LESSON ONE: Cell injury, inflammation, and repair

I. Cell Injury

The stress response at a cellular level

A challenge to homeostatic mechanisms is termed a ‘stress,’ and because stress is a natural phenomenon, cells have a limited ability to adapt to these stresses, usually by altering their form and function. When this stress is removed however, cells may be able to return to a more or less normal state. This is called reversible cell injury. Under chronic stress however, or if the injury is severe enough, the cell may become irreversibly damaged. Irreversible damage ultimately leads to cell death. It is important to note that from a histological perspective, it is difficult to determine when exactly reversible injuries become irreversible, as in chronic stress.

Reversible changes to cell injury

Among the reversible changes observed in cell injury is hydropic swelling, in which the cytoplasm of the cell swells in volume, and although the number of organelles remains unchanged, structural changes may occur. The cisternae of the endoplasmic reticulum may become distended, and membrane-attached polyribosomes may undergo disaggregation. Mitochondria may swell in ischemic conditions, and little portions of the plasma membrane, called blebs, can be seen to pinch off from the injured cell. The granular components of the nucleolus within the nucleus may also undergo changes, and even disappear altogether.

Besides hydropic swelling, a cell under persistent stress may exhibit other adaptations.

Atrophy
Atrophy is the decrease in the size or number of cells that make up a tissue or organ. It is often seen in any state of reduced activity, usually from neuroendocrinal causes or vascular insufficiency, but also from prolonged immobility. In persistent toxic injury atrophic
conditions may result, as in the size and functionality of the bronchial cells in smoking. Aging is another cause of atrophy.

**Hypertrophy**

Hypertrophy is the increase in the size of a cell and as a result, there is usually a marked increase in its functional output. Hypertrophy can be a normal condition, occurring with childhood growth, or in the development of the gonads during puberty, and even an increase in muscle size in physical training. In some endocrinal disorders however, such as in excess TSH (thyroid stimulating hormone) production, the result is a pathological increase in the size and function of the target tissue, as in the enlarged thyroid of goiter. In cardiovascular insufficiency secondary to atherosclerosis there may result an enlargement of the ventricular heart muscle. Similar to hypertrophy, hyperplasia is an increase in the number of cells in a tissue or organ. In severe obesity, there is very often a problem with both hyperplasia and hypertrophy, the latter of which is related to current lifestyle and dietary factors, but the former typically the result of factors (such as diet) during childhood development and adolescence, or genetics. Hyperplasia can also result in the target tissue of a glandular tumor, such as the proliferation of mammary glands in a pituitary tumor.

**Metaplasia**

Metaplasia is the conversion of one kind of cell into another kind of cell type. The most common form of metaplasia occurs when glandular cells are replaced by squamous epithelium, reducing the overall functional complexity of the tissue. In the case of smoking, there are an increased number of squamous cells in the bronchial epithelium, with a loss in the number of mucus-secreting columnar or cuboidal cells. Metaplasia appears to represent a transitional point between normal adaptation and the disease process, and while completely reversible, can also give rise to cancerous changes.

**Dysplasia**

Dysplasia is termed as an alteration in the size, shape and organization of a cell and its components. It can be identified as an aberrance within a tissue of otherwise normal-looking cells. The dysplastic cells may vary in size or shape, being larger or irregularly shaped, and the nuclei more intensely colored. An example is cervical dysplasia, in which surgically removed cells from the cervix can be shown to contain abnormal-looking cells, graded from one to four in severity. Although reversible, dysplasia has been recognized as a precursor state to cancerous changes, and
it can be difficult to determine the difference between severe dysplasia.

Necrosis: another name for death

When a stress persists or manifests in an acute form, a cell may become **irreversibly** injured. This ultimately leads to cell death, or **necrosis**. All forms of necrosis are characterized by a disruption in the permeability of the plasma membrane, resulting in a loss in the equilibrium of concentration gradients, which is a key factor in maintaining cellular function. Necrosis can manifest in a variety of ways. **Coagulative necrosis** is a general term for irreversible structural changes to the organelles of the cells. **Liquifactive necrosis** is the process by which dead cells are liquefied by potent hydrolases released by leukocytes during inflammation or infection. **Fat necrosis** refers to the precipitation of triglycerides from necrotic adipose cells into calcium soaps, most commonly seen in pancreatitis. Two other kinds of necrotic states are caseous necrosis, seen in the lesions of tuberculosis, and **fibrinoid necrosis**, referring to the eosinophilic staining of injured blood vessels.

There are several different causes of cell death, several of which are discussed below:

**Ischemia**

Ischemia is the interruption of blood flow, and a common cause of coagulative necrosis. Alterations to the function of plasma membrane and cytoskeleton are perceived as being key in ischemic cell death. If periods of ischemia are of short duration the condition is reversible. Injury can also occur in ischemic states when the supply of arterial blood is restored, called **reperfusion injury**. This is caused not from ischemic state itself, but due to the generation of **toxic oxygen species** when blood flow is reestablished.

**Reactive oxygen species**

One of the features of higher plants and animals is that they are dependent upon the presence of oxygen to produce energy, in a process called **aerobic respiration**. Energy-rich carbohydrates and fats are oxidized in a step-wise manner within an aerobic cell to release energy, some of it used to fuel the cell’s activities, and the remainder released as heat. The processes of aerobic
respiration are characterized by **oxidation-reduction reactions**. **Oxidation** is the *removal of electrons* from a molecule, resulting in a decrease in its energy content. Reduction is the opposite of oxidation, referring to the *addition of electrons* to a molecule, thereby increasing its energy content. Within biological systems, oxidation and reduction reactions are always coupled. Thus, whenever a substance is oxidized, another is simultaneously reduced. The coupling of these two reactions is referred to as **redox reactions**, and ultimately, all of the energy needed to fuel biological systems comes from the energy of these reactions. Human bodies, just as all other living organisms, are reduced relative to the oxygenated atmosphere in which we live. The large energy difference between the reduced molecules of life, such as carbohydrates, fats and proteins, and the oxidizing atmosphere, provides far more chemical energy than processes that don’t take advantage of oxygen (i.e. anaerobic respiration).

One of the paradoxical features of aerobic respiration is that obligate aerobes are also subject to the toxic effects of reactive oxygen species produced during respiration. Increasingly, researchers are finding that these highly reactive molecules, part of a class of compounds called **free radicals**, are not merely the agents of disease, but also of the aging process itself. Free radicals are oxidizing molecules that have an unpaired electron, making them highly unstable and electrically charged. A free radical becomes reduced only by borrowing an electron from the molecule closest to it, which in turn, causes this adjacent molecule to become unstable. Perhaps the best known example of this process is the role the hydroxyl radical (OH') in **lipid peroxidation**. In this case, OH' removes a hydrogen atom from an unsaturated fatty acid in the cell membrane. This results in the formation of a free lipid radical, which in turn, reacts with molecular oxygen to form a lipid peroxide radical. This lipid peroxide radical then acts as another initiator by removing a hydrogen atom from an adjacent unsaturated fatty acid. Thus a chain reaction is initiated, leading to the destruction of the plasma membrane and the death of the cell.

The oxygen species produced normally and upon reperfusion are but one class of free radicals, referring to three partially reduced molecules that are intermediate between O2 and H2O: **superoxide (O2•−)**, **hydrogen peroxide (H2O2)** and the **hydroxyl radical (OH')**. These partially reduced oxygen species can be created from the therapeutic administration of O2 (causing reperfusion damage), chemical injury, radiotherapy and carcinogens. They are also, however, an important part of immune function. Recently, a role for free ferric iron has been implicated in oxygen toxicity.
When an injury occurs that exposes a tissue to atmospheric oxygen, a series of reactions are initiated among the fatty acids in the plasma membrane of the injured and adjacent cells, promoting the release of local hormones called eicosanoids. These hormones serve the very important role of mediating the inflammatory response, first by causing vasoconstriction to prevent blood loss, and later, by augmenting blood flow to the injured area, as well as stimulating cellular and humoral immune reactions that recycle dead tissue, prevent infection, and stimulate repair. When the repair has been completed and the tissues sealed off from oxygen, the tissues return to their normally reduced state and the inflammatory response subsides.

This same disturbance in the redox potential also occurs when a phagocytic cell is exposed to an antigen and releases lethal oxidants such as \( \text{O}_2^- \) and \( \text{H}_2\text{O}_2 \). This local release of oxidizing agents initiates the same response as if the tissues were exposed to atmospheric oxygen. According to some researchers this change in the redox potential in favor of oxidation facilitates antibody sensitivity to antigens. The basis of this theory suggests that an impaired ability to maintain normally reduced conditions may lead to chronic inflammation and autoimmune disease through the stimulation of antibodies.

The redox potential in tissues is largely determined by the presence of antioxidants, reducing molecules that bind to and deactivate free radicals. Examples of important antioxidants include ascorbate (vitamin C), super-oxide dismutase (SOD) and the sulfur-containing glutathione peroxidase, all of which are constantly working to scavenge the free radicals being produced by normal metabolic processes. When an antioxidant neutralizes a free radical it becomes oxidized itself until it is quickly acted upon by the reducing agents of the cell (i.e. NADH, NADPH and FADH2). Thus antioxidants are recycled, ready to scavenge another free radical after being reduced. Although part of the process is for these antioxidant compounds to become oxidized themselves, the predominant endogenous antioxidant, glutathione, is relatively stable when in an oxidized state and is far less than toxic than reactive oxygen species. Nonetheless, if the level of reducing agents falls, as in ischemia (impairment of blood flow), or there is a peaking of oxidative stress, increasing levels of oxidized glutathione can result in injury or even cell death.

Beyond reactive oxygen species, researchers have found other agents that appear to act as free radicals, such as nitric oxide (NO). NO is an omnipresent biological agent that appears to
regulate several neurological, vascular, and immunological functions. For example, NO functions to relax smooth muscle fibers beneath the endothelium in the arteries to have a vasodilatory effect. NO also functions in the act of penile erection, producing smooth muscle relaxation in the corpus cavernosum, allowing for the inflow of blood. Apart from its role in normal physiological processes however, NO also seems to react with superoxide radicals to promote the formation of peroxynitrite. This chemical is a combination nitrating and oxidizing agent that weakens antioxidant proteins such as superoxide dismutase.

**Chemical Injury**
There are many chemicals that are known to damage cells, some which are cytotoxic and act by direct means, and others that only become toxic when they are metabolized. **Directly cytotoxic chemicals** are highly reactive compounds that produce irreversible cell injury by interacting directly with cellular components, such as destroying the integrity of the plasma membrane, or binding with the DNA in the nucleus or mitochondria and altering their function. With repeated exposure, or a concomitant weakness in immune function, the result may be chronic inflammation or cancer. Examples of cytotoxic compounds include heavy metals such as mercury, lead and arsenic; byproducts of industrial waste such as polychlorinated biphenyls and chlorinated benzenes; and polycyclic aromatic hydrocarbons that are derived from the petrochemical-fueled combustion engine.

**Indirectly cytotoxic chemicals** only exert their toxic effects after being metabolized into a toxin that interacts with the target cell. The commonly used analgesic acetaminophen, for example, is metabolized by hepatocytes into an electrophilic metabolite that reacts with glutathione, thus reducing glutathione levels and inducing oxidative stress. Carbon tetrachloride, a previously common industrial solvent, is metabolized by cytochrome P450 to form a chloride ion and the very powerful CCl₃ radical that promotes lipid peroxidation. Acetaminophen is also acted upon by cytochrome P450, results in the formation of superoxide and hydrogen peroxide. Some drugs such as cimetidine and oral contraceptives can inhibit the metabolism of other drugs, prolonging their effects and increasing the risk of toxicity.

One of the features of the 20th century is that we have been increasingly exposed to a variety of chemical toxins that have found their way into the food chain, water table and atmosphere. Additionally, we have made huge alterations in the way we live our lives. Our diet is now based upon refined foods that are
deplete in naturally occurring antioxidants and high in chemical additives that promote free radical injury and chromosomal damage. We live significantly different lives from that of our forebears, with less exercise and a greater amount of time spent indoors where it is estimated that the level of pollution is 5 – 10 times greater than that of the outdoor environment.

**Viral Infection**

A virus is defined as a minute, intracellular obligate parasite consisting of a core of either RNA or DNA, surrounded by a protein coat called a capsid. Just as the term “parasite” implies, a virus requires the resources of the infected cell for replication. Viruses that infect the body can be broadly organized into two groups: **cytopathic**, or viruses that kill the cell directly; and **indirectly cytopathic**, or viruses that kill cells with the help of the body’s immune system. There are three possible routes of infection, or entry in body tissues: through the skin or mucous membranes, by ingestion, or by inhalation.

The poliovirus is an example of a **cytopathic virus**, consisting of a single strand of RNA surrounded by a capsid. When the poliovirus binds to receptors on the plasma membrane of the target cell, the virus is internalized by exocytosis. The endosome then fuses with a lysosome to form a phagolysosome, which then dissolves the capsid. The virus is then released into the cytosol of the cell and is recognized by the ribosomes as another messenger RNA molecule needed for protein synthesis. The viral genome is then translated into a specific RNA polymerase, which in turn leads to the replication of the virus. The viral genome also leads to the replication of capsular proteins that insert themselves into the plasma membrane and disrupt selective permeability, ultimately causing the death of the cell.

Some RNA viruses, called **retroviruses**, contain an enzyme called **reverse transcriptase** that uses the viral RNA genome to synthesize viral DNA. This viral genome is then incorporated into the host cell’s chromosomal DNA where it may become dormant, cause the cell to mutate, or take over the cell’s machinery to produce more viruses. The virus that is linked to AIDS, human immunodeficiency virus (HIV), is an example of retrovirus.

An **indirectly cytopathic virus**, such as the Hepatitis B virus, consists of a double-stranded DNA genome surrounded by a capsid. After binding to a receptor on the target cell it is internalized by endocytosis, the endosome merging with a phagolysosome and the protein coat digested by proteolytic
enzymes. Unlike RNA viruses, DNA viruses cannot utilize the protein synthesis machinery of the cell until it has been transcribed into viral messenger RNA. The viral DNA genome passes into the nucleus of the cell where it is then acted upon by the host cell’s RNA polymerase. This enzyme then transcribes the viral DNA genome into the corresponding messenger RNA. The viral RNA is then transported into the cytoplasm of the cell where the ribosomes act upon it to manufacture new viral proteins. Once manufactured, these DNA viruses pass through the plasma membrane of the cell to infect other body cells. While no damage is sustained by the host cell in this process, the viral proteins being released by the cell are recognized as antigens and stimulate cellular and humoral immune responses, leading to the death of the virus-infected cell.

**Apoptosis**

Apoptosis is programmed cell death, and unlike the other causes of cell death discussed, is an intriguing example of how an organism regulates its growth and development. Apoptosis is thought to be a genetically determined set of directions that tells the cell when it should self-destruct. Rather than being evidence of disease, apoptosis represents a response of the organism towards homeostasis, seen in a range of activities from shaping the body during neonatal development, to the self-destruction of cells that have become cancerous.

**Calcification**

Calcification refers to the deposition of mineral salts into dead or dying cells, as part of a general inability of the plasma membrane to sustain proper concentration gradients. When there is an extracellular deposition from the circulation or interstitial fluid this is called dystrophic calcification, altering the function of the damaged tissues. Metastatic calcification occurs in altered calcium metabolism, with excessive levels of serum calcium, seen in conditions such as chronic renal failure, vitamin D toxicity and hyperparathyroidism. Calcium can also precipitate in the lumen of the gall bladder, pancreas and urinary tract to form stones.

**Aging and degeneration**

As a model, pathology has not yet been able to identify a cause for cellular aging, with most theories based on in vitro experiments that are limited in their scope and application. In a similar vein to apoptosis, some theories account for aging as a part of a genetic program, with evidence based on identical twin studies and
familial correlations. Some features of aging that begin to appear during mid-life for example, such as baldness and menopause, also appear to be genetically determined. Another theory of aging suggests the accumulated effect of repeated injury as an important mechanism, from dietary factors, to environmental stressors and disease.

II. Inflammation

Inflammation is a result of cellular injury, a reaction within the microcirculation of a tissue characterized by an increased movement of fluid and leukocytes from the blood into the affected tissue. It is thought that inflammation occurs due to the host cell’s attempt to localize and wall off damaged cells, foreign particles, microorganisms and antigens from healthy tissues.

Inflammatory processes are divided into acute and chronic, depending on the duration of the injury, clinical manifestations, and the types of inflammatory responses that have been noted by laboratory testing. Clinically speaking, the hallmark of acute inflammation is characterized by the classical signs of rubor (redness), calor (heat), tumor (swelling), dolor (pain) and functio laesa (loss of function). Inflammation is manifested on a microscopic or histological level by an increased movement of fluid and plasma into the affected tissue, as well as the stimulation of platelets (which are responsible for clotting), and the presence of matured neutrophils called polymorphonuclear leukocytes (PMNs). Chronic inflammation is very often a sequela to acute inflammation, or can be an immune response to a foreign antigen.

The process of inflammation is thought to begin with the initiation of the inflammatory response, followed by its amplification by a variety of chemical mediators, and ending in its termination, by specific inhibitors of inflammation. Inflammation can be seen to have three specific outcomes:

1. Resolution: the source of the injury is removed and normal physiological is restored
2. Abscess: the area of inflammation is walled off from the rest of the tissues by inflammatory cells and the tissues is destroyed
3. Scar: the tissue is irreversibly injured and the normal structure of the tissue is replaced by a scar

Broadly speaking, the mediators of inflammation can be separated into two groups, vasoactive mediators and chemotactic factors.
Vasoactive factors, which include compounds such as histamine, serotonin, and bradykinin, result in vasodilation and increased vascular permeability, resulting in edema. Chemotactic factors recruit and stimulate inflammatory cells such as polymorphonuclear leukocytes (PMNs), platelets and mast cells in acute inflammation, and macrophages, lymphocytes and plasma cells in chronic inflammation. Some of these factors display both vasoactive and chemotactic properties simultaneously.

Acute inflammation

Among the earliest inflammatory responses is a transient vasoconstriction of the arterioles at the site of injury, soon followed by capillary and arteriole dilatation, caused by the release of specific mediators at the site of injury and in the blood. These features occur in Lewis’ triple response, in which a blunt instrument is scratched across the skin to illustrate the changes that occur in acute inflammation. The stroke is marked momentarily by a white line, indicating vasoconstriction, followed by a dull red line indicating capillary dilatation, and then lastly by a red irregular flare that surrounds the injury indicating arteriole dilatation. Collectively, these features are called hyperemia.

From a histological perspective hyperemic tissue states are characterized by an exudation of a protein-rich fluid from the blood vessels into the interstitial tissues. This is facilitated by the activity of specific chemical mediators that induce the contraction of the cells that line the capillary wall, forming gaps into the interstitial tissues. With the opening of these gaps there is a diffusion of plasma and proteins from the blood into the interstitial tissues. This movement of fluid into the tissues is thought to help dilute any toxins that are present. Among the proteins are globulins that act as antibodies to recognize and initiate the destruction of foreign antigens, and fibrin which limits bacterial infiltration and assists in wound healing.

There are a variety of inflammatory chemical mediators, from both cellular and plasma sources, that are generated at the site of injury, some vasoconstrictive and others vasodilatory. As mentioned, vasoconstriction is usually a transient effect to inhibit blood flow.
**Cell-derived inflammatory mediators**

Sources of cell-derived vasodilatory mediators include circulating platelets, tissue mast cells and basophils, and from the injured tissue itself.

Some mediators released at the site of injury are derived from membrane phospholipids and the generation of **arachidonic acid (AA)**. Arachidonic acid is then either converted into pro-inflammatory and vasodilatory prostaglandins and thromboxanes (e.g. PGE₂, PGI₂, PGF₂, and TxA₂) via the **cyclooxygenase pathway**, or into chemotactic leukotriene A₄ via the **lipooxygenase pathway**.

Another common mediator released by injured cells and virtually all inflammatory cells is **platelet activating factor** or PAF. PAF has a wide range of activities that promote inflammation, such as enhancing serotonin and histamine release, promoting platelet aggregation, and augmenting AA metabolism by neutrophils, monocytes and macrophages.

Circulating **platelets**, normally playing a role in clot formation, also release a variety of inflammatory compounds, contained in three distinct kinds of cell inclusions: dense granules (containing serotonin, Ca²⁺, ADP), alpha-granules (containing cationic proteins, fibrinogen and platelet derived growth factor), and lysosomes (containing acid hydrolases). Platelets also produce TxA₂, which enhances inflammatory processes.

**Mast cells** and **basophils** both contain receptors for the immunoglobulin (Ig) E on their cell surface, and when stimulated by an antigen, release a variety of inflammatory mediators contained in dense cytoplasmic granules. These include histamine, leukotrienes (LTC₄, LTD₄, LTE₄), PAF, eosinophilic chemotactic factors and cytokines (e.g. TNF-alpha, IL-4). Mast cells are found in connective tissues, especially along mucosal surfaces of the respiratory and gastrointestinal tract, and in the dermis of the skin, representing a first-line of defense against environmental antigens. Basophils are present in much lower concentrations in the bloodstream.

**Plasma-derived inflammatory mediators**

Within the blood plasma there are several additional sources of inflammatory mediators, including Hageman factor, the inducement of the complement system, anaphylatoxins and opsonization.
Hageman factor, or clotting factor XII, is induced within the plasma by a variety of agents associated with injury, including negatively charged surfaces, bacterial lipopolysaccharides, sodium urate crystals and certain enzymes. Plasmin is generated by activated Hageman factor (clotting factor XII) from plasminogen, resulting in fibrinolysis, augmenting vascular permeability in skin and lung. Plasmin also cleaves components of the complement system to increase vascular permeability. Plasma prekallikrein is converted to kallikrein, which cleaves kininogen and thereby produces bradykinin, which promotes changes to the endothelium that result in increased permeability.

The complement system is a group of 20 plasma proteins with both vasoactive and chemotactic properties when activated. This system helps to ‘complement’ certain immune, allergic, and inflammatory reactions. The key member of the complement system is a plasma protein called C3, which can be activated in two ways, through the classical pathway or the alternative pathway. The classical pathway is the activation of C3 through the formation of antibody-antigen complexes, and thus involves the activities of the immune system. The alternative pathway is the activation of C3 directly by an antigen such as bacteria, fungi, virus, parasite or exogenous toxins. Once C3 is activated, through either the classical or alternative pathways, it activates other complement proteins to promote inflammation and form a membrane attack complex, a macromolecular structure designed to punch holes in plasma membrane of microbe or damaged cell and cause it rupture (cell lysis).

When either the classical or alternative systems are activated complement proteins C3a, C4a and C5a are generated, collectively called the anaphylatoxins. These toxins have potent constrictive effects on smooth muscle and enhance vascular permeability. The anaphylatoxins are also potent chemotactic factors for the migration of neutrophils, monocytes, eosinophils and basophils.

Another kind of plasma-derived inflammatory mediator are a variety of immune molecules such as IgG or C3b that bind to the surface of a bacterium, essentially “tagging” the cell for later recognition by phagocytic cells. This process is called bacterial opsonization.

Cellular recruitment
Within a few hours after inflammatory mediators have been initiated, the second phase of the inflammatory response is activated, characterized by the recruitment of leukocytes into the
injured tissues. Leukocytes traveling through the blood vessels are attracted to the site of injury by a process of margination and adherence. **Margination** is the process by which leukocytes begin to accumulate in the area of injury due to the local slowing of blood flow from increased viscosity and endothelial swelling. **Adherence** occurs with the help of membrane glycoproteins on both leukocytes and endothelial cells that interact with each other and promote the leukocyte to adhere to the endothelial cell. Once the leukocyte is firmly adhered to the endothelium, chemotactic factors released at the site of tissue injury promote the leukocyte to squeeze through the junction between endothelial cells by amoeboid movement. The leukocyte then moves against the concentration gradient of the chemotactic agents to the site of injury. Important chemotactic factors include C5a, cytokines (e.g. interleukins, TNF-alpha, lymphotoxin), products of AA metabolism (e.g. leukotrienes), and bacterial products.

**Phagocytosis**

**Phagocytosis** is the process by which certain inflammatory cells, including PMNs and macrophages, recognize, internalize and digest foreign substances and cellular debris. **Recognition** usually begins with opsonization, in which the substance to be digested is coated in plasma complement proteins and immune complexes. This coating greatly enhances the activity of the phagocyte, which, once it has recognized the substance begins the process of internalization. Once the foreign substance or cellular debris is internalized within the phagolysosome, powerful oxidants and antimicrobial substances are released to begin the process of digestion. Among the oxidizing compounds are superoxide, hydrogen peroxide and the hydroxyl radical. Antimicrobial substances include lysosomal hydrolases, cationic proteins, defensins, lactoferrin and lysozymes.

Although inflammatory cells appear to function to protect the body from foreign invasion and speed up the process of healing, some of these processes actually damage the very tissues they aim to protect. This often occurs as the result of the powerful oxidants and enzymes that are released in the extracellular environment during inflammation.

**Resolution of inflammation**

**Resolution** refers to the complete restoration of normal conditions after the inflammatory response. This state is best achieved is there is minimal tissue damage, the causal agent has been neutralized, and local factors are able to restore the microcirculation and remove cellular debris. In **suppurative**
conditions the immune cells wall off the healthy tissues from the area of bacterial infection. This eventually forms as an abscess and the eventual discharge of pus, a creamy yellowish fluid comprised of living and dead bacteria as well as cellular debris and immune cells.

Chronic inflammation

Chronic inflammation most often occurs as a sequela to acute inflammation when there is significant tissue damage or the cause remains unchecked. Chronic inflammation however may also occur because of continued antigenic reactions. On a clinical level, chronic inflammation may exhibit more subjective signs such as pain and discomfort, as opposed to overt signs of inflammation such as redness and heat. In some cases localized edema can be observed, and in the case of joints crepitus can be felt or heard. On a histological level there will be changes in the types on immune cells involved at the site of injury, with a diminution of PMNs and the increasing presence of macrophages, plasma cells, lymphocytes and eosinophils. When the cause of inflammation cannot be completely digested it may remain more or less in tact inside longer-living macrophages and lymphocytes. This prevents short-lived PMNs from initiating an acute inflammatory response. When immune cells such as macrophages accumulate at the site of injury they undergo a change in their structure and become called epithelioid cells. These kinds of cells are the hallmark of granulomatous inflammation.

III. Wound healing

Wound healing is a response to tissue injury and represents an attempt by the body to restore homeostasis in the affected tissues. It coincides with the inflammatory process, a fact that is an important and often underemphasized component when it comes to medical treatment, as evidenced by the usual application of cold and ice at the site of injury, which while protecting the tissues from oxidative damage, slows down the process of repair and regeneration to a considerable degree. From a herbal perspective, measures are often taken in injuries such as broken bones, factures
and sprains to enhance local circulation and thereby assist the process of healing.

Wound healing begins with the initial inflammatory response, and is comprised of three stages: **contraction**, **repair**, and **regeneration**, which more or less function simultaneously. There are a variety of factors that are responsible for wound healing, including blood clotting, enhanced vascularization, and the migration of fibroblasts immune cells to the site of injury. Additional factors in healing include components of the extracellular matrix such as the collagens, the basement membrane, elastic fibers, fibronectin and the proteoglycans, as well as secretion of cytokines such as epidermal growth factor (ECF) and fibroblast growth factor (FGF).

When a tissue is wounded the initial phase begins with hemorrhage, followed by the formation of a **fibrin clot** that fills the gap of the wound to stop bleeding. Specialized cells called **myofibroblasts** then migrate to the area of the wound to reduce its size, exerting a traction effect on the edges of the wound, in the first stage of healing called **contraction**.

Within 2-3 days of the injury the second stage of healing begins, called **repair**. In and around the damaged tissue new blood vessels can be seen to be formed in a process called **angiogenesis**, in which endothelial cells near the site of injury divide to form capillary sprouts from existing vessels. Migrating fibroblasts from the blood that are now localized at the site of injury become activated by cytokine growth factors, and secrete a variety of extracellular matrix components. These including a group of glycoproteins called **fibronectin** that become cross-linked to matrix components such as fibrin and collagen by the activity of enzymes called **transglutaminases**. This activity, along with the secretion of hyaluronic acid, and later, the secretion of proteoglycans and collagen, helps stabilize the wound and enhance the local proliferation of cells. As the inflammatory continues, phagocytes are recruited to the area of injury to process and remove the cellular debris, and to neutralize foreign cells. The process of immune cell recruitment is enhanced by the binding of fibronectin to cellular components, as well as the process of bacterial opsonization. Some of these leukocytes also produce collagenases and proteases that contribute to the removal of the debris. This stage of healing is noted for the formation of what is called a **granulation tissue**, an older term that originally referred to the formation of small, visible capillary loops that form in the base of the wound, but now generally refers to not only newly
formed capillaries, but the activity of the fibroblasts and phagocytes.

As tissue healing progresses the rate of collagen synthesis by the fibroblasts gradually supercedes its rate of degradation by immune cells, and the accumulating collagen results in the formation of a scar. This process is called fibrosis, in which the highly vascular granulation tissue is transformed into avascular, collagen-rich scar tissue.

The final stage of wound healing is called regeneration, and is the process by which cells lost to injury are replaced by identical ones. The success of regeneration is largely dependent upon the type of cells that have been injured. In the case of labile cells, such as those found in the epidermis, the process of regeneration is ongoing in normal conditions and because of this there is less chance of permanent fibrosis. In stable cells, such as hepatocytes, there is a lessened capacity to regenerate, but such cells still have the ability to regenerate and regeneration is possible. In permanent cells, such as neurons, once they have been damaged they cannot multiply and healing by granulation tissue leads to a permanent loss of function and fibrosis.

In the case of epidermal injury, as long as there is no damage to the basement membrane superficial epithelial cells easily proliferate to reestablish the integrity of the tissue. Reserve epidermal cells then detach from the basement membrane and migrate to the site of injury, flattening to increase their surface area. When the wound surface is completely covered the cells regain their normal shape and re-attach themselves to the basement membrane and undergo squamous differentiation until the thickness of the epithelium is restored. Although each tissue displays individual factors when it comes to healing, the process of healing is more or less the same for all: epidermal wound healing is simply the best-studied homeostatic response to injury.

Factors that influence wound healing include both local and systemic factors:

1. **the size, type and location of the wound**, i.e. small wounds in highly vascularized areas tend to heal faster than large wounds or wounds in relatively avascular areas.
2. **infection**, i.e. the presence of bacteria delays healing and exposes the tissues to continuous trauma
3. **movement**, i.e. the activity and usage of the affected tissue before the tensile strength of the tissue has been reestablished.
4. **circulatory status**, i.e. atherosclerosis (old age, diabetes) impairs blood flow to all tissues, including site of injury
5. **immunodeficiency**, i.e. resulting in an inadequate immune response

6. **malnutrition**, i.e. by not supplying the body with all of the nutrients required in healing, e.g. vitamin A, vitamin C, vitamin E, proteins, zinc etc.

**Bibliography**


LESSON TWO: Immunopathology and neoplasia

I. Immunopathology

Cellular components of the immune response

**Lymphocytes**
Lymphocytes are the primary cell type involved in the immune response through their capacity to recognize and react with specific non-self molecules. All lymphocytes derive from primitive stem cells in either the thymus (T lymphocyte) or bone marrow (B lymphocyte).

As **T lymphocytes** develop in the thymus they undergo different stages of maturation, characterized by the expression of certain CD (cluster designation) adhesion proteins on their plasma membranes that bind the cell to target cells during antigenic stimulation. The result is the formation of two different types of T lymphocyte, those that promote the immune response (‘helper’ CD4 T cells) and those that have cytotoxic/suppressor activities (CD8 T cells) functions. To guard against T cells reacting against self-antigens these immunoreactive cells undergo apoptosis in the thymus before maturation.

**B lymphocytes** arise from stem cells in the bone marrow, and in their immature stage contain cytoplasmic immunoglobulins (Ig) but no surface Ig. As they mature B lymphocytes acquire surface **IgM** and **IgD**, and then enter systemic circulation awaiting activation by a non-self molecule. Antigens present or processed by other cells will crosslink with membrane immunoglobulin receptors on the B cell. The antigen is then taken into the B cell, where it is broken down into fragments and combined with self-antigens, leading to the proliferation and clonal expansion of B cells, a process amplified by cytokines released by local macrophages and T cells. In the absence of antigenic stimulation some of these B cells will go on to present with surface **IgG**, **IgA** or **IgE**. Some B cells will further mature into **plasma cells** that secrete Ig (antibodies) that ‘tag’ non-self molecules for immune destruction.
**Natural Killer cells**
Natural killer (NK) cells are neither T nor B cells that have the capacity to recognize and kill a variety of tumor and virus-infected cells. They are stimulated by IL-2 and suppressed by PgE2.

**Mononuclear phagocytes**
Mononuclear phagocyte is a generalized terms that describes to a variety of phagocytic cells including monocytes, macrophages, Kupffer cells in the liver and fixed tissue phagocytes called histiocytes. Some of these cells line the capillaries of the lung, liver and spleen and form an effective barrier against exogenous substances called the mononuclear phagocytic system. Macrophages are noted for their expression of class 2 major histocompatibility complex, discussed below.

Types of immune responses

Immunity consist of two closely allied immune responses, both triggered by antigens. The first is called cell-mediated immunity, in which T cells proliferate into killer T cells and attack the invading antigen. Cell mediated immunity is particularly active against intracellular pathogens, such as fungi and viruses, some types of cancer cells and foreign tissue transplants. The second type of immune response is called antibody-mediated (humoral) immunity, referring to responses in which B cells transform into plasma cells, and synthesize and secrete antibodies that bind to and deactivate a particular antigen. An antibody (Ab) belongs to a group of glycoproteins called globulins, and thus is called an immunoglobulin (Ig). An antibody combines with a specific antigenic determinant on the antigen that triggered its production, just as a key fits in a lock. There are five classes of immunoglobulins in humans: IgG, IgA, IgM, IgD, and IgE. Each has a distinct chemical structure and a characteristic biological role. Antibody-mediated immunity functions against antigens in body fluids and extracellular pathogens such as bacteria that multiply in body fluids. Often an immune response involves the activation of both types of immune response.

**Antigens**
Antigens (Ag) have two basic characteristics: the ability to provoke an immune response; and the ability to react with a specifically produced antibody (Ab). Antigens are often proteins, but can also be nucleo(proteins), lip(o)proteins, glyco(proteins) and polysaccharides. T cells only respond to antigens that include protein, whereas B cells can respond to proteins, lipids,
polysaccharides and nucleic acids. Large molecules that have repeating subunits such as cellulose and most plastics are generally not antigenic. One of the more impressive features of the human immune system is its capacity to bind to at least a billion different antigenic determinants, or specific portions of antigen molecules. As a rule, antigenic determinants are foreign substances that are not a part of the normal chemical make-up of the body. Sometimes the immune system fails to make a distinction between self and non-self, and this can result in the destruction of self-molecules as though they were foreign. Such a process is called an autoimmune disorder, discussed later in this paper.

**Major Histocompatibility Complex**

With the exception of identical twins, each individual maintains a unique set of glycoproteins that mark all body cells, except red blood cells, called the major histocompatibility complex (MHC). These MHC antigens help T cells recognize foreign invaders, and the lack of these unique glycoproteins on transplanted organs is what is responsible for organ transplant rejection. There are two classes of MHC antigens: MHC I, built into the plasma membrane of all body cells except red blood cells; and MHC II, antigens that are found on the plasma membrane of antigen presenting cells, cells of the thymus gland and activated T cells.

**Pathways of Antigen Processing**

For an immune response to be initiated, B and T cells must recognize the presence of a foreign antigen. B cells can recognize and bind to antigens in the extracellular fluid. T cells however, only recognize fragments of antigenic proteins that have been processed and presented in association with MHC antigens. Most cells of the body can process and present endogenous antigens, foreign antigens that were synthesized in a body cell, such as when a virus infects a cell and uses its metabolic machinery to produce more viruses. Endogenous antigens usually associate with MHC-I molecules. Exogenous antigens are foreign antigens produced by intruders outside body cells, and are processed by special cells called antigen presenting cells (APC), including macrophages and B cells. The first stage of antigen processing begins with the phagocytosis or endocytosis of a foreign antigen. This is followed by the partial digestion of the antigen, in which enzymes split the antigen into short peptide chains, and the synthesis of MHC II molecules by the APC. The partially digested antigen and MHC II molecules then merge, bind together and are inserted into the plasma membrane of the APC. The APC then migrates to lymphatic tissue and is recognized by a T4 cell to trigger a cell
mediated immune response, or is recognized by a B cell to trigger an antibody mediated immune response.

**Cell-Mediated Immunity**

Cell mediated immunity begins with the recognition of particular antigen by a small number of T cells. The T cells then undergo proliferation and differentiation into a clone of effector cells, a population that can recognize the antigen and carry out an immune response and the elimination of intruder. Antigen receptors on T cells are called **T cell receptors (TCRs)**. They recognize and bind to specific foreign antigen fragments that are presented together with self MHC molecules. There are millions of different T cells, each with unique TCRs that can recognize a specific antigen-MHC complex. Most of the time T cells are inactive, and when an antigen enters the body, only a few T cells have TCRs that recognize and bind to the antigen. **Recognition** by a TCR is the first signal in the activation of a T cell. The second signal, called a **costimulator**, is the release of cytokines such as interleukin-2 that stimulate the proliferation of T cells. When a T cell receives these two signals (recognition and costimulation) it becomes activated or primed. The T cell then enlarges, proliferates (divides) and differentiates into more highly specialized cells. The result is a clone, a population of cells that can recognize the same antigen. After the initial immune response there are thousands of T cells to deal with the intruder. Costimulation is an important feature of T cell activation, and apart from stimulating the generation of different T cells, acts a safety switch to prevent the accidental stimulation of an immune response. The are several kinds of T cells that are generated during differentiation. **Cytotoxic T cells (T8 cells)** arise from T lymphocytes that display the CD8 molecule. Cytotoxic cells recognize foreign antigens combined with MHC-I molecules, and when costimulated by interleukin-2 or other cytokines, promote the lysis (cell death) of the microbe. T8 cells also secrete several cytokines such as **lymphotoxin**, a cytokine that fragments the DNA of microbes; **perforin**, acting to perforate the cell membranes of microbes; and along with helper T cells and NK cells, **gamma-interferon**, a cytokine that stimulates phagocytosis and promotes inflammation. **Helper T cells (T4 cells)** arise from T lymphocytes that display the CD4 molecule. After costimulation, T4 cells secrete variety of cytokines that mediate the immune response. **Interleukin-2** acts as costimulator for cytotoxic T cells, and enhances the activation and proliferation of T cells, B cells, and natural killer cells. **Interleukin-4** is a costimulator for B cells, initiates plasma cells to secrete IgE antibodies and promotes the growth of T cells. **Interleukin-5** is a costimulator for B cells, and causes plasma cells to secrete IgA
antibodies. Helper T cells can also secrete gamma-interferon and TNF, both of which promote inflammation. **Suppressor T cells** are specialized T cells with the CD8 marker that produce **cytokine transforming growth factor-β (TGF-β)** that acts to inhibit the activation of T and B cells.Suppressor T cells may also neutralize activated T and B cells by simply destroying them. Other types of T cells include a class that mediates the allergic response, called **delayed type hypersensitivity T cells**. These cells secrete cytokines such as gamma interferon that stimulate macrophages to eliminate the antigen. **Memory T cells** are programmed T cells capable of recognizing a foreign antigen. If at a later time the same pathogen should invade the body thousands of memory cells are available to initiate a swift immune response, destroying the pathogen before symptoms even appear.

**Antibody-Mediated (Humoral) Immunity**
Whereas cytotoxic T cells leave lymphoid tissue to search out and destroy a foreign pathogen in the bloodstream, B cells are stationary in lymph nodes, spleen, and lymphoid tissue in the gastrointestinal tract. When activated, B cells differentiate into **plasma cells** that release specific antibodies into the lymph and blood to reach the site of invasion. **IgG antibodies** represent 75% of the immunoglobulins that are produced by plasma cells, and function by enhancing the phagocytosis of bacteria and viruses, neutralizing toxins, and activating complement. Of the five classes of immunoglobulins only IgG can pass through the placental barrier from the mother to provide immunity to the newborn. **IgA antibodies**, making up close to 15% of all antibodies, are found in tears, saliva, mucosal secretions, breast milk, blood, and lymph. A deficiency of IgA occurs in one in 700 individuals, and levels have been shown to decreases with stress. IgA is an important antibody found in mucosal secretions and a deficiency of IgA is associated with chronic respiratory and digestive infections. **IgM antibodies**, representing between 5 and 10% of all antibodies, are the first antibodies to be secreted by plasma cells when exposed to an antigen. They are found in the blood, lymph, and the surfaces of B cells. When exposed to an antigen, IgM causes agglutination, or the clumping together of microbe-antibody complexes, and promotes cytolysis of the microbe. **IgD antibodies** make up less than 1% of all antibodies and are found in blood, lymph and on the surfaces of B cells as antigen receptors. IgD is involved in the activation of B cells. **IgE antibodies** comprise less than 0.1% of all immunoglobulins and are located on mast cells and basophils that release chemical promoters of the allergic response.
During the activation of a B cell, the antigen binds to antigen receptors on the cell surface. Some of the antigen peptide fragments are then taken into the B cell, combined with MHC II self antigens and moved to the surface of the B cell. Helper T cells then recognize the antigen-MHC II complex, and deliver the costimulation needed for B cell proliferation and differentiation. Some B cells enlarge and differentiate into plasma cells, secreting antibodies at rate of 2000 per second for up to 4 or 5 days, and after which dies. The activated B cells that do not differentiate remain as memory B cells, responding faster and more forcefully should the same antigen appear.

Specific antigens stimulate the proliferation of antigen-specific B cells that develop into plasma cells and their associated memory B cells. Thus, the B cells that developed from the original B cell that was first exposed to the antigen will only secrete immunoglobulins that are specific to that antigen. When antigen-specific immunoglobulins are secreted by plasma cells they enter into circulation to bind with the antigen that originally stimulated its production. The formation of the antibody-antigen complex will then either stimulate phagocytosis or the formation of a membrane attack complex (complement system), both of which resulting in the destruction of the microbe.

**Immunological Memory**

One of the features of the immune response is that it has a capacity to memorize specific antigens that have triggered past immune responses. Immunological memory is due to presence of long-lived antibodies and very long-lived lymphocytes that arise during the proliferation and differentiation of antigen-stimulated B and T cells. During the first exposure to an antigen the immune response is slow and make take several days. After exposure, several thousands of memory cells remain in a resting state, and upon subsequent exposure to the same antigen, memory cells undergo rapid proliferation into antibody-secreting plasma cells and the immune response achieves its maximum intensity within a few hours. Thus the immune response is quicker after the second exposure to an antigen.

