hypertrophy:** an increase in cell size. Increase in skeletal muscle fiber size is a physiologic response to exercise, but the cardiac hypertrophy shown above is a pathologic response to abnormally elevated blood pressure.

**Hyperplasia:** an increase in the number of cells. Postpartum breast lobules undergo hyperplasia for lactation, but endometrial hyperplasia in a postmenopausal woman is abnormal.
This is cardiac hypertrophy involving the left ventricle (Arrow). The number of myocardial fibers does not increase, but their size can increase in response to an increased workload, leading to the marked thickening of the left ventricle in this patient with systemic hypertension.
This is an example of prostatic hyperplasia. The normal adult male prostate is about 3 to 4 cm in diameter. The number of prostatic glands, as well as the stroma, has increased in this enlarged prostate seen in cross section. The pattern of increase here is not uniform, but nodular. This increase is in response to hormonal manipulation, but in this case is not a normal physiologic process.
Here is one of the nodules of hyperplastic prostate, with many glands along with some intervening stroma. The cells making up the glands are normal in appearance, but there are just too many of them.
METAPLASIA
Metaplasia of laryngeal respiratory epithelium has occurred here in a smoker. The chronic irritation has led to an exchanging of one type of epithelium [(the normal respiratory epithelium at the right (Short Arrow)] for another [(the more resilient squamous epithelium at the left (Long Arrow)]. Metaplasia is not a normal physiologic process and may be the first step toward neoplasia.
Metaplasia of the normal esophageal squamous mucosa (Short Arrow) has occurred here, with the appearance of gastric type columnar mucosa (Long Arrow).
This is dysplasia. The normal cervical squamous epithelium (Short Arrow) has become transformed to a more disorderly growth pattern, or dysplastic epithelium (Long Arrow). This is farther down the road toward neoplasia, but dysplasia is still a potentially reversible process.
LIVER CIRRHOSIS

