Cellular Responses to Stress and Toxic Insults: Adaptation, Injury, and Death

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What is pathology?

Pathology is devoted to the study of the

- Structural
- Biochemical
- Functional changes in cells, tissues, and organs that underlie disease.

Pathology: basis of disease.

By the use of

- Molecular
- (Microbiologic)
- Immunologic
- Morphologic techniques, pathology attempts to explain the **whys and wherefores of the signs and symptoms** manifested by patients while providing a rational basis for clinical care and therapy.

It thus serves as **the bridge between the basic sciences and clinical medicine,** and is the scientific foundation for all of medicine.

The four aspects of a disease process

that form the core of pathology are its

- ETIOLOGY cause
- PATHOGENESIS the biochemical and molecular mechanisms of its development
- MORPHOLOGIC CHANGES the structural alterations induced in the cells and organs of the body
- CLINICAL MANIFESTATIONS and the functional consequences of these changes

Etiology or Cause.

Although there are myriads of factors that cause disease, they can all be grouped into two classes:

1. **genetic** (e.g., inherited mutations and disease-associated gene variants, or polymorphisms) and
2. **acquired** (e.g., infectious, nutritional, chemical, physical).

The idea that one etiologic agent is the cause of one disease—developed from the study of infections and inherited disorders caused by single genes—is not applicable to the majority of diseases.

In fact, most of our common afflictions, such as atherosclerosis and cancer, are multifactorial and arise from the effects of various external triggers on a genetically susceptible individual.

Pathogenesis.

- Pathogenesis refers **to the sequence of** cellular, biochemical, and molecular **events** that follow the exposure of cells or tissues to an injurious agent.
- The study of pathogenesis remains one of the main domains of pathology.
- Most of the time the mutated genes underlying a great number of diseases have been identified, but **the functions** of the encoded proteins and **how** mutations induce disease—the pathogenesis—are still not fully understood.
- With more research into clinical genomics it may become feasible to link specific molecular abnormalities to disease manifestations and to possibly use this knowledge to design new therapeutic approaches. For these reasons, the study of pathogenesis has never been more exciting scientifically or more relevant to medicine.

Morphologic Changes.

Morphologic changes refer to the **structural alterations in cells or tissues** that are either characteristic of a disease or diagnostic of an etiologic process.

Traditionally, the practice of diagnostic pathology has used morphology to determine the nature of disease and to follow its progression.

Nowadays, it is about so much more.

seminiferous tubules

Functional Derangements and Clinical Manifestations.

- The end results of changes in cells and tissues
- Will lead to the clinical manifestations: **symptoms and signs** of disease, as well as its **progress** (clinical course and outcome)
- Virtually all forms of disease start with molecular or structural alterations in cells.
- This concept of the cellular basis of disease was first put forth in the nineteenth century by **Rudolf Virchow**, known as the father of modern pathology.

Cellular Responses to Stress and Noxious Stimuli

- The normal cell is confined to a fairly narrow range of function and structure.
- It is nevertheless able to handle physiologic demands, maintaining a steady state called **homeostasis.**
- **Adaptations** are reversible functional and structural responses to changes in physiologic states and some pathologic stimuli, during which new but altered steady states are achieved, allowing the cell to survive and continue to function.

Pathological adaptation

- Left ventricular hypertrophy can develop in response to some factor — such as high blood pressure or aortic stenosis — that causes the left ventricle muscle to work harder.
- In response to this pressure overload inside the left ventricle, heart muscle cells **ADAPT** by getting thicker along the inner walls of the heart. This thickened wall can cause the left ventricle chamber to weaken, stiffen and lose elasticity, which may prevent healthy blood flow.
- Left ventricular hypertrophy is a strong independent predictor of cardiovascular deaths.

Normal, adapted, reversibly injured, and dead myocardial cells

- The **cellular adaptation** shown here is myocardial hypertrophy, caused by increased blood pressure requiring greater mechanical effort by myocardial cells. This adaptation leads to thickening of the left ventricular wall.
- In **reversibly injured** myocardium there are functional alterations, usually without any gross or microscopic changes but sometimes with cytoplasmic changes such as cellular swelling and fat accumulation.
- In the specimen showing **necrosis**, a form of cell death the light area in the posterolateral left ventricle represents an acute myocardial infarction caused by reduced blood flow (ischemia).

Definition and types of degenerations. Parenchymal and fatty degeneration. Organ examples.

