LECTURE 8
CELLULAR INJURY –
CHRONIC CELLULAR ADAPTATIONS

MAMMALIAN PATHOBIOLGY
PATB 4130 / 5130

In the last lecture, reversible and irreversible cellular injuries were covered. Did you wonder what happens to the cells, tissues, and organs that suffer from reversible injury? Did they return to normal or was there some adaptive change that resulted from the injury and/or that permitted survival, albeit mainly in an altered state. Acute, severe injury more likely leads to death of cells or tissues followed either by repair or death of the host. Chronic persistent or intermittent sublethal injury to cells and tissues more commonly leads to adaptation.

OBJECTIVE OF LECTURE 8: To acquaint you with the adaptive changes occurring in cells, tissues, and organs; their causes, and lastly the potential significance of these changes.

AUTOPHAGY AND HETEROPHAGY (slides 2,3)

During the normal process of aging and following injury, cells die and others suffer from sublethal injury. Cells have the capacity to clean up the mess accrued over the years from aging or from cell death and sublethal injury. Two processes may be involved.

Heterophagy: Following cell death, either from the normal aging process or from injury, phagocytic cells such as macrophages can engulf cellular debris or even entire dead and effete cells. At sites of resolving or chronic inflammation, it is not unusual to microscopically visualize entire leukocytes within the cytoplasm of macrophages, a process known as leukophagocytosis. At sites of hemorrhage, phagocytic cells engulf red blood cells (erythrocytes), a process known as erythrophagocytosis. The normal lifespan of red blood cells is approximately 120 +/- days in many mammals. What happens to these cells at the end of their normal life span? The spleen and other fixed macrophages such as Kupffer cells lining the sinusoids of the liver engulf these cells, a process analogous to that following hemorrhage. In both instances, the iron within the hemoglobin is converted to a brown pigment known as hemosiderin. Hemosiderin-laden macrophages can accumulate at sites of bleeding, beginning within three days, and may represent a tell-tale sign of past hemorrhage. Accumulation of abundant hemosiderin in Kupffer cells and in splenic macrophages may indicate increased red blood cell destruction as may occur in the hemolytic anemias.

Autophagy: During the normal aging process or sublethal injury to cells, intracellular organelles may be damaged. These effete organelles fuse with primary lysosomes where digestion occurs. Especially during the aging process, a pigment known as lipofuscin, sometimes called ‘wear and tear’ pigment, accumulates in cells. What types of cells might you be more likely to find wear and tear pigment?
Would you expect to see it in the epithelial cells lining the intestine?

*(NOTE: Pigments will be covered in another lecture)*

**REGENERATION OF CELLS (slides 4-9)**

Following injury, mammals retain the capacity to regenerate an amazing array of different cells types and tissues but, with rare exceptions, cannot regenerate entire organs. If one considers blood vessels to be an organ, mammals have the capacity to generate new blood vessels in damaged tissue; if this were not the case, repair following injury and tissue loss would not be possible. The ability to regenerate and, more importantly, to restore normal function varies greatly depending on the cell and tissue type.

In a previous lecture, we briefly covered the cell cycle and the various types of cells. The concept of labile, stable, and permanent cells dates back to the late 1890’s. Giulio Bizzozero, a pathologist, concluded that all cells fall into three categories based on the number of mitoses he observed in injured tissues. **Labile cells** (epithelia, bone marrow cells) replicate and show mitoses throughout the life of the cell. **Stable cells** (liver, fibrous connective tissue) rarely divide after birth but can be readily stimulated to do so. **Permanent cells** (neurons, striated muscle) never regenerate. This generally accepted paradigm is currently challenged by a variety of observations. Regeneration is possible in one type of striated muscle, skeletal muscle. It is unlikely, however, if regeneration and repair would replace large areas of skeletal muscle loss.

What is the origin or source of regenerating cells in the different organs or tissues? Obviously, some types of adult cells retain the potential to undergo mitotic division and replicate. In many instances, however, mitotically active cells in many tissues arise from reserve (progenitor) cells that are committed to a specific line of differentiation. A good example would be the reserve or basal cells of the epidermis or the cells lining the crypts of Lieberkuhn in the small intestine (slide 8). Stem cells are also another, potentially major source of regenerating cells (slide 9). How do reserve or progenitor cells differ from stem cells? Some would place reserve cells in the stem cell class. A defining point we will use in this class is that reserve cells are committed to a certain line of differentiation. Basal cells of the epidermis will typically become keratinizing stratified squamous epithelial cells. Stem cells on the other hand can differentiate along multiple cell lines depending on the appropriate stimulus. **Totipotential** stem cells, those from the embryo, have the potential to differentiate along virtually any cell line while **pleuripotential** stem cells can differentiate along multiple but not all cell lines. It is possible to experimentally manipulate stem cells in vitro with various growth factors and chemokines to alter lines of differentiation. Another challenge when it comes to therapeutic use is to target stems cells to specific organs to facilitate regeneration and repair of damaged or dysfunctional tissue.