**Self-Recognition and Immunological Tolerance**

To function properly, all B and T cells must have two traits: the ability to recognize MHC molecules, called self recognition; and a lack reactivity to peptide fragments from self proteins, called immunological tolerance (IT). The loss of immunological tolerance leads to autoimmune disorders. Immature B and T cells
that become capable of recognizing self MHC molecules survive and those that don't are destroyed. This is called positive selection. Immature B and T cells with antigen receptors that recognize peptide fragments from self proteins are eliminated, called negative selection. Self-recognition and immunological tolerance ensures that T and B cells will not respond to fragments of molecules that are normally present in body.

Immunologically mediated tissue injury

**Type 1 hypersensitivity: anaphylaxis**

Type I hypersensitivity reactions, also called anaphylaxis, are a local or generalized reaction that occurs within a few minutes of exposure to an antigen to which the individual has been previously exposed. With the first exposure to the antigen there is the formation of a corresponding IgE antibody, and the fixation of this antibody to mast cells and basophils. Upon a second exposure to the antigen IgE promotes mast cell degranulation and histamine release, promoting smooth muscle contraction and enhances vascular permeability. When released locally in the respiratory tract this may manifest in such conditions as hay fever and asthma. Severe type I hypersensitivity reactions can bring about a generalized response called anaphylaxis, leading to bronchial obstruction and circulatory collapse.

It appears that many people who display a tendency to type I hypersensitivity reactions, called atopy, also have a deficiency of an enzyme called delta-6-desaturase. This enzyme is key in the metabolic conversion of dietary linoleic acid into gamma-linoleic acid (GLA), the precursor of the ProgE1 series of prostaglandins that have an antiinflammatory activity. The tendency to atopy is familial with a strong genetic basis, and if both parents are atopic, there is a 75% chance the child will experience the same. Common antigens that can initiate a type I hypersensitivity reaction in some people include penicillin, bee venom, pollen, dust mites and animal dander, as well as certain foods like dairy, wheat, and citrus.

**Type 2 hypersensitivity reactions**

Type II hypersensitivity reactions are also mediated by antibody-antigen reactions, but are directed against foreign cells or altered cell surface antigens. Both IgG and IgM play a role in type II hypersensitivity reactions, and are aided by the activation of the
complement system. Thus, a body cell coated with a particular antigen initiates an immune response that ends up in the destruction of that cell. Autoimmune disorders such as the hemolytic anemias, Grave’s disease, and myasthenia gravis all involve type II hypersensitivity reactions.

**Type 3 hypersensitivity: immune complex disease**

Type III hypersensitivity reactions involve the binding of IgA, IgG or IgM to specific antigens. When these antibody/antigen complexes are deposited in body tissues, such as the kidney, skin, lungs or synovium, they initiate a localized immune response that results in the migration of phagocytes and the release of tissue-damaging proteases and oxygen radicals. Many diseases, including autoimmune disorders such as systemic lupus erythematosus, are mediated by type III hypersensitivity reactions.

**Type 4 hypersensitivity: cell mediated**

Type IV hypersensitivity reactions, unlike the previous three already described, do not involve immunoglobulins, although they often occur simultaneously with antibody reactions. Type IV hypersensitivity reactions, or delayed hypersensitivity reactions, involve macrophages that present an antigen to antigen-specific T-lymphocytes. The resulting inflammation and tissue injury is caused by the release of chemical mediators by the T-lymphocytes.

**Immunodeficiency**

Immunodeficiency diseases involve either a loss of antibody (B cell) or cell mediated (T cell) function, or a combination of both, and can be either congenital or acquired. Congenital forms of immunodeficiency are rare, and are characterized by a susceptibility to infections and chronic diseases such as pneumonia, giardia, candidiasis and chronic rhinitis, including x-linked hypogammaglobulinemia, DiGeorge syndrome, and Wiskott-Aldrich syndrome. Acquired immunodeficiency is associated with a large number of conditions such as malnutrition, autoimmune disorders, cancer, and infection. The most common cause of immunodeficiency is iatrogenesis, most often in patients treated with immunosuppressive drugs or radiotherapy.

Perhaps the best known of the acquired immunodeficiency states is acquired immunodeficiency syndrome (AIDS). The predominant theory of the cause of AIDS is the infection of the human immunodeficiency virus (HIV)-1 and –2. It is thought that
HIV acts principally as a venereal disease, transmitted through the exchange of internal bodily fluids during vaginal and ano-rectal intercourse, but has also been detected in vaginal secretions. According to the AIDS theory, HIV is a RNA retrovirus that contains reverse transcriptase, selectively attacking the CD4 T lymphocyte, although the infection of B lymphocytes, macrophages, glial cells and intestinal epithelial cells have been described. Clinically, AIDS is recognized by a typically gradual decline in the number of T4 helper cells and the development of indicator diseases such as fungal pneumonia (*Pneumocystis carinii*), chronic herpes, mucocutaneous candidiasis, recurrent protozoal and bacterial infection, and Kaposi’s sarcoma. The laboratory features of AIDS includes lymphopenia (an overall decrease in the number of circulating lymphocytes) and a decrease of T4 helper cells relative to T8 suppressor/cytotoxic cells.

The exact mechanism by which HIV kills infected T lymphocytes is still unknown. There are some unanswered questions regarding the validity of the HIV model of AIDS, and several notable researchers including Nobel prize laureate Kary Mullis (1993), have voiced their concern over the HIV model. The history of HIV research and treatment is shrouded with difficulties, including the development of clinical tests for HIV that had a poor specificity and displayed cross-reactivity patients suffering from diseases such as malaria, leprosy, and autoimmune disease. Another difficulty is the lack of data that conclusively states that the virus exists, a feat that is an admittedly technically difficult problem, as viruses are intracellular parasites and are difficult to isolate. Thus ‘HIV markers’ such as antibodies and ‘retro viral proteins’ are used instead to indicate the presence of the virus. Some researchers however, investigating HIV-1 infected T cell cultures, have found that these same markers used in clinical tests could not be associated with HIV.1 Unfortunately the debate between those who support the HIV hypothesis and its skeptics has become antagonistic, and unless some compelling evidence is presented, the debate will likely continue unabated and with misdirected intent.

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Autoimmunity

The term **autoimmunity** refers to a loss of **immunological tolerance** (IT), meaning that the immune system has lost the ability to distinguish self from non-self, and acts against self-antigens. There are a few theories in modern medicine as to why this happens.

The first theory refers to the abnormal development of T cells in the thymus gland. T cells that do not display IT are weeded out by negative selection (apoptosis). If however by some mechanism the T cells are not destroyed and escape from the thymus gland, this can result in a loss of IT. Supporters of this theory point to the often familial incidence of autoimmune diseases, which could imply a genetic defect in the function of T cells.

The second theory of autoimmune disease, and one which is gaining increasing acceptance among medical professionals, is that there is an immunological “cross-reactivity” between infectious microbes and the tissues of the body. In short, an antigen that bears similarity to human tissues is encountered and provokes an immune response. Antibodies are then formed against both the pathogen and the similar tissue. Recently, researchers at Johns Hopkins Medical Institute have shown this to be the case. It was observed that mouse cells infected with the *Salmonella* bacteria displayed molecules on the surface of the plasma membrane that are also found on normal cells in mice that regulate protein shape. The subsequent immune response was then observed to involve the destruction of the infected cell, and the normal cells that carry this similar molecule.

In contrast to the link between pathogens and autoimmune disorders, there is growing amount of evidence that links autoimmune disease with dietary factors. In the early to mid 1980’s researcher D.P. Burkitt provided compelling evidence that autoimmune diseases are simply not seen in primitive societies that eat a traditional diet. Recently, researchers such as Loren Cordian have drawn a link between cereal grains and the rise of the chronic, degenerative diseases common to the West. In societies that were previously healthy, there has been an observed increase in the

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prevalence of all of these “Western” diseases, including autoimmune disorders. Current research for many autoimmune conditions shows that antibodies to a trigger such as gluten (found in wheat) or casein (found in milk) can cross react and attack the host tissues because of a resemblance between the two. Cow’s milk, for example, naturally contains a small amount of bovine insulin that can cross react and initiate the destruction of the beta cells in the islets of Langerhans in the pancreas, suggesting a link between milk and juvenile diabetes.\(^5\) The underlying etiological factor for the pathogenesis of diet-based autoimmune disorders is intestinal permeability, which is itself, linked to dietary factors.

Examples of autoimmune disorders include **systemic lupus erythematosus** (affecting kidneys, joints, serosal membranes and skin), **Sjörgen’s syndrome** (affecting salivary and lacrimal glands), and **Scleroderma** (affecting the skin, blood vessels, kidneys, lungs, heart and digestive tract). These diseases are reviewed in detail in the accompanying pathology text.

### II. Neoplasia

**Cancer**, or **neoplasia**, is an uncontrolled proliferation of anaplastic cells called a **tumor**, with a tendency to invade surrounding tissue and may metastasize through the blood or lymphatics to other tissues. Tumors are classified into two basic types, benign and malignant.

**Benign tumors** do not penetrate to adjacent tissues and nor do they metastasize. They tend to be more highly differentiated than malignant tumors, more closely resembling the tissue of origin. Benign tumors are denoted by the suffix –*oma*, the term preceding it indicating the cell type. Thus a benign tumor of the squamous epithelium is termed an **epithelioma**, and when branched and growing outward is called a **papilloma**. A benign tumor that arises from gland is called an **adenoma**, or **adenomatous**.

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Malignant tumors

Malignant tumors are denoted by the term *carcinoma* when applied to epithelial cancers and *sarcoma* when referring to other connective tissue cells. *Gastric adenocarcinoma* thus refers to a malignant tumor of glandular epithelial tissues in the stomach. A *squamous cell carcinoma* refers to a malignant growth in the skin. In contrast a *chondrosarcoma* refers to the growth of malignant chondrocytes in bone tissue. Despite the attempt to classify the differences between benign and malignant neoplasms in a logical manner, several older terms such as *hepatoma* or *lymphoma* have remained in use, but refer to highly malignant cancers of the liver and lymphatic tissue, respectively. Malignant neoplasms of the blood are designated with the suffix –*emia*, as in *leukemia*.

Malignant cancers can vary to a large degree in their size and shape, and are also classified according to their morphological and functional characteristics. *Papillary* refers to a frond-like structure; *medullary* refers to a soft cellular tumor with little connective tissue; *scirrhous* or *desmoplastic* refers to a tumor with dense fibrous stroma. *Colloid* carcinoma secrete mucus in an island of tumor cells, whereas *comedocarcinoma* is an intraductal neoplasm in which necrotic material can be expressed from the ducts, most commonly seen affecting the mammary glands of the breast.

In order for a tumor to grow it requires enhanced vascular supply. To this end many tumors secrete polypeptides such as *platelet derived growth factor (PDGF)*, *fibroblast growth factor (FGF)* and *transforming growth factor (TGF)* that stimulate the growth of new blood vessels in the host tissue in a process called *angiogenesis*.

**Invasion and metastasis**

Most malignant tumors grow within the tissue of origin where they enlarge and begin to invade surrounding tissues and organs in a process called *invasion*. Examples include squamous carcinoma of the cervix, which may grow and extend into the vagina to produce fistulas and obstruct the ureters. *Metastasis* refers to the transfer of malignant cells from one site to another that is not directly connected to it. In much the same way that a malignant tumor can penetrate the parenchyma of surrounding tissues, neoplastic cells may come into contact with the blood and lymphatics through which they are disseminated to distant locations.
In **hematogenous metastasis** malignant cancer cells invade local capillaries and venous tissue, forming a **thrombus** on the vessel surface. As the thrombus grows particles of the thrombus tend to break off and form **neoplastic emboli** which then travel through the blood. Malignant abdominal tumors spread via the hepatic portal vein and thus are usually responsible for liver metastasis. The invasion of other systemic veins frequently leads to neoplastic emboli being carried to the vena cava, and through the pulmonary vein, to the lungs.

In **lymphatic metastasis** neoplastic cells invade local lymphatic channel, forming microscopic neoplastic emboli in the lymphatic stream. These neoplastic cells are then taken to the nearest lymphatic node, where it invades the tissue, causing it to become enlarged and hard. Lymphatic metastasis frequently involves the occlusion of the affected neoplastic tissue, causing the lymphatic flow and the neoplastic cells contained within it to be directed or reversed to other parts of the lymphatic system. This accounts for the often irregular spread of lymphatic metastasis. As the cancer develops, progressively more and more lymphatic tissue is affected, spreading the cancer to other organs and tissues.

### Causes of cancer

The unregulated growth of cancer cells result from the acquisition of mutations in genes that control cell growth and differentiation. These mutations can be the result of several mechanisms, the most common of which relate to apparently spontaneous errors in DNA replication and repair. The genes that are involved in the pathogenesis of cancer are **oncogenes**, altered versions of normal genes that code for malignant transformation. One of the causes for this alteration is thought to lie in the activity of oncogenic viruses that infect a cell and alter the host DNA to produce a mutant neoplastic cells. Human cells however have also been shown to naturally contain **proto-oncogenes** that when activated, through genetic errors, result in DNA mutation independent of viral stimulation. An important component in oncogenesis are **tumor-suppressor genes** that are involved in normal cellular differentiation and inhibit the proliferative activities of the oncogenes. In this case the evolution of a mutant neoplastic cell is thought to be a failure or loss of tumor suppressor gene activity.

The following lists the basic known causes of cancer:
Chemical carcinogenesis

Chemical carcinogenesis has increasingly been recognized as an important cause of cancer. These chemicals can be termed mutagens, an agent that can permanently alter the genetic structure of a cell. Chemical carcinogens can either cause cancer directly or after they have been metabolized by organs such as the liver. Polycyclic aromatic hydrocarbons are derived from the burning of fossil fuels and tobacco, and can have a wide range of activity in the body, producing cancer in the site of exposure (e.g. the lungs). Similarly, mineral oils and tar products contain benzopyrene and other hydrocarbons that have been shown to produce skin cancer when applied topically. Aflatoxins are natural compounds produced by some Aspergillus species, commonly found as a contaminant in food supply, especially in peanuts and grains that have been stored in warm, moist conditions. Aflatoxin is potent agent in liver cancer. Aromatic amines and azo dyes found in aniline dyes have been shown to promote liver and bladder cancer, after metabolism by the liver. Nitrosamines are potent carcinogens used in food preservation. Metals such as nickel, lead, cadmium, cobalt and beryllium have electrophilic properties and thus can react with the organic constituents of the body, metal ions reacting with the guanine and phosphate groups of DNA. The inhalation of asbestos has been shown promote pulmonary asbestosis and asbestos-associated lung cancers such as mesothelioma. This is by no means a complete list, but represents the most commonly identified chemical toxins. It is important to note that we are exposed to hundreds of different potential chemical toxins, many of which are found in low concentrations in food.

There are several factors that can influence chemical carcinogenesis. For example, a woman that becomes pregnant earlier, has more children and lactates longer has the lowest risk of breast, uterine and cervical cancer in all groups. Conversely, a woman that has an early menarche, a late menopause no pregnancy has the highest risk. In regard to diet low protein, high carbohydrate and low fiber consumption are all factors that have been shown to increase the risk of cancer.

Physical carcinogenesis

Physical carcinogenesis for the most part related to sources of radiant energy. Non-ionizing ultra violet energy from the sun has been associated with basal cell carcinoma, squamous carcinoma and melanoma, and is predominant in white-skinned populations. Ionizing radiation, from sources such as x-rays, the therapeutic administration of radioactive isotopes, industrial mining and
processing of radioactive substances, and from atomic explosion is a potent physical carcinogen, causing disjunction in normal chromosomal structure, with the subsequent random fusing of broken ends leading to mutations in the genetic code.

**Viral carcinogenesis.**
As mentioned earlier, viruses have been shown to be an important factor in cancer, responsible for an estimated 15% of all cancers. Many of these viruses have genes that encode for proteins that interfere with the activities of tumor suppressor genes. Thus these cells become more likely of undergoing neoplasia. Further, once infected, viral DNA is inserted in the host’s genetic structure, either replacing or activating human proto-oncogenes in such a way that they code for malignant transformation. Examples of DNA viruses include the papilloma, herpes, Epstein-Barr and hepatitis B2 virus.

**Immunological defense against cancer**

In order for a cancer cell to be recognized by the immune system it must display antigens on its membrane surface. This has been demonstrated in animal experiments where mice with experimentally induced tumors that were removed before metastasis, can be injected with the same tumor cells afterwards without developing a tumor. This suggests a mechanism of acquired immunity in cancer. The immune system appears to play an important role in preventing new tumor formation by searching and destroying newly transformed cells. While the experimental evidence is far from conclusive, some evidence shows an increased risk of lymphoma, leukemia, Hodgkin’s disease, Kaposi’s sarcoma in immunodeficiency, immunosuppression and autoimmune disease. A few mechanisms that may contribute or mediate immunological cancer cell lysis include the activities of T cells, natural killer cells, macrophage, antibody/antigens and the complement system.

**Systemic effects of cancer**

Cancer patients can be seen to exhibit systemic manifestations of cancer, called *paraneoplastic syndromes*. Generalized manifestations include fever, anorexia and weight loss. In the case of malignant tumors within the endocrinal tissues, there may be an alteration in hormonal secretion that can have systemic effects,
such as Cushing’s syndrome (tumor of the adrenal cortex), and hyperprolactinemia (tumor of the pituitary). Neurological symptoms of cancer may include dementia, cerebellar degeneration, encephalitis and optic neuritis. Upon laboratory investigation there may be erythrocytosis or anemia, granulocytosis, eosinophilia and thrombocytosis.

Cancer epidemiology

Cancer currently accounts for 20% of all causes of mortality, and is the second leading cause of death after cardiovascular disease. Some types of cancers appear to be on the decrease and others on the increase, depending upon geographic and ethnic differences. The rate of nasopharyngeal cancer, associated with EBV, is rare in most parts of the world, significantly higher in parts of East Asia. Esophageal cancer is associated with several factors, including excess alcohol consumption and smoking, occurring in higher rates in Asia, in certain area of Africa, and among African-Americans in the United States. The rates of stomach cancer have undergone a significant decrease in the West since the turn of the last century, but continue to be very high in Japan. It is thought that highly salted foods may promote stomach cancer. The incidence of colorectal cancer is highest in the United States, thought to be associated with low fiber intake. Liver cancer is endemic to sub-Saharan Africa and Asia, thought to be associated with aflatoxin-contaminated food. Skin cancer is noted as being highest among white-skinned people, found highest in Northern Australia and the America South. Lung cancer has undergone a dramatic rise all over the world, and is directly attributed to smoking, as well as the recent increase in environmental air-borne pollutants. Breast cancer is the most common female cancer in North America and Europe, with rates developing countries one-fifth to one-sixth as high. Although the causes are not known, many factors are thought to be responsible, including dietary factors such as saturated fat and the disruptive effects of xenoestrogens (as therapeutic agents or environmental toxins). Cervical cancer has been associated with a low socioeconomic status, as well as early sexual activity and multiple sexual partners, and is associated with venereal disease. The risk of prostatic and testicular cancer in the West has increased dramatically over the last few decades, with very low incidences reported in Asia, particularly in Japanese men.
Bibliography

LESSON THREE: Environmental, infectious and parasitic disease

I. Environmental disease

Environmental pathology is a branch of modern medicine that deals with diseases caused by exposure to external agents of injury. It encompasses a large number of factors, including environmental pollution, as well as behaviors such as smoking, alcoholism and drug abuse. Included as well in environmental pathology are an examination of the issue of iatrogenesis, physical agents of injury such as heat or cold, and common nutrient deficiencies.

Smoking

Tobacco smoking is the single largest preventable cause of death in North America, accounting for roughly one-sixth of the total yearly mortality. Life expectancy is decreased proportionally to the duration of the habit, although former cigarette smokers that have abstained from the habit for at least 15 years have the same risk of mortality as non-smokers.

Among the diseases associated with tobacco smoking are cardiovascular disease, cancer, chronic bronchitis, and chronic obstructive lung disease. In women, the incidence of cigarette smoking increases the risk of osteoporosis and induces menopause at an earlier age by interfering with estrogen metabolism, and appears to be associated with an increased risk of Graves disease (hyperthyroidism). Tobacco smoking in pregnant women has been observed to promote problems associated with the uteroplacental system, and lower than normal birth weight.
Alcoholism

Alcoholism is stated as being the consumption of any amount of alcohol that causes injury to the body. Chronic alcoholism is when these amounts are ingested on a chronic basis. As a general rule, daily alcohol consumption should be less than 40 g, which is equal to 120 mL of 43% (86 proof) alcohol, and amounts in excess of this have been shown to be harmful. On an individual basis however, even small amounts can prove to be harmful, depending on certain factors such as age, ethnicity, gender and the underlying health of organ such as the liver. Women appear to be more sensitive to alcohol than men, and certain populations, such as the Inuit and First Nations people of North America, may also be more sensitive. The rate of alcoholism in North America is stated to be about 10% of the population, although this is not distributed equally through out the population, and certain ethnic groups (e.g. First Nations) the rate of alcoholism can be very high.

The effects of chronic alcohol consumption include alcoholic cirrhosis, acute pancreatitis, alcoholic cardiomyopathy, chronic skeletal myopathy, feminization in men, ulcer and gastric reflux, megaloblastic anemia, and several neurological effects that relate to the toxic effect of alcohol as well as alcohol-induced nutrient deficiencies. In pregnant women alcohol is a teratogen, and if consumed regularly even in relatively modest amounts can promote fetal alcohol syndrome (FAS), which includes growth retardation, central nervous system dysfunction and characteristic facial dysmorphology. FAS is thought to be the most common cause of acquired mental retardation.

Drug abuse

Drug abuse is defined as the use of any substance in a manner that deviates from the accepted medical, social or legal patterns in a given society. As such, what constitutes drug abuse cannot be so easily defined as it much of the definition is based on subjective criteria. That said, some commonly used drugs can definitely be shown to exhibit toxicity, and can dramatically alter the course of an individual’s life. Among the most worrisome drug addictions is heroin, a purified alkaloid derived from Papaver somniferum, a substance first marketed by the German Bayer drug company as a treatment for morphine addiction. Later, heroin could be found in
many OTC products during the early part of the last century, such as in cough syrups, which unfortunately created a relatively large population of addicted users, a ratio in society that appears to be more or less the same today. The greatest problems associated with heroin addiction are contamination and the spread of blood borne illness. Increasingly the focus has on harm-reduction, by the use of more benign agents such as methadone, but also medicinal herbs such as *Eschscholzia californica* and *Avena sativa*, to mediate the symptoms of withdrawal or facilitate decreased usage.

**Cocaine** is an alkaloid derived from the plant *Erythroxylon coca*, and is consumed in variety of ways, either inhaled into the nose or smoked, where it is absorbed by the respiratory mucosa, or is injected directly into the bloodstream. Cocaine acts by inhibiting the metabolism of dopamine, allowing it to linger longer in the synaptic cleft, promoting feelings of euphoria and enhanced sensitivity to sensory stimuli. Large amounts of cocaine may promote anxiety, seizures, cardiac arrhythmia and even death.

**Amphetamines** are another stimulant similar to cocaine, stimulating the fight or flight responses in the body, with effects that are longer lasting than cocaine. One common source of amphetamines are doctor-prescribed treatments for weight loss.

**Hallucinogens** are perhaps the most controversial of supposedly abused drugs, and comprise a large group of unrelated chemicals from both plant and animal sources that alter sensory perception. Some of these agents however are either inherently toxic, e.g. phencyclidine (PCP), or in large doses can lead to respiratory arrest (e.g. lysergic acid dithylamide).

Another commonly abused substance is **organic solvents**, such as fingernail polish, plastic cement, and gasoline, which provide for an inebriated state similar to alcohol. Some of the active compounds are known carcinogens and can are extremely toxic, including benzene, carbon tetrachloride, acetone and toluene. The problem of organic solvent abuse is particularly striking in Canada’s First Nations youth, and is a practice typically found with poverty.

**Iatrogenesis**

Recently, in a review of the US Health care system, the *British Medical Journal* reported that iatrogenesis is the third leading
cause of death in the United States. The source of these mortalities include both physician-prescribed medication, as well as surgery:

- 12,000 deaths/year from unnecessary surgery
- 7000 deaths/year from medication errors in hospitals
- 20,000 deaths/year from other errors in hospitals
- 80,000 deaths/year from nosocomial infections in hospitals
- 106,000 deaths/year from nonerror, adverse effects of medications. (Starfield 2000)

The risk of mortality and adverse reaction appear to be greater for certain kinds of drugs, and with a longer duration of use. In some cases iatrogenesis is caused by a poor selection in medication by the physician, too high a prescribed dosage, a genetic predisposition of the patient, hypersensitivities and drug-drug interactions. Some drugs, such as oral contraceptives and hormone replacement therapy (HRT) have increasingly come under fire for an increased in reproductive cancer.

Environmental toxins

Humans are being exposed to an increasingly wider array of environmental toxins than we have that have seen before, most of which have been produced as a direct result of industrialization. These toxins are now found in both the workplace and in the homes, as well as in our food, air water and bodies. The environmental toxins discussed in this lesson include:

- organic solvents
- pesticides, herbicides, fertilizers
- aromatic halogenated hydrocarbons
- air pollutants
- heavy metals.

Thermal dysregulation

Included within environmental pathology are disruptions to normal thermal regulatory processes, from excess exposure to heat or cold. This includes hypothermia, in which the focal or core body temperature is pushed below 35° C, typically from exposure to cold weather or cold water. In systemic hypothermia there is a net reduction in the core body temperature, a reduction in blood
flow and an increased risk of cardiac arrest. In **focal hypothermia** there is local damage to the endothelium, resulting in inflammation, localized edema and the appearance of blisters. With the occlusion of blood flow there is an increased risk of gangrene.

**Hyperthermia** is a net increase of the in the focal or system body temperature conditions, the mechanisms of injury similar to that of hypothermia, with alterations in vascular permeability, localized edema and the formation of blisters. **Systemic hyperthermia** is an increase in the core body temperature above 41-42˚C, most commonly seen as **heat** or **sun stroke**. Among the complications of heat stroke are lactic acidosis, hypocalcemia, rhabdomyolysis (destruction of skeletal muscle) and acute renal failure. **Focal hyperthermic** conditions are usually the result of **cutaneous burns**. A temperature of 70˚C of higher will cause necrosis of the dermal epithelium. Cutaneous burns are separated into three classifications:

1. **First degree burns** – little necrosis, with mild endothelial injury and inflammation
2. **Second degree burns** – causing necrosis of the epithelium but not dermis, most commonly observed as blisters
3. **Third degree burns** – causing damage to both the epithelium as well as the dermis, and without grafting, cause the formation of a deep scar, with contractures.

Damage to the alveoli and respiratory mucosa can also occur when the air is superheated or the person is exposed to the noxious fumes of burning materials. These are called **inhalation burns**.

### Nutritional disorders

Nutritional pathology for the most part describes overt nutritional deficiencies, rather than the subclinical nutrient deficiencies and ratio imbalances seen in chronic disease. Mostly, these gross nutrient pathologies are seen in extreme poverty, typically in developing countries or in poorer populations of industrialized nations. The most common nutrient deficiency is protein deficiency, followed by a general deficiency in energy consumption. The common end result of protein and energy (calorie) deficiency is **marasmus**, or starvation, in which the body is characterized by a decrease in body weight, diminished fat stores, a protuberant abdomen, muscle-wasting and skin-wrinkling.
It is also very likely that these external changes reflect internal ones, and damage to structures such as the brain may be significant. In children, these symptoms are often accompanied by diarrhea, the most common cause of childhood death in the world. **Kwashiorkor** is caused by a dietary imbalance in children – specifically, protein deficiency combined with a diet that is high in carbohydrates. Clinical manifestations may include some muscle wasting, but subcutaneous fat production appears normal. There may be hepatomegaly, ascites, skin lesions, dermatosis, and the hair becomes depigmented, appearing as sandy or reddish-coloured (considered a “flag” sign for kwashiorkor). This condition is noted for the protruding abdomen, which is caused by hepatomegaly and abdominal edema.

**Gross vitamin deficiencies** such as A, B, C, D, and E, are common in both industrialized and developing countries, as are mineral deficiencies such as **iron, iodine, calcium, magnesium** and **chromium**.

**Obesity** is a nutritional disorder caused by an excessive intake of calories, and a commensurate decrease in physical activity: it is the disease of corpulence and leisure, and the hallmark of affluence. Increasingly, the culprit is not simply recognized as only excess calories or deficient exercise, but similar to Kwashiorkor, represents an imbalance of dietary ratios. Specifically, excessive carbohydrate consumption again appears to be a factor, which promotes insulin resistance and hyperinsulinemia, and is responsible for many of the physical effects such as atherosclerosis seen in obese people.

### II. Infectious and parasitic diseases

Most microorganisms are harmless to humans: indeed, our very own eukaryotic cell can be understood to be several different kinds of microorganisms that evolved into a single physical entity several billion years ago. Thus we are a collection of microorganisms that we attempt to control and modify with our genes. Beyond this however, the external surfaces of our bodies are extensively colonized by bacteria, many of which can be seen to be absolutely key to the maintenance of life. Some organisms may simply compete with more pathogenic bacteria, whereas others interact with our body to participate in activities such as
non-specific mechanisms of defense, such as by fermenting the our bodily secretions to make skin surfaces acidic, or by fermenting indigestible fibers in the colon to help us to assimilate key nutrients such as vitamin K. A few microorganisms, that when present in normal concentrations are otherwise benign, but depending on local factors that enhance their growth and development, they may become pathogenic. An even smaller number of organisms are almost always pathogenic, and typically occur with poor hygiene, contamination of food and water, or food spoilage.

An infection occurs when a microorganisms invades the otherwise sterile tissues of the body. The routes of entry include mucus membranes, ingestion, or inhalation. To combat this, the body maintains several mechanisms to inhibit invasion, including physical barriers such as skin and filtration (e.g. eyelashes), secretions, such as tears, mucus and urine that wash away foreign objects, and certain chemicals such as hydrochloric acid, lysozymes, and components of the immune response. The ability of an organisms to overcome the host defense include volume and virulence of the organism. Virulence is a poorly defined term that includes factors such as the organisms’ ability to withstand the host response, the ability to adhere to the host, the ability to utilize resources within the host, and the production of enzymes that actively destroy host tissues, e.g. hyaluronidase. On an individual basis, a certain pathogenic microorganism can have a variety of effects, producing no symptoms in one person but can be lethal to another. Thus certain factors such as immune health, nutritional status, age and social behaviours can all impact upon the influence of a pathogen.

Viral infections

Viruses are not actually organisms per se, but are minute intracellular obligate parasites comprised of either a single strand or RNA or DNA. Some viruses are directly cytopathic, actively killing cells by disrupting the integrity of the cellular anatomy such as the plasma membrane, whereas others are indirectly cytopathic, the cause of cell death coming from inflammatory and immune responses that recognizes viral antigens on the cell surface. Some viruses infect and persist in cells without altering normal cell functions, called latency. Frequently these latent viruses will only produce disease when the host’s immune response is weakened in some respect. Among the viruses discussed in this lesson are:
• influenza
• respiratory syncytial virus
• viral exanthems (e.g. rubeola and rubella)
• mumps
• the intestinal rotavirus
• hemorrhagic fevers such as yellow fever and dengue fever
• herpes virus (varicella-zoster)
• Epstein-Barr
• cytomegalovirus
• human papilloma virus (HPV, warts).

Bacterial infections

The pathogenesis of bacterial infection consists of the local production of bacterial toxins, the resulting immune response, and tissue invasion. The net result is entry into the blood stream, which is graded in three stages:

1. bacteremia – limited number of organisms, easily handled by the immune response
2. septicemia – numerous organisms posing serious complications
3. pyemia – a large number of organisms, such that they form clumps or thrombi

The kinds of toxins produced by bacteria include exotoxins, such as specific toxins, proteins, and enzymes secreted by the bacteria, or endotoxins, which include components of the bacteria, such as lipid-polysaccharide complex that forms the bacterial cell wall or toxins contained in the bacteria that are released upon lysis.

Bacteria are often classified by their tinctorial properties of their cell wall, such as the Gram stain which is either negative or positive. Round or oval bacteria are called cocci, elongated bacteria are called bacilli, curved bacteria are vibrios, and spiral-shaped bacteria are known as spirochetes.

The different kinds of bacterial diseases discussed in this lesson are:

• pyogenic gram positive cocci (Staphylococcus aureus, Streptococcus pyogenes and Streptococcus pneumoniae)
• childhood bacterial infections (diptheria and pertussis)
• sexually transmitted diseases (gonorrhea and chancroid)
• enteropathogenic bacteria (cholera)
• clostridia and botulism
• tetanus
• plague, anthrax and listeriosis
• Lyme disease
• Chlamydia
• Rocky mountain spotted fever

Fungi

The vast majority of fungi are non-pathogenic to humans, and of those that are, most are opportunists, only infecting the person when immune defenses have been compromised, or if local factors are present that allow for their growth and development.

The different kinds of fungal infections discussed in this lesson are:

• Candida albicans
• Aspergillosis
• Cryptococciosis

Protozoal infections and helminthiasis

Protozoa are unicellular eukaryotic organisms that feed by engulfing their prey, and include the zooflagellates, ciliates, amoeboids and sporozoans. The mechanisms by which protozoa can cause disease in humans is diverse. Pathogenic protozoal infections discussed in this lesson are:

• malaria
• toxoplasmosis
• penumonia
• amebiasis

Helminths, or worms, are common human pathogens that evoke an immune response characterized by eosinophilia.

Pathogenic helminthic infections discussed in this lesson are:

• ascarias
• strongyloidiasis
• trichinosis
• schistosomiasis

**Hygiene hypothesis**
Some researchers have shown that our relative obsession with hygiene and asepsis, seen in the ubiquitous usage of antibiotic agents both internally and environmentally, has facilitated the immune dysregulation that appears to be key in many diseases that affect the western world, such as inflammatory bowel disease (IBD). Researchers have shown that we have steadily lost the number and diversity of intestinal parasites since the turn of the last century, many of which are still commonly seen in developing countries where the incidence of such diseases like IBD are much lower. It has been shown that intestinal worms can dampen components of the immune response, specifically the T helper cell 1 (TH1). Unlike bacteria and viruses, when a T cell detects a helminth the response is to dampen the release of pro-inflammatory cytokines that are normally released with bacterial or viral infection. Instead, helminths promote the activation of another immune pathway, the T helper cell 2 (TH2) response. Some diseases, such as inflammatory bowel disease, are characterized by a TH1 response. With the loss of intestinal parasites it was hypothesized by researchers that the prevalence of TH1 activity in diseases like IBD could be reversed by colonization with intestinal parasites. Human studies with the non-pathogenic helminth *Trichuris suis* (porcine whipworm) tested this hypothesis in a small population of patients with IBD. The results of the study, in which patients ingested sterile eggs, showed that such treatments could indeed successfully dampen the TH1 response and promote the remission of the condition. (Elliott et al 2000)
Bibliography


LESSON FOUR: Cardiovascular disease

I. Arterial disease

Arterial disease accounts for the vast majority of patients that suffer from cardiovascular disease, and may be accompanied by diseases of the veins and heart. The primary arterial disease is atherosclerosis, a progressive disease of large and medium large arteries that is marked by the formation of plaques or atherosclerotic lesions in the endothelium. The term arteriosclerosis is the same pathology, and is used when discussing the atherosclerotic lesions that can occur in the smaller arterioles. The major complications of atherosclerosis include ischemic heart disease, myocardial infarction, and gangrene of the extremities. Atherosclerosis is the leading cause of death in North America, a percentage of the population that has been on the rise steadily since that turn of the last century.

Pathogenesis of atherosclerosis

Atherosclerotic plaques form in the tunica intima of elastic and muscular arteries as a result of the proliferation of intimal smooth muscle cells and the accumulation of fat. As the lesion develops smooth muscle cells release cytokines that stimulates the accumulation of mononuclear phagocytes, lymphocytes and neutrophils in the tunica intima. As the lesion progresses the endothelium ruptures and platelets begin to adhere to it. Eventually small capillaries penetrate the vessel wall and supply blood to the plaque, almost like a kind of malignant tumor.

There are a variety of hypotheses that describe the process of atherosclerotic plaquing. While there is good post-mortem evidence of what components comprises a plaque, and now better data on the risk factors for developing atherosclerosis, the actual mechanisms of how the plaque is formed is severely limited by our inability to actually observe this process in vivo. As a result there are several different theories that describe the mechanism of plaquing. Some of these theories are complimentary and some are antagonistic to each other. The most commonly held belief among medical doctors is the insudation hypothesis, which states that the lipid found in plaques is derived from plasma lipoproteins,
specifically low density lipoproteins (LDL). This theory states that the atherosclerotic lesion begins with a mutation of a smooth muscle cell, perhaps from exposure to chemical or viral mutagens, resulting in focal regions of accumulation. Macrophages then scavenge LDL in the blood and transport the lipid directly into the tunica intima of the blood vessel. For some unexplainable reason there is additional damage to the lesion, exposing circulating platelets to subendothelial collagen, which promotes the release of growth factors by the platelets, as well as by local macrophages, that stimulate the proliferation of smooth muscle cells and make the lesion larger. There is the continued insudation of fat into the lesion by macrophages that then undergo degeneration. Eventually the surface of the plaque begins to ulcerate and a thrombus forms on the injured luminal surface.

The initial lesions found in atherosclerosis are thought to be fatty streaks, flat or slightly elevated lesions that contain lipid. Histologically, these streaks are comprised of lipid containing macrophages referred to as foam cells. While these fatty streaks can be found in both young children and the aged, the distribution of these streaks does not correspond with atherosclerotic lesions in adults. Another candidate for the initial lesion of atherosclerosis are intimal cells masses, which are white thickened areas at branch points in the arterial tree, containing smooth muscle cells but no lipid.

Whatever the initial lesion, the characteristic lesion of atherosclerosis is a fibro-fatty plaque consisting of a fibrous cap and an atheroma. The fibrous cap is a layer of thickened connective tissue containing fat-filled macrophages and smooth muscle cells. The atheroma is a necrotic mass of lipid that forms the middle portion of the lesion. Other components in the lesion of atherosclerosis include other blood-borne cells including lymphocytes. The complicated plaque of atherosclerosis is the clinically significant end-point for the formation of a plaque, characterized by:

1. **Thrombosis:** the aggregation of platelets, fibrin, clotting factors and blood-borne elements on and within the plaque
2. **Neovascularization:** of the cap and edges of lesion
3. **Thinning:** of the underlying tunica media
4. **Calcification:** within the atheroma and fibrous cap
5. **Ulceration:** of the fibrous cap.

The net result of these changes is the occlusion of the blood vessel and the formation of emboli, both of which end up producing
ischemia in the tissues supplied by the atherosclerotic or otherwise occluded blood vessel.

It is thought that the process of atherosclerosis begins early in life, with the formation of intimal cell masses and fatty streaks. Regardless, the characteristic lesion of atherosclerosis requires as long as 20-30 years to form, and the clinically important complicated plaques only after several more decades of progressive development. In this respect atherosclerosis is primarily a disease of older adults. (Rubin and Farber 1990, 355-369)

Etiology of atherosclerosis

The causes of atherosclerosis are still not completely understood, with many convoluted and complicated mechanisms described. In this lesson we will examine the most commonly held belief among the medical profession, as well an alternative to this perspective.

Medicine has defined several risk factors for the development of atherosclerosis, some of which may or may not prove to be entirely true. All of these risk factors are based on a statistical analysis of the data called epidemiology, a process that helps to form researcher of associations between certain factors and the incidence of disease. Although this process may identify groups in a population that are particularly vulnerable to a particular disease, it cannot indicate if a particular person will get a particular disease, and thus cannot take the place of an accurate, individualized health assessment.

The vast majority of the approach now utilized in the prevention and treatment of heart disease is based upon the Framingham Heart study, a cohort study over 5000 adult men and women from the town of Framingham, Massachusetts. Begun in 1948, the participants of the study were analyzed for patterns related to the development of cardiovascular disease (CVD). A second generation cohort study was begun in 1971, involving a similar number of participants comprised of the original participants’ adult children and their spouses. A third generation cohort study is now being implemented. Given the duration and number of participants involved in the study, the Framingham Heart Study has proved to be a rich source of data for all kinds of researchers, who use a number of different methods to analyze the data and identify risk factors for CVD, including high blood pressure, high blood
cholesterol, smoking, obesity, diabetes, and physical inactivity. The Framingham study has also provided additional information on the effects of factors such as blood triglyceride and LDL/HDL cholesterol levels, age, gender, and psychosocial issues. The Framingham data, the analyses and the theories derived from it has played an important role in the development of the modern medical curriculum, and has been influential in establishing hypertension and elevated serum cholesterol as the most prominent risk factors for the development of CVD.

Hypertension is commonly observed in atherosclerosis, simply due to the increased pressure by which the heart has to pump blood through the narrowed and occluded atherosclerotic vessels. Hypertensive patients are at greater risk of myocardial infarction and stroke. There are several causes of hypertension, such as renal artery stenosis or hyperthyroidism and must be ruled out. Essential hypertension is a term that has been given to hypertension when the cause is unknown, or cannot be directly observed. Designating hypertension as a risk factor for atherosclerosis however appears to be irrational – it is far more logical to suggest that essential hypertension is a symptom of the progressive effects of arterial damage. Unfortunately what may seem to be a fairly simple argument has been for the most part ignored by the medical profession, many of whom still encourage hypertensive patients to use medications to lower blood pressure, even though these same medications have no impact upon morbidity and mortality in hypertensive patients, and may directly interfere with normal physiological processes. (Port et al 2000)

Elevated blood cholesterol and triglycerides are stated as being directly correlated with the development of ischemic heart disease and atherosclerosis. The hypophobic nature of lipids in the blood means that fats must be transported with protein carriers, including chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). Chylomicrons are formed by the intestinal villi, and are comprised of globules of triglycerides, phospholipids and cholesterol covered by a protein coating. Chylomicrons are absorbed by the lacteal of a villus, transporting fats through the lymphatic system where they enter into systemic circulation at the left subclavian vein. The triglyceride component of the chylomicron is cleaved by lipoprotein lipase in the blood, where it is taken up by adipose and muscle cells. This leaves a cholesterol-rich lipoprotein remnant that is then taken up by the liver and excreted back into the intestine as bile salts, or repacked with triglycerides into VLDL, where it then reenters into circulation. Once again VLDL
is acted upon by lipoprotein lipase, removing triglycerides from VLDL, forming intermediate-density lipoproteins (IDL) that are eventually converted into cholesterol-rich LDL. LDL is then taken up and processed by a variety of cells, leading to the accumulation of cholesterol within these cells. Unlike VLDL and LDL, which functions to transport cholesterol to peripheral cells, high density lipoproteins (HDL) functions to scavenge cholesterol and return it to the liver for excretion. Thus elevated levels of serum VLDL and LDL have been associated with a greater risk of CVD because they deposit cholesterol into peripheral cells, which according to the insudation hypothesis is the primary cause of atherosclerosis, whereas HDL is correlated with a lower risk because it removes cholesterol from cells. (Rubin and Farber 1990, 355-369)

Despite the elegance of this hypothesis and the determination of what are thought of as useful serum markers (e.g. total cholesterol, VLDL, LDL, and HDL) for the risk of cardiovascular disease, a complete analysis of the data suggests that there are a number of problems with the idea that cholesterol is pathogenic in CVD. When it comes to the argument that dietary cholesterol promotes hypercholesterolemia, the Framingham study clearly shows that men who ate the most cholesterol had exactly the same levels of cholesterol in their blood as those who ate the least cholesterol. And while the Framingham study does show that the highest risk of CVD is associated with total elevated serum cholesterol (18% occurrence), those participants with low to normal levels of serum cholesterol continue to be at significant risk (10-12% occurrence). Furthermore, another more recent cohort study called the Honolulu Heart program that examined 3572 Japanese/American men (aged 71–93 years) found that low serum cholesterol levels in the elderly is an indicator of increased mortality (Schatz et al 2001). All of this becomes extremely confusing.