Definition of degeneration: degeneration is deterioration in the medical sense. Generally, it is the change from a higher to a lower form. More specifically, it is the change of tissue to a lower or less functionally active form.

Degeneration: sublethal injury.

Two features of reversible cell injury can be recognized under the light microscope: cellular swelling and fatty change. **Parenchymal degeneration: cellular swelling. Fatty degeneration: fatty change.**

Cellular swelling appears whenever cells are incapable of maintaining ionic and fluid homeostasis and is the result of failure of energy-dependent ion pumps in the plasma membrane.
Fatty change occurs in hypoxic injury and various forms of toxic or metabolic injury. It is manifested by the appearance of lipid vacuoles in the cytoplasm. It is seen mainly in cells involved in and dependent on fat metabolism, such as hepatocytes and myocardial cells.

MORPHOLOGY

Cellular swelling is the first manifestation of almost all forms of injury to cells. It is a difficult morphologic change to appreciate with the light microscope; it may be more apparent at the level of the whole organ.
When it affects many cells, it causes some pallor, increased turgor, and increase in weight of the organ. On microscopic examination, small clear vacuoles may be seen within the cytoplasm; these represent distended and pinched-off segments of the ER. This pattern of nonlethal injury is sometimes called **hydropic change** or **vacuolar degeneration**. Swelling of cells is reversible.

Cellular swelling

The hallmarks of reversible injury are reduced oxidative phosphorylation with resultant depletion of energy stores in the form of adenosine triphosphate (ATP), and cellular swelling caused by changes in ion concentrations and water influx.

In addition, various intracellular organelles, such as mitochondria and the cytoskeleton, may also show alterations.

Intracellular Accumulations

- One of the manifestations of metabolic derangements in cells is the intracellular accumulation of abnormal amounts of various substances that may be harmless or associated with varying degrees of injury. The substance may be located in the cytoplasm, within organelles (typically lysosomes), or in the nucleus, and it may be synthesized by the affected cells or may be produced elsewhere.
- There are **four main pathways** of abnormal intracellular accumulations.

Intracellular accumulations

- There are four main pathways of abnormal intracellular accumulations:
- Inadequate removal of a normal substance, as in fatty change
- Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects, as in hemosiderosis, amyloidosis
- Failure to degrade a metabolite due to inherited enzyme deficiencies, as in Gaucher's disease
- Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade it, as in anthracosis

Lipid accumulation

All major classes of lipids can accumulate in cells: triglycerides, cholesterol/cholesterol esters, and phospholipids.

In addition, abnormal complexes of lipids and carbohydrates accumulate in the lysosomal storage diseases.

We discuss triglyceride and cholesterol accumulations.

Fatty change, fatty degeneration, steatosis

- Definition: the terms steatosis and fatty change describe abnormal accumulations of triglycerides within parenchymal cells. Fatty change is often seen in the liver because it is the major organ involved in fat metabolism but it also occurs in heart, muscle, and kidney.
- Etiology: the causes of steatosis include toxins, protein malnutrition, diabetes mellitus, obesity, and anoxia.

In developed nations, the most common causes of significant fatty change in the liver (fatty liver) are alcohol abuse and nonalcoholic fatty liver disease, which is often associated with diabetes and obesity.

Pathogenesis

- Short-term ingestion of as much as 80 gm of alcohol (six beers or 8 ounces of 80-proof liquor) over one to several days generally produces mild, reversible hepatic steatosis.
- Daily intake of 80 gm or more of ethanol generates significant risk for severe hepatic injury, and daily ingestion of 160 gm or more for 10 to 20 years is associated more consistently with severe injury.
- Only 10% to 15% of alcoholics, however, develop cirrhosis.

Pathogenesis

- Exposure to alcohol causes steatosis, dysfunction of mitochondrial and cellular membranes, hypoxia, and oxidative stress.
- Hepatocellular steatosis results from
- (1) shunting of normal substrates away from catabolism and toward lipid biosynthesis, as a result of generation of excess reduced nicotinamide adenine dinucleotide (NADH + H+) by the two major enzymes of alcohol metabolism, alcohol dehydrogenase and acetaldehyde dehydrogenase;
- (2) impaired assembly and secretion of lipoproteins; and
- (3) increased peripheral catabolism of fat.