- FIBROSIS
- FIBROPLASIA
The liver injury with chronic alcoholism leads to fibrosis and regeneration of the hepatocytes in nodules. This firm, nodular appearance of the liver as seen here is called cirrhosis.
INFLAMMATION
The white arrows mark areas of abscess formation in the upper lobe of this lung. The liquefactive necrosis of an abscess is apparent, because the purulent contents are draining out to leave a cavity. On a chest radiograph, the liquefied central contents of an abscess can appear as an "air-fluid level".
With a poor immune response to the agents producing granulomatous inflammation, there can be extensive spread of infection with the production of a "miliary" pattern of granulomas, as seen here in the lung of a patient with miliary tuberculosis. The 1 to 2 mm granulomas are scattered around like millet seeds (millet is a type of cereal grain).
Microscopically, this abscess has a mixture of inflammatory cells, but the wall of the abscess is "organizing" with ingrowth of capillaries (filled with red blood cells) and fibroblasts. As organization continues there is resolution with decreasing size of the abscess, until only a scar remains. If the body's defensive systems cannot contain the agent causing the abscess, then the process may continue and even spread.
Granulomatous inflammation occurs in response to some agents which persist for a long time and require a more orchestrated immune response to fight them. The granuloma seen here demonstrates the typical rounded and focal nature of this type of inflammation. A couple of spherules of *C. immitis* are present in the giant cell in the center.
• Granulomatous disease can become quite extensive. Here are numerous confluent granulomas in upper lung fields in a case of active pulmonary tuberculosis.
These are epithelioid cells around the center of a granuloma. They get their name from the fact that they have lots of pink cytoplasm similar to squamous epithelial cells. Their nuclei tend to be long and stringy.
NEOPLASIA
At high magnification, the normal cervical squamous epithelium (YELLOW AR.) at the left merges into the dysplastic squamous epithelium (RED AR.) at the right in which the cells are more disorderly and have darker nuclei with more irregular outlines.
Benign neoplasms can be multiple, as is shown in this uterus opened anteriorly to reveal leiomyomas of varying size, but all benign and well-circumscribed firm white masses. Remember that the most common neoplasm is a benign nevus (pigmented mole) of the skin, and most people have several. As a general rule, without additional transforming influences, benign neoplasms do not give rise to malignant neoplasms.
This renal cell carcinoma demonstrates distortion and displacement of the renal parenchyma by the tumor mass in the lower pole of the kidney. This malignant neoplasm has a variegated appearance on its cut surface, with yellow to white to red to brown areas.
Neoplasms can be benign as well as malignant, though it is not always easy to tell how a neoplasm will act. Here is a benign lipoma on the serosal surface of the small intestine. It has the characteristics of a benign neoplasm: it is well circumscribed, slow growing, non-invasive, and closely resembles the tissue of origin (fat).
This is an example of metastases to the liver. Note that the tan-white masses are multiple and irregularly sized. Like many large metastatic lesions, there is central necrosis (Arrow). A primary neoplasm is more likely to appear within an organ as a solitary mass. The presence of metastases are the best indication that a neoplasm is malignant. The original clone of cells that developed into a neoplasm may not have had the ability to metastasize, but continued proliferation of the neoplastic cells and acquisition of more genetic mutations within the neoplastic cells can give them the ability to metastasize.
• This is the view on colonoscopy of an adenocarcinoma of the colon. This is a bulky mass (Arrow) which spreads over the colonic mucosal surface. It has areas that appear red because it is bleeding, and this led to a positive occult blood in stool which was the screening method for detection. Neoplasms may not maintain the structure of normal tissues, so there is often irregular growth with necrosis and hemorrhage, particularly in larger and more aggressive neoplasms.
Here is a fleshy mass (FM) arising in the soft tissues of the lower leg. The tibia (T) and the fibula (F) are seen in cross section. This neoplasm proved to be a malignant fibrous histiocytoma. Sarcomas tend to invade locally, as can be seen here by the ill-defined margins (Arrow) of the mass.
Here is an osteosarcoma of bone. The large, bulky mass arises in the cortex of the bone and extends outward.
Features of a carcinoma are seen in this **electron micrograph**. This squamous cell carcinoma demonstrates many desmosomes (Arrow), along with cytoplasmic tonofilaments (T) streaming to the left.
This excision of skin demonstrates a malignant melanoma, which is much larger and more irregular than a benign nevus. From the history provided by the patient, we know that it grew quickly in size in 3 months. In contrast, a benign nevus hardly seems to change at all over many years.
In contrast, this hepatocellular carcinoma is not as well circumscribed (note the infiltration of tumor off to the lower right (Arrow)) nor as uniform in consistency. It is also arising in a cirrhotic (nodular) liver.
This is a squamous cell carcinoma of the lung. It is a bulky mass that extends into surrounding lung parenchyma.
By electron microscopy (EM), features of a carcinoma can be seen. This adenocarcinoma demonstrates several features typical of a neoplasm of epithelial origin, including the junctional complex (tight junction at the asterisk and the desmosomes at crosses). The mucin granule (M) and lumenal microvilli at the upper right are also typical for an adenocarcinoma. EM is occasionally employed as a diagnostic tool for neoplasms.
ATHEROSCLEROSIS AND THROMBOSIS
Here is occlusive coronary atherosclerosis. The coronary at the left is narrowed by 60 to 70%. The coronary at the right is even worse with evidence for previous thrombosis with organization of the thrombus and recanalization such that there are three small lumens remaining, one of which contains additional recent thrombus (Arrow).
Here is a coronary artery with atherosclerotic plaques. There is recent hemorrhage (Arrow) into the plaque. This is one of the complications of atherosclerosis. Such hemorrhage could acutely narrow the lumen and produce an acute coronary syndrome with ischemia and/or infarction of the myocardium.
• Here is the anterior surface of the heart with the left anterior descending coronary artery opened longitudinally. This is coronary thrombosis, one of the complications of atherosclerosis. The occlusive dark red thrombus (Arrow) is seen within the lumen of the coronary artery. This produces an acute coronary syndrome.
A coronary thrombosis (Arrow) is seen microscopically occluding the remaining small lumen of this coronary artery. Such an acute coronary thrombosis is often the antecedent to acute myocardial infarction.
This cross section through the heart reveals a large myocardial infarction involving the anterior left ventricular wall and septum. The infarct is beginning to heal, but still has a necrotic center. The ejection fraction from the left ventricle would be significantly reduced.
Atherosclerosis may weaken the wall of the aorta such that it bulges out to form an aneurysm. An atherosclerotic aortic aneurysm (Arrow) typically occurs in the abdominal portion below the renal arteries, as shown here. Aortic aneurysms that get bigger than 6 or 7 cm are likely to rupture.
General Principles of Cell Injury