Much of the impetus behind the cholesterol hypothesis is based on animal experimentation, such as the landmark study published by David Kritchevsky in 1954, who described the effects of feeding cholesterol to rabbits causing the formation of atheromas (Kritchevsky et al 1954). In another study published the following year Kritchevsky published a paper that described the benefits of consuming polyunsaturated fatty acids for lowering cholesterol levels. Some researchers criticized Kritchevsky’s research – after all, rabbits are herbivores and don’t normally eat cholesterol, unlike humans, who are omnivores and have a long history of eating cholesterol and saturated fat. Kritchevsky’s research marks the beginning of a drawn out campaign to get North American consumers to substitute traditionally-consumed cholesterol-rich
foods such as butter for low cholesterol innovations such as refined corn oil. This marketing campaign had already begun much earlier in the century, but with a highly selective presentation of the preliminary scientific evidence, the industry-funded American Heart Association began to encourage the North American public to substitute butter, lard, beef and eggs with corn oil, margarine, chicken and cold cereal (Enig and Fallon 2003). Unfortunately these changes have been marked by an increasing incidence of cardiovascular disease in North America, which from 1900 to the mid 1960’s increased by 300%, and is now the single leading cause of death (Bergner 1997, 202-03)

The reason for the exclusion of data such as these from conventional medical thinking on CVD risks is unknown, but when considered it radically alters the perception that cholesterol-rich foods are responsible for elevated serum cholesterol, or that elevated serum cholesterol is an important a risk factor CVD. Of particular concern is the relatively recent use of a new class of drugs called statins, derived from red rice yeast, which are used to interrupt the synthesis of cholesterol and reduce LDL/cholesterol levels in the blood. Unfortunately, while statins indeed have been shown to reduce the risk of cardiovascular disease in patients with a history of myocardial infarction, they have also been shown to have number of adverse effects that make them unsuitable for general prevention in patients presenting with dyslipidemia. Some researchers have stated that the benefit of statins has nothing to do with the benefits of lowering cholesterol, but of promoting the stabilization of the lesion.

Metabolic Syndrome X

While the cholesterol hypothesis has been the primary model of CVD, it has been observed for a number of years that non-insulin-dependent diabetes mellitus (NIDDM), hypertension, dyslipidemia (hypertriglyceridemia and/or low HDL-cholesterol), obesity, and coronary artery disease are common clinical manifestations that often occur in one patient. For some time now cardiologists have used a term called “syndrome X” to identify a patient with angina pectoris and a positive stress-test, but who had no evidence of coronary arterial stenosis: in the case the “X” meant an unknown factor. Further study demonstrated that these patients often have a decreased cellular response to insulin. In 1988 medical researcher Gerald Reaven theorized that these metabolic and cardiovascular disorders are a part of a multifaceted syndrome characterized by
insulin resistance with compensatory increased insulin secretion of the pancreas leading to hyperinsulinemia (elevated levels of insulin in the blood). Further studies have revealed that increased plasma insulin concentrations caused by decreased insulin sensitivity are positively correlated with an increased risk of hypertension, dyslipidemia and non-insulin dependent diabetes mellitus (NIDDM). These clinical studies have consistently supported Reaven’s hypothesis that insulin resistance and hyperinsulinemia increase the risk of developing CVD.

Insulin resistance is a multifaceted syndrome that can express itself in many ways, depending on an individual's genetic background. There is much evidence to suggest that the prevalence of this dynamic, coined by the term metabolic syndrome X, affects 60% or more of the U.S. population, even though only about 15% have blood sugar irregularities or NIDDM.

The clinical manifestations of metabolic syndrome X include:

• abdominal obesity (i.e. “apple shape,” “beer gut,” “love-handles”)
• elevated triglycerides
• decreased HDL cholesterol
• hypertension
• atherosclerosis and related diseases
• thrombotic diseases
• hypoglycemia
• NIDDM

Apart from these more commonly found features, there are a number of other secondary manifestations that can result from a failure of insulin to facilitate the entry of nutrient into the cell, or the negative effects of chronically elevated insulin levels, including:

• osteoporosis
• clinical depression
• cognitive problems
• Alzheimer's disease
• erectile dysfunction

Syndrome X and atherosclerosis

Within the medical community there is an ongoing debate on the role of hyperinsulinemia in the development of atherosclerosis, with most of the research directed to the pathogenesis of adult onset diabetes mellitus, which is characterized by insulin resistance and compensatory increase in insulin secretion leading to a state of
hyperinsulinemia. Insulin resistance is caused by a defect in the capacity of peripheral tissues such as skeletal muscle to take up glucose, which causes a commensurate rise in blood glucose. In response, the insulin-secreting pancreatic cells increase the secretion of insulin to lower the blood sugar, leading to a state of high serum levels of insulin.

The effect of hyperinsulinemia on the development of atherosclerosis has been studied from epidemiologic as well as experimental perspectives. Initial studies indicated little relationship between the two, but more recent studies such as the Quebec Cardiovascular Study demonstrated a relationship between elevated insulin levels and coronary artery disease (Despres et al 1996).

Experimental studies linking hyperinsulinemia and increased cardiovascular risk have shown that a prominent candidate is plasminogen activator inhibitor type 1 (PAI-1), which acts to impair fibrinolysis. Elevated PAI-1 levels are associated with an increased risk of myocardial infarction, and hyperinsulinemia results in an increase in PAI-1 gene expression and ultimately higher serum PAI-1 levels. There is also preliminary evidence that PAI-1 may be a predisposing factor to the formation of lipid-rich plaques in the arterioles rather than relatively cell-rich plaques. The high lipid content may make these plaques particularly prone to rupture and may precipitate acute coronary events. Sobel et al have performed immunohistochemical staining of human coronary artery atherectomy specimens to grade the content of PAI-1 in subjects with and without diabetes matched for severity of coronary disease. The atheromatous material from patients with diabetes exhibited significantly more PAI-1 than that obtained from nondiabetic patients. (Sobel et al 1998)

Hyperglycemia and atherosclerosis

Prolonged exposure to hyperglycemia has also been recognized another factor in the pathogenesis of atherosclerosis. Hyperglycemia induces a large number of alterations at the cellular level of vascular tissue that potentially accelerate the atherosclerotic process. Animal and human studies have indicated three major mechanisms that encompass most of the pathological alterations observed in the atherosclerosis:

1. nonenzymatic glycosylation
2. oxidative stress
3. protein kinase C (PKC) activation (Aronson and Rayfield 2002)

One of the important mechanisms responsible for the accelerated atherosclerosis in diabetes is the nonenzymatic reaction between glucose and proteins or lipoproteins in arterial walls, collectively known as Maillard, or browning reaction. Glucose forms reversible early glycosylation products with reactive amino groups of circulating or vessel wall proteins to form advanced glycosylation end products (AGEs). AGEs normally accumulate with normal aging and at an accelerated rate in diabetic patients. In situations in which the local redox potential has been shifted to favor oxidant stress, AGEs formation is increased substantially, and can accelerate the atherosclerotic process (Aronson and Rayfield 2002).

Oxidative stress is another commonly described pathogenic mechanism for atherosclerosis. Hyperglycemia can increase oxidative stress through several pathways promoting the intracellular production of reactive oxygen species (ROS). There is also evidence that hyperglycemia may compromise natural antioxidant defenses. Reduced glutathione as well as reduced vitamin E have been reported in diabetic patients. Plasma and tissue levels of vitamin C are 40–50% lower in diabetic patients compared with nondiabetic subjects (Aronson and Rayfield 2002).

High glucose concentrations have been shown to activate the protein kinase C, a family of at least 12 isoforms of serine and threonine kinases. In vascular smooth muscle cells, PKC activation has been shown to modulate growth rate, DNA synthesis, and growth factor receptor turnover. Hyperglycemia-induced PKC activation also results in increased platelet derived growth factor-beta receptor expression on smooth muscle cells and other vascular wall cells, and increases the expression of transforming growth factor-beta (TGF-beta), which is thought to lead to thickening of capillary basement membrane (Aronson and Rayfield 2002).

Aneurysms

An aneurysm is a localized dilatation of blood vessels caused by a congenital or acquired weakness in the structure of the vessel, be it an artery or vein. They are classified according to their location, configuration and causes. The most common manifestation of an
Aneurysm is called an **atherosclerotic aneurysm**, occurring more often in men over the age of 50, about half of whom are also hypertensive. The clinical features of aortic aneurysms are asymptomatic and are only discovered by palpation of a mass in the abdomen or with radiological examination. **Dissecting aneurysms** refer to the entry of blood into the arterial wall and its extension along the length of the vessel. With an aortic dissecting aneurysm the patient presents with a severe “tearing” pain in the anterior chest, sometime misdiagnosed as a myocardial infarction.

**Varicose veins**

A **varicose vein** is an enlarged, tortuous vessel in the venous system in filled with stagnant deoxygenated blood. Unlike the arterial system that relies upon the high pressures induced by heart contraction and the wave-like peristaltic movements of the arteries, the venous system has no independent pumping mechanism of its own, instead, relying upon a series of one way valves to direct the blood back to the heart as well as the pumping activity of muscular contraction. Deoxygenated blood is collected from tissues in venous capillaries at relative low pressures, essentially oozing out of tissues and moved along by one-way valves. The blood is then directed to superficial veins and then into the deep veins that lay next to the major arteries to direct conduct the blood to the heart. Once the blood is in the deep veins the pressure can increase dramatically through the pumping effect if muscular contraction. Unlike the arteries that are can distend with an increase in pressure, the deep veins are constructed in such as way that it prevents distension, and thus the maintenance of these pressures ensure that the blood is directed upwards to the heart. The superficial veins however are constructed differently, and can become dilated when there is too high an increase in venous pressure, either because of an obstruction in venous flow, because muscular contraction is insufficient, or because of a failure of the one-way valves. Once a one-way valve fails, it promotes an increase in pressure in the local venous network, leading to the sequential failure of the other valves. After this process has continued for some time, the superficial veins become increasingly dilated and tortuous.

Factors that promote the obstruction of venous flow include tight clothing around the waist and especially pregnancy, which as the fetus grows, compresses the veins that drain legs, causing an increase in pressure and the manifestation of varicosities. Hormones released during pregnancy facilitate this dynamic by
making vessels more pliable. Other more serious causes include a thrombosis in the deep veins, and should be ruled out. The most common cause of varicose veins is physical inactivity, especially if it is complexed with the effects of gravity. Thus people who are required to stand for long periods without moving or completely contracting the legs of the muscles are much more prone to varicosities. Researchers have also pointed out the importance of accessory nutrients such as flavonoids that play a key role in the function and repair venous tissue (e.g. aesculin, derived from *Hippocastanum*), and thus dietary deficiencies of such nutrient can be seen to promote or exacerbate this condition. While generally not all that serious of a condition, varicose veins can be very painful, and if untreated can eventually ulcerate and become infected (see below). (Berkow 1992)

Deep vein thrombosis

Thrombophlebitis describes the inflammation and secondary thrombosis of the small veins, as part of a local reaction to bacterial infection. Phlebothrombosis is the same as above but is not attributable to inflammation or infection. The term deep vein thrombosis is the formation of a thrombus associated with decreased cardiac output and extended bed rest, typically forming in the deep veins of the iliac and femoral veins. The primary concern in such cases is that the thrombus could embolize to the lungs. (Berkow 1992)

II. Heart disease

The most common cause of heart failure is ischemic heart disease, which accounts for more than 80% of deaths from heart disease. The most common cause relates to atherosclerotic plaquing within the vessels that supply the heart. Left sided heart failure is more common, resulting in an increase in pulmonary venous pressure leading to pulmonary congestion. Right sided heart failure is usually a complication of the former.

The most common symptom of heart disease is angina pectoris, typically occurring in patients with ischemic heart disease when they exert themselves physically or are emotionally excited.
A **myocardial infarction** is focal damage to the myocardium from sustained ischemia due to occlusion of the coronary arteries. This topic is covered in detail in the accompanying textbook.

**Rheumatic heart disease** is an inflammatory disease of the myocardium that occurs during acute rheumatic fever, caused by group A *Streptococcus*, resulting in deformities of the heart valves. **Bacterial endocarditis** is the invasion of the cardiac valves by bacteria, most commonly *Staphylococcus aureus* and *Streptococcus pyogenes*. Since the advent of antibiotics the incidence of bacterial endocarditis has diminished substantially, but can occur in intravenous drug users (using infected needles), in patients with prosthetic valves, and from dental procedures that expose the tissues to oral bacteria. In the later case antibiotics are often given after dental surgery to prevent infection.

Other diseases of the heart covered in this lesson include **non-bacterial endocarditis**, **calcific aortic stenosis** and **mitral valve prolapse**. The section on **congenital heart disease** should also be reviewed.
Blood disease

Anemia

The term anemia refers to a decrease in the numbers of red blood cells (RBCs) or hemoglobin (Hb) content caused by a limited number of mechanisms that can function independently or occur synergistically. The term anemia is often used incorrectly as a diagnosis, but like hypertension, is really a symptom of an underlying pathology. Thus different types of anemia are defined according to the pathophysiology.

The rate by which RBCs develop in red bone marrow is dependent upon the status of hemoglobin, which ensures the proper oxygenation of the tissues. This process is maintained by a negative feedback mechanism that is stimulated by hypoxic conditions in the affected tissues, which in turn, promotes an increase in RBC synthesis until tissue oxygen levels are restored to normal. RBCs develop from pluripotent hematopoietic stem cells to progenitor cells, when then form into proerythroblasts, reticulocytes and then erythrocytes (RBCs) in a process requiring a variety of growth factors and cytokines including erythropoietin. Once formed, RBC precursor cells are released into circulation as reticulocytes where they remain in circulation for about one day until they lose their nucleus. This causes the center of the cell to indent and form the distinctive concave shape of a mature RBC. Since erythrocytes have no nucleus they rely upon anaerobic and aerobic glycolytic pathways for energy, and as the cell ages the levels of these enzymes gradually decrease. After 120 days worn and damaged RBCs are destroyed by phagocytic cells in the liver and spleen. Thus the body requires that at least 1/120 the number of RBCs are produced on a daily basis to maintain homeostasis and prevent hypoxia. (Berkow 1992; Rubin and Farber 1990, 553-563)

The unique concave shape of an RBC functions to increase the surface area for gas exchange. This shape also ensures that RBCs are highly deformable, and can bend in upon themselves allowing them to squeeze through the narrow openings of capillaries into the tissues. Each RBC contains approximately 280 million molecules of hemoglobin (Hb), contained in a lipid membrane and supported by a cytoskeletal network. (Berkow 1992; Rubin and Farber 1990, 553-563)
Generally speaking, there are three primary causes of anemia:

1. blood loss  
2. deficient erythropoiesis (decreased production of RBCs)  
3. excessive hemolysis (increased RBC destruction)

A number of conditions can cause anemia, including:

• external blood loss: e.g. trauma, injuries, menorrhagia, and stomach ulcers  
• iron deficiency: iron is an important component in the production of hemoglobin  
• chronic disease: any long-term disease can lead to anemia  
• kidney disease: through decreased erythropoietin secretion  
• pregnancy: water gain during pregnancy is thought to dilute the RBCs (hemodilution); the fetus also robs the mother of iron during pregnancy  
• poor nutrition: inadequate source of dietary iron and accessory nutrients (e.g. B complex); also common in alcoholism (Berkow 1992)

More uncommon causes of anemia include bleeding disorders, liver disease, thalassemia, infection, cancer, arthritis, enzyme deficiency, sickle cell disease, hypothyroidism, toxins, or hereditary conditions.

Signs and symptoms of anemia include:

• black and tarry stools (sticky and foul smelling)  
• maroon, or visibly bloody stools  
• rapid heart rate  
• rapid breathing  
• pale or cold skin  
• jaundic  
• hypotension  
• heart murmur  
• fatigue  
• dyspnea  
• chest and/or abdominal pain  
• weight loss  
• weakness  
• vertigo and fainting, especially upon standing

Apart from external blood loss from trauma or injury, the two primary metabolic mechanisms of anemia are deficient RBC
production and excessive RBC destruction. (Berkow 1992; Rubin and Farber 1990, 553-563)

**Deficient erythropoiesis**

Anemia is often classified according to RBC morphology, which can give an indication of the cause of the anemia, and thus terms such as microcytic anemia, normochromic-normocytic anemia, and macrocytic anemia are often used. These terms describe the different kinds of anemias that are caused by deficient erythropoiesis.

**Microcytic anemia** indicates an alteration in heme or globin synthesis, such as in iron deficiency, thalassemia (and related Hb-synthesis defects), and anemia of chronic diseases (e.g. infection, inflammation). **Iron-deficiency anemia** is the most common anemia, and is a chronic condition characterized by small, pale RBCs and iron depletions. The most common cause is **blood loss**, from chronic bleeding (e.g. erosive gastritis), excessive menstruation, or from a developing fetus. Other prominent causes include a dietary deficiency of iron, malabsorption from intestinal damage (e.g. inflammatory bowel disease or bowel surgery), or from the excess consumption of iron-chelating agents in diet (e.g. phytates in cereals and legumes, tannins and oxalates in certain plants, etc.). The most common clinical presentation is fatigue, dizziness, headache, insomnia, pallor, weight loss and poor immunity. The conjunctiva, buccal mucosa and nail bed may be pale. In severe cases the patient may display **pica** (a craving for dirt, paint, chalk, glue, hair or ice), **glossitis** (inflammation of the tongue), **cheilosis** (sores about the lips and mouth), and **koilonychias** (thinning, concave nails). (Berkow 1992)

**Normochromic-normocytic anemia** refers to state of the RBCs that appears otherwise normal upon microscopic examination, but are diminished in number. Thus, this type of anemia suggests a failure to produce the necessary number of RBCs to accommodate those that are no longer viable and are removed from circulation by the spleen and liver. Normochromic-normocytic anemia is either hypoproliferative or hypoplastic. **Hypoproliferative anemia** is caused by a deficient production of erythropoietin (EPO), commonly associated with renal disease (which produces EPO), hypometabolic states (e.g. hypothyroidism), and protein deficiency. In contrast, **hypoplastic or aplastic anemia** results from a loss of RBC precursors due to a defect in the stem cell pool or an injury to the red marrow from which the RBCs are generated. The cause of such anemias are typically related from exposure to
certain industrial chemicals (e.g. benzene, inorganic arsenic), radiation, or drugs (e.g. chemotherapy, antibiotics, NSAIDs, anticonvulsants). In some cases the cause is unknown and termed idiopathic aplastic anemia. (Berkow 1992)

**Macrocytic or megablastic anemia** refers to a state of deficient RBC production, but one in which the RBCs appear unusually large. This results from defective DNA synthesis but with continued RNA synthesis, resulting in an increase in RBC cytoplasmic mass. This form of anemia is typically related to a dietary deficiency or impaired metabolism vitamin B₁₂ and/or folic acid (folate), as well as the use of cytotoxic and immunosuppressant drugs that impair proper DNA synthesis. (Berkow 1992)

A vitamin C deficiency can also promote anemia, usually associated with hypochromic anemia, but also normocytic and occasionally microcytic anemia. Vitamin C plays a key role in iron utilization. (Berkow 1992)

**Excessive hemolysis**
Excessive hemolysis refers to the excessive destruction of RBCs, usually by phagocytic cells in the spleen, liver, and bone marrow. There are a variety of factors that promote the destruction of RBCs including defects in the RBC itself, or external factors such as the presence of anti-RBC immunoglobulins, trauma or infectious disease. Depending upon the cause, excessive hemolysis can be acute, chronic, or periodic.

A common clinical or laboratory finding for hemolysis is jaundice, occurring when the conversion of Hb to bilirubin exceeds the liver's capacity to form bilirubin glucuronide and excrete it into the bile, promoting unconjugated bilirubinemia. Increased catabolism is also manifested by an increase in stercobilin in the stool and urobilinogen in the urine, as well as pigment-gallstones particularly in the course of the condition is chronic.

Abnormalities within the RBC that promote hemolysis are either related to some dysfunction within the cell or the cell membrane. There are a number of rare, congenital red cell membrane disorders including hereditary spherocytosis, congenital hemolytic jaundice, chronic acholuric jaundice, familial spherocytosis and spherocytic anemia. Acquired red cell membrane disorders include as stomatocytosis (caused by alcoholism) and hypophosphatemia (caused by several factors including starvation, diabetic acidosis, diuretics, vomiting, corticosteroids etc.), the latter of which results
Anemias caused by disorders of red cell metabolism relate to a failure of the RBC to use glucose effectively to produce ATP and are rare genetic disorders. Anemias caused by defective hemoglobin synthesis are similarly caused by genetic abnormalities. **Sickle cell anemia** is a RBC defect that is found mostly in people of African descent, and to a lesser extent those of Mediterranean and Middle Eastern descent. It characterized by a sickle-shaped RBC caused by the homozygous inheritance of Hb S, an abnormal form of hemoglobin that clumps together, making RBCs sticky, stiff, and more fragile, causing them to assume a curved, sickle shape. The distorted and inflexible RBCs adhere to vascular endothelium and end up plugging small arterioles and capillaries, leading to occlusion, hypoxia and local cell death. There are a variety of other congenital diseases that relate to impaired or improper hemoglobin synthesis and cause anemia, including hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease. Of note is the relatively common **thalassemia major** and **thalassemia minor**, a group of chronic, inherited, microcytic anemias characterized by defective Hb synthesis and ineffective erythropoiesis resulting from decreased production of beta, alpha, gamma, or delta polypeptide chains. Thalassemia is particularly common in persons of Mediterranean, African, and Southeast Asian ancestry. (Berkow 1992; Rubin and Farber 1990, 553-563)

Hemolysis caused by defects external to the red cell is determined when no intrinsic RBC abnormality can be identified. Causes include:

• **Hypersplenism**: characterized by a mechanism that produces splenomegaly (spleenic enlargement) with increased filtering of RBCs and phagocytic function. Mechanisms include infection (e.g. bacterial endocarditis, mononucleosis), hereditary conditions (e.g. spherocytosis, thalassemia major), congestive conditions (e.g. splenic vein thrombosis, portal hypertension), myeloproliferative disease (e.g. chronic myeloid metaplasia), infiltrative diseases (e.g. sarcomiosis) and cancer (e.g. chronic lymphocytic leukemia, lymphomas).

• **Autoimmune hemolytic anemia (AIHA)**: identified by the presence of anti-RBC immunoglobulins. More frequent in women than in men, usually with an abrupt onset, producing a severe and potentially fatal anemia.
• Traumatic hemolytic anemia: caused by some kind of trauma such as hand-drumming or karate, or from roughened endothelial surfaces in the heart (e.g. calcific aortic stenosis) or arterioles (atherosclerosis); in the latter case, increases in blood pressure can also promote RBC damage

• Infectious hemolytic anemia: from reacting to toxins produced by infectious organisms in the body (e.g. *Clostridium perfringens*, hemolytic streptococci, meningococci), or when RBCs are actually infected themselves (e.g. *Plasmodium* and *Bartonella spp.*). (Berkow 1992; Rubin and Farber 1990, 553-563)
References

LESSON FIVE: Respiratory disease

Diseases of the respiratory tract are a major health issue in North American society, with lung cancer accounting for more deaths than any other kind of cancer, and even relatively benign conditions such as an upper respiratory tract infection accounting for more work days lost than any other cause. The increasing prevalence of respiratory disorders can certainly be linked to lifestyle behaviors such as smoking, but also to the now ubiquitous presence of airborne environmental toxins, often found in high concentrations indoors in the home and the workplace, from sources that include building materials (e.g. carpets, fiberboard), synthetic perfumes, solvents, ventilation systems, and household cleaning agents. This situation is often compounded by deficiencies of dietary nutrients and antioxidants that can help to limit the effects of these toxins in the body.

I. Upper respiratory tract

Rhinitis

The term rhinitis, or coryza, refers to inflammation of the mucus membranes of the nose, typically characterized by swelling of the mucosa and a nasal discharge. In many cases rhinitis will be accompanied by sinusitis, which is a similar inflammatory process located in the paranasal sinuses. Rhinitis can have several different causes and clinical manifestations, and is therefore classified into several different groups, including acute rhinitis, allergic rhinitis, atrophic rhinitis and vasomotor rhinitis. The most common cause of rhinitis is the common cold (coryza), the symptoms related to a local viral infection and the accompanying immune response. Acute rhinitis simply refers to nasal inflammation that has an acute onset, typically experienced with upper respiratory tract infection. Allergic rhinitis, or hay fever, refers to localized type 2 hypersensitivity reaction, typically to allergens such as dust, animal dander or grass and tree pollen. In some cases the inflammatory processes can extend into the ears, eyes, throat, lungs and skin. Chronic allergic rhinitis is particularly susceptible to secondary infection. Atrophic rhinitis refers to the atrophy of the mucus membranes in the nasal passages, with impaired ciliary function leading to drying and crusting of the
mucus membranes. In some cases there may be a fetid-smelling discharge that is undetected by the patient due to a concomitant loss of smell. It is particularly seen in subacute or chronic forms, and is often mediated by allergic triggers, toxic exposure (e.g. smoke), after surgery, or in areas of low humidity. **Vasomotor rhinitis** refers to varying degrees of nasal blockage and a watery nasal discharge, often accompanied by an impairment in taste and smell. The cause of vasomotor rhinitis is not known, but is often triggered by extremes of temperature and humidity, exposure to bright sunlight or sleep deprivation. In many respects vasomotor rhinitis is the endpoint of what was thought to be allergic rhinitis when conventional treatment fails. **Nasal polyps** can form in patients with chronic nasal inflammation, and are comprised of inflammatory mucosa that often form on the middle turbinate bones and in the maxillary sinuses. (Berkow 1992; Rubin and Farber 1990, 690-91; Govan et al 1991, 290-91)

**Sinusitis**

**Sinusitis** is the inflammation of one or more of the paranasal sinuses (frontal, sphenoid and maxillary sinuses), often presenting as a complication of rhinitis. With the inflammation of the nasal mucus membranes the openings from the sinuses may be obstructed promoting the accumulation of sinus secretions, causing pain, pressure, headache, fever and local tenderness. Sinusitis can be either acute or chronic, but it can be difficult to distinguish between the two, and as both are attributed to bacterial infection they are treated identically with antibiotics. (Berkow 1992; Rubin and Farber 1990, 690-91; Govan et al 1991, 290-91)

It is estimated that 37 million people in the United States suffer from chronic sinusitis, making it one of the most commonly experienced conditions. Similar to acute sinusitis, chronic sinusitis is thought to be bacterial in origin, and is typically treated with antibiotic therapy. Most patients however, while obtaining some temporary benefit, find that their symptoms return with a matter of a few weeks. In a recent study of chronic sinusitis patients, researchers at the Mayo clinic found that 93% of 210 consecutive patients diagnosed with chronic rhinosinusitis were found to be suffering from fungal infections, and that all cases were characterized by the presence of eosinophils in the nasal tissue and mucus. Thus the routine use of antibiotics may be contraindicated in chronic sinusitis, and may end up making the problem worse by tipping ecological factors in favour of the fungi (Ponikau et al 1999).
Laryngitis

Acute laryngitis is a typically mild and self-limiting condition usually due to infection by adenoviruses and parainfluenza viruses, sometimes followed by secondary infection by organisms such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Neisseria catarrhalis*. It is characterized by fever, local lymphadenitis, and swelling of the larynx, sometimes accompanied by mild epiglottitis. The characteristic symptom found in laryngitis is a loss of voice, due to the temporary swelling of the vocal cords. In chronic laryngitis the mucus glands may become hyperplastic leading to enhanced mucus secretion. Another possibility with chronic laryngitis is squamous metaplasia, which results in a loss of ciliary function and a tendency to recurrent infection. The most common cause of chronic laryngitis is smoking, but other factors such as excessive talking or singing, chronic allergic reactions or chronic exposure to noxious inhalants. (Berkow 1992; Govan 1991, 292-93)

Pharyngitis

Pharyngitis, or sore throat, refers to the inflammation of the pharynx or throat, and can have a variety of causes including the rhinoviruses, influenza viruses, adenoviruses and EBV, as well as bacteria such as Group A *Streptococcus*, Corynebacterium, Arcanobacterium, *Neisseria gonorrhoeae* and *Chlamydia pneumoniae*. In up to 30% of cases, no infectious agent can be identified, indicating that other factors such as excessive talking or singing and allergic reactions could play a role. The condition may be accompanied by fever, headache, and local lymphadenitis. In severe cases a throat swab is usually performed to rule out Group A *Streptococcus*, which causes strep throat. Complications of strep throat include rheumatic fever, and glomerulonephritis (kidney inflammation). In particularly severe forms of pharyngitis airway obstruction may occur. (Berkow 1992; Rubin 2001)

Epiglottitis

Acute epiglottitis is a very serious condition usually caused by *Haemophilus influenza* type B, or in some cases streptococci. It causes an acute and rapid swelling of the epiglottis, leading to the obstruction of air flow, the retention of CO$_2$ and hypoxia. Clinically, it is characterized by inspiratory stridor (wheezing upon
inhalation), often with an accompanying pharyngitis and fever. Acute treatment consists of re-establishing airflow, and in such cases either a nasotracheal tube or a tracheostomy is implemented. Internal therapy typically consists of intravenous antibiotics, once the specific pathogen is identified. (Berkow 1992; Rubin 2001)
II. The lungs

Bronchiectasis

**Bronchiectasis** is the irreversible dilation of bronchi due to the destruction of the muscular and elastic components of the bronchial walls. It may result from a mechanical obstruction from the inhalation of foreign bodies, tumors, mucus plugs in asthma and compressive lymphadenopathy. In most cases however bronchiectasis is a complication of respiratory infections, chronic bronchitis, or from genetic defects of the defense mechanisms that protect the airway from infection (e.g. cystic fibrosis). The clinical features of bronchiectasis include a chronic, productive cough, sometimes with hemoptysis from the rupture of bronchial arteries. Pneumonia is a typical complication, and long-standing conditions are at risk of hypoxia and pulmonary hypertension. (Berkow 1992; Rubin 2001)

Pneumonia

**Pneumonia** is a general term that refers to an acute infection of the lung parenchyma including the alveolar spaces and interstitial tissues, and can be caused by a variety of microorganisms, including viruses, bacteria, and fungi. Many of these organisms are commonly found in the ears, nose and throat, and reach the alveoli by the inspiration of secretions. Its involvement may be confined to an entire lobe (**lobar pneumonia**), a segment of a lobe (**segmental** or **lobular pneumonia**), in the alveoli contiguous with the bronchi (**bronchopneumonia**), or in the interstitial tissue (**interstitial pneumonia**). Factors that predispose patients to pneumonia include smoking, chronic bronchitis, alcoholism, hospitalization, malnutrition and diabetes. In developing countries pneumonia is the second leading cause of death in children, next to diarrhea. Although bacteria are usually assumed to be the cause in most forms of pneumonia, between 30-50% of cases demonstrate no identifiable pathogen. (Berkow 1992; Rubin 2001; Rubin and Farber 1990, 320-21)

Pneumonia typically begins after the first few days of an upper respiratory tract infection. Some common signs and symptoms include fever, chills, cough, unusually rapid breathing, chest pain, dyspnea, and using a stethoscope, bronchial breath sounds and late inspiratory crackles over the involved areas. In extreme cases, a bluish or grayish color of the lips and fingernails can be seen.
(cyanosis). Most often the sputum is cultured to determine the pathogen, but these are unreliable due contamination of the sputum with the normal oropharyngeal flora. (Berkow 1992; Rubin 2001)

Among infants, children and the elderly, **viral pneumonia** is most commonly caused by the respiratory syncytial virus, parainfluenza virus, and influenza A and B viruses. In otherwise healthy adults, the most frequently identified viral pathogens are influenza A and B viruses. Patients with compromised immune systems frequently develop infections from latent viruses such as the cytomegalovirus (CMV). (Berkow 1992; Rubin 2001)

**Pneumococcal pneumonia** is caused by *Streptococcus pneumoniae*, accounting for up to two thirds of all cases of pneumonia. Pneumococcal pneumonia occurs more frequently in winter, and is more common in the young, elderly and immunocompromised. The bacilli can travel to the lungs by inhalation or aspiration, lodging in bronchioles where they proliferate. This initiates the release of inflammatory cells and the resultant alveolar hemorrhage identified in the rusty-colored sputum. Upon percussion the lung will sound solid, like the liver (called “red hepatization”). (Berkow 1992; Rubin 2001; Rubin and Farber 1990, 320-21)

**Pneumocystis carinii pneumonia** is a disease found only in immunocompromised patients, such as in cancer, chemotherapy and AIDS. About 30% of patients with HIV infection have *P. carinii* pneumonia as the initial AIDS-defining diagnosis, and become particularly vulnerable to infection when the CD4 helper cell count is < 200/µL. At one time *P. carinii* was thought to be a protozoan, but is now classified as a fungus. (Berkow 1992; Rubin 2001; Rubin and Farber 1990, 320-21)

**Tuberculosis**

**Tuberculosis** is a chronic or recurrent granulomatous infection of the lungs or other tissues, caused by *Mycobacterium tuberculosis*, *M. bovis*, and *M. africanum*. It is generally transmitted by the inhalation or ingestion of infected droplets, the bacteria multiplying in the alveoli due to a failure of local macrophages to effectively kill the organism. *M. bovis* can be found in unpasteurized milk. Tuberculosis is separated into primary and secondary manifestations.
Primary tuberculosis represents the first stage of the disease, consisting of a Ghon complex, a parenchymal granuloma found more often in the lower lobes of the lungs, that disseminates via the lymphatic system to produce prominent infected mediastinal lymph node. Bacteria engulfed by local macrophages result in the formation of tubercles, an organized aggregation of enlarged macrophages surrounded by fibroblasts, macrophages, and lymphocytes. In many cases the central region of tubercle undergoes a characteristic caseous necrosis to produce a "soft" tubercle, the most characteristic hallmark of tuberculosis. The organism itself does not produce any toxin, but as the bacillus degrades it releases tuberculin, which serves as a positive marker for tuberculosis. Most cases of primary tuberculosis are asymptomatic, the lesions remaining localized and eventually heal. In about 10% of cases however the bacteria spread to other parts of the lung, seen more often in children and immunosuppressed patients. The most common symptoms are a non-specific cough usually attributed to other causes (e.g. smoking), accompanied by a yellow-green mucus. Eventually the cough becomes progressively more productive. Chest pain, weight loss, and night sweats may occur as the condition progresses, with dyspnea occurring with pleural effusion or a rupture of the lung. Hemoptysis is not a typical symptom of primary tuberculosis. The tubercle bacilli may also spread into blood vessels to affect the nervous system, the genito-urinary tract, the peritoneum, the pericardium, the digestive tract and liver, and the bones and joints. (Berkow 1992; Rubin 2001)

Secondary tuberculosis refers to the reactivation of primary tuberculosis or a new infection in a previously infected patient. The initial reaction is different from primary tuberculosis, the lesions typically appearing in the apical and posterior portions of the upper lobes. Furthermore, because of the cellular immunity acquired in the initial infection, the tubercle bacilli are rapidly phagocytized and destroyed by activated macrophages. As a result, the lesions remain localized and dissemination is usually prevented. The hypersensitivity response promotes a more rapid caseation and fibrotic walling-off of the focal infection. (Berkow 1992; Rubin 2001)

Unfortunately the success of antibiotic treatment for tuberculosis has been the catalyst for the emergence of a new wave of drug resistant tuberculosis. Drug-resistant tuberculosis was first observed in 1948 subsequent to the first trials of streptomycin. As a result, patients were prescribed multiple antibiotics to control the infection. The emerging pattern of drug-resistant tuberculosis has
Fungal infection

Most fungi are not pathogenic but are opportunists, only becoming pathogenic in a compromised host. Fungal infections often have a geographic distribution, confined to the inhabitants or travelers in that area. The characteristic feature of fungal infections is their chronic course, with symptoms that rarely become intensified, although fever, chills, night sweats, anorexia, weight loss, malaise, and depression may occur.

**Histoplasmosis** is an infection with *Histoplasma capsulatum*, and occurs from inhalation dust that is contaminated with the fungal spores. It has a world-wide occurrence. Histoplasmosis has three main forms: **acute primary histoplasmosis** which is usually asymptomatic or similar to a typical upper respiratory tract infection; **progressive disseminated histoplasmosis** characterized by a primary pulmonary lesion and dissemination into the blood, with ulcerations of the oropharynx and gastrointestinal tract, with hepatomegaly, splenomegaly, lymphadenopathy and adrenal necrosis; and **progressive disseminated histoplasmosis** which is one of the defining opportunistic infections for AIDS, leading to severe acute pneumonia. (Berkow 1992; Rubin 2001)

The fungus *Coccidioides immitis* can cause **coccidioidomycosis** (Valley Fever; San Joaquin Fever) manifesting as a usually asymptomatic or a self-limiting respiratory infection, sometimes disseminating to other area of the body including the skin, lymph nodes, bones, internal organs and the brain. The course of the disease is slow but have a rapid progression in immunodeficiency syndromes. In the United States it is endemic to the southwestern regions of the country, including California, Arizona, New Mexico, and Texas. (Berkow 1992; Rubin 2001)
Aspergillosis is an infection caused by any species of the *Aspergillus* genus, in the lungs typically *A. niger* or *A. fumigatus*. The disease usually manifests with the inhalation of the fungal spores, but can be acquired from exposure to open wounds. *Aspergillus spp.* are a very common environmental mold, often found in decaying vegetation such as compost piles, as well as in building materials and ventilation systems. *Aspergillus* is typically noninvasive but may colonize preexisting pulmonary lesions, leading to the formation of a fungus ball (aspergilloma), a tangled masses of hyphae, with fibrin exudate and few inflammatory cells, typically encapsulated by fibrous tissue. Aspergillomas usually arise and may enlarge gradually within pulmonary cavities originally caused by bronchiectasis, neoplasm, tuberculosis, other chronic pulmonary infections. In most cases aspergilliosis is only a progressive condition in immunosuppressed patients. Some patients may display a hypersensitivity reaction to the fungal spores leading to hayfever or asthma. Some *Aspergillus* are also common food molds, invading improperly stored foods, and producing aflatoxins that can promote liver toxicity and cancer. (Berkow 1992; Rubin 2001)

Diffuse alveolar damage

Diffuse alveolar damage (DAD), or adult respiratory distress syndrome is a general reaction to lung injury from a variety of causes, characterized by edema of the lungs, respiratory distress, and hypoxemia. Conditions that commonly promote DAD are numerous, including pneumonia, chest trauma, inhalation of smoke or other toxic gas shock, and near drowning. Iatrogenic causes include procedures such as blood transfusions and reperfusion, cardiopulmonary bypass and certain drugs. The pathogenesis of DAD is thought to be mediated by lymphocytes and platelets that accumulate in the lungs, releasing chemical mediators that inflame and injure the tissues, promoting fibrosis and impairing normal lung function. When the capillaries and alveoli in the lungs are damaged in DAD, plasma and fluids into the alveoli and reduces the surfactant activity, thus leading to collapsed lungs (atelectasis). DAD usually develops within 24 to 48 hour after the initial injury or illness, manifesting as dyspnea and shallow, rapid breathing. The skin may appear bluish in color indicating cyanosis, and upon auscultation breath sounds may include crackles, rhonchi or wheezes. As the pathology continues over a 2-3 week period the fibrosis becomes extensive, leading to impaired lung function, severe hypoxemia, and pulmonary hypertension. As the result of impaired lung function a possible complication includes is a
secondary bacterial infection. (Berkow 1992, 643-45; Rubin and Farber 1990, 325-28)

Chronic bronchitis

Chronic bronchitis is a chronic pulmonary obstructive disorder (CPOD) that is defined as a chronic, productive cough experienced for more than a two-year period. The primary pathological features are characterized by an increase in goblet and mucus cells with a commensurate loss of serous glands and ciliated epithelium, resulting in a thick, viscous sputum that is difficult to expectorate. With repeated inflammation there is fibrosis and a thickening of the bronchial wall, which further impairs airflow. In progressed conditions hypertrophy of the right heart ventricle (cor pulmonae) can occur. In most cases the patient is a smoker, although environmental pollution is another important factor and is probably an increasing trend, especially in highly congested urban areas. Nutrient deficiencies such as vitamin A, essential fatty acids and accessory antioxidants also facilitate the condition. Chronic bronchitis is often concurrent with emphysema (see below) (Berkow 1992, 658-661; Rubin and Farber 1990, 328; Govan 1991, 300-301)

Emphysema

Emphysema is another type of CPOD in which there is a permanent enlargement of the airspaces distal to the terminal bronchioles, caused by the destruction of the elastic tissues in the walls of the small airways. As a result, there is an impairment in the normal recoil of these tissues, leading to an expansion of lung volume and capacity, but with a diminished capacity for gas exchange. The most common symptoms include breathlessness, wheezing, and a productive cough (see chronic bronchitis), but usually only manifests by about the 6th decade of life. In some cases the enlargement of the airspaces in the lungs presents as a patient with a “barrel chest.” As the condition progresses, it leads cyanosis, peripheral edema, cor pulmonae and right heart failure, making it difficult to differentiate from other conditions such as congestive heart failure. A commonly used clinical test for emphysema is to ask the patient to take a deep breath and forcibly exhale – if it takes more than 4-6 seconds to expire this is considered to be a positive indicator of emphysema. (Sharma 2005; Berkow 1992, 661; Rubin and Farber 1990, 333-36)
The primary factor in emphysema is smoking, which is thought to enhance the activity of neutrophils that release protease enzymes such as elastase that catabolize the protein elastin. Normally the activity of these enzymes is regulated by a glycoprotein synthesized in the liver called alpha₁-antitrypsin (AAT), but it appears that the inhaled smoke inhibits its activity, facilitating elastin destruction. A significant number of cases of emphysema are also caused by an inherited deficiency of alpha₁-antitrypsin (which also affects liver function) – patients that have this disorder are distinguished by concurrent liver disease and an earlier onset of emphysema. Patients with AAT deficiency and smoke are at highest risk for developing the disease. (Sharma 2005; Berkow 1992, 658-661; Rubin and Farber 1990, 333-36)

Asthma

Asthma is another COPD, characterized by inflammation and obstruction of the bronchus and bronchioles, mediated by a hyperreactivity to a variety of stimuli, including smoke, noxious gases, pollen, animal dander and dust, as well as the heaving breathing that accompanies exercise, laughing, crying or emotional stress. Recently, the role of volatile organic compounds (VOCs) found in carpeting and building materials have been identified in the pathogenesis of asthma. Another factor is a concurrent respiratory infection, such as coryza or pneumonia. With asthma it is thought that these factors or combination of factors initiates the release of inflammatory mediators promoting the release histamine and arachidonic acid metabolism. When activated these inflammatory chemicals promote the smooth muscle spasm of the bronchial wall and edema of the mucosa, enhancing mucus production and bronchial injury by activated immune cells (primarily eosinophils, lymphocytes and neutrophils). It is important to note that production of inflammatory mediators is enhanced by a pre-existing deficiency of vitamins, minerals and accessory nutrients such as n-3 PUFAs and flavonoids that counter or prevent inflammation. (Berkow 1992, 646-47; Rubin and Farber 1990, 329-332)

The frequency and severity of asthma attacks vary to a large degree. Some patients have only occasional episodes that are mild and brief, whereas others experience a chronic cough and mild bronchial congestion that is interrupted by severe episodes of bronchospasm, usually after exposure to some type of stimuli that enhances bronchial hypersensitivity. An asthma attack typically has an acute onset, with sudden wheezing, coughing, and dyspnea,
sometimes preceded by pruritis over the neck and chest. The cough of an asthma attack is distinctively tight, hard and sharp, generally unproductive, and accompanied by wheezing, a sensation of chest constriction and the subsequent distress this causes the patient. In less severe attacks a dry cough may be the only presenting symptom. After the attack subsides many patients will produce a thick, tenacious mucus. (Berkow 1992, 647-48; Rubin and Farber 1990, 329-332)

Asthma is classified into four categories according to the severity of symptoms. In many cases a patient will move back and forth between these categories, depending upon treatment and the presence of stimuli that promotes hypersensitivity:

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild and intermittent dyspnea.</td>
<td>Moderate, with obvious dyspnea and</td>
<td>Severe, with obvious distress, visible</td>
<td>Severe distress, lethargy,</td>
</tr>
<tr>
<td>Lung capacity 50-80% of normal.</td>
<td>wheezing. Lung capacity 50% of normal.</td>
<td>cyanosis. Lung capacity 25% of normal.</td>
<td>confusion, 'pulsus paradoxus’ (decrease in</td>
</tr>
<tr>
<td>Pulmonary (Pa) CO₂ levels</td>
<td>Usage of accessory muscles. PaCO₂</td>
<td>Marked use of accessory muscles. PaCO₂</td>
<td>systolic pressure and pulse amplitude).</td>
</tr>
<tr>
<td>normal or decreasing. pH normal</td>
<td>decreasing, pH increasing; PaO₂</td>
<td>normal or rising. pH normal or decreasing;</td>
<td>Lung capacity 10% of normal. Marked</td>
</tr>
<tr>
<td>or increasing; PaO₂ normal or</td>
<td>decreasing.</td>
<td>PaO₂ decreasing dramatically.</td>
<td>use of accessory muscles. PaCO₂ rapidly</td>
</tr>
<tr>
<td>decreasing.</td>
<td></td>
<td></td>
<td>increasing, pH rapidly decreasing; PaO₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dramatically diminished (Berkow 1992, 648).</td>
</tr>
</tbody>
</table>
Tumors of the lungs can be benign or malignant, either originating in the lung (primary origin) or secondarily by metastasizing from primary cancers in other organs and tissues. Primary lung tumors include bronchogenic carcinoma (the most common type of lung cancer), bronchial carcinoid tumor, and a number of rarer types.