**ATROPHY OF CELLS, ORGANS, AND TISSUES (Slides 10-18)**

**Atrophy** indicates an acquired decrease in the size of cells, tissues, or organs as a whole. Mechanistically, this can occur either because of a decrease in the size of individual cells or a
decrease in the number of cells. If atrophy is an acquired condition, what is meant by the terms **hypoplasia** and **aplasia**? The term **involution** in some ways is synonymous with atrophy but is used to refer to a normal physiological reduction in size of tissues or organs such as the pregnant uterus after parturition or the expected decrease in size of the thymus that occurs early in life.

**Causes of atrophy:**

- **Decreased use:** An example here would be decreased size of the skeletal muscle mass when a limb is immobilized in a cast following a fracture. Slide 12 is a microscopic illustration of muscle atrophy due to disuse using an ATPase stain to differentiate Type 1 and Type 2 muscle fibers. The photo on the left is normal. Taken at the same magnification, the muscle fibers on the right are much smaller (atrophic) than normal. Type 1 and type 2 fibers are both affected but type 2 more severely.

- **Decreased or faulty nutrition:** Atrophy of body fat stores happens during periods of dieting or frank starvation. When this occurs in starvation, the body’s normally white or tan fat stores are converted to a translucent, gelatinous tissue substance due to mobilization of fat to replace the deficient nutrition. This process is called **serous atrophy of fat**. Starvation also results in atrophy of the liver and other tissues.

- **Inadequate blood flow:** Sudden abrupt and complete cessation of blood flow typically causes necrosis of the affected tissue called **infarction** and the resultant lesion is an **infarct**. Examples include blood clots (thrombi or emboli) occluding blood vessels in the brain or heart causing stroke or heart ‘attack’. On the other hand, partial or slow gradual cessation of blood flow commonly results in atrophy. Slide 13 is an example of liver atrophy. The figure illustrates a shunt between the portal vein and the caudal vena cava (will be pointed out in class) as revealed by injecting a dye into the portal vein. Shunting of the blood from the portal vein and into the caudal vena cava reduces the blood supply to the liver limiting its supply of oxygen and nutrients. Hence, **ischemia** results not only in oxygen starvation but also faulty nutrition. Slide 14 shows atrophy of the liver. On the left is normal liver. On the right, note the comparatively small size of hepatocytes.

- **Increased local pressure:** Any space occupying lesion can increase pressure in surrounding tissues resulting in atrophy. Examples would include an abscess or a tumor. In horses with chronic distension of the large bowel, atrophy of the left liver can occur. Other excellent examples of pressure atrophy, this time due to increased hydrostatic pressure, include hydronephrosis and hydrocephalus (Slide 15).

- **Hormones:** Hormones are chemicals produced in one part of the body that exert their effects on tissues distant from the site of production or on the body as a whole. Atrophy is commonly due to deficiency of a hormone. **Ovariectomy** can result in marked atrophy of target tissues such as uterus and mammary gland. Slide 16 shows atrophy of the thyroid gland. Secretion of thyroid hormone is regulated by thyroid stimulating hormone (TSH) produced by secretory neurons in the hypothalamus. If this area of the hypothalamus is destroyed, no TSH is produced and thyroid glands atrophy.

- **Old Age:** Many tissues suffer from some degree of atrophy during the aging process. In humans, this typically begins between the ages of 45-55 years. The total body mass decreases and there are decreases in the weight of some organs such as brain, liver, kidney, and spleen.
• **Denervation**: Denervation atrophy is most applicable to skeletal muscle. When the motor nerves that supply a group of skeletal muscles are damaged, the muscle becomes small and atrophic. Slide 17 is an example of denervation atrophy. In this case, there is damage to the left recurrent laryngeal nerve resulting in atrophy of the cricoarytenoideus muscle.

• **Immune mechanisms**: Sometimes the body develops antibodies against its own tissues. In **pernicious anemia** of humans, **autoantibodies** are produced against parietal cells of the gastric lining (mucosa) resulting in a loss of these cells and atrophy of the mucosa. Along with HCl, parietal cells produce another chemical called **intrinsic factor**. The **pathogenesis** of the anemia is as follows: 1) intrinsic factor, required for the absorption of vitamin B₁₂ from the small intestine is deficient, 2) vitamin B₁₂ is a cofactor for enzymes required for normal production of red blood cells. Another example of atrophy due to autoantibodies is **Hashimoto’s thyroiditis**.