• The cellular response to injurious stimuli depends on:
  • the type of injury, its duration, and its severity

• The consequences of cell injury depend on:
  • the type and adaptability of the injured cell

• **Cellular function** is lost far before morphologic changes of cell

• The “**point of no return**” at which cell death has irreversibly occurred is difficult to determine
Possible Biochemical Mechanisms of Cell Injury

1) ATP depletion.

2) Generation of reactive oxygen free radicals.

3) Loss of $\text{Ca}^{++}$ homeostasis.

4) Defect in plasma membrane permeability.

5) Mitochondrial damage.
1-ATP depletion

- **ATP is essential for every cellular process**:  
  - Maintenance of cell osmolarity  
  - Transport processes  
  - Protein synthesis  

Therefore, loss of ATP results in rapid shutdown of most critical homeostatic pathways.
2-Free Radical Mediation of Cell Injury

- **Definition Of Free Radicals**
  Extremely unstable, highly reactive chemical species with a single unpaired electron in an outer orbital

- In cells they attack and degrade nucleic acids, proteins, lipids and carbohydrates

- They initiate autocatalytic reaction, i.e. molecules that react with free radicals are converted into free radicals

- **Examples Of Free Radicals**
  - Hydroxyl (OH·)
  - Hydrogen (H·)
  - Superoxide (O₂⁻)
Free Radical Mediation of Cell Injury

• Free radicals constitutes an important mechanism of cell injury

• It Contributes To:
  – Chemical and radiation injury
  – Oxygen and other gaseous toxicity
  – Cellular aging
  – Microbial killing by phagocytic cells
  – Inflammatory damage
  – Tumor destruction by macrophages
  – Others
3-Increased Cytosolic Calcium:

- **Sources**
  - mitochondria
  - endoplasmic reticulum
  - external to the cell

- **Consequences (activates enzymes)**
  - ATPase
    - decreased ATP
  - phospholipase
    - decreased phospholipids
  - protease
    - disruption of membrane and cytoskeletal proteins
  - endonuclease
    - nuclear chromatin damage
Increased Cytosolic Calcium, source and consequences

Injurious agent

Mitochondrion

Increased cytosolic Ca++

ATPase
Decreased ATP

Phospholipase
Decreased phospholipids

Protease
Disruption of membrane and cytoskeletal proteins

Endonuclease
Nuclear chromatin damage

Endoplasmic reticulum
4-Defects in Plasma membrane permeability:

- **Causes:**
  1. Direct damage by toxins (bacterial, viruses, complement, physical or chemical injury)
  2. Damage secondary to ATPase loss or from calcium-mediated phospholipase activation

- **Effects:**
  Loss of Mb barriers → breakdown of the concentration gradient of metabolites
5-Mitochondrial damage

- Mitochondrial integrity is crucial for cell survival

**Causes:**
Increase Cytosolic calcium, free radicals

**Effects:**
No ATP generation
Release of cytochrome c into cytoplasm
Ischemic and Hypoxic Injury

**Mechanism:**

1. Decreased oxidative phosphorylation
2. Increased anaerobic glycolysis
3. Detachment of ribosomes/reduced protein synthesis
4. Worsening mitochondrial function
5. Increasing membrane permeability
6. Cytoskeleton dispersion
7. Swelling of mitochondria, endoplasmic reticulum, and entire cells