**Bronchogenic carcinoma**
Bronchogenic carcinoma is a highly malignant primary lung tumor that accounts for more than 90% of all cases of lung cancer. It is the second most common cancer in men and the third most common in women, and with a very poor prognosis is the leading cause of cancer death. The etiology of bronchogenic carcinoma appears to be directly related to smoking, accounting for 87% of all lung cancers. A small proportion of lung cancers appear to be related to occupational hazards, often in concomitant with smoking, including asbestos, radiation, arsenic, chromates, nickel, chloromethyl ethers, mustard (poison war) gas, and coke oven emissions. The exact role of air pollution has yet to be defined, but given the increasing pollution of urban areas probably plays a significant role. (Berkow 1992; Rubin and Farber 1990, 314-17)

Four histologic types of bronchogenic carcinoma are typically described:

1. **Squamous cell carcinoma** refers to a proliferation of malignant epithelial cells. The cytoplasm of cells is eosinophilic suggesting keratin production and there is squamous "pearl" formation. Cytologically the nuclei are pleomorphic (vary in size and shape) and hyperchromatic (increased chromatin, darker stained).

2. **Undifferentiated small ("oat") cell carcinoma** is composed of small round to oval cells with little cytoplasm and dark nuclei. The cells are slightly bigger than lymphocytes and are called oat cells. There may also be spindle-shaped forms. Nuclei are hyperchromatic and exhibit nuclear molding. **Undifferentiated large cell** is composed of large polygonal cells with no evidence of glandular or squamous differentiation.

3. **Adenocarcinoma** refers to the malignant proliferation of epithelial cells that produce glandular structures with central lumina some of which contain intraluminal mucinous-like material. (Berkow 1992; Rubin 2001; Rubin and Farber 1990, 314-17)
The clinical manifestations of bronchogenic carcinomas depend on where the tumor is located and how it has spread. Most bronchogenic carcinomas are contained with the bronchial passage and thus patients typically present with a cough, some with hemoptysis. In an ulcerated bronchial tumor the bleeding is usually not excessive, but will often be streaked with blood and contain pus. As the tumor progresses symptoms include fatigue, weakness, lethargy, a worsening cough, difficulty in breathing, decreased appetite, weight loss, and pain. Carcinomas of all types usually metastasize to the regional lymph nodes, in particular the hilar and mediastinal nodes. The most common site of extranodal metastasis is the adrenal gland. (Berkow 1992; Rubin 2001; Rubin and Farber 1990, 314-17)

**Bronchial carcinoid tumors**

Bronchial carcinoid tumors are a group of neuroendocrine, pulmonary neoplasms derived from the pluripotent basal layer of the respiratory epithelium. Bronchial carcinoid tumors may be benign or malignant, occur equally in both sexes, and do not appear to be related to smoking. Bleeding from the overlying mucous membrane often occurs, and recurrent pneumonia within the same lung zone and localized overlying pleural pain are common. Metastases are uncommon but may occur to regional lymph nodes. (Berkow 1992; Rubin 2001; Rubin and Farber 1990, 314-17)
Bibliography

LESSON SIX: Gastrointestinal disease

In traditional medicine most forms of disease are seen as some kind of affliction of the digestive tract, usually related to weak digestion and the consumption of inappropriate foods. This concept is almost wholly unknown in modern medicine, to the extent that gastroenterologists will routinely ignore the effect that diet has on the induction and pathogenesis of gastrointestinal disease. A surprisingly large number of people suffer from gastrointestinal disease, judging from the sale of OTC H₂ (histamine) antagonists and antacids, the sales of which extend into the hundreds of millions of dollars in Canada alone. Most of these treatments of course are simply suppressive in nature, or end up making the problem worse. In your practice, digestive disorders are likely to be among the most common presenting conditions.

I. Upper digestive tract

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a relatively new classification of disease that was at one time known simply by the generic term of ‘heartburn,’ but has since become a highly pathologized state, although it is also a normal physiologic phenomenon experienced occasionally by healthy individuals. The most common symptom of GERD is a burning sensation or discomfort behind the breastbone or sternum, and may be accompanied by regurgitation of gastric contents into the mouth or the lungs. In patients with significant reflux dysphagia is a common complaint and can indicate stricture of the esophagus. Pulmonary manifestations such as asthma, coughing, or intermittent wheezing and vocal cord inflammation with hoarseness may occur in some patients. Complications of GERD include esophageal erosion, esophageal ulcer, and esophageal stricture. In a chronic state there may be a replacement of the normal squamous esophageal epithelium with abnormal columnar (Barrett’s) epithelium, which is considered to be precancerous. In many cases there is a diminished secretion of saliva, with increased risk of tooth decay and gum recession. (Berkow 1992, 748-49; Rubin and Farber 1990, 355)
Most episodes of GERD occur during the day, usually after eating, although some sufferers will also experience reflux during sleep. The nocturnal form of GERD is associated with a higher risk and more severe indications of esophagitis because the sleeping patient produces less saliva and swallows less often, to clear out and neutralize the acid. (Berkow 1992, 748-49; Rubin and Farber 1990, 355)

The typical etiology of GERD is usually attributed to a dysfunction of the lower esophageal sphincter (LES), with delayed stomach emptying, ineffective esophageal clearance, and decreased salivation. Pathologists recognize smoking, caffeine, chocolate, fatty foods, overeating, tight clothing, a hiatal hernia, and certain medications as being associated risk factors. In herbal medicine, the issue of GERD is recognized as an issue of poor gastric tone, with poor motility. Fundamentally, GERD is recognized as a stomach deficiency. Additional factors that are recognized and treated by herbalists are the consumption of flour products, which has a glue-like consistency and promotes poor motility, as well as poor food combinations, i.e. animal proteins with carbohydrates, which similarly impair gastric function. In some cases gastric impairment is a symptom associated with system pathologies such as scleroderma in which the dysfunction of the LES is attributed to autoimmune-induced fibrosis. (Berkow 1992, 748-49; Rubin and Farber 1990, 355)

Hiatus hernia

The term hiatus hernia refers to a protrusion of the stomach above the diaphragm. Technically speaking the usage of the term “hernia” is incorrect, as a hernia specifically refers to the protrusion of an organ through an abnormal opening. In the case of a hiatal hernia it is the protrusion of the fundus of the stomach through the normal opening of the esophageal hiatus, a hole that pierces the diaphragm and allows the esophagus to meet up with the stomach. The conventional medical perspective states that the etiology of hiatus hernia is often idiopathic, but in a minority of cases is related to a congenital abnormality or is secondary to trauma, such as a tear in the diaphragm. An alternate explanation, and one that would suit the vast majority of cases, is that a hiatus hernia is caused by the elongation or rupture of the phrenoesophageal ligament (PEL), which extends from the diaphragm and adheres the external esophageal sphincter to the internal esophageal sphincter located in the wall of the esophagus. This displacement of the PEL allows a portion of the stomach to
rise above the diaphragm. The cause of this is not entirely known but it is thought that the PEL becomes displaced because of an increase in the intra-abdominal pressure, which forces the stomach upwards. Thus anything that increases intra-abdominal pressure, such as bending or lifting, especially after eating, would put an upward pressure upon the stomach, forcing a portion of it through the esophageal hiatus. In a **sliding hiatus hernia** the gastroesophageal junction and a portion of the stomach are pushed up above the diaphragm. In **paraesophageal hiatus hernia** the gastroesophageal junction is in the normal location but a portion of the stomach is adjacent to the esophagus rises above the diaphragm. (Berkow 1992, 750; Rubin and Farber 1990, 354-55)

Approximately 40% of the population suffers from hiatus hernia, although in many cases these patients are asymptomatic or only occasionally affected (i.e. by overeating, or eating certain foods such as flour products, spicy foods, etc.). A paraesophageal hiatus hernia is generally asymptomatic but unlike a sliding hiatus hernia, it may become occluded and strangulate. Small amounts of blood or even a massive hemorrhage may occur with either type of hiatus hernia. (Berkow 1992, 750; Rubin and Farber 1990, 354-55)

**Esophageal carcinoma**

Esophageal cancer is cancer of the esophagus, more common in smokers and alcoholics, and linked to gastroesophageal reflux disease (GERD) that promotes metaplastic changes in the cell types lining the esophagus to the precancerous Barrett’s esophagus. The clinical presentation of esophageal cancer manifests as a difficulty in swallowing solid food that progresses over a period of several weeks, and a commensurate loss in body weight. In many cases there are the only symptoms, while others may present with chest pain that radiates to the back. As the condition progresses it produce vomiting, hematemesis and a subsequent anemia, as well as cough and pneumonia. The tumor frequently metastasizes to the liver and lungs. (Berkow 1992, 745-46; Rubin and Farber 1990, 357-58)

While there are a number of different types of esophageal cancer, most are either epidermoid (squamous cell) carcinomas or adenocarcinomas. **Epidermoid (squamous cell) carcinoma** is relatively uncommon in North America, found more often in China, Puerto Rico, Singapore, South Africa, Switzerland, France, and in northern Iran. It is most often associated with alcohol and tobacco ingestion. **Adenocarcinoma** has a rising incidence in
North America and is related to the metaplastic tissue changes seen Barrett's esophagus. Barrett's esophagus is characterized by the replacement of the normal squamous epithelium with a columnar, glandular, stomach-like mucosa. (Berkow 1992, 745-46; Rubin and Farber 1990, 357-58)

Gastritis

Gastritis refers to inflammation of the gastric mucosa, and can be classified in a number of different ways:

1. **severity**: gastritis can be either **erosive** or **nonerosive** based on the severity of damage to the mucous membranes.
2. **location**: gastritis can be classified on the basis of what part of the stomach is involved, including the cardia (upper stomach), corpus (middle stomach), and antrum (lower stomach).
3. **onset and duration**: gastritis can also be classified on the basis of either an **acute** onset or **chronic** manifestation, based in part on the case history, but also from a histological examination of the inflammatory cells. (Berkow 1992, 796).

**Acute gastritis** is a very serious and life-threatening condition that usually occurs in very ill patients, typically experienced as a vague abdominal discomfort. Life-threatening clinical manifestations include hemorrhaging from the mouth or nose, and symptoms of gastric perforation. Histological examination reveals an infiltration of polymorphonuclear leukocytes in the gastric mucosa, usually in the antrum or corpus. The most common cause of **acute erosive gastritis** are drugs such as anti-inflammatory drugs and other NSAIDs (e.g. acetaminophen, acetyl salicylic acid), as well as alcohol consumption and acute emotional stress. If the patient has a history of chronic NSAID they may present with anemia, indicating chronic gastric bleeding. Less common but important causes include radiation burns, viral infections (e.g. cytomegalovirus), vascular injury, and direct trauma (e.g. nasogastric tubes). In very ill patients the overall mortality can be between 40-50%. (Berkow 1992, 762; Rubin and Farber 1990, 359-61)

Patients with **chronic erosive gastritis** typically present with a vague dyspepsia, with epigastric pain and nausea, and can even be asymptomatic. Endoscopy reveals the presence of multiple punctate or aphthous ulcers, while further histological examination will show some degree of atrophy or metaplasia. If it involves the antrum there will be a loss of G cells and thus decreased gastrin
secretion, or if the corpus, a loss of oxyntic glands facilitating reduced HCl, pepsin, and intrinsic factor secretion. The causes of chronic gastritis are essentially the same as for its acute forms. (Berkow 1992, 763; Rubin and Farber 1990, 359-61)

**Nonerosive gastritis** is typically associated with *Helicobacter pylori*, a spiral-shaped, gram-negative bacteria that thrives in the high acid environment of the stomach. It is thought that infection with *H. pylori* invariably leads to gastric mucosal inflammation, which in turn alters gastric secretion, leaving the mucosa more susceptible to damage by acid. The highest concentrations of *H. pylori* are typically found in the antrum. (Berkow 1992, 764-65; Rubin and Farber 1990, 359-61)

*H. pylori* is a very common chronic infection, and in developing countries is most frequently acquired in childhood, although infection of children is much less common in industrialized societies. Although the exact mode of transmission is unclear, the organism has been cultured from stool, saliva, and dental plaque, which suggesting an oral-oral or fecal-oral transmission. Infections tend to predominate in families and in hospital workers, frequently in nurses and gastroenterologists. (Carroll 2005; Sepulveda 2005b)

Although *H. pylori* is fingered as the cause of almost all cases of nonerosive gastritis, less than 20% of all *H. pylori* infected persons will develop significant clinical consequences in their lifetime, suggesting that *H. pylori* may not be as pathogenic as previously thought. There are many different strains of *H. pylori*, with apparently different degrees of virulence. Furthermore, *H. pylori* appears to have co-evolved in humans and is thought by many to be a commensal. The typical treatment of *H. pylori* is the use of several different kinds of antibiotics, administered over a long period of time. This treatment will result in the destruction of beneficial bacterial strains and may provoke esophageal disease or gastric cancer of the cardia. (Hunt et al 2001; Sepulveda 2005)

Autoimmune factors can also promote chronic nonerosive gastritis. Auto-antibodies are produced against the parietal cells and intrinsic factor, leading to a reduction or complete inhibition of gastric secretion. Further investigation usually reveals increased serum gastrin (due to G-cell hyperplasia in the antrum) and gastric enterochromaffin-like hyperplasia due to gastrin stimulation. (Sepulveda 2005b; Rubin and Farber 1990, 359-61)
The mildest form of nonerosive gastritis is **superficial gastritis**, which even more than the other, more serious forms of gastritis, can yield very mild symptoms. The inflammatory process can involve all parts of the stomach but is not accompanied by atrophic or metaplastic changes. Upon histological examination the infiltrating cells are usually found to be lymphocytes, plasma cells and neutrophils. (Rubin and Farber 1990, 359-61)

**Atrophic gastritis** is often an evolute of chronic, superficial gastritis, typically presenting as a definite but nonetheless mild dyspepsia. Histological examination yields lymphocytes and plasma cells often penetrating the mucosa all the way to the muscularis. The condition also involves degenerative changes in HCl and pepsin secreting cells leading to a loss of gastric secretions, including intrinsic factor which promotes a vitamin B\textsubscript{12} deficiency (Berkow 1992, 765; Sepulveda 2005a).

**Gastric metaplasia** is common in chronic nonerosive gastritis, typically occurring with severe atrophy of the gastric glands, which are progressively replaced by mucous glands, typically in the antral mucosa. The gastric mucosa may resemble small intestinal mucosa, with goblet cells, endocrine (enterochromaffin or enterochromaffin-like) cells, and rudimentary villi, and may even assume functional (absorptive) characteristics. In complete metaplasia, gastric mucosa is completely transformed into small intestinal mucosa, with the ability to absorb nutrients and secrete peptides. In incomplete metaplasia, the epithelium assumes a histologic appearance closer to that of the large intestine and frequently exhibits dysplasia. Both cell types are associated with an increased risk of stomach cancer. (Sepulveda 2005b; Rubin and Farber 1990, 359-61)

**Peptic ulcer disease**

**Peptic ulcer disease** refers to an excoriated segment of the gastrointestinal mucosa, typically in the stomach (gastric ulcer) or first few centimeters of the duodenum (duodenal ulcer), which proceeds to penetrate through the muscularis. The ulcers may range in size from several millimeters to several centimeters. The etiology of peptic ulcer disease was at one time considered to be due to excess gastric acid secretion but this theory has given way to factors that disrupt normal mucosal defense mechanisms, including \textit{H. pylori} infection and NSAIDs usage, which make the mucosa more susceptible to the effects of the stomach acid. Gastric ulcers typically arise from chronic nonerosive gastritis, and
in most cases patients secrete less acid than healthy individuals. (Berkow 1992; Rubin and Farber 1990, 361-65)

The mechanism by which *H. pylori* promotes damage to the gastric mucosa is thought to be a result of the organism synthesizing the enzyme urease that breaks down urea into ammonia. This chemical reaction allows the organism to survive the acidic environment of the stomach, but at the same time erodes the mucous membrane. *H. pylori* also produces cytotoxins that promote epithelial damage, as well as mucolytic enzymes such as protease and lipase. The host response to these events are thought to promote the release of cytokines that further promote damage and the process of ulcerogenesis. (Berkow 1992; Rubin and Farber 1990, 361-65)

NSAIDs promote damage to the gastric mucous membranes through a directly toxic effect and by modifying the host response on a systemic basis. When ingested NSAIDs diffuse into gastric epithelial cells and promote the release of H+ ions, promoting mucosal injury. NSAIDs also inhibit the cyclooxygenase pathway and the synthesis of prostaglandins that maintain gastric integrity. The interruption of this metabolic pathway results in significant changes to the gastric mucosa, inhibiting blood flow, reducing mucus and HCO₃ secretion, and inhibiting cellular repair mechanisms (Berkow 1992; Rubin and Farber 1990, 361-65)

The signs and symptoms of peptic ulcer disease can vary. While in some cases, such as in the elderly, the pain can be minimal or even absent, others can experience a burning pain in the epigastrum that refers to the back. In some cases the pain is relieved by eating, whereas for others it makes little difference. When very often the symptoms come and go. Pyloric ulcers are often associated with symptoms of obstruction such as bloating, nausea, vomiting. In duodenal ulcers the pain tends to be consistent, frequently absent when the patient awakens but appearing later in midmorning. The pain of duodenal ulcers is often relieved by food but recurs within a few after eating. (Berkow 1992, 768-69)

The most common complication of peptic ulcer disease is hemorrhaging, and occurs in up to 20% of patients. Symptoms include vomiting of blood (“coffee grounds”), occult blood in the stools and iron-deficiency anemia. The penetration of the gastric or duodenal wall by an ulcer results in stomach acids leaking into the abdominal cavity, causing peritonitis, and can attack the pancreas or liver. The overall mortality rate for perforated ulcers is
10-40% with gastric ulcers, and 5-13% with duodenal ulcers. 
(Berkow 1992; Rubin and Farber 1990, 361-65)

Gastric adenocarcinoma

Gastric adenocarcinoma accounts for 95% of malignant tumors of the stomach, and varies worldwide, with the highest rates in Japan, Chile, and Iceland, more common in North America among the poor, increasing in prevalence with age. The cause of gastric cancer is idiopathic. Gastritis and intestinal metaplasia of the gastric mucosa is often found in gastric cancer, and in 1994 the World Health Organization declared Helicobacter pylori to be a grade I carcinogen for gastric adenocarcinoma and mucosa-associated lymphoid tissue tumors of the stomach. Other factors include the consumption of starchy foods, smoked meat and fish and pickled vegetables. Of particular concern are the nitrites and nitrates added to preserved food that may be converted into cancer-causing nitrosamines by the gastric bacteria. (Berkow 1992, 778-79; Rubin and Farber 1990, 366-67)

Early-stage stomach cancer is usually asymptomatic. Satiety after eating is common if the cancer obstructs the pyloric region. Loss of weight or strength is among the first symptoms, although sometimes the first symptoms are the result of metastasis (e.g. enlarged liver, jaundice, ascites, skin nodules, and fractures) – the initial gastric tumor is asymptomatic. Other findings may be occult blood in the stools and anemia. By the time most gastric cancers are detected they have penetrated beyond the submucosa into the muscularis and serosa. Such cancers are classified according to their morphology, and including polypoid (fungating) carcinoma, ulcerating carcinoma and diffuse adenocarcinoma. The latter form in particular is associated with Barrett's esophagus. (Berkow 1992, 779; Rubin and Farber 1990, 361-65)

Gastroenteritis

Gastroenteritis refers to the inflammation of the lining of the stomach and intestines, manifested by upper GI tract symptoms such as anorexia, nausea, vomiting, as well as diarrhea and abdominal pain. Gastroenteritis is a general term for these symptoms, whether the cause can be identified or not, the specific
cause denoted by the descriptive term, ‘bacterial,’ or ‘viral.’ In most cases gastroenteritis is a relatively benign and self-limiting condition, but in debilitated patients and in children can be fatal due to a loss of electrolytes and the resultant dehydration.

**Enterotoxins** are synthesized by certain bacteria, which function to impair intestinal absorption and stimulate the secretion of electrolytes and water into the lumen of the bowel. Examples of bacteria that produce such toxins are *Vibrio cholerae* (cholera) and *Escherichia coli*. Rather than producing enterotoxin some bacteria including *Shigella*, *Salmonella*, and *E. coli* species actually penetrate the mucosa of the intestine, causing ulceration, bleeding, and the discharge of pus, along with the secretion of electrolytes and water. (Berkow 1992, 813; Govan et al 1990, 395)

*Campylobacter jejuni* is the most common bacterial cause of gastroenteritis illness in North America, primarily through infection from domesticated animals or contaminated poorly cooked food. Person-to-person transmission is especially common with gastroenteritis caused by *Shigella* and *Escherichia coli*. *Salmonella* infection may be acquired through contaminated food or water, contact with reptiles (e.g. frogs, turtles) or from insects (e.g. cockroaches). (Berkow 1992, 813)

Viral causes of gastroenteritis include the Norwalk virus and similar viruses, as well as rotaviruses, adenoviruses, astroviruses, and caliciviruses. Epidemics of viral diarrhea in infants, children, and adults are typically spread via contaminated water or food or via the fecal-oral route. Norwalk virus infections occur year-round and cause about 40% of outbreaks of gastroenteritis in children and adults. During the winter in temperate climates, rotaviruses are the major cause of serious gastroenteritis in young children. (Berkow 1992, 813)

A number of intestinal parasites can also cause gastroenteritis by invading the bowel mucosa. *Giardia lamblia* is a protozoan that inhabits the crypts in between and on the villi surface, and can cause symptoms that range from mild colic and poorly formed stools to severe cramping, diarrhea and fever. Infections can persist for a number of years, causing chronic diarrhea, flatulence, malabsorption, and weight loss. Both humans and animals are reservoirs for *Giardia*, and is spread by the fecal-oral route. *Giardiasis* or ‘beaver fever’ is common in the colder climates of North America, Europe and Asia, acquired by drinking water from contaminated creeks and streams. Another common intestinal parasite is *Cryptosporidium parvum*, usually acquired by drinking contaminated water. *Cryptosporidiosis* promotes a watery
diarrhea that is sometimes accompanied by abdominal cramps, nausea, and vomiting. It is usually a mild and self-limiting disease in healthy individuals, but in the immunocompromised, as well as young children and the elderly, the infection can be severe, causing significant electrolyte and fluid loss. Non-infectious causes of gastroenteritis include the ingestion of toxins found in fungi and plants (e.g. poisonous mushrooms, potato leaves), heavy-metals (e.g. arsenic, lead, mercury, and cadmium) and antibiotics, the latter of which promote GI dysfunction by altering the normal gut flora. (Berkow 1992, 237)

The signs and symptoms of gastroenteritis vary to a large degree, depending on host resistance, the virulence or toxicity nature of the etiological agent, and the duration of its activity. Symptoms of gastroenteritis are often quite sudden, and can include anorexia, nausea, vomiting, borborygmi (intestinal ‘gurglings’), colic, and diarrhea with or without blood and mucus. Other symptoms may include fatigue and lethargy, muscle aches, and fever. With either vomiting or diarrhea excessive fluid loss can occur, promoting symptoms of dehydration including muscular spasm, nervous irritability, shock, vascular collapse and renal failure. (Berkow 1992, 237).

**Malabsorption syndromes**

There a number of different malabsorption syndromes, a clinical term given to an impaired ability to properly absorb nutrients in the small intestine. Broadly speaking, malabsorption issues can be divided into two components: a dysfunction of digestive processes that break down the ingested food in the lumen of the bowel, and a dysfunction of processes that take place on and in the intestinal villi that ensure the absorption of these nutrients into the blood. Factors that impair absorption in the lumen of the small intestine include the deficient secretion of pancreatic enzymes and/or bile, as well as the gut flora that can synthesize enzymes that deconjugate bile salts. Surgical procedures such as the surgical removal of the gall bladder or resection of the bowel can also impair the secretory functions of the intestine. Factors that impair absorption at the intestinal level include inherited deficiencies of certain enzymes produced by the intestinal villi or from inflammatory processes that cause damage to the absorptive villi. Common signs and symptoms of malabsorption include weight loss, glossitis, foot cramps and spasms, and absence of tendon.
reflexes, bruising, gas, bloating, and colic. (Berkow 1992; Rubin and Farber 1990, 371-72)

**Carbohydrate Intolerance**

A carbohydrate intolerance is an inability to properly digest simple carbohydrates such as the disaccharides or lactose because of an inherited deficiency to produce the enzymes that break them down. Common clinical symptoms include gas, bloating and diarrhea usually with an hour after consumption. When such sugars remain undigested they interrupt normal osmotic mechanisms in the gut and thus promote diarrhea. Undigested, commensal bacteria then ferment these sugars, leading to an increase in fecal bulk and a lowering of the colonic pH, producing gas and bloating. The most common carbohydrate intolerance is to lactose due to a deficiency of the enzyme lactase, stated to be about 75% world-wide, highest among those of East Asian descent, and supposedly lower in Northern Europeans. Inherited deficiencies of other sugars such as glucose, galactose, sucrase, and isomaltase are quite rare. (Berkow 1992; Rubin and Farber 1990, 371)

**Celiac Disease**

Celiac disease is a malabsorption disorder caused by an intolerance to the gliadin fraction of gluten, a protein found in wheat and rye, and to a lesser extent in barley, oats and other grains. Within the intestinal mucosa gliadin forms an immune complex that promotes inflammation and mucosal damage. Celiac disease has a chronic course when the gliadin antigen is consumed regularly, although many patients may be entirely asymptomatic. Common clinical presentations may include varying degrees of steatorrhea, with diarrhea, colic, gas and bloating. In chronic cases patients may present with asthenia, recurrent aphthous stomatitis, dermatitis herpetiformis, anemia, bone pain, edema, and skin disorders. In many cases the diagnosis is missed because not all patients present with acute GI symptoms. In children that otherwise consume sufficient protein celiac disease can manifest as impaired physical development, a sallow complexion, wasting, and a large, distended abdomen. Family incidence is often a good indicator of the disease when clinical symptoms are mild or largely unmanifest. Although considered a disease, there is considerable evidence that celiac disease and its sub-chronic variants is a natural condition in humans, who did not consume grains and grain products until relatively recently. (Berkow 1992; Rubin and Farber 1990, 371-72)
II. Lower Digestive tract

Diverticulosis and diverticulitis

**Diverticulosis** is a term that describes a condition in which small pouches or sacs of the colonic wall called **diverticuli** herniate through the mucosa and submucosa of the colon. Although they can occur anywhere in the colon the vast majority occur in the sigmoid, giving rise to symptoms such as rectal bleeding and abdominal pain. The actual number of diverticuli can range from only a few to several hundred, and are usually one cm or less. (Berkow 1992; Rubin and Farber 1990, 378)

Diverticulosis is uncommon those below that age of forty, but become more common with increasing age. The epidemiological evidence indicates that diverticulosis is almost entirely a disease of Western, industrialized nations, it is becoming increasingly clear that diet plays a major role. Specifically, it appears that a low fiber diet is a major cause, which promotes alterations in fecal consistency that increases intraluminal pressure (particularly when a patient strains to evacuate the bowels), promoting the process of herniation. (Berkow 1992; Rubin and Farber 1990, 378)

When diverticuli become impacted with feces they can become inflamed, called **diverticulitis**, which could form abscesses that can perforate and cause peritonitis. Symptoms of diverticulitis include left lower quadrant pain and fever. (Berkow 1992; Rubin and Farber 1990)

Crohn’s disease

**Crohn's disease** is chronic **inflammatory bowel disease (IBD)** that typically affects the distal portions of the small intestine (i.e. the ileum) and/or proximal regions of the colon (i.e. the ascending colon). About 45% of Crohn’s patients suffer from both ileal and colonic inflammation, whereas about 35% involve the ileum only, and 20% involve only the colon. In some cases the entire small intestine may be involved, and in rare cases the stomach, duodenum and esophagus. In about 10-15% of patients the anorectal fistulas are the dominant presentation. (Berkow 1992; Rubin and Farber 1990)
The cause of Crohn's disease is idiopathic, with a number of theories to suggest its prevalence, including chronic infection and autoimmunity. Epidemiological evidence suggests that Crohn’s is for the most part a disease of industrialized, Western nations and has a strong familial predisposition. Although much neglected by medical researchers, the data suggests that environmental factors such as diet are very important.

The inflammation of Crohn's disease typically involves all layers of the bowel wall, and is thus called a **transmural inflammatory disease.** The inflammation however is discontinuous, interrupted by normal patches of intestinal tissue. The earliest lesion of the disease is intestinal crypt injury which progress to aphthous ulcers, often located over lymphoid nodules. In some cases the lesions regress, but in others the inflammatory process continues, with the local proliferation of inflammatory cells. The continued spread of inflammation eventually leads to mucosal edema and a thickening of the bowel wall from fibrosis. As the condition progresses further the mucosa develops a **cobblestone** appearance, comprised of both longitudinal and transverse ulcers with intervening mucosal edema. (Berkow 1992; Rubin and Farber 1990, 379-389; Gowan 1990, 403-4)

Patients with Crohn's disease typically present with abdominal pain, fever, anorexia, weight loss, and a very tender right lower quadrant mass or fullness upon palpation. Up to a third of patients may also have a prior history or present with anal fissures or fistulas. The disease also has extra-intestinal manifestations, and is closely associated with ankylosing spondylitis and other arthropathies (e.g. sacroilitis), aphthous stomatitis, primary sclerosing cholangitis and anterior uveitis. (Berkow 1992; Rubin and Farber 1990, 379-389; Gowan 1990, 403-4)

Crohn’s disease is characterized by periods of exacerbation and remission, which can be spontaneous and in many cases idiopathic. Dietary factors, stress, and other illnesses appear to have an influence but a cause and effect relationship can be difficult to establish. While the surgical resection of the affected bowel portions is a rather drastic method of putting the condition into ‘remission,’ in many cases the disease will begin to manifest in adjacent regions of bowel, suggesting the continuous of the caustive factors that promote the disease. Patients with long-standing Crohn's disease of the small bowel are at increased risk of small-bowel cancer, and patients with Crohn's disease of the colon have a long-term risk of colorectal cancer equal to that of
Ulcerative colitis

Similar to Crohn’s disease, **ulcerative colitis** is a chronic, inflammatory bowel disease, but unlike the former, is confined to the colon, usually affecting the distal portions of the bowel. While its cause or causes are unknown, it has a similar prevalence and distribution as Crohn’s, with a familial pattern, more commonly found in Europe and North America and much less frequently in Africa and Asia. (Berkow 1992; Rubin and Farber 1990, 381-82; Gowan 1990, 418-20)

The inflammation and ulceration of ulcerative colitis can extend from the most distal part of the rectum all the way to the proximal regions of the colon, but generally not into the small intestine. Unlike Crohn’s, which is a transmural disease, the ulceration extends only to the mucosa and not the deeper layers of the colon.

Signs and symptoms are typified by a recurrent, bloody diarrhea interspersed with asymptomatic periods. The degree of symptoms can vary, and often have a discrete onset, beginning as a mild diarrhea that gradually becomes more intense, accompanied by LLQ pain, and blood and mucus in the stool. In some patients however the onset can be acute, with a very watery diarrhea accompanied by fever and indications of peritoneal inflammation. Other clinical features may include malaise, fever, anemia, anorexia, and weight loss, while laboratory investigations reveal leukocytosis, hypoalbuminemia, and an elevated ESR. One particularly severe complication of ulcerative colitis is a **toxic megacolon**, which occurs when the ulceration results in intestinal obstruction and peritoneal inflammation. As this condition progresses the colon begins to dilate over a period of hours or days, and the patient presents with fever, and severe abdominal pain. (Berkow 1992; Rubin and Farber 1990, 381-82; Gowan 1990, 418-20)

The incidence of colon cancer in ulcerative colitis is increased when the entire colon is involved and when the disease lasts for more than 10 years, at a rate of about 0.5 to 1% per year. Although the cancer incidence is highest when the ulceration involves the entire colon, the risk is significantly increased when any portion beyond the sigmoid is involved. Similar to Crohn’s disease, extra-intestinal manifestations include inflammation of other tissues...
including the joints, muscles, skin and eyes. While classified separately based upon the target and characteristics of inflammation and ulceration, most gastroenterologists group ulcerative colitis and Crohn’s disease together as **Crohn’s-colitis**, which accounts for the similar prevalence, distribution and etiological factors. (Berkow 1992; Rubin and Farber 1990, 381-82; Gowan 1990, 418-20)

**Polyps of the colon and rectum**

A **polyp** is a small outgrowth of tissue that arises from the bowel wall and protrudes into the lumen of the colon. While pathologists can use numerous criteria to classify them, they are generally classified into either benign, **hyperplastic** types, or potentially malignant **adenomatous** types. There are also a number of other kinds of polyps, including juvenile polyps, inflammatory polyps and lipomas. Most polyps (90%) of the colon are hyperplastic, and are only discovered upon autopsy. Among the adenomas there are two primary forms based on their pathology and histology: tubular and villous. The etiology is usually attributed to a low fiber, high fat diet. (Berkow 1992; Pearlman 2005; Rubin and Farber 1990, 383-85; Gowan 1990, 421-23)

**Tubular adenomas** are the most common type of polyp (75%), and develop from the crypt cells between the intestinal villi in the sigmoid and rectal colon, reaching a size of about 2 diameters. They contain tightly packed glandular epithelial cells, and as it grows develops a pedicle comprised of the mucosa and muscular mucosae, developing a mushroom-like appearance. Malignancy is largely a determinant of the penetration of the glandular cells past the muscular layer into the lymphatic system. (Rubin and Farber 1990, 383-85; Gowan 1990, 421-23)

**Villous adenomas** are a much less common type of polyp, arising from the superficial epithelium of the rectum. As they enlarge they become progressively papiliform or “cauliflower-like,” containing fibrovascular tissues that are essentially identical to the lamina propria lined by epithelial cells. The tumor is sessile, has a broad base and can become quite large, up to 10 cm in diameter. (Rubin and Farber 1990, 383-85; Gowan 1990, 421-23)

**Familial polyposis coli** is a rare, inherited autosomal dominant condition characterized by the progressive development of numerous adenomas. The first symptoms appear in late childhood and by about the age of 40 the entire colon is studded with
numerous adenomatous polypi that inevitably leads to carcinoma of the colon. (Rubin and Farber 1990, 383-85; Gowan 1990, 421-23)

Most patients with polyps are asymptomatic, with rectal bleeding being the most frequent complaint. Other symptoms such as cramping, abdominal pain, or fecal obstruction can be a sign of a large polyp. In some cases a pedunculated polyp can prolapse through the anus. (Berkow 1992)

Colorectal cancer

Colorectal cancer is the second most common cancer in North America. It begins with the formation of benign polyps, which may increase in size and become cancerous. Among the factors that are associated with colorectal cancer are age, ulcerative colitis, hereditary polyposis, genetic factors and diet. Most forms of colorectal cancer are adenocarcinomas

The prognosis of colorectal cancer is reflective of the extent to which the tumor invades through the wall of the colon. To assess the nature of the tumor, oncologists use a combination of TNM staging (T = primary tumor, N = regional lymph node, M = remote metastasis) and Dukes classification:

• Stage A: tumor confined to the mucosa
• Stage B₁: tumor invading into the muscularis propria
• Stage B₂: tumor invading into the serosal, without lymph node involvement
• Stage C₁: B₁ tumors with metastases to local lymph nodes
• Stage C₂: B₂ tumors with metastases to local lymph nodes
• Stage D: distant metastases

The clinical features of colorectal cancer include intestinal bleeding, either as dark, tarry stools or bright red blood depending on whether the tumor is distal or proximal to the rectum. This is usually accompanied with severe anemia from blood loss. In the cecum and ascending colon tumors can grow to a large size without obstructing normal bowel function, but when the tumor affects the left side there are usually symptoms of obstruction, with flatulence and pain. The primary treatment for colorectal cancer is surgery. The five year survival rate for patients with stage B tumors is 70%, and 50% for stage C. (El-Deiry 2005; Berkow 1992; Rubin and Farber 1990, 386-87).
Hemorrhoids

Hemorrhoids are considered to be a kind of varicosity of the hemorrhoidal plexus, a specialized arteriovenous shunt similar to the corpus cavernosum of the genitalia, filled with oxygenated blood (hence the bright red color). External hemorrhoids are located below the anal sphincter, lined with squamous epithelium, whereas internal hemorrhoids are located above the sphincter and are covered by the rectal mucosa. (Berkow 1992; Rubin and Farber 1990, 383)

In many cases hemorrhoids are asymptomatic but they can protrude, bleed, and cause pain. Any kind of rectal bleeding should only be attributed to hemorrhoids after other, more serious conditions are excluded, such as diverticulosis or colorectal cancer. The volume of blood that is discharged following defecation is usually self-limiting, and rarely leads to complications such as anemia or hemorrhage, but in chronic bleeding can be a cause of iron deficiency anemia. Over the course of the condition both external and internal hemorrhoids can protrude and then regress, and in most cases can be reduced temporarily by manually pushing them back inside the rectum. In some cases however they cannot be reduced manually and can become strangulated, ulcerated or thrombotic, causing severe pain. In some cases internal hemorrhoids can cause a discharge of mucus and a sensation of incomplete evacuation following defecation. External hemorrhoids often present some difficulty in properly cleansing the anal region, which can lead to irritation and itching. (Berkow 1992; Rubin and Farber 1990, 383)

III. Liver, gall bladder and pancreas

Cholelithiasis and cholecystitis

Cholelithiasis refers to the formation or presence of calculi (gallstones) in the gallbladder, and accounts for most clinical disorders of the extrahepatic biliary tract. Factors that increase the probability of (cholesterol) gallstones include female sex, obesity, increased age, North American Indian ethnicity, a Western diet, and a positive family history.
Most gall stones (75%) consist of cholesterol, the remainder consisting of calcium bilirubinate or other calcium salts. The pathogenesis of **cholesterol stones** relates to the supersaturation of bile, which precipitates in the gall bladder as solid cholesterol crystals. This appears to be related to a deficiency of 7-hydroxylase, an enzyme that is involved in the production of bile salts from cholesterol. From a herbal perspective, this enzyme deficiency occurs in poor liver function, i.e. ‘hepatic torpor,’ caused by dietary factors, xenobiotic insult, excess liver burden, and a lack of bitter foods (which stimulate bile excretion and synthesis). The formation of **pigment stones** appears to be unrelated to the risk factors that predispose the formation of cholesterol stones, and is related specifically to unconjugated bilirubin in the bile. (Berkow 1992; Rubin and Farber 1990, 439-441)

The signs and symptoms of cholelithiasis can vary, with many patients remaining with symptoms for long periods, some never presenting with any at all. During periods of transient duct obstruction from a stone lodging somewhere in the biliary tree the result is **cholecystalgia**, a condition characterized by nausea, vomiting and epigastric or right upper quadrant pain that often radiates to the lower right scapula. When the obstruction persists it usually produces inflammation, resulting in acute **cholecystitis** and when the obstruction promotes the reflux of pancreatic juices **acute pancreatitis**. Perforation of the gall bladder and the release of bile into the peritoneum is a complication of acute cholecystitis, usually occurring as the result of a secondary bacterial infection. (Berkow 1992; Rubin and Farber 1990, 439-441)

**Pancreatitis**

**Pancreatitis** refers to the acute inflammation of the pancreas, and is divided into either acute or chronic forms. Up to 80% of **acute pancreatitis** are either caused by diseases of the biliary tract (e.g. cholecystitis or alcoholism). Iatrogenic causes can also be seen, including certain drugs such as azathioprine, sulfasalazine, furosemide, valproic acid, and estrogen. Other potential causes include infection (e.g. mumps), vascular diseases (e.g. hypotension), hypertriglyceridemia, trauma, hyperparathyroidism and hypercalcemia, as well as structural abnormalities of the pancreatic duct. **Chronic pancreatitis** is most often caused by either chronic, excessive alcohol consumption, or biliary diseases such as cholelithiasis. (Berkow 1992; Rubin and Farber 1990, 445-49)
The pathogenesis of both acute and chronic pancreatitis caused by cholelithiasis relates to the impaction of a gallstone in the sphincter of Oddi: acute forms are associated with a large stone whereas chronic forms relate to the temporary obstruction of the sphincter by smaller stones. The obstruction of the sphincter promotes an increase in ductal pressure and the reflux of pancreatic enzymes back into the pancreatic ducts. Other causes that promote an increase in ductal pressure occur with the sclerosis or stenosis of the sphincter of Oddi, or its dysfunction. (Berkow 1992; Rubin and Farber 1990, 445-49)

Chronic alcohol consumption also plays a major role in pancreatitis, particularly when more than 100 g of ethanol is consumed on a daily basis. While ethanol is thought to have a number of dysfunctional activities in the biliary tree, such as the spasm and edema of the sphincter of Oddi, ethanol specifically increases the protein content of the pancreatic juice, leading to the formation of protein plugs that accumulate within the small ductules of the pancreas. As these plugs accumulate the pancreas releases enzymes to digest them, resulting in acute inflammation. (Khoury 2005; Berkow 1992; Rubin and Farber 1990, 445-49)

The signs and symptoms of pancreatitis depend upon either its acute or chronic manifestations. Acute pancreatitis typically presents as an acute epigastric pain that can radiates to the upper back, usually accompanied by nausea and vomiting. The patient can be in pain for several hours or even days without respite, and often has a fever, is sweating, has an elevated pulse rate. Laboratory investigations reveal an elevated WBC count. Death from acute pancreatitis within the first few days after onset is thought to be associated with the circulation enzymes and toxins, causing cardiovascular, renal and/or renal respiratory failure, and in some cases heart failure. Chronic pancreatitis can follow a similar course, but is usually not as severe. (Khoury 2005; Berkow 1992; Rubin and Farber 1990, 445-49)
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LESSON SEVEN: Liver and kidney disease

The liver and kidneys play extremely crucial roles in the body, responsible for a variety of metabolic functions including the neutralization and elimination of toxins in the body. This lesson provides an overview of the major pathologies found in the hepatobiliary and renal systems.