Morphology - macroscopy

- Macroscopically, the fatty liver of chronic alcoholism is a large (as heavy as 4 to 6 kg), soft organ that is yellow and greasy. Although there is little or no fibrosis at the outset, with continued alcohol intake fibrous tissue develops around the terminal hepatic veins and extends into the adjacent sinusoids.
- Liver enlargement: hepatomegaly
- Severe liver fibrosis: hepatic cirrhosis

Morphology - microscopy

Hepatic Steatosis (Fatty Liver). After even moderate intake of alcohol, **microvesicular** lipid droplets accumulate in hepatocytes.
With chronic intake of alcohol, lipid accumulates creating large, clear **macrovesicular** globules that compress and displace the hepatocyte nucleus to the periphery of the cell.
The fatty change is completely reversible if there is abstention from further intake of alcohol.

Micromorphology

Fat accumulation is partial first (centrolobular or peripherolobular), finally it becomes panlobular.

Clinical manifestations

Hepatic steatosis (fatty liver) may become evident as hepatomegaly, with mild elevation of serum bilirubin and alkaline phosphatase levels.

Severe hepatic dysfunction is unusual.

Alcohol withdrawal and the provision of an adequate diet are sufficient treatment.

More organ examples

Fatty change in the heart: It most often reflects poor oxygenation (i.e., chronic severe anemia). It is distributed away from the vessels, and produces a "tiger-stripe„ heart.

Accumulation of fat in phagocytic cells is a common theme in pathology. The fat is usually made up largely of cholesterol esthers. Xanthomas, cholesterolosis.

Atherosclerosis: In atherosclerotic plaques, smooth muscle cells and macrophages within the intimal layer of the aorta and large arteries are filled with lipid vacuoles, most of which are made up of cholesterol and cholesterol esters.

GLYCOGEN ACCUMULATION

- Glycogen ordinarily is present in the livers of people in the fed state, and is abundant if the patient has an IV line infusing glucose.
- In HYPERGLYCEMIA, it is common to see glycogen "in" hepatic nuclei, pancreatic beta cells, and in the proximal tubular epithelial cells. These accumulations are probably harmless.
- The various GLYCOGEN STORAGE DISEASES result from inborn errors of metabolism.

ACCUMULATIONS OF COMPLEX LIPIDS AND CARBOHYDRATES

- These typically result from inborn errors of metabolism. Typically the substance is stored in lysosomes. Eventually enough accumulates to compromise organ function.
- In Gaucher's disease glucocerebroside accumulates, the disease results from mutation in the gene that encodes glucocerebrosidase.

Gaucher's disease

Gaucher disease results from mutation in the gene that encodes glucocerebrosidase.

There are three autosomal recessive variants of Gaucher disease resulting from distinct allelic mutations.

Common to all is variably deficient activity of a glucocerebrosidase that normally cleaves the glucose residue from ceramide.

This deficit leads to an accumulation of glucocerebroside, an intermediate in glycolipid metabolism, in the mononuclear phagocytic cells and their transformation into so-called Gaucher cells.

Normally the glycolipids derived from the breakdown of senescent blood cells are sequentially degraded by the phagocytic cells of the body particularly in the liver, spleen, and bone marrow. In Gaucher disease, the degradation stops at the level of glucocerebrosides, which accumulate in the phagocytes.

These phagocytes—the Gaucher cells—become enlarged, with some reaching a diameter as great as 100 μm, because of the accumulation of distended lysosomes, and acquire a pathognomonic cytoplasmic appearance characterized as "wrinkled tissue paper".

Hyaline

- Hyaline is a histopathologic generic term for homogenous amorphous masses of protein (usually a single protein).
- Eosinophilic
- Intra or extracellular
- When patients are losing lots of protein trough their glomeruli, it's common to see eosinophilic protein droplets in the proximal renal tubules.

Hyalin examples

- RUSSELL BODIES are round accumulations of monoclonal protein that are (or used to be) inside the endoplasmic reticulum, usually immunogloublin within plasma cells.

Hyalin examples

- MALLORY'S (ALCOHOLIC) HYALINE is scrambled prekeratin intermediate filaments typically in liver cells. This usually reflects heavy drinking (alcoholic hepatitis) or years of overeating and not exercising ("bad NASH").

Hyalin examples

- Excess basement membrane and other proteins "hyalinizes" the body's small arteries in high blood pressure and diabetes.
- Amyloid, mentioned above, is another extracellular accumulation that always has a hyaline appearance.
- Fibrin, when the meshwork is crunched down, can be intensely eosinophilic and appear "hyaline".
- Fibrinoid is a special "material" seen in the walls of blood vessels that are dead but still contain flowing blood. A mix of plasma proteins and dead cell debris solidifies in the media and stains intensely pink.