**The Significance of Atrophy**

Atrophy implies loss of function but the significance of atrophy varies greatly according to the organ or tissue. Significance can also vary according to the cause. Atrophy of thyroid glands, even though a very small organ can have significance including changes in the skin and disturbances in fat metabolism that can lead to **atherosclerosis**. Atrophy of the liver, even though one of the largest organs in the body has great functional reserve and atrophy, per se, would have little effect. If the liver atrophy is caused by a portavacal shunt, however, there is great significance; causing a condition known as **hepatic encephalopathy**. Encephalopathy is not due to the atrophy but to the fact that the vascular anomaly shunts blood around the liver. The functional capacity for eliminating potential toxins from the body such as ammonia is there but can’t be used.

**CELLULAR ADAPTATIONS (Slides 19-39)**

Cells can adapt to chronic or repeated low-level injury over time (see Slide 21). Some of these changes are beneficial, some have functional consequences, and one, dysplasia, for all practical purposes, is bad.

**Hypertrophy**: Hypertrophy is an increase in the size of an organ or tissue due to an increase in the **SIZE** of individual cells. Slides 23 and 24 illustrate good examples of right-sided cardiac hypertrophy. In slide 23, the normal cardiac silhouette is on the left and the heart with right ventricular hypertrophy is on the right. Slide 24 is a transverse plane of the heart cut through the ventricles. Note that the thickness of the right ventricular wall, interventricular septum, and left ventricular wall are approximately equal. In a normal heart, the thickness of the right ventricle should be only about one-third of the left ventricle.

**Hyperplasia**: Hyperplasia is an increase in the size of an organ or tissue due to an increase in the **NUMBER** of cells. Slides 26 and 27 are an example of **congenital** hyperplastic **goiter**. We see congenital goiter in small ruminants on a fairly common basis here in Wyoming and the thyroid glands can be sufficiently large to cause **dystocia**. In slide 27, normal thyroid gland consists of follicles lined by cuboidal or columnar epithelial cells. The dense pink-staining proteinaceous fluid content of the follicles is called colloid. In the goitrous gland on the right, note the marked
increase in the number of cells and, at best, poorly formed follicular structures. Goiter, including the congenital form, can be due to a number of factors including gene defects in thyroglobulin synthesis, iodine deficiency, and toxin/poisons. Paradoxically, too much iodine can also lead to goiter.

The concepts of hypertrophy and hyperplasia are relative. In most instances, both occur together to result in an increase in size. Earlier, the paradigm of three cell types was mentioned (slide 5). Although not valid for all situations, this paradigm remains useful when discussing the capacity for hypertrophy versus hyperplasia in various tissues and organs. As a general rule, permanent cells undergo hypertrophy while, in contrast, labile cells have a great capacity to proliferate and tissues composed mainly of these cells enlarge because of hyperplasia. Take the example of right ventricular cardiac hypertrophy; at the light microscopic level this change seems to be entirely due to hypertrophy of cardiac myocytes, one type of striated muscle. There is however, a subtle and often overlooked increase in connective tissue and small blood vessels due mainly to hyperplasia. When we speak of this, however, pathologists refer to the dominant change, i.e. cardiac hypertrophy, NOT cardiac myocellular hypertrophy and stroma/vascular hyperplasia.

The causes of hypertrophy and hyperplasia are varied. Furthermore, these adaptive changes can be a normal physiological response or can be pathological.

- **Increased functional demand.** The enlargement of a body builder’s skeletal muscles and an athlete’s heart are examples of a normal physiological response to increased workload. **Brisket disease** (high altitude disease) in cattle is an example of a pathological response. The low oxygen tension at high altitudes results in reflex constriction of pulmonary arteries that, in turn, increases intravascular pressures and the work load on the right ventricle of the heart causing it to enlarge. Ultimately, in many cases, the right ventricle eventually fails resulting in right-sided congestive heart failure. This process is called cor pulmonale (right-sided heart failure secondary to increased vascular resistance in the lung).

- **Hormonal stimulation.** Enlargement of the mammary glands at puberty and during pregnancy is a physiological response. From a disease standpoint, can you think of a disorder caused by a hormonal imbalance that results in an increased in the size of an organ or tissue? How about acromegaly or Cushing’s disease? The latter is also called hyperadrenocorticism. In one form of the disease, there is a tumor of the pituitary gland that secretes excess ACTH. How about the bone marrow response to anemia (erythropoietin)?