I. Liver disease

Jaundice

Jaundice is a term that refers to a yellowing of the skin, sclerae (whites of the eyes), and other tissues caused by an excess of circulating bilirubin. Bilirubin is a water-insoluble waste product derived mostly from the heme portion of degenerating RBCs, as well as from RBC precursors in the marrow and heme proteins of liver and other tissues. Bilirubin is released by phagocytes and other cells into circulation where it is bound with albumin, transported and taken up by the liver. Bilirubin is then conjugated with glucoronic acid to form bilirubin diglucuronide, and is then secreted into the bile. Within the colon the bacterial flora deconjugate bilirubin into stercobilinogen, most of which is excreted in the feces as a brownish coloured pigment. Significant amounts are absorbed however, and then directed back to the liver where they are again excreted in the bile, or via the kidneys in urine as urobilinogen. (Berkow 1992; Rubin and Farber 1990, 396-400)

Abnormalities in the production and excretion of bilirubin often result in jaundice. Elevated levels of unconjugated bilirubin in the blood can be the result of an increased production of bilirubin, an impairment in liver uptake, or inefficient conjugation by the liver. In contrast, elevated levels of conjugated bilirubin is caused by impaired biliary excretion. In both liver disease and cholestasis the patient will often present with a mixed hyperbilirubinemia, with both conjugated and unconjugated serum bilirubin. (Berkow 1992; Rubin and Farber 1990, 396-400)

Cases of mild jaundice in the absence of a dark-coloured urine would tend to indicate an unconjugated hyperbilirubinemia, caused
by either hemolysis or Gilbert's syndrome (see below). In contrast, more severe indications of jaundice, and/or a very dark urine is a definite indication of an overt liver or biliary disorder. Accompanying signs such as ascites or pruritis usually suggests a chronic rather than acute pathology. Patients will often report a darkening of their urine before the skin discoloration of jaundice occurs, and in the case history is a better indication of the original onset of the pathology and should be noted. Where nausea and vomiting proceeds jaundice this is most often an indication of acute hepatitis or an obstruction of the cystic duct by a stone – when abdominal pain is a dominant symptom it is more likely to be caused by cholecystitis. Jaundice concurrent with symptoms such as poor appetite, weight loss and fatigue suggest alcoholic liver disease or chronic hepatitis. (Berkow 1992; Rubin and Farber 1990, 396-400)

Common disorders of bilirubin metabolism include unconjugated hyperbilirubinemia, Gilbert's syndrome, obstructive jaundice, and neonatal jaundice. Other more rare causes include inherited diseases such as Crigler-Najjar disease, which like Gilbert’s syndrome is manifested by decreased bilirubin conjugation, and Dubin-Johnson syndrome, which relates to the decreased intracellular transport of conjugated bilirubin. (Berkow 1992; Rubin and Farber 1990, 396-400)

**Unconjugated hyperbilirubinemia** is the result of a hemolytic anemia, a premature destruction of the RBCs, occurring in association with some infectious diseases, with certain inherited red-cell disorders, or in response to drugs and other toxic agents. (Berkow 1992; Rubin and Farber 1990, 396-400)

**Gilbert's syndrome** is an inherited autosomal dominant, mild and chronic, unconjugated hyperbilirubinemia often misdiagnosed as chronic hepatitis. It may affect as many as 5-10% of the population. The pathogenesis appears to be related to defects in the liver's uptake of plasma bilirubin. While Gilbert’s syndrome is not associated with any overt liver pathology, patients will often experience some degree of malaise and weakness. (Berkow 1992; Rubin and Farber 1990, 396-400)

**Obstructive jaundice**, or **cholestasis**, results from impaired bile flow, from any point between the liver cell canaliculi and the ampulla of Vater. Typically, a distinction is made between intrahepatic and extrahepatic causes. The most common **intrahepatic** causes are hepatitis from drug toxicity and alcoholic liver disease, but less common forms include primary biliary
cirrhosis, cholestasis in pregnancy and metastatic carcinoma. The most common extrahepatic causes are a common duct stone and pancreatic cancer, with less common causes being a benign stricture of the common duct (usually related to surgery), ductal carcinoma, pancreatitis and sclerosing cholangitis. (Berkow 1992; Rubin and Farber 1990, 396-400)

**Neonatal jaundice** is in most cases a normal event experienced by up to 70% of newborns, called “physiologic jaundice,” the cause of which is poorly understood. It is usually a transient condition that can be easily treated by having the baby lie in the direct sunlight for 5-10 minutes each day. Other causes of neonatal jaundice are more serious such as infection or extrahepatic biliary atresia. (Berkow 1992; Rubin and Farber 1990, 396-400)

### Hepatomegaly

**Hepatomegaly** refers to an enlargement of the liver, and usually indicates some kind primary or secondary liver disease. Although the normal liver displays some variation in placement, the lower border of a normal liver is often palpable at or slightly below the right costal margin, and the upper border is identified by a dull sound upon percussion over the rib cage. Upon palpation the edge of the normal liver feels rubbery and smooth, whereas a cirrhotic liver feels firm and irregular. Liver tenderness, often over diagnosed because the patient anticipates tenderness or is anxious about the examination, is correctly identified by a deep-seated ache upon palpation. In such cases the liver feels enlarged, with a tender, smooth edge, and can suggest either liver inflammation or venous stasis (i.e. secondary to right heart failure). (Berkow 1992)

### Portal hypertension

**Portal hypertension** refers to the increased pressure in the portal venous system. The portal vein unites the superior mesenteric and splenic veins, draining the lower portions of the gastrointestinal tract, as well as the spleen and pancreas. The blood directed to the liver via the portal vein provides up to 75% of the liver’s total blood supply, 60% of its total oxygen supply, and is rich in a slurry of nutrients derived from the GIT. Portal hypertension occurs when there is an increased flow of blood directed to the liver, or when there is an increased resistance to the flow of blood, and can be classified as prehepatic, intrahepatic or posthepatic. **Prehepatic**
**portal hypertension** relates to blood disorders that cause splenomegaly, increasing the flow of blood in the portal vein. **Intrahepatic portal hypertension** is related to an increased resistance to the flow of blood, when the portal venules and liver sinusoids are damaged by fibrosis (i.e. cirrhosis), or are obstructed by parasites (i.e. schistosomiasis). Causes of posthepatic portal hypertension include hepatic vein obstruction caused by Budd-Chiari syndrome, or an obstruction of the vena cava or in diseases of the heart. Portal hypertension can manifest as splenomegaly or ascites, and may present with life-threatening hemorrhaging of lower esophagus or upper stomach, requiring immediate emergency care. Herbalists recognize a subclinical form of portal hypertension called **portal congestion**, which underlies many pathologies of the abdomen and lower parts of the body, including both gynecological disorders such as dysmenorrhea and male reproductive disorders such as chronic prostatitis, as well as hemorrhoids and varicosities of the legs. (Berkow 1992; Rubin and Farber 1990, 426-428)

### Ascites

**Ascites** is the accumulation of fluid in the peritoneal cavity, representing either a disorder of the liver, diseases of the heart and kidneys, or can be an indication of abdominal diseases such as cancer or tuberculosis (the latter causing peritonitis). Liver disease remains the most common cause of ascites, and includes cirrhosis, chronic hepatitis, alcoholic liver disease and hepatic vein obstruction caused by Budd-Chiari syndrome. The specific factors that promote ascites range from an impaired production of serum albumin (decreasing the osmotic pressure of the blood), or an increase in portal venous pressure. Ascites is diagnosed is a clinical setting by percussion, which reveals a dull rather than hollow sound, and with advanced cases noting an abdomen is distended and tight. The primary difference between ascites caused from liver disorders as opposed to systemic conditions such as congestive heart failure is noted by abdominal edema that is disproportionate to peripheral manifestations, whereas in the latter condition peripheral edema is more marked. (Berkow 1992; Rubin and Farber 1990, 426-428)

### Alcoholic liver disease

Alcohol consumption has a long history in human civilization, dating back to the early neolithic, with references to the problem of
alcoholism noted in the ancient medical texts of India and other cultures. At one time it was thought that alcoholic liver disease (ALD) was solely related to the nutritional deficiencies caused by using alcohol as the primary source of dietary calories, but it is now understood that excessive alcohol consumption promotes specific degenerative changes in the liver that are responsible for the clinical manifestations of ALD, which progresses from fatty liver, to alcoholic hepatitis, and finally cirrhosis. Only about 15% of people with alcoholism however will go on to experience cirrhosis of the liver. (Berkow 1992; Rubin and Farber 1990, 412-415)

The pathogenesis of ALD relates primarily to the quantity of alcohol consumed and the duration of consumption, as well as the patient's overall nutritional status and a number of genetic and metabolic characteristics. Consuming as little as 20 grams of ethanol, equal to 60 mL of 40% whiskey, 200 mL of 12% wine, or 500 mL of 5% beer can produce liver injury when consumed daily over a period of years. In cases of alcoholic hepatitis a patient will consume up to 80 grams of alcohol daily for almost a decade, whereas cirrhosis is typically seen with the consumption of 160-200 g daily over the same period. (Berkow 1992; Rubin and Farber 1990, 412-415)

Alcohol is a potent source of carbohydrates, and thus decreases the appetite, promoting malabsorption through its toxic effects on the gut and pancreas. The net result of this is malnutrition, which tends to hasten the negative effects of alcohol, and promoting aging and susceptibility to other diseases. (Berkow 1992; Rubin and Farber 1990, 412-415)

When ingested alcohol is quickly absorbed from the GI tract, and directed to the liver where it is metabolized by oxidative mechanisms that involve alcohol dehydrogenase and the microsomal ethanol oxidizing system. Alcohol dehydrogenase produces acetaldehyde as the major catabolite, which is toxic to both the liver and other organs, and is further oxidized to acetate. This process increases the redox state of the liver, which interferes with normal functions, inhibiting gluconeogenesis and protein synthesis, and increasing fatty acid synthesis and lipid peroxidation (seen in fatty liver). Alcohol metabolism also induces a local hypermetabolic state that promotes hypoxic damage, as well as induces microsomal P-450, which is involved in drug metabolism. As a result of this, alcoholics tend to acquire an increased tolerance to alcohol and drugs, often leading to multiple drug abuse patterns. Women in particular appear to be more susceptible to alcohol,
thought to be because females tend to produce less alcohol dehydrogenase in the gastric mucosa than males. (Berkow 1992; Rubin and Farber 1990, 412-415)

**Fatty liver** or **steatosis** is the initial manifestation of acute or chronic excess alcohol consumption, the liver becoming enlarged and yellowed from the accumulation of fat droplets that can coalesce as larger cysts. These fatty changes to the liver however are completely reversible, and usually presents no more symptoms that the malaise and discomfort of the typical symptoms of ‘hangover’ experienced the next day. (Berkow 1992; Rubin and Farber 1990, 412-415)

If ethanol is consumed on a regular basis and to excess however, the injury to the liver persists and the result is **alcoholic hepatitis**, which is usually superimposed upon the fatty changes. The swollen and injured hepatocytes undergo degeneration and a localized inflammatory reaction develops in response. Cellular necrosis and hypoxia stimulates fibrosis, often around the central vein, and in severe cases can be totally obliterated, surrounded by dense fibrous tissue called **central hyaline sclerosis**. Clinically, the effects of alcoholic hepatitis are noted by malaise, anorexia, right upper quadrant pain and jaundice, with laboratory investigation revealing leukocytosis and elevated serum aminotransferase activity. In about 10-30% of the cases the result is death. In those that survive and persist in drinking the acute illness will eventually be followed by chronic hepatitis, usually resulting in cirrhosis within a few years. Even for those patients that abstain from drinking at this point only about 25% fully recover by 6 months, and 20% will continue on to experience cirrhosis regardless of abstinence. For most patients recovery is very slow, and will show some degree of liver disease even after a year of abstinence. (Berkow 1992; Rubin and Farber 1990, 412-415)

**Cirrhosis** represents the end-stage disease of ALD, with hepatocellular necrosis and generalized fibrosis that surrounds the few remaining hepatocellular nodules. Essentially, the liver becomes shrunken and fibrotic, and patients will often die from esophageal hemorrhage (secondary to portal hypertension) or from complete hepatic failure. (Berkow 1992; Rubin and Farber 1990, 412-415)
Acute viral hepatitis

**Acute viral hepatitis** refers to liver inflammation caused by certain viruses, including the hepatitis A, B, C, D and E viruses. Other viruses that affect the liver include EBV, herpes simplex, yellow fever and cytomegalovirus, and are usually considered as separate disorders.

**Hepatitis A virus (HAV)**

Hepatitis A virus (HAV) is a single-stranded RNA picornavirus. Upon investigation the viral antigens may be found in the blood, stool, and liver but only during acute infection. A characteristic of the early, acute stage of the disease is a temporary elevation of IgM antibody followed by the development of protective IgG antibody that persists for the remainder of the patient’s life. The transmission of HAV depends on transmission from person to person via the oral-fecal route. Epidemics usually occur in unsanitary conditions although improperly cooked shellfish may also transmit the infection. The infection is particularly high among homosexuals via the oral-anal route. HAV is mostly benign, self-limiting disease that does not play a role in the pathogenesis of chronic hepatitis or cirrhosis. (Berkow 1992; Rubin and Farber 1990, 402-10)

**Hepatitis B virus (HBV)**

Hepatitis B virus (HBV) is a liver-specific DNA virus that causes both acute and chronic liver disease. The virus is comprised of an inner core and a surface coating. The HBV viral core contains a circular double-stranded DNA molecule and DNA polymerase that can only replicate within the nuclei of liver cells. The surface coating of the virus consists of a mixture of carbohydrates, lipids and proteins that is synthesized independently of the virus in the cytoplasm of an infected liver cell. Although not infectious this surface coating can be detected in the blood by laboratory methods as the hepatitis B surface antigen (HBsAg). The intact and infectious virus is also found in the serum as the Dane particle, consisting of both the inner core and the surface coating. (Berkow 1992; Rubin and Farber 1990, 402-10)

HBsAg usually appears during the viral incubation period, one to six weeks before clinical symptoms develop and then disappears as the patient recovers. The corresponding protective antibody (anti-HBsAg) appears weeks or months later after recovery, and usually persists for life, indicating past HBV infection and a relative immunity to the virus. The HBV viral core antigen (HBeAg) can be found in infected liver cells but is not detectable in serum
except by specialized laboratory techniques. Antibody to HBcAg (anti-HBc) usually appears at the onset of illness, and only gradually diminishes over a period of years or for life. (Berkow 1992; Rubin and Farber 1990, 402-10)

It is estimated that 300 million people worldwide are chronic carriers of HBV, the carrier rates as low as 0.3% in industrialized nations and up to 20% in developing countries. Humans are the only significant reservoir for HBV, and unlike HVA which is spread via the oral-fecal route, HBV is not and nor does it contaminate water supplies. HBV has been found in secretions of the blood, saliva and semen and is through to be transmitted either through infected blood products, injection drug users, or through intimate contact (with a higher prevalence in homosexual communities). (Berkow 1992; Rubin and Farber 1990, 402-10)

Unlike HAV, HBV is associated with significant liver diseases, including acute self-limiting hepatitis, fulminant hepatitis, and chronic hepatitis. **Acute self-limiting hepatitis** is associated with the majority of infected persons, with complete recovery and lifelong immunity. **Fulminant hepatitis** is experienced much less of the time, characterized by hepatocytes necrosis, hepatic failure and a high mortality. In 5-10% of HBV infections patients do not develop anti-Hbs, and the infection persists leading to chronic hepatitis B. **Chronic hepatitis** is discussed later in this lesson. (Berkow 1992; Rubin and Farber 1990, 402-10)

**Hepatitis D virus (HDV)**

The **hepatitis D virus (HDV)** is a defective RNA virus that can only replicate only in the presence of either acute or chronic HBV infection, and usually increases the severity of existing chronic hepatitis. A combination HBV and HDV infection accounts for a large proportion of fulminant HBsAg-positive hepatitis. (Berkow 1992; Rubin and Farber 1990, 402-10)

**Hepatitis C virus (HCV)**

Although grouped along with HAV and HBV, the **hepatitis C virus (HCV)** is considered to be quite a different pathogen, from the family known as Flaviviridae, close cousin to the viruses that cause bovine diarrhea, hog cholera, and yellow fever. Researchers have identified more than 100 strains of the virus and grouped them into six major "genotypes," which tend to be in specific regions around the world. (Berkow 1992; Rubin and Farber 1990, 402-10)

The evolution of HCV began when clinicians observed a small fraction of transfusion recipients suffering from short-lived flu-like
symptoms followed in some cases by liver disease years later. To distinguish the disease from HAV and HBV, they originally called it non-A, non-B hepatitis. Researchers from Chiron Corp. and the Centers for Disease Control and Prevention (CDC) finally determined the infectious agent in 1988, and published paper describing it and a method for testing for it in blood samples. (Berkow 1992; Rubin and Farber 1990, 402-10)

There is no evidence pointing to where or when HCV first infected humans, as no other species appears to serve as a natural host. Studies clearly have established that the main routes of transmission are by tainted blood transfusions and non-sterile needles. The development of a screening test in 1990 has virtually eliminated the spread of HCV through blood transfusions in industrial countries, and now sharing contaminated needles is the most common route of infection. Although the numbers of infected persons has dropped dramatically since testing began, the CDC estimates that perhaps 1.8% of the U.S. population harbors the virus, and as these patients age, HCV-related liver disease, accounting for 8000 to 10,000 annual deaths in the United States, is the single most common reason for liver transplants. (Berkow 1992; Rubin and Farber 1990, 402-10)

Apart from direct blood contact HCV appears to be a very difficult agent to transmit, with only 6% maternal-to-fetal transmission is low. Some have suggested that HCV can be transmitted sexually, the CDC officially stating that sex accounts for between 10% and 20% of the infection in the United States. The actual evidence however is far from convincing, with little data to support these numbers. (Berkow 1992; Rubin and Farber 1990, 402-10)

The severity of HCV varies enormously from person to person and there are few reliable indicators to predict who will do well or badly. It is estimated that 15% to 25% of people infected with HCV will effectively deal with the virus during initial infection, with the remaining proportion of patients developing a chronic infection. The prevalence of any significant clinical complication of the disease is estimated to be between 10-20% of chronically infected people, with an even smaller percentage developing hepatocellular carcinoma. Several studies show however that the majority of patients have none of these symptoms even 20 years after infection. In one seven year study of more than 400 patients who had tested positive for HCV, and whose infection could in most cases be traced to a transfusion or injection, only 13% of 81 patients who had undergone liver biopsy had evidence of severe hepatitis (8%) or cirrhosis (5%), despite a duration of infection that
generally exceeded 15 years (Alter et al 1997). These results closely parallel other studies that have shown that HCV is generally not associated with any significant liver pathology. There is little correlation between the viral load in the patients serum and the progression of the disease. More significant factors include alcohol consumption, cocaine and intravenous drug use, body piercing and tattoos, and in older patients, blood transfusion. Although HCV is stated to be a blood borne disease, researchers have identified a few alcoholics with HCV who do not have any other risk factors (Verbaan et al 1993). Even commonly relied upon indicators such as elevated serum alanine aminotransferase (ALT), an enzyme released by liver cells when they die, is not an indicator of the progression of HCV-related disease (Ghany et al 1996).

The biggest issue when it comes HCV is the lack of a culturing system for HCV. As of 2005, no researcher has been able to culture HCV. In every other infectious disease there is a cause and effect relationship between the etiological agent and the disease, except it HCV. The testing for HCV is based upon a proprietary test used to detect specific HCV antibodies to a yet to be identified pathogenic agent. While somewhat suspicious, this only becomes problematic when these tests are used as the basis for the aggressive anti-retroviral therapies currently being utilized, many of which have severe side-effects. Since HCV is in most cases an asymptomatic disease, especially in those that abstain from drug and alcohol use, there seems to be little indication for the usage of therapies such as interferon and ribavirin that have severe, debilitating side-effects. While these drugs have been shown to reduce the viral markers for HCV in the patient’s blood at the end of treatment, the net result is the creation of a host of other diseases that have a dramatic impact upon the health of the individual. In otherwords, one can be “cured” of HCV, but end up being much, much more ill than at the time of diagnosis. Perhaps even more significantly, these drugs are not necessarily effective for all the different strains of HCV that exist, and thus reinfection may occur. (Berkow 1992; Rubin and Farber 1990, 402-10)

**Signs and symptoms.**

In acute viral hepatitis the liver acini are affected by hepatocellular necrosis and mononuclear inflammation. The symptoms and signs can vary from a minor flu-like illness to a fulminant liver failure that can cause death, depending on the patient's immune response as well as a number of other factors that have yet to be fully elucidated. The initial onset of viral hepatitis usually begins quite suddenly, with poor appetite, fatigue, nausea and vomiting, and fever, with skin eruptions and joint pain (particularly in HBV).
Between 3 and 10 days after the prodromal symptoms occur the urine darkens and signs of jaundice manifest, but the patient often feels somewhat better, with a decline in systemic symptoms. With jaundice there is hepatomegaly and liver tenderness upon palpation, with splenomegaly present in up to 20% of patients. Blood tests often reveal an elevation in the enzymes AST (aspartate amino transferase) and ALT (alanine amino transferase), which are released by damaged hepatocytes. WBC counts are usually low to normal, and with cholestasis tests may also reveal an elevation in alkaline phosphatase. (Berkow 1992; Rubin and Farber 1990, 402-10)

The prognosis for acute viral hepatitis is good, especially in HAV, and in most cases there is a spontaneous remission within four to eight weeks. With HBV however, elderly or hospitalized patients have an increased risk of mortality, and up to 10% of cases develop into a chronic hepatitis leading to cirrhosis or hepatocellular carcinoma. Infection with HCV is more likely to become chronic, appearing mild at the outset of the illness and for many years afterwards, with cirrhosis occurring only after several years if not decades. The vast majority of patients with HCV and who require a liver transplant have a significant history of chronic drug and alcohol use. (Berkow 1992; Rubin and Farber 1990, 402-10)

**Chronic hepatitis**

Chronic hepatitis refers to the presence of inflammation and necrosis in the liver for more than six months, although pathologists admit this is a somewhat arbitrary designation. Rather than defining hepatitis as chronic, the medical emphasis is to note the specific etiological and pathological factors involved in the disease, e.g. chronic HCV with periportal inflammation, autoimmune hepatitis with cirrhosis, etc.

HBV and HCV are the major causes of chronic hepatitis, mediated through the host response to infection, rather than the virus itself. Iatrogenic causes of chronic hepatitis include drugs such as isoniazid, methyldopa, nitrofurantoin, and acetaminophen, although many more can be added to this list. The role of alcohol in chronic liver disease has already been discussed in detail. The clinical features of chronic hepatitis includes lethargy, anorexia, and fatigue, sometimes with low-grade fever and epigastric discomfort. In many cases there will be no noticeable evidence of overt pathology, and characteristic signs of liver injury such as
jaundice, as splenomegaly, spider nevi, ascites may only evolve over a period of several years. In the autoimmune variant of hepatitis that tends to be more common in women, there can be systemic complications including acne, amenorrhea, joint pain, ulcerative colitis, fibrosis of the lungs, thyroiditis, nephritis, and hemolytic anemia. The overall prognosis for chronic hepatitis is highly variable, depending upon the removal of etiological factors (e.g. drugs or alcohol). In cases of HBV or HCV liver inflammation and damage progresses slowly, and are difficult to treat with standard medical therapies, although the many hepatoprotective herbs such as Curcuma, Silybum, and Cynara would seem to be indicated. Autoimmune forms of chronic hepatitis are generally treated with immunosuppressive drugs such as corticosteroids, and although they can be effective in limiting the acute manifestation of disease, the side-effects can promote immunodeficiency. (Berkow 1992; Rubin and Farber 1990, 402-10)

Benign tumors of the liver

**Benign liver tumors** are relatively common and although most do not usually manifest any clinical symptoms, they can be associated with hepatomegaly, URQ pain or intraperitoneal hemorrhage. Most cases are discovered as part of a routine examination, such as ultrasound or palpation. Upon laboratory investigation liver function tests appear normal, or may show a mild elevation in liver enzymes. (Berkow 1992; Rubin and Farber 1990, 435-39)

**Hepatocellular adenoma** is another common benign tumor of the liver, usually occurring in women age taking oral contraceptives. Although they do not typically undergo malignant transformation, a few cases have been reported in the literature. In most cases the adenomas resolve once oral contraceptives are discontinued. (Berkow 1992; Rubin and Farber 1990, 435-39)

**Focal nodular hyperplasia** is often association with hepatocellular adenoma, and the use of oral contraceptives. Upon histological examination the tumors resemble the same kind of tissue changes as cirrhosis. (Berkow 1992; Rubin and Farber 1990, 435-39)

**Hemangiomas** are the most common benign tumor of the liver, and are usually small and do not promote any symptoms. Post-mortem research has indicated that they are present in as many as
7% of the population. (Berkow 1992; Rubin and Farber 1990, 435-39)

Cirrhosis

Cirrhosis is the end stage of any chronic liver disease, in which the functional liver essentially devolves into a shrunken, fibrotic cord of tissue that surrounds small nodules functional hepatocytes. Fibrosis can occur as the result of chronic infection (e.g. viral hepatitis), chronic exposure to toxins (e.g. drugs, alcohol), autoimmune mechanisms, biliary obstruction, vascular impairments, or some combination of these factors.

The clinical manifestations of cirrhosis can range from an asymptomatic state that can exist for years, to more generalized symptoms such as asthenia, poor appetite, lethargy, and fatigue. If the fibrosis has progressed such that bile flow is obstructed jaundice is its natural evolute, with accompanying indications of poor appetite, poor fat digestion, and eventually, essential fatty acid and fat-soluble vitamin deficiencies. Upon palpation the liver is often firm and displays a blunt edge, but in other cases the liver may be too small to palpate. Ascites is a potential presentation and may be present with splenomegaly. With portal hypertension cirrhosis can present as a life-threatening esophageal or gastric bleeding secondary. (Berkow 1992; Rubin and Farber 1990, 418-20)

Hepatocellular carcinoma

The most common type of primary liver cancer is hepatocellular carcinoma, a liver tumor that arises from malignant hepatocytes. Although much less common than metastatic liver cancer, which is secondary to primary cancers of the lung, breast, stomach, pancreas and colon, it is especially prevalent in certain areas of Africa and SE Asia where HBV is endemic. Carriers of HBV have a dramatic 200-fold increase in the risk of liver cancer. In these carriers the viral DNA becomes incorporated into the genome of infected hepatocytes leading to malignant transformation. Environmental carcinogens are also thought to play a role in hepatocellular carcinoma, such as the ingestion of food contaminated with aflatoxins produced by certain species of fungi that infect improperly stored foods in the warm, humid climate of Africa and SE Asia. Chronic HCV infection is also associated with hepatocellular carcinoma although the mechanism of carcinogenesis is unclear, thought to be related to the fibrotic
changes seen in cirrhosis. (Berkow 1992; Rubin and Farber 1990, 435-39)

The signs and symptoms of hepatocellular carcinoma include abdominal pain, anorexia, and a large palpable mass in the right upper quadrant of the abdomen. The prognosis for hepatocellular carcinoma is very poor and medical intervention is usually unsuccessful. Failing a liver transplant the patient with hepatocellular carcinoma eventually succumbs cachexia, severe hemorrhage caused by the rupture of the tumor, or hepatic failure. (Berkow 1992; Rubin and Farber 1990, 435-39)
II. Kidney disease

Polycystic kidney disease

**Polycystic kidney disease (PKD)** refers to a group of inherited disorders that are characterized by the accumulation of renal cysts that increase the kidney size but impair its overall function. PKD may be autosomal recessive (ARPKD) or autosomal dominant (ADPKD), the former of which is comparatively rare.

**Autosomal dominant polycystic kidney disease**

The incidence of **autosomal dominant polycystic kidney disease (ADPKD)** occurs in about 1 in 1000 patients, and is often asymptomatic, slowly progressing over many years. Clinical manifestations typically occur in early to middle adult life, although in some cases the disease is only discovered post mortem. Typical symptoms relate to the effects of the cysts, including lower back pain and hematuria. Chronic infection is frequent event and contributes to the progression of the disease. Around 30% of patients also present with similar cysts in the liver, and with the destruction of the nephron hypertension is a frequent presenting symptom. About half of those with ADPKD develop uremia, referring to a toxic accumulation of urea in the blood. Without dialysis or transplantation the patients usually die as a result of this or from complications related to hypertension. (Berkow 1992; Rubin and Farber 1990, 457-58)

Glomerular disease

**Glomerular diseases** are a diverse group of diseases that affect the glomerulus, and may be primary or secondary to systemic disease. In many ways they cannot be thought of as diseases per se but as syndromes based on specific clinical and laboratory indications. The etiology is highly diverse and often mixed, and different pathological conditions can produce the same syndromes. The major categories are **inflammatory (nephritic syndrome)** and **hemodynamic (nephrotic syndrome).**

**Nephritic syndrome**

Nephritic syndrome is disease by inflammation of the glomerulus, characterized by clinical signs such as hematuria, hypertension, renal insufficiency and edema. It is has two primary forms: acute
and chronic. **Acute nephritic syndrome** is characterized by the sudden onset of hematuria, and is usually accompanied by hypertension, edema, and azotemia. Acute ephritic syndrome is associated with the infection of certain strains of group A-hemolytic streptococci and the formation antigen-antibody complexes. These immune complexes are deposited in the subepithelium of the glomerular basement membrane and stimulate localized inflammatory responses. The disease is most common in children under 3 years of age and in young adults, but 5% of patients are more than 50 years old. The prognosis is usually good if the initial renal damage is not severe. (Berkow 1992; Rubin and Farber 1990, 466-73)

**Chronic nephritic syndrome** (syn. **chronic glomerulonephritis**) is a syndrome caused by several diseases of different etiologies, characterized by diffuse sclerosis of the glomeruli accompanied by proteinuria, hematuria, hypertension and a gradual loss of renal function over a period of years. The etiology is complex, but most conditions are associated with immune-mediated inflammatory reactions. (Berkow 1992; Rubin and Farber 1990, 466-73)

**Nephrotic syndrome**

Nephrotic syndrome (NS) is a complex of signs and symptoms that results from a severe, prolonged increase in glomerular permeability for protein. This can be related to a number of different pathologies, including primary renal diseases such as focal glomerulosclerosis and IgA nephropathy, secondary diseases such as diabetes and systemic lupus erythematosus, the use of drugs such as NSAIDS and heroin, or other conditions including allergies, malignancies and various infective agents. The primary clinical feature of nephritic syndrome is a pronounced proteinuria, often with hypalbuminemia, generalized edema, lipiduria, and lipemia. It can occur at any age but is more common in children between the ages of 1 and 4 years. The early sign of NS is frothy urine due to protein, as well as clinical features such as anorexia, lethargy and fatigue, puffy eyelids, abdominal pain, and wasting of the muscles. Severe proteinuria promotes protein malnutrition, promoting a range of symptoms including brittle hair and nails, hair loss, impaired growth and development, and the demineralization of bone. (Berkow 1992; Rubin and Farber 1990, 457)

**Diabetic nephropathy**

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease in North America. The pathogenesis is complex, but the mechanisms responsible are related to the hormonal and metabolic abnormalities seen in poorly controlled
diabetes. Similar to its role in atherosclerosis, hyperglycemia causes the glycosylation of glomerular proteins, which results in vascular endothelial damage. (Berkow 1992; Rubin and Farber 1990, 476)

Urolithiasis

Urinary calculi (syn. kidney stones, nephrolithiasis, urolithiasis) refers to the presence of calculi in the urinary tract, varying from microscopic crystalline granules to calculi several centimeters in diameter. Depending on their location in the UT, this condition is given different names: within the bladder, the condition can be termed vesical calculi, bladder calculi, vesical stones, or bladder stones; within the kidneys, the condition is termed nephrolithiasis, kidney calculi or kidney stones.

In North America about 80% of the stones found in urolithiasis are comprised of calcium salts, as calcium oxalate or calcium phosphate. Between 5-10% are comprised of urates, another 5-10% are struvite (magnesium ammonium phosphate), and between 1-2% are comprised of cysteine. There are a variety of theories that describe the etiology and pathogenesis of urolithiasis, each depending upon the type of stone formed. Generally speaking, the underlying etiological factors in most types of urolithiasis is related to an impairment in bladder emptying due to anatomical problems (e.g. prostatitis, tumors), neurogenic bladder (e.g. spinal cord injury, multiple sclerosis), the presence of foreign bodies in the UT that act as a nidus or “seed” that promotes stone formation (e.g. surgical staples, ureteral stents), or bladder inflammation (e.g. radiation, schistosomiasis). (Berkow 1992; Smith 2005)

Although often asymptomatic, urinary calculi can cause pain, bleeding, urinary obstruction, and secondary infection. Renal colic frequently occurs when the calculi obstructs urination excretion into the bladder, and can be excruciating, originating in the lower back and radiating across the abdomen into the crotch and inner thigh. If calculi obstruct the bladder the pain is typically localized in the suprapubic region. Gastrointestinal symptoms such as nausea, vomiting, and abdominal distention are frequent, and as the stone is being passed additional symptoms such as chills, fever, hematuria, and frequent urination are very common. (Berkow 1992; Smith 2005)
Hydronephrosis

**Hydronephrosis** refers to structural or functional changes in the urinary tract that hinders normal urine flow. The result of this is that the renal pelvis and calyces become progressively dilatated, flattening the papillae and in some cases leads to renal dysfunction or atrophy. In men the most common cause of obstruction is chronic prostatitis and benign prostatic hyperplasia, but may also be caused by prostate cancer, the presence of a foreign body, vesicular spasm or congenital structural abnormalities. In women urethral obstruction is less common, but may occur secondary to a tumor, radiotherapy or surgery, or urologic instrumentation (usually repeated dilation). **Anuria** (absence of urination) is a frequent manifestation if both ureters are obstructed. (Berkow 1992; Rubin and Farber 1990, 485)

Renal failure

**Renal failure** refers to a decline in the glomerular filtration rate, with resultant increases in **urea blood nitrogen (azotemia)** and **serum creatinine**. **Acute renal failure** results from injury or damage to any portion of the kidney, whereas **chronic renal failure** (CRF) is an end stage renal disease resulting from any major cause of renal dysfunction including diabetic nephropathy, polycystic kidney disease and prostatic hypertrophy. CRF can manifest with numerous signs and symptoms, including hypertension, muscular spasm and convulsion, peripheral neuropathies, poor appetite, nausea and vomiting, GI ulceration, malnutrition, and asthenia. Very frequently the skin has a yellowish brown cast and is pruritic, and the mouth has an ammonia-like taste because of excess urates in the saliva. In very rare cases the skin excretes excess urates in the sweat, forming a whitish crystalline excretion called a **uremic frost**. (Verrelli 2005; Berkow 1992)

Renal cell carcinoma

Renal cell carcinoma accounts for about 2% of adult cancers, and 90% of all renal cancers in adults. It is associated with smoking, obesity and the use of analgesic drugs. The signs and symptoms include hematuria, flank pain, and palpable mass. (Rubin and Farber 1990, 486)
Bibliography


LESSON EIGHT: Genitourinary and reproductive disease

I. Female reproductive tract

Vaginal inflammation

Vaginitis refers to a non-specific irritation and inflammation of the vagina with burning and irritation, sometimes with discharge, in which no specific pathogenic agent can be identified. The underlying mechanism is often a deficiency of the bacteria that act upon the vaginal secretions to make the vagina slightly acidic. The intensity of the vaginal secretions typically reach their height during ovulation, but gradually decrease during the luteal phase and during menopause. Thus, the susceptibility to vaginitis increases late in the luteal phase just before menstruation, and also during menopause when vaginal secretions naturally diminish. Other factors however can negatively affect the pH of the vagina, including antibiotics, diabetes, pregnancy, frequent douching, and a diet high in refined carbohydrates. Factors that promote the irritation of the vagina include sensitivities or allergies to sexual lubricants, topical contraceptives and scented hygiene products, as well as frequent or unlubricated sexual intercourse. Hygiene is an important issue, Synthetic fibers, tight clothing around vagina and sitting for long periods on vinyl seats (as in a long car trip) all can facilitate the growth of micro-organisms such as Candida, leading to yeast infections and vaginitis. Poor toilet habits (i.e. wiping back to front after a BM) can also lead to vaginal infection.

Sexually transmitted diseases (STDs)

All healthy women experience some kind of vaginal discharge, which ranges from simple, clear mucosal secretions, the egg-white cervical secretions that indicate fertility, to menstrual blood. Any change in the quality and quantity of the vaginal secretions may be indicative of pathological changes. Beyond that of abnormal menstruation, which will be covered later, these changes are usually indicative of some kind of inflammatory or infective process. A watery, bloody discharge however suggests malignancy, so care must be taken in the diagnosis.
The term commonly used to describe an abnormal discharge is **leucorrhea**, and could include a number of infectious causes including trichomoniasis, yeast infections, gardnerella, gonorrhea, or chlamydia.

**Trichomoniasis**

*Trichomoniasis* is caused by *Trichomonas vaginalis* is a protozoa found in roughly 65% of women, and is responsible for up to 30% of all cases of vaginitis. Characteristic symptoms include itching, burning and a thin pale yellow to greenish malodorous discharge. With acute inflammation there may be “strawberry” colored spots in the mucosa. Symptoms often appear after menses. As many women are asymptomatic carriers for this protozoa, the manifestation of symptoms are often related to other causes, such as a secondary vaginal infection, emotional stress, and lowered resistance and immunity. Sexual partners may also be affected and thus treatment should be to both the woman and her partner to avoid a cycle of reinfection. (Berkow 1992, 1786-88)

**Vaginal candidiasis**

*Vaginal candidiasis*, or a yeast infection, is an overgrowth of the fungus *Candida albicans*, a naturally occurring microbe in the vagina. The infection may be localized in the vagina, but is commonly a reflection of a systemic yeast infection. Both within the vagina and in the gut *Candida* is kept in check by the *Lactobacillus* bacteria, and in the vagina specifically by the relatively low pH. The symptoms of a yeast infection can range from mild chronic irritation to a thick white (cottage cheese) discharge with a strong smell, with intense itching, inflammation, and burning upon urination. Candidal infection is more common among women who have diabetes, who use IUDs, who have recently used an antibiotic (e.g. tetracycline for acne), who use corticosteroids regularly, or who are immunodeficient. (Berkow 1992, 1786-88)

**Gardnerella**

*Gardnerella* is caused by the *Gardnerella vaginalis* is a gram-negative bacterium and a frequent cause of vaginal infection. Although it is classified as a sexually transmitted disease, it is a normal constituent of the vaginal flora, and its manifestation is linked with recurrent vaginal irritation, alterations in vaginal pH, emotional stress, and lowered resistance and immunity. The primary symptom of gardnerella is a thin, greyish discharge with a ‘fishy’ odour. (Berkow 1992, 1786-88)
**Chlamydia**

*Chlamydia* is caused by the bacteria of the genus *Chlamydia*, a unique bacteria that acts like virus in that it invades a host cell in order to reproduce. *Chlamydia trachomatis* is found in humans, and lives in the conjunctiva of the eye, and in the urethra and cervix. In poor countries such as Nepal, chlamydia is the primary cause of blindness. Chlamydia is thought to affect up to half of all sexually active women, although as many as 60% of these women are not bothered by symptoms. As a result, chlamydia often goes untreated and can result in a low grade chronic inflammation that negatively affects fertility. When symptoms do manifest they may include a yellowish or greenish discharge from the cervix, bleeding of the cervix from a Pap smear, irregular vaginal bleeding, lower abdominal pain, and pain upon urination. It is difficult to diagnose chlamydia as it is hard to culture it from vaginal swabs and urine samples, and as a result there is probably a high false negative rate in diagnosis. Women who are at risk for chlamydia are under the age of 24, have multiple sexual partners, and are not using barrier methods of contraception (i.e. condoms). The use of oral contraceptives enhances the likelihood chlamydia infection, as do many surgical procedures that artificially dilate the uterus such as a fitting for an intrauterine devices (IUDs), abortion, dilatation and curettage (D&C), and fetal monitoring. (Berkow 1992, 1786-88)

**Genital herpes**

While herpes simplex virus (HSV) is not a cause of leucorrhea, it does promote genital ulcers. Any ulceration however should be carefully assessed, to rule out syphilis. Most HSV genital infections are due to HSV type 2, and infection typically occurs during intimate contact with someone shedding the virus. After an incubation period of 5 to 7 days small vesicles appear, releasing the virus over a 4-5 day period until the lesions completely crust over. During the initial infection, the virus ascends via the peripheral nerves into the sacral plexus, where it resides permanently, and thus serves as a reservoir for recurrent infection. The initial infection is usually associated with malaise, regional lymphadenopathy, and fever, which usually resolves in about one week. The herpetic lesions are very tender and heal over a 10-21 day period. Recurrent infections, which tend to be milder and localized, are typically preceded by a prodrome of numbness or tingling at the site. Reactivation of the virus during late term pregnancy can result infection of the infant during birth, which can be fatal. (Berkow 1992, 270; Rubin 2001, 508-9)

**Genital warts**

Genital warts are caused by the human papillomavirus (HPV), of which there are several types (1, 2, 6, 11, 16, 18), and is
typically transmitted through intimate contact with an infected individual. It is the most common viral STD, with a reported incidence of 6% in women aged 20 to 34 years. Pathologists have identified several different some of which are involved in cervical dysplasia and invasive cervical cancer. **Condyloma acuminatum** is a benign lesion of the external genitalia and rectum that can result from HPV infection, appearing first as a papule, plaque or nodule, eventually growing as a spiked or cauliflower-like growth. In many cases these patients will have other infections as well, suggesting the virus replicates and grows with lowered immunity. (Berkow 1992, 271; Rubin 2001, 508)

**Urethritis, cystitis and pyelonephritis**

The urinary tract is typically sterile and highly resistant to bacterial colonization through the secretion of protective antibodies and by mechanical washing during urination. Women of reproductive age have a much greater incidence of infection, up to 50 times greater than men of the same age, due to the proximity of the urethral opening to the vagina and the relatively short length of the urethra.

Gram-negative aerobic bacteria cause most bacterial UTIs, the vast majority occurring when colonizing bacteria ascend from the vagina into the urethra (causing **urethritis**) to the bladder (causing **cystitis**), and in some cases, up the ureter to the kidney causing **pyelonephritis**. *Escherichia coli* is the most common bacterium isolated, accounting for upwards of 80% of infections, *Staphylococcus saprophyticus* accounting for about 10%, the remaining organisms typically **Klebsiella** or **Proteus**. In most cases the urine will be acidic, having a pH less than 7. In some cases, such as in **Klebsiella** or **Proteus** the urine pH will be elevated. (Berkow 1992, 1714)

Bacteruria is more frequent among sexually active women, especially with the concurrent use of spermicides that induce changes in the vaginal flora, promoting an overgrowth of *E. coli*. Although the relationship between frequent bacterial infection and diet isn’t entirely clear, many women who consume a diet rich in carbohydrates are particularly prone to recurrent cystitis, suggesting a complex disruption of the vaginal flora, beginning with the overgrowth of **Candida** followed by secondary bacterial infection. Pregnant women are frequently affected by cystitis due to a functional and anatomic obstruction of ureters and bladder, which leads to urinary stasis and an increase in the risk of infection.
The onset of cystitis is typically sudden, with frequency, urgency, and burning pain upon urination, with small volumes of urine voided. Nocturia, with suprapubic and low back pain is common. The urine is often turbid, and bleeding occurs in about 30% of patients. (Berkow 1992, 1714; Rubin 2001, 488-89).

**Cervicitis**

**Cervicitis** refers to inflammation of the cervix, usually resulting from infection, particularly those organisms that colonize the vaginal mucosa, including *Streptococcus*, *Staphylococcus* and *Enterococcus*. In acute cervicitis the cervix is red and swollen, with a mucopurulent fluid exuding from the external os. In **chronic cervicitis** the mucosa is similarly inflamed, sometimes with epithelial erosions. (Rubin 2001, 513)

An **endocervical polyp** is the most common kind of cervical growth, and is non-cancerous. It often appears as a single mass typically less than 3 cm at its greatest dimension. It occurs in less than 5% of women, presenting with vaginal bleeding or discharge. (Rubin 2001, 513)

**Cervical cancer** is the third most common malignancy in women, occurring usually by the age of 50, but may occur in young women as early as 20 years. Cervical cancer is considered to be a sexually transmitted disease, with the risk inversely related to age at first intercourse, and directly related to the lifetime number of sexual partners. Interestingly, risk is also increased for sexual partners of men whose previous partners had cervical cancer. **Human papillomavirus (HPV) infection** and the development of cervical neoplasia are strongly associated, as is cervical neoplasia and cigarette smoking. (Rubin 2001, 513-16)

The precursor cells of cervical cancer develop over a number of years, called **cervical dysplasia (CIN)**. The grading of cervical dysplasia is classified as mild, moderate, and severe, corresponding to **CIN grades I, II, and III**. These changes are often detected by a **Papanicolaou smear (Pap smear)**, although very recently researchers have discovered that common household vinegar, which when used to wash the cervix, turns any potential dysplastic lesions white. Both this method as well as the Pap smear have a fairly high rate of false positives however, and as a result a biopsy is usually performed to ensure the diagnosis of cervical dysplasia. (Rubin 2001, 513-16)
Squamous cell carcinoma accounts for 80 to 85% of all cervical cancers with adenocarcinomas accounting for most of the rest. Sarcomas and small cell neuroendocrine tumors are rare. Invasive cervical cancer usually spreads by direct extension into surrounding tissues and the vagina or via the lymphatics to the pelvic. (Rubin 2001, 513-16)

Cervical dysplasia is usually asymptomatic and discovered because of an abnormal Pap smear. Patients with early-stage cervical cancer usually present with irregular vaginal bleeding, which is usually experienced after sexual intercourse, but metrorrhagia (intramenstrual bleeding) may occur. Patients with larger cervical cancers or advanced-stage disease may present with foul-smelling vaginal discharge, abnormal vaginal bleeding, or pelvic pain. Obstructive uropathy, back pain, and leg swelling are manifestations of late-stage disease. (Rubin 2001, 513-16; Berkow 1992, 1824)

Uterus

Menorrhagia

Menorrhagia refers to excessive menstrual bleeding, and can be of two types: functional, which is heavy bleeding during an otherwise normal menstrual cycle; and secondary, with heavy bleeding during menstruation, usually the result of uterine fibroids. Any kind of irregular bleeding however should be investigated by analyzing the case history, and performing pulse, tongue, and iris examination. If no cause is ascertained a laparoscopy, D&C (dilatation and curettage), or hysteroscopy may be required to determine the nature of the bleeding. Functional menorrhagia is in some way related to a prostaglandin imbalance, usually PGI₂, leading to reduced clotting and dilated blood vessels during menstruation. It is often related to a relative estrogen excess and/or a diet high in saturated fat (which facilitates the growth of bacteria in the lumen of the intestine that deconjugates conjugated estrogens in the bile). The diagnosis of functional menorrhagia requires that hormonal causes are weeded out, best assessed by using a symptothermal chart to assess for ovulation, or any other method, such salivary testing. If hormonal causes can be ruled out, then several other possibilities exist, including poor uterine tone, a prostaglandin imbalance, nutritional deficiencies, weakness and a lack of vitality, or liver congestion. (Trickey 1998, 174-79; Berkow 1805-06)
Metrorrhagia
Metrorrhagia or dysfunctional uterine bleeding (DUB), can be the result of several causes. Endometrial hyperplasia is a possible cause, the result of excessive estrogen and deficient progesterone secretion, resulting in an excessive stimulation of endometrial cells. Uterine cancer is a more common cause of DUB in postmenopausal women over 40. The aggravation of cervical or endometrial polyps after sexual intercourse or medical examination is another cause of DUB. Cervical dysplasia may also be the cause of metrorrhagia, and is a precancerous change in the cervical tissue, with bleeding indicative of a progression of dysplastic changes. Cervicitis is another possible cause of DUB, and is often secondary to chronic pelvic inflammation. Sometimes the bleeding is the result of cervical abnormalities such as cervical eversion, which can be congenital or the result of chronic infections. Other possible causes include ovarian cysts, oral contraceptive use, and excessive exercise. (Trickey 1998, 192-97; Berkow 1807-08)

Amenorrhea
Amenorrhea refers to the absence of menstruation and is of two types: primary amenorrhea, in which menstruation has not begun by late puberty, even if other signs of physical maturation are present; and secondary amenorrhea, which is the cessation of menstruation for more than 3 cycles in a post-pubescent woman. There are many possible causes of amenorrhea, including:

• intrauterine adhesions
• cervical stenosis
• obstruction of menstrual flow
• hypothalamic dysfunction
• GnRH inhibition
• weight loss
• rigorous exercise
• severe chronic illness
• drugs such as the phenothiazines (antiemetics), antihypertensives and antipsychotics
• after using oral contraceptives
• polycystic ovarian disease
• breast feeding
• hypothyroid conditions (leads to decreased SHBG and thus increased estrogen)
• hyperthyroid (conversion of androgens to estrogens)
• excessive glucocorticoids (e.g. Cushing's syndrome)
• premature ovarian failure (perhaps an autoimmune disease?)
• ovarian damage or destruction (from ischemia) (Trickey 1998, 209-212; Berkow 1992, 1798, 1802)
The most common causes of amenorrhea are hyperprolactinemia, and a relative androgen excess. **Hyperprolactinemia** is a condition in which there are increased levels of prolactin in the bloodstream. The signs and symptoms include galactorrhea (breast milk production), menstrual irregularities, decreased GnRH and LH levels, elevated androgens (with decreased 5-alpha-reductase activity), decreased SHBG, and decreased bone density. Possible causes of hyperprolactinemia include pituitary tumors, hypothyroidism, prolonged stress, excessive breast stimulation (Chinese "Deer" exercises), excessive exercise, drugs (phenothiazines, dopamine antagonists, antihypertensives, antiulcer drugs, estrogen oral contraceptives, opiates, cocaine) and alcohol (especially beer because of the Hops, which is a galactagogue). (Trickey 1998, 213-216)

**Androgen excess** is another possible cause of amenorrhea, and describes a condition in which there are higher than normal levels of circulating androgens. Possible causes include PCOD (polycystic ovarian disease), an androgen-secreting adenocarcinoma of the adrenal gland, adrenal hyperplasia, steroidal drugs (synthetic progesterone, cortisone), post-menopause, and obesity. The signs and symptoms of androgenization include hirsutism, alopecia, acne, and elevated blood pressure. Other, more rare symptoms include the deepening of the voice, clitoral enlargement, and decreased breast size. Laboratory evidence will typically show elevated serum testosterone and DHEA. Some cases of androgenization are the result of an increased sensitivity to androgens rather than an androgen excess, and thus will not show up with lab tests. (Trickey 1998, 217-219; Berkow 1992, 1800)

**Dysmenorrhea**

Dysmenorrhea refers to the uncoordinated contractions of the uterus just before and during menstruation, resulting in a decreased volume of blood flow through the uterus and the resultant pain and cramping. Typically the pain experienced is dull, with a sense of pelvic heaviness or congestion. There may also be symptoms of fatigue, bowel irregularity, shivering, sweating, leg pain, nausea and vomiting, faintness, and mood swings. **Primary dysmenorrhea** is common in young women and rare after childbirth, whereas the usual onset of **secondary dysmenorrhea** is in the 30's, or after childbirth. The most common cause for primary dysmenorrhea is an eicosanoid imbalance, with excessively high levels of PGE₂ and PGF₂, and in severe cases, high levels of the leukotrienes LTC₄ and LTD₄. The usage of oral contraceptives seems to reduce the symptoms, which suggests a relative estrogen excess and a progesterone deficiency. Secondary dysmenorrhea is
most often associated with other gynecological conditions such as uterine inflammation, fibroids, endometriosis, pelvic inflammatory disease (PID), and occurs with premenstrual syndrome (PMS). In secondary dysmenorrhea, the underlying cause for the pain, such as fibroids or PID must be resolved. (Trickey 1998, 223-26; Berkow 1992, 1792-93)

**Premenstrual syndrome**

Premenstrual syndrome (PMS) refers to the different kinds of symptoms experienced by some women during the luteal and menstrual phase of the estrus cycle. It affects upwards of 75% of all women of menstruating age in varying degrees. The most common physical symptoms of PMS are abdominal distension, breast swelling and tenderness, headaches, changes in appetite, food cravings, fatigue, dizziness, weight gain, fluid retention, joint pain, pelvic congestion, poor immunity, constipation or diarrhea, herpes outbreak, and acne. Psychological symptoms might include insomnia, poor memory, grief, irritability, anger, anxiety, poor concentration, and confusion. Such symptoms, when recognized by the physicians of the middle ages, gave rise to all kinds of interesting ideas, such as the concept of a "wondering womb" that searched the body looking for a baby, and in its journey caused the myriad symptoms that we now define as PMS. The modern medical approach to this condition is little better however, and the prevailing notion is that PMS is nothing but a kind of female nervous tension best treated by sedation. (Trickey 1998 35-37; Berkow 1992, 1791)

Although the causes of PMS are varied, in her book *Women, Hormones and the Menstrual Cycle*, author Ruth Trickey illustrates some common themes, all of which are related to neuroendocrine control:

- **Estrogen**- Elevated levels of estrogen relative to progesterone 5 – 10 days prior menses is thought to cause feelings of irritability and aggression by elevating norepinepherine in the brain.
- **Progesterone**- A relative deficiency of progesterone 5 – 10 days prior menstruation allows for the elevation of aldosterone, enhancing sodium retention and the resulting edema. The progesterogenic effects of the luteal phase are also inhibited by elevated norepinepherine from emotional stress and elevated estrogen.
- **Aldosterone**- Aldosterone is a cause of premenstrual fluid retention, and is enhanced with stress, low progesterone, high estrogen, and a deficiency of magnesium.
- **Prolactin**- Women with PMS are thought to have an excessive sensitivity to, or mildly elevated levels of, prolactin. Prolactin is
normally secreted in high levels during lactation, and prolactin is implicated in the increased breast sensitivity and swelling of some forms of PMS.

• **Endorphins** - Endorphins are natural opiates that elevate mood, and when decreased, can give rise to symptoms of depression. Additionally, endorphins appear to regulate the secretion of the gonadotropins.

• **Dopamine** - Dopamine in a prolactin antagonist, and is decreased under the influence of estrogen and a deficiency of magnesium and vitamin B₆. Dopamine also appears to regulate mood, and a deficiency is implicated in anxiety, irritability, and emotional lability. (Trickey 1998, 109-118)

Other factors in PMS include a prostaglandin imbalance and the overgrowth of *Candida albicans*, the latter of which is linked to a relative estrogen excess. A deficiency of vitamin B₆ is often implicated in PMS, and treatment with this nutrient may provide relief from depression and anxiety. The breast swelling and tenderness associated with elevated prolactin levels may be relieved by supplementation of vitamin B₆ through the enhanced synthesis of dopamine. Vitamin B₆ is also a cofactor in the production of the series 1 prostaglandins and can normalize cellular magnesium levels. Magnesium too is a factor in dopamine synthesis, and a deficiency can lead to depression, anxiety, and cyclic breast pain. (Trickey 1998, 109-118)

There are five different subcategories of PMS, first devised by G.E. Abraham, and each of these subtypes have a unique set of symptoms and metabolic abnormalities associated with them. The following chart describes these subtypes and the mechanisms that could cause them. It is important to note that a woman with PMS may experience more than one subtype.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Symptoms</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMS A</td>
<td>Anxiety Nervousness Mood Swings Nervous tension</td>
<td>Estrogen excess Progesterone deficiency Liver congestion</td>
</tr>
<tr>
<td>PMS C</td>
<td>Craving for sweets Increased appetite Palpitations Fatigue Dizziness Headaches</td>
<td>Hypoglycemia Magnesium deficiency Prostaglandin imbalance Often occurs in association with PMS A</td>
</tr>
<tr>
<td>PMS H</td>
<td>Breast tenderness Bloating Weight gain Edema</td>
<td>Elevated aldosterone Estrogen excess Progesterone deficiency Elevated prolactin</td>
</tr>
<tr>
<td>PMS D</td>
<td>Depression Poor memory</td>
<td>Estrogen deficiency</td>
</tr>
</tbody>
</table>

©2003 by Todd Caldecott and the Wild Rose College of Natural Healing
Grief
Confusion
Insomnia

PMS P
P= pain

Lower back pain
Abdominal pain
Joint pain
Headaches

Estrogen excess
Prostaglandin imbalance

(Trickey 1998, 118-121)

**Uterine fibroids**

**Uterine fibroids** (syn. **Leiomyomas**) are non-cancerous tumors of the uterus, affecting 20 –25% of the female population over the age of 35. Fibroids can vary in size, shape, position and number, some causing symptoms of pressure and uterine enlargement, while others are small and discrete. They are composed of dense muscular fibers arranged in circular layers, and encapsulated in a layer of smooth muscle. Fibroids may be located within the uterus (intrauterine), in the wall of the uterus (myometrial), or outside of the uterus (extrauterine). Intrauterine fibroids can inhibit fertility by interfering with implantation. Myometrial fibroids can place pressure on adjacent organs, and in some cases, can affect renal function by placing pressure upon the ureters. Extrauterine fibroids are located under the serous membrane of the uterus, and can be on or near the fallopian tubes and can inhibit fertility. (Trickey 1998, 184-87; Berkow 1992, 1807)

Fibroids are of two basic types. They can be discrete, fibrous, encapsulated and roughly spherical in shape, or can be large pendunculated fibroids. The former are usually of little concern, and although they should be monitored, do not present any problems. Preventative measures, such as the use of phytoestrogens should be encouraged however. Large pendunculated fibroids are of concern due to the likelihood of torsion. Such an event is very painful and may require immediate surgery. Such fibroids are also associated with an increased risk of sarcoma. Although the specific causes of fibroids remain elusive, it is known that they are dependent upon estrogen for their growth. They are rare before menarche (the first period) and typically resolve with menopause. Fibroids have also been found to contain higher amounts of DDT than other uterine tissues, which as a xenoestrogen could promote their growth. Some herbalists have speculated that fibroids act as a kind of “second liver” within the uterus, walling off toxic compounds from the rest of the uterus. (Trickey 1998, 184-87; Berkow 1992, 1807)

The most prominent symptoms of uterine fibroids are menorrhagia, sensation of abdominal pressure and pelvic congestion, urinary frequency, abdominal enlargement, lower back pain, and
dysmenorrhea. The primary risk factors for fibroids include the regular consumption of coffee and obesity, with a slight risk associated with oral contraceptive use. The risk of fibroids declines with repeated pregnancies, and the incidence is lower in smokers. (Trickey 1998, 184-187; Berkow 1992, 1807; Rubin 2001, 523)

Pelvic inflammatory disease
Pelvic Inflammatory disease (PID) or salpingitis are general terms for the inflammation of the pelvic organs, and is given different names according to the location of inflammation, such as endometritis (endometrium), oophoritis (ovaries), and peritonitis (peritoneum). The primary cause of PID is bacterial infiltration from the vagina, more common after childbirth, miscarriage, abortion, IUD insertion, and D&C. The most common pathogenic factors include Chlamydia and Trichomonas, but Neisseria gonorrhoea (i.e. gonorrhea) and Ureaplasma urealyticum (mycoplasma) can also promote PID. The signs and symptoms of PID include a dull ache or acute pain in the lumbar region, pain after intercourse, cramping, fever, abnormal vaginal discharge, dysuria, pain upon defecation, inguinal lymphadenopathy, nausea and vomiting, metrorrhagia and/or menorrhagia, and pain upon ovulation (mittleschmerz). Not all of these symptoms may be present and what symptoms there are may come and go over a period of years in a cycle of exacerbation and remission. Abscesses may develop in the fallopian tubes, ovaries and pelvis during the inflammatory stage. (Trickey 1998; Berkow 1992, 1789-90; Rubin 2001, 524)

Endometriosis
Endometriosis refers to the growth of endometrial tissue outside of the uterine cavity or into the uterine wall. The cyclic variations of the estrus cycle cause this misplaced endometrial tissue to undergo both proliferative and secretory stages, but without elimination during menstruation. The cyclical hemorrhaging of extrauterine (ectopic) endometrial tissue can give rise to a variety of symptoms, and with repeated hemorrhaging the implanted endometrial tissue begins to enlarge. Endometriosis is a disease of women of reproductive age and regresses with artificially induced or natural menopause. It is believed to affect upwards of 10% of women, and is slightly more common in women in their late 20's to mid 30's. It has been estimated that 25-50% of infertile women have endometriosis. The sites most commonly affected, in order of decreasing frequency, are the ovaries, fallopian tubes, uterus, pouch of Douglas, uterosacral ligaments, urinary bladder, ureters, vagina, lower gastrointestinal tract, and rarely, in distant areas such as the lungs, pleura, and extremities. (Trickey 1998, 239-249; Berkow 1992, 1809-12; Rubin 2001, 518-19)
Although the etiology is unclear, there are four possible causes of endometriosis:

• the retrograde flow of menstrual fluid into pelvic cavity
• relative estrogen excess, increasing number of cells and sites receptive to estrogen
• immunological and inflammatory factors
• fetal developmental of ectopic endometrial tissue

The first possible cause of endometriosis is the retrograde flow of menstrual fluid into pelvic cavity, in which foci of the menstrual tissues regurgitate into the fallopian tubes and become implanted upon the various pelvic organs. Factors that can enhance the retrograde flow of menstrual fluid include cervical stenosis, uterine or cervical adhesions, imperforate hymen, exercise during menstruation, and excessive uterine spasm and fallopian dilation during menstruation, mediated by excessive PGE₂. (Trickey 1998, 239-249; Berkow 1992, 1809-12; Rubin 2001, 518-19)

The second and third causes are somewhat related, with elevated levels of estrogen having a negative effect upon immune activity that might otherwise 'clean up' the regurgitated tissues. Further, women exposed to high levels of estrogen are more likely to develop endometriosis. Women now menstruate far more often then our forebears, and complexed with influence of xenoestrogens and oral contraceptives, women are generally overexposed to estrogen. The immune response too can have a negative impact upon the situation, and an enhanced localized immune response promotes inflammation, and can result in macrophage-induced infertility during the initial stages of endometriosis. Note as well that high levels of circulating estrogen facilitates the production of the antiinflammatory prostaglandins. With the progression of the disease the immune response declines, but the scarring from inflammation remains and inhibits fertility. (Trickey 1998, 239-249; Berkow 1992, 1809-12; Rubin 2001, 518-19)

The fourth possible cause of endometriosis is linked fetal development. All reproductive tissues develop from the same embryonic tissue. During embryonic development the tissues may fail to differentiate properly, giving rise to an ectopic endometrium. The risk factors for endometriosis are numerous, including lifestyle, familial and dietary aspects. As mentioned already, women who menstruate early, and/or who never have children or lactate, have a higher incidence of endometriosis due to
the negative effects of excessive estrogen. (Trickey 1998, 239-249; Berkow 1992, 1809-12; Rubin 2001, 518-19)

Sexual intercourse during menstruation is also thought to increase the retrograde flow of endometrial fluid, and many cultures for this and other reasons prohibit sexual intercourse during menses. There also appears to be familial link, and immediate family members of a woman who has endometriosis are seven times more likely to develop it. Additionally, daughters of mothers with endometriosis have an increased risk of endometriosis. The use of an intrauterine device (IUD) is associated with an increased risk of endometriosis, possibly because the device enhances retrograde flow, as do tampons. Women taking oral contraceptives appear to have a negligible risk for endometriosis, but former OC users are at a higher risk of developing endometriosis than women who have never taken the Pill. Other risk factors include the regular use of caffeine and alcohol in the diet. Factors that appear to decrease the risk of endometriosis include pregnancy and lactation, with the risk of endometriosis decreasing with each successive pregnancy. Exercise too appears to have a beneficial effect because it can reduce estrogen production, but strenuous exercise, and in particular aerobic exercise, is thought to enhance retrograde flow. (Trickey 1998, 239-249; Berkow 1992, 1809-12; Rubin 2001, 518-19)

There are two primary forms of endometriosis, adenomyosis, and extraterine or ectopic endometriosis. **Adenomyosis** is the growth of endometrial tissue into the muscular wall of the uterus. It is more likely to occur in women over the age of 35 and in women who have carried more than one full term pregnancy. In 50% of cases it is associated with fibroids. When the uterus is palpated it feels hard, large and may have an irregular shape. The symptoms of adenomyosis include severe dysmenorrhea (related to implants of ectopic endometrium on the uterosacral ligaments that swell just before menstruation), infertility, menorrhagia, increased frequency of menstruation, and uterine enlargement. **Extra-uterine or ectopic endometriosis** is the growth of endometrial tissue outside of uterine cavity. If implanted upon the ovaries it can lead to the development of ovarian cysts, which occurs in about 60% of all cases. The formation of the cyst is due to the ovary trying to contain endometrial growth by encapsulating it. These endometrial cysts are called endometriomas, and are filled with clotted dark brown blood that gives rise to their more common name of chocolate cysts. The size of an endometrioma varies from a small cyst that has a tendency to rupture at each period, to large cysts which do not rupture, but only get larger, upwards of 20 cm in
diameter. When large cyst rupture there is acute abdominal pain and shock, and require immediate surgery. Small rupturing cysts cause on the other hand cause chronic irritation, inflammation, and pain within the pelvic cavity. Other sites of implanted endometrial tissue often include the fallopian tubes, pouch of Douglas, the uterosacral ligaments, and other pelvic organs such as the bowel, urinary bladder, ureters, and urethra. The implanted tissue forms raspberry-like clusters of endometrial tissue that are in various stages of development. Typically the implanted endometrial tissue may bleed for a few months, and then be replaced by fibrous tissue called adhesions. Endometriomas that occur peripherally may manifest as bluish swellings under the skin that because increasingly painful and may even bleed as menstruation approaches. The symptoms of extrauterine endometriosis includes severe dysmenorrhea, infertility, pain with sexual activity, increasing pain as luteal phase progresses, pain at ovulation, one sided pelvic pain, pelvic heaviness, and irritable bowel syndrome. (Trickey 1998, 239-249; Berkow 1992, 1809-12; Rubin 2001, 518-19)

**Endometrial cancer**

In North America *endometrial cancer* is the most common gynecologic malignancy and the fourth most common malignancy in women after breast, colorectal, and lung cancer. It is far more common in industrialized countries in which dietary fat intake is high and fiber intake is low. The most significant risk factor is obesity, which increases risk by 3 to 10 times. Endometrial cancer is more common in women with conditions that tend to result in unopposed estrogen (high circulating levels of estrogen with no or low levels of progesterone), such as unopposed estrogen replacement therapy, obesity, PCOD, nulliparity (never carried a child), late menopause, estrogen-producing tumors, anovulation, or oligo-ovulation. Women with a history of pelvic radiation therapy or with a personal or family history of breast or ovarian cancer are at increased risk. (Rubin 2001, 519-22; Berkow 1992, 1822-23)

Endometrial cancer can spread to other tissues of the body, either directly, into the cervix or peritoneum, from the fallopian tube to the ovaries, or indirectly, via the bloodstream or lymphatics (Berkow 1992, 1822).

Adenocarcinoma accounts for more than 60% of cases of endometrial cancer, with sarcomas accounting for only about 5% of all uterine malignancies. Sarcomas tend to be more aggressive, are more likely to produce local, regional, and distant metastases, and have a worse prognosis. More than 90% of patients with endometrial cancer have abnormal uterine bleeding, and about one-
third of women with postmenopausal bleeding have endometrial carcinoma. In postmenopausal women, a vaginal discharge may precede bleeding by several weeks or months. (Rubin 2001, 525-34; Berkow 1992, 1822-24; Winter 2005)

The initial diagnosis is based on clinical signs and symptoms. A Pap smear does not accurately detect endometrial malignancies and thus tissue biopsy is usually required, followed by ultrasound, serum chemistry studies, liver function tests, chest x-ray, and pelvic and abdominal CT. The prognosis is influenced by the tumor's histologic appearance and grading, the patient's age (older women have a poorer prognosis), and metastatic spread. Overall, 63% of patients are cancer-free 5 years after treatment. (Rubin 2001, 525-34; Berkow 1992, 1822-24; Winter 2005)

Ovaries

Ovarian cysts refer to the development of cysts within ovarian tissue, and can range from being otherwise benign to cancerous. Up to 20% of all women have some degree of cyst formation in their ovaries at some point, although the vast majority are symptom-free. Ovarian cysts are often discovered by routine examination, or from the investigation of abdominal pain, discomfort, or pain upon intercourse. An ultrasound will indicate the presence of an ovarian cyst, but without performing a biopsy it is difficult to identify the kind of cyst. The most common form of ovarian cysts are physiological cysts, as well as those associated with polycystic ovarian disease (PCOD). Other less common types of ovarian cysts include the cystadenomas, fibromas, dermoid cysts, and Brenner cysts. Most cysts are symptom-free unless they rupture or twist upon their stalk (pedicle). Some cysts are malignant, and others, called functioning cysts, have the ability to produce hormones. (Berkow 1991, 1784; Trickey 1998, 258-269; Rubin 2001; 524-25)

Physiological cysts are simple cysts that do not produce hormones, and represent a deviation in the normal functioning of the ovary. Follicular cysts are formed due to a problem with the developing follicle in which the mature follicle either fails to release the ovum and continues to enlarge, or one of the developing follicles fails to disintegrate. The symptoms are minimal and require little in the way of treatment. Luteal cysts form during the luteal phase of the estrus cycle after the corpus luteum has formed. Typically the cysts are small and require no treatment, but sometimes the cysts will
become quite large and be filled with blood. Luteal cysts may interfere with the normal cycle, delaying menstruation and can cause an alteration in blood loss during the period. Luteal cysts typically resolve after one cycle and require little in the way of treatment. (Trickey 1998, 258-269; Rubin 2001, 524-25)

**Polycystic ovarian disease (PCOD)**
The term 'polycystic' refers to the formation of many cysts within the ovaries. **Polycystic ovarian disease (PCOD)** represents a dysfunction of the endocrinial activities of the ovaries, with erratic ovulation and menstrual dysfunction in association with a tendency to excessive androgen secretion. The signs and symptoms of PCOD are ovulatory failure, infertility, hirsutism, obesity, and abnormal menstruation. A smaller percentage of women with PCOD may also experience male pattern hair growth, a deepening of the voice, and a loss of feminine contour. Diagnostically, an ultrasound is used to detect ovarian cysts, and blood tests will reveal high levels of LH with relatively constant or low FSH. The differential diagnosis includes Cushing's syndrome, adrenal hyperplasia, adrenal adenocarcinoma, hyperprolactinemia, and thyroid dysfunction. (Trickey 1998, 264-269; Rubin 2001, 524-25)

The causes of PCOD relate to the abnormal function of the ovaries, with the excessive production of androgens within the developing follicle. Obesity is recognized as an underlying factor, and about 40% of women with PCOD are obese. With obesity there is the increased conversion of ovarian androgens into estrone by the fatty tissues of the body by the enzyme aromatase, leading to chronically high estrogen levels. Obese women, and in particular those women with truncal or abdominal obesity, display a greater proclivity to insulin resistance, leading to elevated blood sugar levels, hyperinsulinemia, and a greater risk of cardiovascular disease and diabetes. Women with PCOD may also display abnormal adrenal function, with an excessive production of androgens that results in their conversion to estrone. High levels of estrone without the normal cyclic variation then stimulates excess LH production. This secretion of LH then adds fuel to the fire by triggering ovarian androgen production. Further, the levels of FSH, due to the high levels of circulating estrogens, remain suppressed. Low FSH reduces the ability of cells in the ovarian follicle to convert androgen into estrogen. Although elevated levels of LH are generally accepted as being caused by an androgen excess, some researchers have suggested that the cause may be abnormal hypothalamic function with the improper secretion of GnRH. This could lead to elevated LH levels, resulting in elevated androgens, which in turn, initiates LH secretion in a self-perpetuating cycle. Playing into this whole cycle of low ovarian estrogen, high
peripheral estrogen, and excess androgen, is SHBG (sex hormone binding globulin). Normally, SHBG binds to both estrogens and androgens to reduce the bioactivity of these hormones. With obesity and elevated androgens however, the level of SHBG declines, and the masculinization effects of the excess androgens begins to be seen. (Trickey 1998, 264-269; Rubin 2001, 524-25; Berkow 1992)

**Ovarian cancer**

Ovarian cancer is the second most commonly diagnosed gynecologic malignancy and the fourth leading cause of cancer-related deaths in women in the USA. There are three primary types of ovarian tumors, including those of epithelial, germ cell, stromal origin. The vast majority (90%) of tumors are of epithelial origin, with most being serous, followed by mucinous, endometroid, clear cell and transitional cell tumors. (Rubin 2001, 525-34; Berkow 1992, 1827-28)

Ovarian cancer affects primarily perimenopausal and postmenopausal women, with a significantly higher incidence in industrialized countries, which researchers correlate with the increased consumption dietary fat coupled with low fiber intake. Other risk factors include nullparity, infertility, and delayed menopause. Ovarian cancer can spreads by direct extension, by intraperitoneal implantation, by lymphatic dissemination in the pelvis and aortic region, and, less commonly, via the blood to the liver or lungs. (Rubin 2001, 525-34; Berkow 1992, 1827-28; Trickey 1998, 260)

Up to three-quarters of women with ovarian cancer present with the advanced-stage disease, and have vague, nonspecific symptoms, such as dyspepsia, bloating, anorexia, gas pains, and backache. Ovarian tumors are commonly found as an abdominal mass, discovered as part of a routine pelvic examination. Some patients however will present with severe abdominal pain, secondary to torsion of the ovarian tumor. Late in the course of the disease other symptoms such as pelvic pain, anemia, cachexia, and abdominal swelling from the tumor mass or ascites often occurs. (Rubin 2001, 525-34; Berkow 1992, 1827-28; Trickey 1998, 260)

**Breast diseases**

**Fibrocystic breast disease (FBD)**

Fibrocystic breast disease (FBD) is a common benign condition of premenopausal women that may or may not occur with the
variance in hormonal levels experienced during the estrus cycle. Although many women display areas of relatively indistinct breast lumpiness, FBD refers to small benign tumors that are well-circumscribed and feel a like slippery marble to the touch. The primary symptoms of FBD are irregularly lumpy and swollen breasts that feel heavy, aching and sore. In most cases the pain is worst just prior to menstruation and as such can be considered to be a form of PMS (see PMS A and PMS H). In other cases however, the pain is ongoing with no cyclical change. It is important to get an accurate diagnosis as some of the symptoms resemble that of breast cancer. The exact cause of FBD still eludes researchers but it appears that it is aggravated by a relative estrogen excess. During the follicular phase of the estrus cycle estrogen stimulates the production of lactiferous glands and the supporting stromal layers of the breast. After ovulation, when progesterone elevations are elevated, prolactin levels begin to increase to trigger glandular changes in the breast. If implantation does not occur however, the newly formed breast apparatus begins to break down. It is thought that in FBD however, that the growth and development of new tissues in the breast is faster than the process of degeneration and resorption. Small pockets of cellular debris and trapped secretions are formed, and these may coalesce to form fluid-filled cysts. Although the cysts can be surgically excised the frequently reappear, and thus little treatment is offered. Women who have FBD however, have 4 times the risk of developing breast cancer, and thus some form of preventative treatment is appropriate. Further, women with low thyroid function have a greater incidence of FBD as well as breast cancer. (Trickey 1998, 123-26; Berkow 1992, 1814-15; Rubin 2001, 540-42)

Breast cancer

Breast cancer (carcinoma of the breast) is one of the most common cancers in North America, and in the most recent Canadian statistics (2003), actually accounts for slightly more cases of cancer (21,200) than lung cancer (21,100) (NCIC 2003, 19). In North America, women have about a 13% chance of developing breast cancer in their lifetime (Boik 1996, 2). Within Canada, it is estimated that 22% of breast cancer cases occur in women under age 50, 48% occur in women aged 50 to 69, and 31% in women aged 70 and over. In Canada, breast cancer is the third leading cause of cancer-related deaths (NCIC 2003, 19).

The risk factors for developing breast cancer include a family history, in which first-degree familial prevalence (parent, sibling, child) doubles to triples a woman's risk. When two or more first-degree relatives have had breast cancer the risk may be 5 to 6 times higher. Breast cancer rates in developing countries are only about
one-fifth to one-sixth as high as in the West, suggesting a number of unique risk factors at play that are reflective of a number of social and environmental factors. These include nullparity, an early menarche, late menopause, a late first pregnancy, a history of FBD, obesity, a diet high in fat and low in fiber, the regular use of alcohol and cigarettes, and the use of hormone replacement therapy. Other factors include the long term use of oral contraceptives, previous radiotherapy, and trauma to the breast (e.g. lacerations sustained from a seat belt during an MVA). The most current recommendations suggest that routine screening should only involve the age groups at highest risk of developing breast cancer, between the ages of 50 and 70 years. (Rubin 2001, 524; Berkow 1992, 1815-17; Rigby et al 2002; Rossouw et al 2002)

About 5% of women with breast cancer carry one of the two breast cancer genes, BRCA1 or BRCA2. Women who do not have a family history of breast cancer in at least two first-degree relatives are not thought to carry this gene. The BRCA1 gene is located on the 17th chromosome, and has been linked as a hereditary factor in both breast and ovarian cancers, with women who have this mutated gene have up to an 85% risk of developing the disease. BRCA2 is located on chromosome 13, and mutations in it account for up to 70% of cases of inherited breast cancer. Another gene at play are mutations in the p53 gene, responsible for breast cancer in young women, conveying a risk of about 1% in women below the age of 40 (Rubin 2001, 542).