- **Excess nutrition.** Obesity is a great example but, unknown to many, excessive nutrition also results in a dramatic increase in protein synthesis throughout the body.

- **Increased blood flow.** Vascular tumors, fractures, and osteomyelitis can sometimes increase the length of a limb, an effect partially due to increased blood flow. Wound healing is also a perfect example that will be covered in another lecture. Increased delivery of trophic substances via the blood also plays a likely role, however.

- **Mechanical factors.** An example here would be a skin callus at points of mechanical stress.
Hypertrophy and hyperplasia are generally considered to be beneficial but there are obvious exceptions. Additionally, in some situations, there is a limit to the extent that hypertrophy and hyperplasia can maintain or restore normal function. Considering the previous example of cor pulmonale, there is a limit to how much the myocardium can hypertrophy. Beyond this limit, the myocardium will weaken, ventricles then dilate, and the heart is no longer able to pump blood efficiently resulting in heart failure.

**Metaplasia.** Metaplasia is a conversion of cells in a tissue or organ from one type to another, usually of the same class, i.e. epithelial cell to epithelial cell and connective tissue cell to another connective tissue cell.

The potential causes of metaplasia are generally limited and in some instances unknown. Metaplasia is typically a response of labile and stable cells.

- Chronic irritation is often cited as the most common cause of metaplasia. Following permanent tracheostomy, there is a conversion of the normal ciliated stratified columnar epithelium (similar to slide 32 and like slide 36) to stratified squamous epithelium analogous to the skin and oral cavity. Why does this occur? The air passing through the **osteon** is neither warmed nor moistened, particulate matter is not cleared by passage through the nasal cavity, and there is also increased air turbulence resulting in an entirely different and irritating environment. Connective tissue metaplasia occurs at sites where there is florid **fibroplasia** as in areas of repair or in neoplasms with a proliferative connective tissue component. Here the fibrous tissue is converted to bone, a transformation called **osseous metaplasia**.

- Nutritional deficiency, Vitamin A. Vitamin A is required for the integrity of many sensitive epithelial tissues in the body but the biochemical mechanisms have not been resolved. Vitamin A deficiency results in the conversion of columnar epithelial to stratified squamous epithelium in many tissues (i.e. ducts, urinary and respiratory systems). Slide 33 illustrates this effect on the submucosal glands of the esophagus in an avian species. Similar effects occur in other ducts such as that of the **lacrimal** gland.

- Hormone excess, estrogen. One neoplasm that develops in the testes of dogs is called a Sertoli cell tumor. Sertoli cell tumors in dogs and other species secrete estrogen. One effect of the hyperestrogenism is a conversion of prostatic epithelial cells to stratified squamous epithelium.

What is the significance of metaplasia? In many cases, connective tissue metaplasia is of little to no clinical consequence; it represents an incidental finding. Epithelial metaplasias on the other hand can be highly significant. Squamous metaplasia of submucosal glands in the esophagus (slide 33) can result in blockages and accumulation of keratinaceous debris in the duct lumens. Even more significant, squamous metaplasia of the urinary system in birds can lead to at least partial obstruction, retention of urates, and **gout** (covered in another lecture). Slide 36 is a photo of normal tracheal epithelium. How would squamous metaplasia affect the function of this tissue? Another possible significant outcome of metaplasia is that it may precede development of certain cancers.
Dysplasia. Dysplasia, a somewhat imprecise term, essentially means disordered development or adaptation. Dysplasia typically refers to a proliferative response where there is disorderly replication and maturation of cells.

Causes include cellular injury over time or when there is constant low-grade injury that damages but does not kill the cells. Since the change results in disorderly proliferation and maturation of cells, there is inference that damage involves the control mechanisms of the cell cycle such that abnormalities such as DNA damage may persist through subsequent divisions. Significantly, dysplasia is regarded as a preneoplastic change. You are all well aware of the effects of solar radiation. Repeated, life-long exposure to solar radiation predisposes the skin to the development of malignancies including melanoma, basal and squamous cell carcinomas in humans. This is not, however, just a condition related to humans; many examples can be found in animals.

- Squamous cell carcinoma of the conjunctiva and cornea of horses and cattle, mainly affecting breeds or individuals with little melanin pigmentation.
- Squamous cell carcinoma of the nasal planum and tips of the ears in white-haired cats.
- Squamous cell carcinoma and hemangioma/hemangiosarcoma of sparsely-haired lightly pigmented abdominal skin in certain breeds of dogs.

When examining a tissue microscopically, the dividing line between dysplasia and overt neoplasia can be vague (slide 39).