Breast cancer is classified according to the histology and location of the cancer. In situ carcinoma is contained entirely within the breast duct, with no invasion of adjacent normal tissues. Such cancers now account for more than 15% of all breast cancers diagnosed in North America. It is divided into three histological types: intraductal, lobular and papillary, with each form having the capacity to become invasive. Both intraductal and lobular carcinoma arises from the terminal duct lobular unit, but in the case of lobular carcinoma in situ, the cancer cells are smaller, causing less distension, and do not undergo central necrosis as in the intraductal forms. As its name suggests, papillary carcinoma forms papillary structures, with small fenestrations rather than a solid tumor. (Rubin 2001, 544)

Among the invasive carcinomas ductal carcinoma in situ (DCIS) accounts for 43% of breast cancers diagnosed in women aged 40 to 49, and 92% of cases diagnosed in women aged 30 to 39. It is characterized by the stromal invasion of the breast by malignant
cells that arise from the terminal duct of the lobular unit, usually with a pronounced fibroblastic proliferation. This creates a hard, palpable mass called a scirrhous carcinoma. Lobular carcinoma in situ (LCIS), or lobular neoplasia, occurs predominantly in premenopausal women and is usually found incidentally because it typically does not form a palpable mass, instead, forming single strands of malignant cells that infiltrate between the stromal fibers of the breast. Invasive ductal and lobular tumors are the most common histologic types of invasive cancer (about 90%). Other less common histologic types include medullary or tubular carcinoma. (Rubin 2001, 544-47; Berkow 1992, 1817-18)

Oncologists assess the status of hormone receptors and other tumor markers in breast cancer cells to guide treatment and determine the prognosis. Generally speaking, cancers in which the cells express the estrogen receptor (ER) in their nuclei will have a better prognosis, because the cells are generally better differentiated and they can respond to hormonal manipulation (e.g. tamoxifen). Some 35% of breast cancers in women of childbearing age are estrogen-dependent. Symptoms are often dramatically decreased by the removal of the ovaries, which is the major source of estrogen. The significance of the progesterone receptor (PR) in breast cancer is less well understood, and are generally found in association with ER positive cancers. Breast cancer cells that are PR positive but not ER positive however, may have a worse prognosis. Other markers that are used to identify breast cancer include HER-2 and cathepsin D. HER-2 is a gene that helps control how cellular growth, proliferation and repair. Cancers with too many copies of the HER-2 gene or too many HER-2 receptors tend to proliferate too quickly, and are associated with invasion and metastasis. Cathepsin D is an acidic lysosomal protease, synthesized under the influence of steroid hormones such as estrogen. Although its specific role is unclear, cathepsin D is associated with an increase in mortality with increased levels. (Rubin 2001, 544-47; Berkow 1992, 1817-18)

II. Male reproductive tract

Urethra and bladder

Urinary tract infection in men is less than 50 years of age are uncommon, most often due to urological abnormalities, or in men who engage in unprotected anal intercourse, who are uncircumcised (small increase in risk), in unprotected intercourse
with a woman whose vagina is colonized with uropathogens, and AIDS. Bacteriuria is more common in elderly men because of abnormal micturition and significant residual bladder urine. Chronic bacterial prostate infection is the most common cause of recurrent UTI in men due to reintroduction of infection into the bladder. The onset is of urethritis is gradual and the symptoms are mild, the patients typically presenting with a urethral discharge, which is purulent when due to *N. gonorrhoeae* and whitish mucoid when nonspecific. Symptoms of cystitis are suprapubic and lower back pain, with burning micturation. Enlarged lymph nodes in the groin typically indicate a genitourinary tract infection such as prostatitis or urethritis, most often caused by gram negative bacteria such as a *Escherichia coli* (accounting for 80% of all cases) and *Staphylococcus saprophyticus* (11%), as well *Klebsiella* and *Proteus*. (Berkow 1992, 1714-15; Rubin 2001, 489)

**Scrotum and groin**

**Inguinal and scrotal inflammation**

A lump or a swelling found in the groin or scrotum is a common clinical presentation in both boys and men. Most lumps are either hernias or enlarged inguinal nodes. **Inguinal herniations** are more common than femoral herniations by a ratio of 4:1. Within the scrotum, lumps could be a varicocele, a hydrocele of the tunica vaginalis, a hydrocele of the spermatic cord (spermatocele), a lipoma of the spermatic cord, a cyst of the epididymis, inflammation of the epididymis, or an enlargement of the testes (orchitis). It is necessary to get an accurate medical diagnosis however, to rule out the possibility of testicular cancer, or to determine the nature of a pathogenic agent. Inguinal and femoral hernias usually require corrective surgery. (Swash 1995, 100-101; Berkow 1992, 1745)

**Varicocele**

A varicocele is the tortuous dilation of the pampiniform venous complex of the spermatic cord, forming a soft, elastic swelling that can cause pain but are more often asymptomatic. Essentially, a varicocele is a varicosity of the spermatic vein, in which the blood flows backwards to engorge the vein. Varicoceles are more common in the left testicle because the left testicular vein connect to the renal vein at a right angle, whereas the right testicular vein drains directly into the vena cava. Varicoceles of the right testicular vein however, may indicate an obstruction of the vena cava. In regard to examination, a varicocele is apparent upon standing rather than lying down, and feels like a "bag of worms"
superior to the testicle. Varicoceles account for roughly 30 – 40% of cases of male infertility, and occurs in about 15 – 20% of the population. Although the cause of the infertility is unknown, it is thought that the increase in testicular temperature from the enhanced blood flow may inhibit spermatogenesis and sperm motility. Varicoceles and can be diagnosed with examination, ultrasound, or venography (x-ray of testicles). (Swash 1995, 100-101; Berkow 1992, 1745; Junnila and Lassen 1998)

**Hydrocele, Hematocele and Spermatocele**

A hydrocele is common intrinsic swelling of the scrotum resulting from an excessive accumulation of peritoneal fluid between the parietal and visceral layers of the tunica vaginalis. In infants, a hydrocele is the result of the persistence of the processus vaginalis, a diverticulum of the peritoneal membrane. This defect typically closes spontaneously within the first year of life and requires no specific therapy. In adults, a hydrocele may be due to a diminished resorptive capacity of the lymphatic and venous vessels, from inflammation due to trauma or infection, or from testicular torsion or neoplasm. A hematocele is a solid mass of the tunica vaginalis comprised of blood, and is usually secondary to trauma. A spermatocele is a cyst of the epididymus or areas adjacent to the epididymus that contains dead sperm. Hydroceles and spermatoceles are easily distinguished from other scrotal masses by tensing the scrotal skin gently over the swelling and shining a bright light behind it. Both of these masses will transmit light, whereas a hematocele will not. The difference between a hydrocele and a spermatocele is that in the former the testis is not palpable separately from the swelling. In contrast, a spermatocele lies adjacent to the epididymis, superior and posterior to the testes, suggesting a "third testis." In very large spermatoceles however, it may difficult to differentiate it from a hydrocele, in which case ultrasonography may help with the diagnosis. (Swash 1995, 100-101; Berkow 1992, 1745; Junnila and Lassen 1998)

**Epididymitis**

Epididymitis is an acute or chronic inflammation of the epididymis, a complication resulting from sexually transmitted diseases, ascending urinary tract infections, or prostatitis. It is the most common cause of scrotal swelling in postpubescent males. Pyuria, or leukocytes in the urine, is a laboratory feature of epididymitis, and the absence of pyuria makes the diagnosis of epididymitis unlikely. In males under the age of 35 the organism typically involved is *Chlamydia trachomatis*, but could be *Neisseria gonorrhoeae*. In prepubescent males and males over the age of 35, the most common cause of epididymitis is a bacterial
infection of the urinary tract. Gram's stain and culture should be obtained however, in order to rule out a sexually transmitted disease. If the test is positive for an STD, the patient's sexual partner(s) should be treated as well. It should be pointed out that epididymitis can be tubercular in origin. Symptoms include difficult urination, fever, chills, groin pain, and a tender, swollen epididymus that may difficult to distinguish from the testis. (Swash 1995, 100-101; Berkow 1992, 1745; Junnila and Lassen 1998)
Testes

**Orchitis**

Orchitis is an acute inflammation of one or both testicles, presenting as a sudden onset of testicular pain, high fever, abdominal pain, and nausea and vomiting. The testis is enlarged (about 2 – 3 times larger), swollen, and tender upon palpation. The causes of acute orchitis must be clearly established before treatment, as both testicular trauma and torsion require immediate surgery to prevent permanent damage to the testis. Without such an indication, orchitis may be a complication of a urinary tract infection, a sequela to gonorrhea, syphilis or tuberculosis, a complication of prostate surgery, and most commonly, the result of viral parotitis (mumps). In some cases, orchitis may be an autoimmune response to spermatozoa, more common in older men and after a vasectomy. Orchitis as a complication of parotitis occurs in about 20% of postpubescent men, presenting as a unilateral swelling of the testes that accompanies or follows the inflammation of the salivary glands. Some degree of testicular atrophy may ensue, and in about 4% of cases inflammation of both testes results in a loss of spermatogenesis, although androgenic activity is maintained. The swelling typically resolves on its own in about 7 – 10 days, and if the testes appear smaller than before the swelling, atrophy is indicated. The medical treatment of orchitis is based upon the causative factor. *Chlamydia trachomatis* is most often the organism implicated in non-viral orchitis, and other diseases such as tuberculosis, syphilis, or mycotic (fungal) infections are now rare. (Swash 1995, 100-101; Berkow 1992, 1745; Junnila and Lassen 1998)

**Testicular cancer**

Testicular cancer is an abnormal growth of cells in the testicle, responsible for 1-2% of cancer in men and typically strikes those aged 18-44 years. The cancer usually occurs in only 1 testicle. Less than 5% of the time, it can occur in both testicles. Testicular tumors account for most solid tumors in males more than 30 years old. The incidence is 2.5 to 20 times higher in patients with cryptorchidism, even if the undescended testis has been brought down surgically. The normally descended testis however is also at risk for tumor. The cause of testicular cancer is unknown. Embryonic exposure to xenoestrogens during pregnancy, such as diethylstilbestrol (DES), an estrogen compound that was once used for women with breast cancer, has been identified as a causative agent. Testicular atrophy from mumps, torsion (loss of blood supply after twisting upon its cord), or trauma are also risk factors, as are decreased exercise, increased sexual activity, sitting with
legs crossed (increases testicular temperature), and HIV. There is no increased risk of testicular cancer if a family member has the disease. (Swash 1995, 100-101; Berkow 1992, 1745; Junnila and Lassen 1998)

The usual presenting sign is a scrotal mass, sometimes associated with pain. Many patients discover the mass in association with minor trauma. Hemorrhage into the tumor may produce local pain and tenderness. Any firm mass in the testis is cause for immediate clinical suspicion of testicular tumor. An ultrasound is among the first diagnostic method used to detect a tumor, and if positive, is followed by a chest x-ray and CT scan of the abdomen and pelvis are used to look for further spread of the disease. Blood tests are used to look for tumor markers such as fetoprotein and human chorionic gonadotropin, which are substances released into the blood by the tumor tissue, may assist in predicting the type of cancer, its extent, and how it might respond to treatment. The prognosis depends on the histology and extent of the tumor, but generally speaking is very good. If diagnosed early, nearly 100% of men are cured. Even those with advanced disease have over an 80% cure. (Berkow 1992, 1745; Junnila and Lassen 1998)

Prostate

Prostatitis is the inflammation of the prostate gland, differentiated into an acute or chronic bacterial prostatitis, a chronic nonbacterial prostatitis, and benign prostatic hypertrophy.

Bacterial prostatitis
Acute bacterial prostatitis is an acute infection of the prostate gland, the patient presenting such symptoms as chills, fever, urinary frequency and urgency, burning upon urination, hematuria, and perineal and lumbar pain. Upon examination the prostate will feel swollen, tense, and warm to the touch, and laboratory investigation of the cultured prostatic secretions will yield a high bacterial count, most commonly enteric, gram-negative organisms. Chronic bacterial prostatitis is similar to the former, except the symptoms are less acute and display a greater degree of variability. The symptoms are distinguished by a relapsing urinary tract infection, that can range from being asymptomatic except for bacilluria, to urinary frequency and urgency, burning upon urination, hematuria, and perineal and lumbar pain. With chronic infection, the scrotal contents may become affected presenting as epididymitis and/or orchitis. Upon examination the prostate may
be boggy or irregularly swollen and tense, and somewhat tender. (Berkow 1992, 1715)

**Chronic nonbacterial prostatitis**

Chronic nonbacterial prostatitis is more common than bacterial prostatitis but the cause is unknown. The symptoms resemble those of chronic bacterial prostatitis, and although laboratory investigation may show an elevation of leukocytes in the urine, cultures of the urine and prostatic secretions fail to indicate a pathogenic organism. In herbal medicine chronic nonbacterial prostatitis is a congestive state of the pelvic circulation. In many cases patients spend much of their time sitting, more than our forebears, such that it is not uncommon for men to sit for more than 8 hours a day, 5 days a week. Such inactivity, often complexed with dietary factors that inhibit liver and digestive function such as stress, a diet high in refined foods and saturated fats, as well as methylxanthine containing beverages, promotes pelvic congestion. Prostatic congestion can also be a symptom of non-ejaculatory sex and extended periods of arousal, both of which enhance prostatic circulation, but inhibit elimination. Some commentators, such as James Green in his book *The Male Herbal*, note that men are now exposed to overt sexual stimuli in an increasing fashion, from books and magazines, to television and movies. Green suggests that such chronic stimuli congests sexual energy, promoting prostatic enlargement and inflammation (Green 1991, 113). There are other factors that may underlie prostatitis. Men who bicycle frequently are at an increased risk of prostatitis, and should be counseled to try many of the newly designed bicycle seats that take some of the pressure off of the perineal region. Excessive sexual activity may also irritate prostate function, as might the habitual consumption of spicy foods that are traditionally said to inhibit male sexual function. The regular excessive consumption of alcohol, and especially beer, may also tax the prostate through the distension of the urinary bladder and excessive diuresis. Another factor traditionally ascribed to prostatic inflammation is the suppression of urination. The call to eliminate should never be ignored, and many men can actually trace the cause of their prostatitis to an occasion in which the suppression of urination caused acute pain. Such an event is likely to cause permanent damage and chronic inflammation, and although the exact cause in unclear, it most likely stems from the acute distension of the urinary tract and the retrograde flow of urine.

**Benign prostatic hypertrophy (BPH)**

Benign prostatic hypertrophy (BPH) refers to the adenomatous enlargement of the periurethral prostate gland, promoting obstruction of the urethra and bladder opening. It is a disease
commonly seen in men over the age of 50, and although the etiology is unclear, may involve alterations in hormonal balance associated with aging. BPH is less common in the Orient and more frequent in the Western world, and within North America, has a higher frequency among blacks than whites. With aging however, the incidence of BPH increases in all populations, and by about 80 years of age, 75% of men have prostatic hypertrophy. (Berkow 1992, 1736; Rubin 2001, 501-02)

In the initial stages of the disease multiple nodules derived from epithelial, stromal and smooth muscle cells begin to occur in the periurethral region of the prostate. Five types of nodules have been found, with fibromyoadenomatous nodules being the most common. Histologically, the hyperplastic tissue is glandular, with varying amounts of stromal tissues interposed. Gradually, the progressive growth of these hyperplastic nodules begin to distort and compress the urethra, and place pressure upon the peripheral areas of the prostate. With progressive compression and urinary obstruction there is an increased risk of secondary infection, and the development of urinary calculi. The bladder becomes distended, and the retrograde flow of urine can impair renal function and promote hydronephrosis. In the latter stages the flow of urine may become completely blocked, causing acute pyelonephritis, uremia, and death. In the vast majority of cases however, BPH rarely progresses beyond being an annoying chronic condition. The symptoms of BPH are a progressive frequency and urgency, difficulty initiating urination, decreased urine flow and force, and nocturia. Upon rectal examination the prostate is enlarged and has a rubbery consistency, and an abdominal exam may reveal a distended bladder that is palpable or percussible. The congestion of the superficial veins of the prostate and the trigone muscle of the bladder can cause hematuria if the patient strains while trying to void. Burning sensations and fever indicate secondary infection. Although testosterone levels typically decline with aging, it is clear that testosterone plays a role in the pathogenesis of the hyperplasia. Specifically, it is the conversion of testosterone into 5-alpha-dihydrotestosterone by 5-alpha-reductase within the prostate that is thought to cause the hypertrophy. 5-alpha-dihydrotestosterone is about fives times more potent than testosterone and thus has a greater stimulatory effect. Additionally, with the declining levels of testosterone estrogen levels begin to increase. Some researchers have speculated that the prostate is divided into an inner and outer mass, the outer mass responsive to testosterone and the inner to estrogen. With the relative increase of estrogen with aging, complexed with the ubiquitous influence of xenoestrogens from dietary and
environmental sources, causes this inner prostatic mass to enlarge. Cadmium has also been found to induce prostatic hyperplasia in animals, and has been found to be elevated in prostatic tissues in patients with BPH, proportional to the elevated levels of 5-alpha-dihydrotestosterone. (Berkow 1992, 1736-37; Rubin 2001 501-02; Green 1991, 104-05; Brys et al 1997; Hoffmann et al 1985; Habib et al 1976)

**Prostate cancer**

**Adenocarcinoma** of the prostate accounts for 95% of all forms of prostate cancer, and is the most frequently diagnosed malignancy among men and the second leading cancer cause of death in men more than 50 years of age, the incidence increasing with each decade of life. The cause or causes of prostate cancer are unknown, but hormonal influences are thought to play an important role in the etiology of adenocarcinoma, primarily the activity of the androgens, although this is far from conclusive. Incidence rates of prostate cancer are high in northern Europe and North America, intermediate in southern Europe and Central and South America, and low in eastern Europe and Asia. This data in conjunction with migration studies suggest that environmental factors, such as diet, may play a significant promoting role in the development of a prostate cancer. Specifically, a high-fat diet may lead to increased risks, while a diet rich in phytoestrogens (e.g. soy) may be protective. Other data shows that omega-6 fatty acids are positive stimulants of prostate cancer cell growth, while omega-3 fatty acids are negative stimuli. Deficiencies of vitamins A, D and E, as well as selenium are also thought to play a role. (Berkow 1992, 1750; Rubin 2001, 503-04; Fleshner et al 2004; Meyer et al 1999; Trichopoulou et al 2000; Hodge et al 2004; Green 1991, 111-12)

Generally speaking, prostate cancer is slowly progressive and may cause no symptoms – most cases are found upon autopsy, suggesting that in some respect it is a natural manifestation of aging. In progressive cases, the late-stage disease symptoms include bladder obstruction, ureteral obstruction, and hematuria. Metastases to the pelvis, ribs, and vertebral bodies may cause bone pain. Locally advanced prostate cancer may exhibit extension of induration to the seminal vesicles and fixation of the gland.

**Gynecomastia**

**Gynecomastia** is the enlargement of the breast, most usually in pubescent males as a transient swelling of breast tissue under the areolae that appears as a hardened disk. Gynecomastia may also
occur with aging, or may accompany hepatic disease, regular marijuana consumption, and with the use of various pharmaceutical drugs. Obesity is also a risk factor for gynecomastia, due to the conversion of androgens into estrogen by adipose tissue. (Berkow 1991, 1815; Rubin 2001, 549)

Sperm dysfunction and infertility

Male infertility is often linked with various forms of sperm dysfunction. Semen analysis is an invaluable tool to evaluate male fertility, to determine the success of a vasectomy or if the male is infertile. Among the factors analyzed are:

• **Volume**: a low volume indicates an anatomical defect or inflammation
• **Morphology**: in a normal sample at east 60% of the sperm show good motility
• **Count**: sperm counts below 20 million/mL often indicate infertility
• **Liquefaction**: delays liquefaction of more than two hours suggests enzyme defects in the seminal fluid or inflammation of the accessory organs
• **Morphology**: no more than 30 – 35% of the spermatozoa should have abnormal shapes, such as a poorly formed head or tail;
• **pH**: a rise in pH indicates prostatic inflammation
• **Fructose**: absence indicates obstruction from inflammation or congenital defects of the accessory structures. (Berkow 1992, 1769)

**Oligospermia** is a low sperm count, which apart from anatomical issues, usually relates to hormonal deficiencies. **Asthenospermia** is poor sperm motility, and can be indicative of a genitourinary infection. **Teratospermia** is poor sperm morphology, which in association with poor motility often indicates an autoimmune reaction to the spermatozoa. **Pyospermia** is a high white blood cell count in semen, and is indicative of a genitourinary infection.

The ubiquitous presence of xenoestrogens in the diet and environment may be responsible for a variety of effects upon male fertility. Reduced sperm counts, a rise in anatomical defects such as undescended testes, hermaphroditism, and rise in reproductive cancers can all be correlated to the influence of xenoestrogens. The rates of male infertility have risen sharply since the early 1980's, and over the last 50 years there has been a substantive decrease in the quality and quantity of sperm. In Britain, for example, the
testicular cancer rate has tripled in the last 50 years, and is now the most common cancer in men under 30 (Joffee 1996). Two studies published in the *Lancet* that showed that men who ate pesticide-free foods produced roughly double the average number of sperm than those that did not eat organic food (Jensen et al 1996; Abell 1994).

**Erectile dysfunction**

**Erectile dysfunction (ED),** also called **impotence** or **sexual arousal disorder**, refers to the inability to attain or sustain an erection satisfactory for sexual intercourse. There are two primary forms of ED. **Psychogenic ED** is caused by psychic factors, such as an abnormal fear of the vagina, sexual guilt, fear of intimacy, or depression. **Organic ED** can result from vascular, nervous, or hormonal causes. At one time, psychogenic ED was thought to be the primary form of ED, but it is now recognized that organic ED accounts for up to 80% of all cases. In some situations however, psychogenic effects occur simultaneously with organic causes. (Berkow 1992, 1575; Brosman 2005)

There are many conditions associated with ED, including aging, chronic disease (cardiovascular disease, liver disease, renal disease), endocrine abnormalities (hypogonadism, hyperprolactinemia, hyper/hypothyroidism, hyperinsulinemia and diabetes), lifestyle habits, neurogenic causes (e.g. multiple sclerosis, spinal cord injury, herniated disk), penile injuries, drugs, psychological issues, pelvic trauma or surgery, and pelvic radiation. The most common medical conditions associated with ED are those conditions in which there is an impairment of arterial flow to the erectile tissues, or disruption of the neuronal circuitry. Patients with diabetes mellitus have the highest rates of ED as a result of vascular disease and autonomic dysfunction. Up to 25% of ED cases are caused by medication, most commonly those used to treat hypertension (e.g. diuretics, beta-blockers, and sympatholytics) and psychiatric disorders (e.g. antipsychotics, anxiolytics, and antidepressants). Additionally, both the regular consumption of alcohol and smoking has been associated with an increased incidence of ED. With aging there is typically a diminution of spontaneous erectile function with erotic thoughts or activity. The easy to achieve erection that occurs in youth begins to become less a feature of male sexuality by about mid-life. Often, some form of consistent tactile stimulation is required to sustain an erection, and when achieved, may not be as hard as experienced in youth. With these changes, the man may become increasingly
anxious about his sexuality, which may further exacerbate the condition. (Berkow 1992, 1575; Keene and Davies 1999; Brosman 2005)
References


LESSON NINE: Endocrinal disease

I. Thyroid

Goiter

Goiter, or more specifically non-toxic goiter or euthyroid goiter, is an enlargement of the thyroid gland but without any evidence of thyroid dysfunction. Goiter is the most common cause of thyroid enlargement, seen more frequently during puberty, pregnancy, and menopause. The most prominent cause relates to an iodine deficiency, but other causes include the excess consumption of goitrogens (e.g. cruciferous vegetables), and drugs, including aminosalicylic acid and lithium. Somewhat paradoxically, high amounts of iodine may decrease the synthesis of thyroid hormone. (Rubin 2001, 600-01; Berkow 1992, 1080)

Gross iodine deficiency is very uncommon in the West but is the most common cause of goiter worldwide. Iodine is ingested in food and water, and is actively taken up by the follicular cells of the thyroid gland, which under the influence of thyroid stimulating hormone (TSH), uses it and the amino acid tyrosine to form thyroxine, of which there are two primary forms: T3 (triiodothyronine, comprised of three iodine atoms) and T4 (tetraiodothyronine, comprised of four iodine atoms). These hormones are then released by the thyroid where they are bound to thyroid hormone-binding serum proteins for transport. Thyroxine-binding globulin (TBG) accounts for 75% of thyroid hormone-binding proteins, and has high affinity but low capacity for T4 and T3. Other thyroid hormone-binding proteins include transthyretin (prealbumin), which has high affinity but low capacity for T4, and albumin, which has low affinity but high capacity for T4 and T3. Approximately 0.03% of the total serum T4 and 0.3% of the total serum T3 are free from carrier proteins. (Berkow 1992, 1071-72)

Increased levels of free thyroid hormones T3 inhibit TSH secretion from the pituitary, whereas decreased levels of T4 and T3 result in an increased TSH release from the pituitary. TSH secretion however is also influenced by thyrotropin-releasing hormone (TRH), an amino acid peptide synthesized in the hypothalamus.

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1 Although iodine is key in thyroid function, there are several other minerals are involved in the production of thyroid hormone, including iron, manganese, zinc, copper, chromium, selenium, cobalt, sodium, lithium, calcium, magnesium and possibly other trace minerals. Selenium specifically is involved in the conversion of T4 into T3.
which binds to a specific TRH receptor on the thyrotropic cells of the anterior pituitary and causes the subsequent release of TSH. (Berkow 1992, 1071)

The thyroid hormones act to increase protein synthesis and O$_2$ consumption in virtually every body tissue, increasing or enhancing the metabolic rate. Although T4 is much more abundant among the thyroid hormones, only T3 is thought to be metabolically active. Once taken up by a cell however, T4 can be deiodinated into T3. (Berkow 1992, 1071)

About 20% of the circulating T3 is produced by the thyroid and the remaining 80% is produced by the monodeiodination (removal of one iodine atom) in the outer ring of T4. The monodeiodination of the inner ring of T4 results in reverse T3 or rT3, mostly occurring in peripheral tissues. Unlike normal T3, rT3 has minimal metabolic activity and increases in certain diseases, e.g. chronic liver and renal disease, acute and chronic illness, starvation, and carbohydrate-deficient diets. Reverse T3 may also act to inhibit T4 conversion into the metabolically active T3, and is used as marker to rule out hypothyroidism (in which T3 levels are decreased). Some researchers speculate that rT3 may block T3 receptor sites, competitively inhibiting the activity of T3. (Berkow 1992, 1071)

Goiter is evidenced by a soft, symmetric, smooth mass in the neck. Goiter can range in size from a doubling of the thyroid gland to a massive enlargement that weigh several hundred grams. The early indications of the disease include follicular hypertrophy and hyperplasia, and as the condition progresses this is followed by an increasingly nodular configuration. Serum TSH may be slightly elevated and serum T4 may be low-normal or slightly low, but serum T3 is normal or slightly elevated. Thyroid antibodies are typically measured to rule out Hashimoto's thyroiditis as the cause. (Berkow 1992, 1084-85; Rubin 2001, 600-01)

Hypothyroidism

Hypothyroidism or myxedema is group of signs and symptoms that characterize a thyroid hormone deficiency. Primary hypothyroidism is the most common form, and is most common is the fifth and sixth decades of life, and is more common in women. Up to 75% of hypothyroid patients have circulating antibodies to thyroid antigens, which suggest an autoimmune component (see thyroiditis below). The second most common
form is post-therapeutic hypothyroidism, primarily due to the administration of radioactive iodine therapy or surgery for hyperthyroidism. Secondary hypothyroidism occurs when there is failure of the hypothalamic-pituitary axis because of deficient TRH secretion from the hypothalamus or lack of TSH secretion from the pituitary. Rare inherited enzymatic defects can alter the synthesis of thyroid hormone and cause goitrous hypothyroidism. Mild hypothyroidism is common and is more often found in elderly women. (Berkow 1992, 1080-81; Rubin 2001, 600-01)

The signs and symptoms of hypothyroidism are often quite subtle and insidious, with initial symptoms such as lethargy, increased cold sensitivity and difficulty concentrating. The facial expression becomes progressively more and more dull in appearance, and the voice is hoarse and speech is slowed. Proteoglycans begin to accumulate in the extracellular matrix and bind with water, promoting the characteristic symptoms referred to as myxedema, including facial puffiness, puffy eyelids, peripheral edema and a swollen tongue. Changes begin to occur in the skin, including pallor and dryness, and the hair begins progressively more and more sparse: hair loss and a loss of the lateral eyebrows specifically is a common finding. The term myxedema madness refers to a worsening of the nervous afflictions, from poor concentration and forgetfulness to depression, anxiety and paranoia. Weight gain is a common symptom, mostly from decreased metabolism and fluid retention. The early symptoms of myxedema include a reduction in heart rate and volume from a decrease in both thyroid hormone and adrenergic stimulation, and as the condition progresses the heart may be enlarged, with pleural or abdominal effusions. Decreased peristalsis becomes an important clinical feature, and patients will often complain of chronic constipation and sometimes present with fecal impaction (myxedema megacolon). The continuing deposition of proteoglycans and proteins in the extracellular matrix, especially around the ligaments of the wrist and ankles produces nerve compression and carpal-tarsal tunnel syndrome. Women with hypothyroidism often develop menorrhagia, and as a result iron-deficiency anemia is often present, although in some cases the anemia may be related to impaired $\text{B}_{12}$ absorption. (Berkow 1992, 1080-81; Rubin 2001, 600-01)

The challenge in the diagnosis of hypothyroidism is to differentiate it from its primary and secondary forms. Secondary hypothyroidism, caused by a failure of the hypothalamic-pituitary axis is comparatively uncommon, and in women presents with a history of amenorrhea rather than menorrhagia, skin
depigmentation and hypoglycemia. Laboratory testing demonstrates a low level of circulating TSH in secondary hypothyroidism whereas in primary hypothyroidism serum TSH levels are typically elevated. It generally takes 6 weeks however for TSH levels to reflect the status of thyroid hormone in the blood because TSH in normally released in a pulsatile fashion, peaking during the night, and the changes in response are subtle, with TSH gradually responding to excess or diminished thyroid hormone. Thus TSH may not be a reliable indicator of thyroid function at the time of diagnosis. Serum T3 and T4 levels are also investigated, and in both forms levels are typically decreased, although patients with primary hypothyroidism may have normal circulating levels of T3. Certain medications however such as estrogen, as well as chronic illnesses and liver problems can cause alterations in protein concentration, and thus the total T4 and T3 measurements typically utilized may not accurately represent thyroid function. To this extent, laboratory tests that measure the free T3 and T4 levels are far more accurate determinants of thyroid function and should be used in preference. (Berkow 1992, 1080-81; Rubin 2001, 600-01)

Hyperthyroidism

Hyperthyroidism is a condition that encompasses several different diseases, all of which are characterized by hypermetabolism and elevated serum levels of free thyroid hormones. It is the result of the excess secretion of thyroid hormones from the thyroid gland, with or without their increased synthesis. The most common causes of hyperthyroidism include Grave’s disease and toxic multinodular goiter and toxic adenoma.

Grave’s disease

Grave's disease is the most common cause of hyperthyroidism, and is an autoimmune disease that has a chronic course with remissions and relapses. The etiology of Grave's disease relates to the production of IgG antibodies against the thyroid TSH receptor, which results in the continuous stimulation of the gland to synthesize and secrete excess quantities of T4 and T3. It is sometimes associated with other autoimmune disorders, including insulin-dependent diabetes mellitus, vitiligo, premature graying of hair, pernicious anemia, collagen diseases, and polyglandular deficiency syndrome. It is far more common in women than in men, and has been observed to occur in periods of emotional stress. (Berkow 1992, 1075-77; Rubin 2001, 604-05)
The clinical features of Grave’s disease typically involve a gradual onset of non-specific symptoms such as nervousness, emotional irritation, tremor, weakness, weight loss and tachycardia. Patients are intolerant of heat and tend to sweat profusely. One of the more striking features of Grave’s is exophthalmos, a protruding of the eyeballs characterized by the enlargement of intraocular muscles from the accumulation of fluid, fibroblasts and lymphocytes. The thyroid is often symmetrically enlarged from increased metabolic activity. (Berkow 1992, 1075-77; Rubin 2001, 604-05)

The thyroid storm of hyperthyroidism is characterized by the rapid onset of acute symptoms of hyperthyroidism, including fever, marked weakness and muscle wasting, extreme restlessness with emotional irritability, confusion, psychosis, hepatomegaly with mild jaundice. The patient may present with cardiovascular collapse and shock, and is a life-threatening emergency. (Berkow 1992, 1076)

The diagnosis of hyperthyroidism is concluded by noting the elevation of T3 and T4, and/or by the increased uptake of radioactive iodine. TSH levels are typically very low or undetectable. In Graves' disease specifically, the antibody against the thyroid TSH receptor is measured. (Berkow 1992, 1075-77; Rubin 2001, 604-05)

**Toxic nodular goiter**

Toxic nodular goiter (TNG) is the second most common cause of hyperthyroidism after Graves disease in the Western world, representing about 15-30% of cases, and in areas of endemic iodine deficiency it is the most common cause. TNG represents a spectrum ranging from a single hyperfunctioning nodule within a thyroid that contains other nonfunctioning nodules to multiple areas of hyperfunctioning nodules throughout the gland. TNG is most often seen to arise from a simply goiter, secondary to an iodine deficiency. A deficiency of iodine results in low levels of circulating thyroxine (T4), and through a feedback mechanism, promotes thyroid cell hyperplasia. Increased thyroid cell replication predisposes single cells in the thyroid to mutations of the TSH receptor, resulting in the formation of multiple nodules. (Berkow 1992, 1077; Rubin 2001, 605-06)

**Toxic adenoma**

Toxic adenoma (Plummer’s disease) refers to a solitary, hyperfunctioning follicular neoplasm in an otherwise normal thyroid. These neoplasms function independent of TSH, and the hyperactivity of the nodule eventually suppresses the remainder
of the thyroid, which then atrophies. As the condition progresses TSH levels decline. It is most common in the fourth and fifth decades of life, but the patients do not typically express symptoms of hyperthyroidism until the adenoma has grown more than 3 cm in diameter. Adenomas are typically treated by surgery. (Berkow 1992, 1077; Rubin 2001, 605-06)

**Thyroiditis**

The term *thyroiditis* relates to diverse group of inflammatory diseases of the thyroid gland, usually caused by autoimmune factors, and sometimes by infectious agents (e.g. mumps virus).
Hashimoto's thyroiditis

Hashimoto's thyroiditis is a chronic inflammatory disorder of the thyroid characterized by the infiltration of thyroid by autoantibodies. It is thought to be the most common cause of primary hypothyroidism in the Western world, and is eight times more prevalent in women than in men. (Berkow 1992, 1083; Rubin 2001, 606)

The pathogenesis of Hashimoto’s thyroiditis relates to high circulating autoantibodies against thyroid peroxidase (which acts to oxidize iodide into organic iodine), thyroglobulin (which serves as a substrate for the iodination of tyrosine in the thyroid), and the TSH receptor. There is a familial tendency for Hashimoto’s thyroiditis, with both patients and their relatives having a higher incidence of other autoimmune diseases (e.g. IDDM, Addison’s disease, myasthenia gravis, pernicious anemia, RA, SLE, Sjögren's syndrome). (Berkow 1992, 1083; Rubin 2001, 606)

Patients with Hashimoto’s typically present with a non-tender enlargement of the thyroid gland or fullness of the throat that can promote some discomfort in swallowing. Upon examination the thyroid is enlarged, smooth or nodular, and firm. Many patients have hypothyroidism when first seen, and may present with other autoimmune diseases such as SLE and RA. Laboratory investigation typically yields normal T4 and TSH levels, with high levels of thyroid peroxidase antibodies and sometimes anti-thyroglobulin antibodies. As the disease progresses the patient develops clinically evident hypothyroidism, with decreased T4, decreased thyroid radioactive iodine uptake, and increased TSH. (Berkow 1992, 1083; Rubin 2001, 606)

Thyroid carcinoma

There are four general types of thyroid cancer: papillary (including mixed papillary-follicular), follicular, medullary (solid, with amyloid struma), and undifferentiated and anaplastic (rare). Most thyroid nodules are benign, and thyroid cancers generally are not highly malignant and are compatible with normal life expectancy if treated properly. Papillary thyroid cancer, which accounts for 75% of all thyroid cancers, is linked to an iodine excess in the diet, radiation and genetic factors. Although thyroid nodules are found in as many as 10% of the population, malignant thyroid cancers account for only 1% of cancers and 0.4% of cancer-related deaths. (Berkow 1992, 1084; Rubin 2001, 608)
Parathyroid dysfunction

The parathyroid glands are attached to the posterior surface of the thyroid gland and function to maintain proper calcium metabolism through the secretion of parathyroid hormone (PTH). PTH functions to increase the number and activity of osteoclasts, which results in the breakdown of bone matrix and the elevation of serum Ca^{2+} and phosphates (HPO_4^{2-}). PTH also increases the rate at which Ca^{2+} and Mg^{2+} is resorbed from urine back into the blood, and the rate at which HPO_4^{2-} is excreted. Thus, PTH decreases serum HPO_4^{2-} and increases serum Ca^{2+} and Mg^{2+}. PTH also acts on the kidneys to promote the formation of calcitrol, the active form of vitamin D_3, increasing calcium, phosphate and magnesium absorption into the blood. These activities of the parathyroid glands are paired with the thyroid’s secretion of calcitonin, which functions to lower the amount of serum Ca^{2+} and HPO_4^{2-} by inhibiting the activity of the osteoclasts (i.e. the rhyme “calcitonin bone-in”)

Hypoparathyroidism relates to either the decreased secretion of parathyroid hormone (PTH) or from a marked decrease in sensitivity to PTH. Symptoms relate primarily to hypocalcemia, which increases neuromuscular excitability that can range from a mild tingling in the hands to severe muscle cramping and convulsions, sometimes including psychiatric manifestation including depression and psychosis. Hypoparathyroidism often has a familial prevalence, related to adrenal insufficiency and candidiasis, and may be an autoimmune disorder. (Rubin 2001, 612)

Hyperparathyroidism relates to the excessive secretion of PTH. Most cases (80%) are caused by a parathyroid adenoma, but other causes include familial parathyroid hyperplasia and parathyroid carcinoma. A chronic vitamin D deficiency is the cause of secondary hyperparathyroidism, which promotes impaired intestinal Ca^{2+} absorption leading to a compensatory hyperparathyroidism. (Rubin 2001, 612)
II. Adrenals

Adrenocortical insufficiency

Adrenocortical insufficiency relates to the deficient production of the adrenocortical hormones. It can result from stress, injury or destruction of the adrenal gland, pituitary or hypothalamic dysfunction, or the chronic usage of corticosteroids. Adrenocortical insufficiency is really only recognized as an overt disease in pathology, but herbalists recognize a subclinical form that affects people under chronic stress.

Addison’s disease

Addison’s disease is a chronic, progressive disease caused by a failure of adrenocortical secretion, characterized by a deficiency of glucocorticoids, mineralcorticoids and androgens. The etiology of Addison’s disease in most patients (75%) is unknown, but is thought to be related to an autoimmune process, as patients typically present with other autoimmune endocrinal diseases. Immune mechanisms include The remainder of cases relate to granulomatous conditions from infection (e.g. tuberculosis), as well as amyloidosis, cancer, adrenal hemorrhage, sarcoidosis, and the treatment of fungal infections with ketoconazole. (Rubin 2001, 615-16; Berkow 1992, 1088)

Clinically apparent indications of Addison’s only occurs after 90% or more of the adrenal gland is destroyed. The initial symptoms are insidious, including weakness, poor appetite, and asthenia. As the condition progresses there is increased pigmentation, caused by increased melanocyte-stimulating activity of pituitary pro-opiomelanocortin, which is commensurate with an increase in ACTH secretion. This is characterized by a diffuse “tanning” of both exposed and unexposed portions of the body, including on bony regions, skinfolds, and scars. Another common feature is the appearance of blackish freckles over the forehead, face, neck, and shoulders, as well as bluish-black discolorations of the areolae and mucous membranes. In some cases vitiligo may be present. Hypotension (e.g. 80/50 mm Hg) occurs as the result of mineralcorticoid insufficiency, from the resulting low serum sodium. As the condition progresses signs and symptom include nausea, vomiting, diarrhea, and cold intolerance. (Rubin 2001, 616p; Berkow 1992, 1088)

An adrenal crisis is a life threatening emergency that results from an abrupt loss of adrenocortical function. Symptoms typically
relate to a deficiency in mineral corticoid secretion, and are characterized by hypotension and shock, commensurate with profound weight loss, abdomen pain, and lower back and leg pain. If untreated renal failure with azotemia is a result. The crisis can be caused by the stress of acute infection or surgery, and in some cases from sodium loss due to excessive sweating. **Waterhouse-Friederichsen syndrome** relates to the acute injury of the adrenal glands secondary to meningococcal or pseudomonal infections of the blood, usually occurring in young patients and typified by sudden vascular collapse, hypotension, fever, myalgia and pupura. In most cases an adrenal crisis is caused by the **abrupt withdrawal** of corticosteroid therapy. (Rubin 2001, 616p; Berkow 1992, 1088)

**Adrenocortical hyperfunction**

*Adrenocortical hyperfunction* relates to the hypersecretion of one or more adrenocortical hormones. With the excessive production of androgens the result is adrenal virilism; with the hypersecretion of glucocorticoids the result is Cushing's disease; and with the excess secretion of aldosterone the result is hyperaldosteronism (aldosteronism). In some patients these syndromes can occur concurrently. (Berkow 1992, 1092)

**Adrenal virilism**
The term *adrenal virilism* relates to any syndrome, either congenital or acquired, in which there is an excessive output of adrenal androgens. The signs and symptoms effects depend upon the sex and age of the patient. In adult women, adrenal virilism is caused by adrenal hyperplasia or an adrenal tumor. In either case, symptoms and signs include hirsutism, baldness, acne, deepening of the voice, amenorrhea, atrophy of the uterus, clitoral hypertrophy, decreased breast size, and increased muscularity. Libido may increase. Hirsutism may be the only sign in mild cases. Mild hirsutism and virilization with amenorrhea and elevated plasma testosterone may be seen in polycystic ovarian disease. (Berkow 1992, 1092)

**Cushing’s syndrome and Cushing’s disease**
*Cushing’s syndrome* refers to signs and symptoms that stem from chronically elevated serum levels of cortisol and related corticosteroids (hyperadrenocorticoolemia). This can be the result of excess ACTH secretion (corticotropin dependent, or more properly Cushing’s disease) or it may be independent of ACTH (corticotropin-independent). In Cushing’s disease the ACTH-
dependent hyperfunction of the adrenal cortex is typically due to either the hypersecretion of ACTH by a pituitary tumor, or the hypersecretion of ACTH by a nonpituitary tumor, such as small cell carcinoma of the lung (i.e. ectopic ACTH syndrome). This results in a bilateral hyperplasia of the adrenal cortex. ACTH-independent causes of hyperadrenocorticoolemia include an adrenal tumor, such as an adrenal adenoma or carcinoma, but by far the most common cause is the result of long-term glucocorticoid administration (e.g. prednisone). (Rubin 2001, 619-20; Berkow 1992, 1093)

The signs and symptoms of Cushing disease include a progressive obesity, of the face (e.g. "moon" face), neck ("buffalo hump"), trunk and abdomen, commensurate with some degree of muscle wasting and weakness. The skin is thin and atrophic, with a loss of subcutaneous fat, poor wound healing and easy bruising. The enlargement of the abdomen produces purplish striae (stretchmarks). There is often increased bone resorption, causing osteoporosis and renal calculi. Hypertension is another common feature, relating to excess mineralcorticoid secretion. Glucose intolerance and hyperinsulinemia is caused by the stimulation of gluconeogenesis by glucocorticoids. In both sexes there is a loss of secondary sexual characteristics and libido: in women, signs and symptoms of virilization such as menstrual disturbances, acne, alopecia and hisutism; and in men, impotence and gynecomastia. Psychiatric manifestations include emotional irritability, depression and paranoia. (Rubin 2001, 619-20; Berkow 1992, 1093)

**Hyperadrenocorticism in liver disease**
In some patients with chronic liver disease, and especially in alcoholics, there are signs and symptoms are similar to Cushing's syndrome. Elevated plasma cortisol levels result from the reduced ability of the damaged liver to oxidize cortisol.

### III. Pancreas

**Metabolic syndrome X**

It has been observed for a number of years that conditions such as adult onset diabetes, hypertension, elevated blood levels of cholesterol, elevated serum levels of low-density lipoproteins, obesity, and coronary heart disease are common disorders that often occur in one patient. In 1988 medical researcher and
Endocrinologist Gerald Reaven theorized that these metabolic and cardiovascular disorders are a multifaceted syndrome characterized by **insulin resistance** and **hyperinsulinemia** (the resultant elevation of insulin levels in the blood). Subsequent studies have shown that increased insulin concentrations in the blood, as a marker of decreased insulin sensitivity, can be correlated with an increased risk of hypertension, hyperlipidemia and non-insulin dependent diabetes (NIDDM). These studies support Reaven's hypothesis, coined **metabolic syndrome X (Syndrome X)**, that insulin resistance and hyperinsulinemia may increase the risk of developing cardiovascular disease, as well as other disease such as cancer. There is increasing evidence to suggest that this condition affects 60% or more of the U.S. population, a figure that likely reflects its prevalence in the Canadian population as well.

The clinical manifestations of Syndrome X include truncal abdominal obesity, elevated blood triglycerides, decreased HDL cholesterol and elevated LDL cholesterol, hypertension atherosclerosis, thrombotic diseases (e.g. deep vein leg thrombosis), hypoglycemia, and non-insulin-dependent diabetes mellitus (NIDDM). Other clinical manifestations may include osteoporosis, clinical depression, cognitive problems (i.e. poor memory and concentration), Alzheimer's disease and erectile dysfunction. All the above clinical manifestations are related either to the failure of insulin to facilitate the entrance of nutrients into the cell, which disrupts cellular function, or the negative effects of elevated levels of insulin upon the vascular system and in tissues that have not yet become insulin resistant.

Insulin is the body's primary anabolic or tissue-building hormone, and is secreted by the beta cells of the pancreas. Insulin promotes the uptake and storage of nutrients within the cell, including glucose, free fatty acids, and amino acids. The primary stimulus for insulin secretion is the ingestion of carbohydrates, whereas the consumption of a diet rich in proteins and fats tends to limit the secretion of insulin. When its activities predominate insulin prevents the breakdown of fat and protein.

When a cell does not respond to normal levels of insulin it is said to be insulin-resistant. Such a situation can develop from numerous factors:

- **Consuming foods with high glycemic index.** These are foods that contain a relatively large volume of simple sugars, which upon digestion, elevate blood glucose levels and stimulate the release of insulin.
• **Low fat diets.** Although widely marketed as being the basis of a healthy lifestyle, low fat diets are not necessarily beneficial. Significant portions of fat in a meal lowers the glycemic index by delaying stomach emptying.

• **Deficiencies of chromium and magnesium.** Deficiencies of these nutrients facilitate insulin resistance to create a vicious cycle pattern. Other common nutritional deficiencies include zinc, manganese, and the B-vitamins.

• **Sedentary lifestyle and lack of exercise.** Insulin resistance in the liver increases after five days of no exercise. Trained muscle does not require insulin for the uptake of blood glucose, whereas a lack of trained muscle mass in the body promotes systemic insulin resistance.

• **Excess insulin secretion.** Excess insulin secretion promotes insulin resistance in a vicious-cycle relationship. When a cell is exposed to elevated levels of insulin it begins to down-regulate its response to insulin and reduce the number of its insulin receptors.

• **Obesity.** Weight gain, particularly truncal-abdominal weight gain, promotes insulin resistance, which in turn, promotes elevated levels of insulin secretion preventing the breakdown of fat.

Not all tissues become insulin resistant at once. The liver, which is exposed to insulin-rich blood from the portal vein, becomes resistant first. Later, muscle and fat cells may become resistant, followed by platelets and other cells. Skin cells however do not become insulin resistant. Ultimately, the effects of insulin resistance depend on which tissues are involved.

As a tissue becomes insulin resistant, the uptake of blood glucose becomes more difficult, and as a result blood glucose levels begin to rise and continue to be elevated over an increasingly longer period of time. The pancreas, in turn, responds by secreting progressively higher levels of insulin until the glucose is effectively stored. In such situations insulin secretion is not only elevated but prolonged, such that the total hours of insulin exposure in the body may become elevated by 50-100% beyond that of normal.

There are several possible effects of prolonged hyperinsulinemia:

• **Hyperinsulinemia disrupts sodium metabolism and promotes water retention and hypertension.**

• **Hyperinsulinemia increases the oxidative load in some tissues, promoting oxidative damage and initiation of atherosclerosis and neoplasia (cancer).**
• Hyperinsulinemia decreases the total daily secretion of growth hormone with negative effects throughout the body. One notable effect of this is to inhibit the conversion of T4 into T3, creating a functional hypothyroidism that is difficult to detect with routine laboratory tests.
• Chronic hyperinsulinemia may be accompanied by chronic compensatory hypercortisolemia (high blood cortisol levels), poor tolerance to stress, depressed immunity, and eventually, adrenal exhaustion.
• Chronic, high levels of insulin secretion will eventually exhaust the beta cells of the pancreas, increasing the likelihood of a functional deficit of these tissues, resulting in adult-onset diabetes.

The diagnosis of Syndrome X is determined by measuring fasting insulin levels, or by measuring insulin changes to a glucose challenge. Unfortunately, most physicians and labs cannot run these tests as there are several practical and technical challenges that make this procedure difficult. Clinicians may determine Syndrome X with a fairly large degree of certainty however, based on patient history and physical examination. The most important physical feature that is indicative of Syndrome X is truncal-abdominal obesity, such that the circumference of the abdomen at the navel is greater than that of the hips. For men the ratio between these two measurements should be no greater than one, i.e. the abdominal girth should be equal to or less than the waist circumference. For women, the waist-hip ratio should be less than 0.8, i.e. the circumference of the waist should be less than 80% than the circumference of the hips. Another good indicator of Syndrome X are consistent readings of elevated triglycerides in routine blood tests, which tends to parallel insulin secretion.

Diabetes mellitus

Diabetes mellitus is a disease characterized by hyperglycemia resulting from absolute or relative impairment in insulin secretion and the activity of insulin. Patients with type I diabetes mellitus (DM), also known as insulin-dependent DM (IDDM) or juvenile-onset diabetes, are at risk of developing diabetic ketoacidosis (DKA). Patients with type II DM, also known as non-insulin-dependent DM (NIDDM), are at risk of developing hyperosmolar hyperglycemic nonketotic coma (HHNC). Common complications in both conditions include retinopathy, nephropathy, peripheral and autonomic neuropathies, as well as more overt indications of cardiovascular disease such as atherosclerosis. This condition relates to the effect of oxidizing...
effects of uncontrolled blood sugar and insulin upon cardiovascular tissue. Thus in IDDM, cardiovascular disease is the result of iatrogenesis, by recommending a high carbohydrate diet and the need for progressively larger amounts of injected insulin. (Berkow 1992, 1106-12; Rubin 2001, 630-36)

**Classification and pathogenesis**

**IDDM** most commonly develops in childhood or adolescence and is the predominant type of DM diagnosed before age 30. This type of diabetes accounts for 10 to 15% of all cases of DM and is characterized clinically by hyperglycemia and a tendency to develop DKA. The pancreas produces little or no insulin. IDDM results from an immune-mediated, destruction of more than 90% of the insulin-secreting cells. The pancreatic islets of IDDM patients are inflamed, characterized by an infiltration of T lymphocytes accompanied by macrophages and B lymphocytes. The antibodies present at diagnosis usually become undetectable after a few years. (Berkow 1992, 1106-07)

Some researchers believe that susceptibility to IDDM is inherited as an autosomal dominant recessive trait, although fewer than 20% of these patients have a parent or sibling with the disease. Identical twin studies have cast further doubt on the idea that IDDM is an inherited disorder. Up to 95% of patients with IDDM express either HLA-DR3, HLA-DR4, or both, compared with only 20% of the population at large, which may suggest a susceptibility to IDDM. Given the inconclusive findings of genetic research however, environmental factors are still considered to be of prime importance, including viruses (congenital rubella, mumps, and coxsackie B viruses may incite the development of autoimmune -cell destruction) and exposure to cow's milk (a specific sequence of albumin from cow's milk may cross-react with islet protein). This latter factor may explain the very high incidence of IDDM in Scandinavian countries, for whom milk is not a traditional food. (Rubin 2001, 630)

**NIDDM** is usually diagnosed in patients older than 30 years of age, but is being diagnosed with increasing frequency in children and adolescents. It is characterized clinically by hyperglycemia and insulin resistance, and can be thought of as a worsening or progression of the same factors that promote the Syndrome X pattern. Such patients that are able to implement a strategy to lose truncal-abdominal weight and train muscle can be observed to have normal serum glucose levels. Some cases of NIDDM occur in young, nonobese adolescents (maturity-onset diabetes of the young [MODY]) with an autosomal dominant inheritance. Many families
with MODY have a mutation in the glucokinase gene. (Rubin 2001, 632-33; Berkow 1992, 1109-10)

Chronic pancreatitis, particularly in alcoholics, is frequently associated with diabetes. Such patients lose both insulin-secreting and glucagon-secreting islets. These patients may be mildly hyperglycemic and sensitive to low doses of insulin. Given the lack of effective counterregulation (exogenous insulin that is unopposed by glucagon), they frequently suffer from rapid onset of hypoglycemia. In Asia, Africa, and the Caribbean, DM is commonly observed in young, severely malnourished patients with severe protein deficiency and pancreatic disease. NIDDM can be secondary to Cushing's syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism, or somatostatinoma. Most of these disorders are associated with peripheral or hepatic insulin resistance. Many patients will become diabetic once insulin secretion is also decreased. The prevalence of NIDDM is increased in patients with certain autoimmune endocrine diseases, such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease (Rubin 2001, 632-33; Berkow 1992, 1109-10)

**Diabetic ketoacidosis**

IDDM is often first diagnosed with an emergency presentation from the effects of uncontrolled hyperglycemia and **diabetic ketoacidosis (DKA)**. DKA is an acute, life threatening complication of uncontrolled IDDM in which there is a loss of urinary loss of water, potassium, ammonium and sodium, resulting in hypovolemia (decreased blood volume), electrolyte imbalance, very high blood glucose levels, and the breakdown of free fatty acids causing acidosis. (Rubin 2001, 632-33; Berkow 1992, 1122)

**Ketoacidosis** is an extension of normal physiological mechanisms that compensate for starvation. In the fasting state the body changes from metabolism based on carbohydrate, to the oxidation of fat. Free fatty acids produced in adipose cells are transported to the liver, bound to albumin, where they are broken down into acetate, and then turned into ketoacids (i.e. acetoacetate and beta-hydroxybutyrate). The ketoacids are then exported from the liver to peripheral tissues (notably brain and muscle) where they can be oxidized. During ketosis a relatively small amount of acetone is produced giving ketotic patients their typical odour, often described as 'fruity'. DKA represents a derangement of this mechanism. Although there are large amounts of circulating glucose from the diet, it cannot be used owing to lack of insulin. Ketogenic pathways are thus initialized, but the supply of ketones soon exceeds peripheral utilization, and ketosis results. The
resultant change in blood chemistry, called **acidosis**, is marked by an increase in hydrogen ion concentration and the widespread disruption of homeostatic mechanisms. Untreated, DKA leads to coma and death. DKA rarely occurs in NIDDM. (Berkow 1992, 1122)

**Hyperosmolar hyperglycemic nonketotic coma**

Patients with severe NIDDM are at risk for developing **hyperosmolar hyperglycemic nonketotic coma (HHNC)**, a condition characterized by decreased consciousness, extreme dehydration and extremely high blood glucose levels. Normally the kidneys compensate for high glucose levels in the blood by excreting excess glucose in the urine. However, when water is scarce, the kidneys conserve fluid and glucose levels become higher, resulting in intracellular dehydration. Despite the name, coma is present in fewer than 10% of cases. HHNC most commonly develops in diabetic patients who have some concomitant illness that leads to a reduced fluid intake. (Berkow 1992, 1124-25)

**Complications of diabetes mellitus**

Complications only occur after several years of poorly controlled hyperglycemia, which, concomitant with insulin-resistance and compensatory hyperinsulinemia, results in both macro and microvascular damage (see Lesson Four: Cardiovascular disease). Macrovascular diseases such as atherosclerosis may lead to symptomatic coronary artery disease, claudication, skin breakdown, and infections. Amputation of a lower limb for severe peripheral vascular disease, intermittent claudication, and gangrene remains common. Background retinopathy can progress to macular edema or proliferative retinopathy with retinal detachment or hemorrhage, which can cause blindness. About 85% of all diabetics eventually develop some degree of retinopathy (e.g. age-related macular degeneration, AMD). (Rubin 2001, 633-36; Berkow 1992, 1109-11)

**Diabetic nephropathy** develops in about one third of IDDM patients and in a smaller percentage of NIDDM patients. Diabetic nephropathy is usually asymptomatic until end-stage renal disease develops, but it can cause nephrotic syndrome. (Rubin 2001, 633-36; Berkow 1992, 1109-11)

**Diabetic neuropathy** is characterized by a loss or reduction of sensation in the feet, and in some cases the hands, and pain and weakness in the feet. Nerve damage is likely due to a combination of factors, including hyperglycemia and hyperinsulinism, and
ischemia. The symptoms of diabetic neuropathy are insidious and mild at onset, usually experienced as numbness, pain, or tingling in the hands, feet, or legs. After several years this may lead to weakness in the muscles of the feet. Occasionally, diabetic neuropathy can flare up suddenly and affect a specific nerve that may result in double vision or drooping of the eyelid, or weakness and atrophy of the thigh muscles. Nerve damage caused by diabetes generally occurs over a period of years and may lead to problems with internal organs including the digestive tract and sexual organs. These problems can then tend to cause indigestion, diarrhea or constipation, dizziness, bladder infections, and impotence. The loss of sensation in the feet is important as it may increase the possibility of injuries of which the patient is not aware. These foot injuries can develop into ulcers or lesions that can become infected. In some cases, ulcers may not heal and amputation may be required. (Rubin 2001, 633-36; Berkow 1992, 1109-11)

The risk of infection from fungi and bacteria is increased because of decreased cellular immunity caused by acute hyperglycemia and circulatory problems caused by chronic hyperglycemia. Peripheral skin infections and oral and vaginal thrush are most common. A fungal infection may be the initial pathogen, leading to lesions, cracks, fissures, and ulcerations that favor secondary bacterial invasion. Patients with infected foot ulcers frequently feel no pain because of neuropathy and have no systemic symptoms until late in the disease. (Rubin 2001, 633-36; Berkow 1992, 1109-11)
References

LEsson ten: Musculoskeletal disease

I. Disorders of bone

Osteomyelitis

Osteomyelitis is the inflammation and subsequent destruction of bone tissue caused by a number of different microorganisms, including bacteria and fungi. Infection can be secondary to the vascular complications of diabetes, typically found in the vertebrae and in the bones of the feet, or from infections introduced by injury or surgery. The blood-borne infection settles in the developing or cancellous bone of the metaphysis, usually long bones in children. (Berkow 1992; Govan 1990, 804-5; Rubin and Farber 1990, 708-9)

Hematogenous osteomyelitis is the subsequent infection of bone tissue from already infected bone, such as from infected implants (e.g. prosthetic joints), fractures and bone surgery. Fungi and mycobacteria can also infect bone, but don’t tend to spread. Once the organisms penetrate the bone they proliferate in the marrow, forming an abscess filled with pus. As the abscess becomes larger it eats away at the bone cortex and accumulates between the cortex and periosteum, interrupting and occluding the flow of blood and nutrients to the bone. Eventually the infection breaks through the periosteum, invading the joint or penetrating the skin to create a draining, sinus ulcer. Complications include chronic infection, degenerative joint disease (e.g. bacterial osteoarthritis), fractures, squamous cell carcinoma and amyloidosis. (Berkow 1992; Govan 1990, 804-5; Rubin and Farber 1990, 708-9)

The signs and symptoms of acute osteomyelitis is fever, weight loss and fatigue, and in indications of inflammation in the areas of infection. In vertebral osteomyelitis however, the only symptom may be back pain that does not respond to the typical anti-inflammatory treatments. In the absence of effective treatment chronic osteomyelitis results, causing intermittent bone pain, tenderness, and in some cases, chronic sinusitis. (Berkow 1992; Govan 1990, 804-5; Rubin and Farber 1990, 708-9)
Osteoporosis

**Osteoporosis** is a generalized term for a group of diseases of a number of different etiologies that results in the progressive loss of bone density, and the subsequent fragility of the skeleton. Osteoporotic bones usually display normal mineralization but the bone cortex and trabecular suffer from an increasing loss of density and thickness, although the osteoid seams remain normal. (Berkow 1992; Govan 1990, 796-98; Rubin and Farber 1990, 708-9)

The primary pathology that characterizes osteoporosis is that the processes of bone resorption are greater than those of bone formation. In normalcy, both these events are balanced, such that the rate of bone reabsorption is identical to that of bone formation. The most common etiological feature appears to be a facet of aging and a decrease in sex hormone production in men and women. Both estrogen and testosterone inhibit osteoclast activity, but with the natural decline in the secretion of these hormones that occurs with aging osteoclast activity begins to outpace osteoblast activity, promoting a net loss in bone density. Osteoporosis is more common in women due to the relatively rapid cessation in estrogen production during menopause, whereas healthy men continue to produce significant amounts of testosterone even into old age. The greatest period of bone density is about the middle of the third decade of life, which continues to plateau for about a decade. This is then followed by loss of bone density at a rate of about 0.3 to 0.5% per year. With the onset of menopause the rate of bone loss can increase to a rate of about 3 to 5% per year. Physical activity however is a method that can prevent bone loss, and thus physical inactivity in the elderly hastens the osteoporotic process (Berkow 1992; Govan 1990, 796-98; Rubin and Farber 1990, 708-9)

Osteoporosis is divided into two main forms: primary and secondary. **Primary osteoporosis** is associated with menopause in women and normal aging in men. Overall, women are six times more likely to suffer from osteoporosis. **Secondary osteoporosis** accounts for less than 5% of osteoporosis cases and includes a diverse number of causes, including endocrinal diseases (e.g. hyperthyroidism, Cushing’s disease, diabetes, lactation and pregnancy, hypogonadism, hyperparathyroidism), cirrhosis, inflammatory joint disease, chronic pulmonary diseases, immobilization, drugs (e.g. anticonvulsants, heparin, glucocorticosteroids, ethanol, tobacco), cancer and malabsorption.
syndromes. (Berkow 1992; Govan 1990, 796-98; Rubin and Farber 1990, 708-9)

The primary clinical manifestations of osteoporosis are bone fractures, usually occurring in the proximal humerus, lower forearm, hip, spine and pelvis. These can cause chronic pain, but not all patients with low bone mass will experience fracture. Radiologic and ultrasonic investigation will yield a finding of thin bone cortices, called osteopenia (‘little bone’); findings in an individual are compared against the typical density of bone found in a healthy individual of the same age, sex and size (‘age-matched’) against the optimal peak bone density of a healthy young adult of the same sex (‘young normal’). The typical osteoporotic patient is of North European descent, female, a smoker, with a history of breastfeeding several children and a lack of sun exposure. As we will explore, these factors are related to important hormonal shifts in large part brought about by environmental factors. (Berkow 1992; Govan 1990, 796-98; Rubin and Farber 1990, 708-9)

The processes regulating bone formation and reabsorption are complex. The process begins with osteoblasts that lay down the organic matrix of bone and mineralize it, followed by osteoclasts that function to resorb bone. Their activities are controlled by a number of hormones including parathyroid hormone [PTH], calcitonin, and estrogen, as well as nutritional sources of vitamin D and locally acting cytokines. As previously stated, the most common cause of osteoporosis is attributed to declining levels of estrogen, which enhances the secretion of a cytokines such as interleukin-1, tumor necrosis factor alpha, granulocyte-macrophage colony-stimulating factor and interleukin-6, which in turn, promotes the recruitment, differentiation and activation of osteoclasts. Interestingly enough, obesity is not a risk factor for osteoporosis, and is actually associated with a higher bone density. It is known that fat serves as a source of estrogen after menopause, and thus women that maintain a good waist to hip ratio with a little extra padding on the hips and thighs, i.e. ‘pear-shaped,’ can reduce their risk of osteoporosis AND diseases associated with the ‘apple-shape’ of truncal abdominal obesity (e.g. diabetes, CVD, cancer, etc.) (Berkow 1992; Govan 1990, 796-98; Rubin and Farber 1990, 708-9)

Nutritional factors are stated to promote a secondary osteoporosis, such as protein malnutrition and scurvy, but can also be seen to play into the pathogenesis of the primary form, namely, with regard to the insufficient dietary intake of Ca, Mg, P, and vitamin
D. Among these, **deficient dietary calcium** is typically suggested as the major dietary component responsible for osteoporosis, and thus many women are suggested to drink milk and take calcium supplements to prevent osteoporosis. Recent studies however have disproved this hypothesis, showing that vitamin D is a more important factor to maintain proper bone mass (Feskanich et al 2003). In temperate countries, the population is a greater risk for **vitamin D deficiency** due to decreased sunlight hours during winter, increased amount of time spent indoors from previous generations, and the decreased consumption of foods naturally rich in vitamin D such as animal liver and eggs. Moreover, populations that tend to consume less calcium appear to have a **decreased** risk for osteoporosis (Fujita and Fukase 2000), as in the Japanese, who only consume 400-500 mg of calcium per day, mainly as soybean products, small fish with bones, and vegetables. One recent study suggested that some traditional Japanese foods, such as leafy green vegetables and natto (fermented soybeans) provide higher serum levels of **vitamin K2 (menaquinone-7; MK-7)**, with a statistically significant inverse correlation was found between the consumption of these foods and the incidence of hip fractures in women (Kaneki et al 2001).

**Magnesium** is an important accessory element required for bone production that is comparatively low in recommended foods such as dairy. Specifically, magnesium is required for the activation of alkaline phosphatase, an enzyme involved in forming calcium crystals in bone (Iseri and French 1984) and for the conversion of vitamin D into 1,25-dihydroxyvitamin D3, its biologically active form (Rude 1985). Researchers evaluated the effect of magnesium supplementation on apparent calcium absorption, bone metabolism and dynamic bone strength in ovariectomized rats as a model of postmenopausal women. The results of this study indicated that magnesium supplementation reduces apparent calcium absorption, but promotes bone formation and prevents bone resorption in ovariectomized rats. Moreover, the results indicated that magnesium supplementation increases the dynamic strength of bone (Toba et al 2000).

The body's **acid-base balance** is also an important factor in osteoporosis, and the more acidic the blood the greater requirement for alkalization (i.e. bicarbonate ions), at the expense of bone. Thus a diet high in protein without the consumption of alkalizing foods may increase the risk of osteoporosis. Other factors in osteoporosis include a late menarche and early menopause, nulliparity, caffeine ingestion, alcohol use, and cigarette smoking are also important determinants of decreased bone mass. Another
factor that is typically not taken into account is the prevalence of **celiac disease**, which may be more common than previously suspected (Nelsen 2002). Chronic celiac disease, which may present with little or no clinical symptoms, impairs the ability of the gut to absorb minerals such as calcium.

**Osteomalacia and rickets**

**Osteomalacia** is a group of bone disorders characterized defective mineralization of newly formed bone matrix. **Rickets** is a similar disorder but found only in children, in which the epiphyses are still open, thus causing the defective mineralization of as well. The usual cause of both conditions is a **vitamin D deficiency**, but other factors include intestinal malabsorption syndromes (e.g. Crohn’s, celiac disease), as well as inherited renal disorders. (Berkow 1992; Govan 1990, 799-800; Rubin and Farber 1990, 709-11)

Vitamin D is a fat-soluble vitamin that plays a key role in the absorption of calcium from the gut, and proper bone metabolism. It occurs in two forms: **ergocalciferol** (activated ergosterol or vitamin D2), found in irradiated yeast, and is used to fortify milk; and **cholecalciferol** (activated 7-dehydrocholesterol, vitamin D3), formed by a phytochemical reaction in the skin when exposed to UV (sun)light, and also found in fish liver oils and egg yolks (Berkow 1992). Unlike vitamin D3, no metabolite of vitamin D2 is normally detectable in the blood of humans or primates. Although the conventional medicine states that vitamin D2 is equivalent with vitamin D3, it is an assumption based on sixty year old evidence that was recognized as weak, even at the time. The more biologically active form of vitamin D is cholecalciferol, which is about four times as potent as ergocalciferol (Veith 2001).

Although called such, vitamin D is in fact a **prohormone** with a number of active metabolites that have hormonal activities. The process of vitamin D production begins with the epidermal synthesis of 7-dehydrocholesterol. When exposed to UV light this chemical in the skin is slowly isomerized into cholecalciferol (vitamin D3), and is gradually released into the bloodstream. In the liver a hydroxyl group is added (hydroxylation) to the 25th carbon of the vitamin D3 molecule to produce **25(OH)D3 or calcidiol**. This molecule is then further hydroxylated in the kidneys under the influence of **parathyroid hormone (PTH)** to produce the metabolically active or **1, 25(OH)D3 or calcitriol**. (Berkow 1992; Govan 1990, 799-800; Rubin and Farber 1990, 709-11)
The typical cause of a vitamin D deficiency relates to the inadequate exposure to sunlight, deficient dietary intake or impaired intestinal absorption. In temperate regions and especially regions hampered by cold weather there is a tendency to not spend enough time outside (up to 45 minutes required on a daily basis) to ensure proper cholecalciferol production. This is exacerbated by recent shifts in the diet that have deprived people of important dietary sources of cholecalciferol, such as liver and eggs. Osteomalacia is almost unheard of in the tropics, although rickets is sometimes seen in infants because of the tradition of swaddling infants for extended periods, and keeping them out of sunlight. Other causes of vitamin D deficiency include intestinal diseases (e.g. Crohn’s, celiac, tuberculosis), hypoparathyroidism and familial hypophosphatemia. (Berkow 1992; Govan 1990, 799-800; Rubin and Farber 1990, 709-11)

Benign tumors of bone

**Osteochondromas** are the most common benign tumors of bone, usually found persons aged 10 to 20, with a slightly greater tendency to occur in males. They may be single or multiple, and although can arise from any bone tend to occur near the ends of long bones, usually the distal femur and proximal tibia. Such tumors are likely caused by either a congenital defect or trauma, or more rarely the autosomal-dominant osteochondromatosis. They are usually formed of cartilage capped by bony growths that grow away from the surface of the affected bone. **Chondromas** are a benign tumor of the cartilage and are usually asymptomatic. They are often found coincidentally when x-rays are taken for another reason. **Chondroblastoma** is a rare benign cartilaginous tumor that is usually found in the epiphysis of long bones, such as the femur, humerus and tibia. Signs and symptoms include pain and swelling. Chondroblastomas frequently recur after surgical excision, particularly if the lesion is large or is located in the proximal femur or pelvis. **Chondromyxofibromas** are very rare and occur before age 30. (Berkow 1992; Govan 1990, 807-10; Rubin and Farber 1990, 715-22)

**Osteoid osteoma** is a small painful, benign tumor that is characterized by a vascularized center of woven bone that becomes progressively larger and more painful. It most frequently occurs in young adults, three times more frequently in males. Pain is usually highly localized and worse at night. **Giant cell tumor** (**osteoclastoma**) is an uncommon tumor that occur most commonly in persons aged 20-30. The lesions usually occur in the
epiphyses, expanding outwards so that the bone cortex becomes very thin and is subject to rupture, causing fracture. Although excision is usually resorted to, giant cell tumors are notorious for their tendency to recur. (Berkow 1992; Govan 1990, 807-10; Rubin and Farber 1990, 715-22)

Malignant tumors of bone

**Multiple myeloma** is the most common type of malignant bone tumor, and usually occurs in older adults. Technically speaking, multiple myeloma isn’t a malignant bone tumor at all, but rather, a malignant tumor of plasma cells that inhabit the bone marrow. Normally, plasma cells comprise up to only 5% of the marrow tissue, but upon malignant transformation can increase to comprise up to 10% of the marrow mass, eroding bone and displacing other cells in the red marrow, leasing to anemia and immune deficiency. Multiple myeloma is most commonly found in the spine, skull, ribs, sternum and pelvis but can affect any bone with red marrow. Berkow 1992; Govan 1990, 799-800; Rubin and Farber 1990, 709-11)

**Osteosarcoma** is the most common primary bone tumor and is highly malignant. Osteosarcoma is most common in persons aged 10 to 20, although it can occur at any age, especially in the elderly secondary to Paget’s disease. In young patients the lesions are usually found at the end of long bones, most frequently in the region of the knee on the femur, tibia or fibula. Clinical indications of the disease typically occur only in the late stage, with localized pain and inflammation, and a palpable mass. Osteosarcoma most commonly metastasizes to the lung. Berkow 1992; Govan 1990, 799-800; Rubin and Farber 1990, 709-11)

**Chondrosarcomas** are malignant tumors of cartilage, developing in approximately 10% of patients with benign osteochondromas. It is most commonly seen in the 5-6th decade of life, more frequently in men, usually affecting the pelvis, sacrum, long bones, ribs, and scapula. Berkow 1992; Govan 1990, 799-800; Rubin and Farber 1990, 709-11)

**Ewing's tumor (Ewing's sarcoma)** is an uncommon malignant tumor of the long bones, especially the humerus, tibia and femur, but can occur on any bone. It most common affects patients younger than 20 years, and males are more frequently affected than females. Pain and swelling are the most common symptoms. Ewing's tumor tends to be extensive and can involve the entire
shaft of a long bone. Ewing's sarcoma frequently metastasizes to the other bones, as well as the lung and brain. (Berkow 1992; Govan 1990, 799-800; Rubin and Farber 1990, 709-11)

II. Inflammatory joint disease

Osteoarthritis

There is perhaps no disease that is as close to the human condition as arthritis, or joint pain. It is among the earliest diseases described in the ancient medical literature, and is clearly found throughout the anthropological record, such as in bone and fossil remains. Researchers from many fields tell us that it is a disease we share with a great many animals, including our fellow mammals, as well as birds, reptiles and fish. For all of us, the sad commonality is that it is apparently inevitable: a simple process of wear and tear to joints over a lifetime of use. Interestingly enough, some mammals that hang upside down such as bats and sloths don’t seem to experience this kind of joint damage, although mammals supported by water such as whales do (Berkow 1992). In yogic tradition this might be seen as evidence that inverse postures (asanas) such as headstands promote the proper flow of energy that overcomes stagnant energy… in the philosophical tradition of ancient India this is represented by Bodhi, or Enlightenment tree, which as it grows sends its branches back down into the earth…

Broken down, busted up and good ol' fashioned deee-generating joint problems got a high falootin’ name in western medicine: osteoarthritis (OA). It nonetheless has a precise definition, to differentiate it from the other forms of arthritis such as rheumatoid, gouty, or bacterial. OA is mild inflammatory joint disease characterized by a gradual loss of articular cartilage and the subsequent hypertrophy of bone producing osteophytes. Its prevalence increases with age, as does its severity, with a usual onset of it more symptomatic forms in the fourth to fifth decades of life (or usually earlier with sports injuries). Men typically have an earlier onset than women, but women get it at an increasing frequency with age. (Berkow 1992; Rubin and Farber 1990, 723)

OA is classified as either primary (idiopathic) or secondary to some identifiable cause. Primary OA involves the distal and proximal interphalangeal joints, the first carpometacarpal joint, the intervertebral disks and zygapophyseal joints in the cervical and
lumbar vertebrae, the first metatarsophalangeal joint, the hip, and knee. Secondary OA may present as above, but has a known underlying cause, including congenital joint abnormalities, genetic defects, crystal deposits, infection, metabolic diseases, endocrinopathies, inflammatory disease (e.g. RA, gout), and trauma from fracture or simple “wear and tear.” (Berkow 1992; Rubin and Farber 1990, 723)

Joints are an amazing feature of anatomical mechanics. Cartilage is a spongy, dense tissue covering the articular surfaces of bones, comprised mostly of extracellular matrix managed by a small number of very long-lived chondrocytes. This spongy surface is bathed in an extremely slippery synovial fluid filled with nutrients to feed the chondrocytes and support cartilage health. Surrounding the synovium is a series of tough fibrous tissues and muscles to unite the joint, and maintain stability. As the cartilage is compressed with movement, fluid is pumped out of it and into the joint space. In essence, this action squeezes the wastes from out of the spongy cartilage, to be absorbed by the capillaries and then venules of the muscosa. As the cartilage is released the cartilage expands, swelling back up with nutrient-rich, slippery synovial fluid. As a result, normal joint movement is essential to joint health, and because joints have a very coefficient of friction, they should maintain themselves almost indefinitely with normal activity. The primary pitfall with cartilage is that it is an avascular tissue, as well as both aneural and alymphatic: or in other words, a part of the body that we have an inherent capacity to take for granted (aneural), but can take a very long time heal (vascular, alymphatic). (Berkow 1992; Rubin and Farber 1990, 723)

The earliest changes of osteoarthritis are the loss of proteoglycans and type II collagen, which is the principal structural elements of cartilage, from the surface of the articular cartilage, followed by the death of the chondrocytes. This process may take several years. Overtime, the articular surface develops microfractures, and the synovial fluid works its way down into these fissures, extending the cracks deeper. Neovascularization from the epiphysis and subchondral bone extends into the areas of the fissures, inducing subchondral osteoclastic bone resorption. Adjacent osteoblastic activity occurs simultaneously, resulting in a thickening of the subchondral bone plate in the area of the crack. Fibrocartilage plugs then form as a substitute for the articular cartilage, and the subchondral bone becomes exposed as it grinds against the opposite joint surface, which is usually undergoing a similar process. These thick, shiny smooth areas or subchondral bone are described as eburnated, or “ivory-like.” This eburnated
bone then cracks, allowing synovial fluid to extend into the subchondral bone marrow, leading to a **subchondral bone cyst**. An **ostearthroplasty** or **bone spur** then develops, consisting of bone and a mixture of connective tissues with a coating of fibrocartilage and sometimes islands of hyaline cartilage within the osteophyte. The degree of formation of these spurs varies among the joints, in proportion to the underlying cause. Finally, **bony cysts** (**pseudocysts**) form in the marrow below the subchondral bone, resulting from extrusion of joint fluid through the hyaline cartilage into the marrow, with a fibroblastic and osteoblastic cellular reaction. The gross pathology includes a roughening, pitting, and irregularity of the hyaline cartilage surface, proceeding to gross ulceration with focal and then diffuse areas of complete loss of cartilage, leaving only eburnated bony surfaces. By the time symptoms appear, synovial proliferation and some mild synovitis are virtually always present. (Berkow 1992; Rubin and Farber 1990, 723)

The signs and symptoms of OA are insidious and gradual, usually involving one or only a few joints. Pain with movement and morning stiffness are among the earliest symptoms of OA. As the condition progresses joint movement is impaired, with crepitus, tenderness, grating sensations or muscle spasm. Overtime the joint can become edematous and swollen, with the proliferation of the various joint tissues. With improper treatment and repeated injury the chances for recovery become progressively less and less. (Berkow 1992; Rubin and Farber 1990, 723)

**Rheumatoid arthritis**

The *Merck Manual* defines **rheumatoid arthritis (RA)** as a “chronic syndrome characterized by nonspecific, usually symmetric inflammation of the peripheral joints, potentially resulting in progressive destruction of articular and periarticular structures,” with or without generalized manifestations (Berkow 1992, 1305).

RA usually manifests in a diarthrosis, or freely moveable joint. A distinguishing characteristic of this kind of joint is the presence of a synovial cavity that separates the articulating bones. A sleeve-like articular capsule attached to the peristeme of the articulating bones is composed of two layers: a **fibrous capsule** externally and a **synovial membrane** internally. The fibrous capsule provides for the strength and flexibility of the joint, and is composed of dense irregular connective tissue, sometimes arranged in bundles called
ligaments. The synovial membrane is composed of areolar connective tissue, elastic fibres and a variable amount of adipose tissue and secretes synovial fluid, which fills the synovial cavity, lubricates and provides nourishment to the joint. *Synovial fluid* consists of hyaluronic acid and interstitial fluid formed from blood plasma, and is quite viscous during inactivity and becoming less so during activity. As well as providing lubrication and nourishment, the synovial fluid contains phagocytes that remove microbes and debris from the joint, as well as metabolic wastes from the chondrocytes of the articular cartilage. Examples of different kinds of synovial joints are the knee, the radial-ulnar joint, and the hip and shoulder joints. (Berkow 1992; Rubin and Farber 1990, 725-29; Hickling and Golding 1984)

RA has worldwide distribution, but tends to be more prevalent in temperate climates. Between 1 and 3% of all populations are affected, with women two to three times more commonly than men. Onset may be present at any age but typically occurs between the ages of 25 and 50 years, the prevalence increasing with age. A genetic disposition towards rheumatoid arthritis seems plausible, but it is a complex process and little has been understood. In animal research at least two genes have been involved in the transmission of rheumatoid arthritis to offspring, halotype HLA-DW4 and alloantigen HLADRW4. (Berkow 1992; Rubin and Farber 1990, 725-29; Hickling and Golding 1984)

The pathology of RA is characterized by inflammation of the synovial membrane, which proliferates and thickens, forming villi that encroach upon space in the joint. This characteristic inflammatory tissue contains numerous polymorphs, lymphocytes and plasma cells and is highly vascular. Histologically the synovial fluid becomes inundated with leukocytes (e.g. T helper cells, macrophages), which produce cytokines and proteolytic enzymes that degrade the macromolecular complexes of the mucopolysaccharides that give the synovial fluid its viscous quality. Occasionally the cell content of the fluid becomes so high as to give the appearance of pus. The inflammatory membrane then produces an abnormal granulation tissue, called a pannus, that adheres to the surface of the articular cartilage. At the point of contact between the pannus and the hyaline cartilage, proteolytic enzymes are released and begin to digest the articular cartilage and subchondral bone. The process usually begins at the outer margins of the joint but then gradually spreads across the articular surface. Hyaline cartilage has a very limited power of regeneration and healing is by fibrosis. When the cartilage is destroyed, fibrous tissue joins the exposed articulating bones. The tissue begins to
ossify and fuses the joint together so that it becomes immovable. The distortion, so often seen in the hands and fingers of patients with rheumatoid arthritis is typical of the growth of this granulation tissue. Rheumatoid arthritis however, may never progress beyond the initial stages of swelling and inflammation, and it is only a small percentage that the disease will progress to a more serious state. (Berkow 1992; Rubin and Farber 1990, 725-29; Hickling and Golding 1984)

The cause of rheumatoid arthritis is unknown. For the longest time some form of infection was thought to be responsible, but the absence of a bacterial or mycoplasmic pathogen in the early stages of the disease has ruled this out. The possibility of it being a viral infection has attracted much attention, as viruses can resist detection by incorporating themselves in the nuclei of cells. Viral particles however would be recognized as antigenic, initiating a specific immune response that could identified, and so far, this has escaped the notice of researchers. Other hypothetical causes of RA such as poor nutrition, metabolic disorders, endocrine dysfunction, occupational and climactic factors have not withstood the rigors of epidemiological analysis.

There is an increasing amount of evidence however that damage to the gut wall plays a role in autoimmune diseases like RA (Cuvelier et al 1987; De Keyser et al 2002). For example, A significantly high number of patients with ankylosing spondylitis, a rheumatoid-like condition of the axial skeleton and large joints, have been shown to have histological indications of chronic gastrointestinal inflammation and damage. It appears that in many of these patients the remission of the condition occurs in tandem with the remission of digestive inflammation, and vice versa. These findings have given rise to the theory of intestinal permeability, which suggests that some agent or combination of agents initiates an inflammatory response in the digestive tract. Persistent GI inflammation eventually disrupts the integrity of the mucosal lining of the gut, and tiny perforations allow for molecules larger than usual to pass across this barrier, including molecules from dietary protein and fats, bacteria, parasites and fungi. In response to this infiltration, an immune response is initiated and the body begins to manufacture specific antibodies to these antigens. Unfortunately, human tissues have antigenic sites almost identical to those substances that pass across a permeable intestinal wall. These antibodies then circulate throughout the body and “look” for more antigens. When an antigen is found, such as a tissue that has similar markers to an exogenous antigen, the antibody initiates an immune response and the tissue begins to be destroyed. Factors
that directly or indirectly promote gut irritation and inflammation include antibiotics, alcohol, caffeine, parasites, pathogenic bacteria, peroxidized fats, some food preservatives and food additives, enzyme deficiencies (e.g. celiac disease, lactose intolerance), NSAIDs, corticosteroids, refined carbohydrates, oral contraceptives and mycotoxins (from stored grains and dried fruit).

In most cases RA is a disease of alternating cycles of exacerbation and remission. The onset is often abrupt, with simultaneous inflammation in multiple joints, but is gradual in other cases, with progressive joint involvement. The affected joints are tender, red and swollen. Joint involvement may or may not be symmetrical, but if so it usually manifests in the hands, wrists, elbows, ankles and feet. Joint stiffness lasting more than thirty minutes upon arising in the morning or after prolonged inactivity is very common. An intense cycle of exacerbation called a flare may begin for no apparent reason, promoting acute inflammation – these have been reported during changes of weather, periods of emotional stress, or in reaction to dietary articles. If the inflammation persists there is progressive joint deformity, with subcutaneous rheumatoid nodules in the later stages of the disease. Other manifestations could include visceral nodules, vasculitis (causing leg ulcers), pleural or pericardial effusions, lymphadenopathy, Sjögren's syndrome (dry mouth and eyes) and episcleritis. Neurological manifestations include carpal tunnel syndrome, caused by the compression of the median nerve under the flexor retinaculum at the wrist by inflammatory rheumatoid tissue. A low grade fever may also be present as well as generalized aches, malaise, loss of appetite, depression, weight loss, anemia and cold sweaty hands and feet. (Berkow 1992; Rubin and Farber 1990, 725-29; Hickling and Golding 1984)

Any four criteria must be present to diagnose rheumatoid arthritis; criteria 1 through 4 must have been present for more than 6 weeks.

1. Morning stiffness for ≥ 1 hour
2. Arthritis of ≥ three joints
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatic nodules
6. Serum rheumatoid factor, by a method positive in < 5% of normal control subjects
7. Radiographic changes (erosions, decalcification) (Berkow 1992)
Laboratory investigations factors include rheumatoid factor, an IgM, IgG and/or IgA subclass of immunoglobulins that is directed against the Fc fragment of IgG. Although given much importance, up to 25% of people with positive RF are healthy, and thus cannot be considered sufficient to rule RA in or out. Rather, RF is an effective measure of the severity of RA. Other diagnostic techniques include elevated ESR and normocytic anemia. Aspiration of the synovial fluid itself typically reveals low viscosity, high inflammatory cell count (mostly neutrophils), low glucose, high protein and positive RF. (Berkow 1992; Rubin and Farber 1990, 725-29; Hickling and Golding 1984)

Ankylosing spondylitis

**Ankylosing spondylitis (AS)** is a systemic rheumatic disorder characterized by inflammation of the axial skeleton and large peripheral joints. AS is three times more frequent in men than in women and begins most often between the ages of 20 and 40. It is 10 to 20 times more common in first-degree relatives of AS patients than in the general population, and is associated by class I histocompatibility antigens, in particular, HLA-B27. AS is differentiated from RA by sero-negativity for rheumatoid factor and other serological markers for RA. (Berkow 1992)

The most frequent symptom is recurrent back pain, often experienced at night, but the condition may also begin in any of the peripheral joints. Concomitant symptoms and signs may include impaired breathing from costovertebral involvement, a low-grade fever, fatigue, impaired appetite, weight loss and anemia. Mild to moderate symptoms come and go, and may go into remission for decades with stiffness as the only complaint – in other cases however the condition can promote deformities including kyphosis. Approximately 7% of patients with AS have psoriasis, and up to 20% of patients with ulcerative colitis or Crohn’s suffer from arthropathies such as AS. Full-blown systemic manifestations such as uveitis or pericarditis occur in about a third of patients, and is usually acute and self-limiting. (Berkow 1992)

Gout

**Gout** is a group of heterogenous diseases characterized by a recurrent acute or chronic arthritis of the peripheral joints that
Entirely result from sustained increases in serum uric acid levels. Due to its poor solubility, **monosodium urate crystals** begin to accumulate in and about the joints of the extremities, in the cartilage initially, and then into the bones and tendons. This initiates an inflammatory response that results in a granuloma-like tissue comprised of giant cells and activated mononuclear cells. As the condition progresses a white chalky deposit on the articular surfaces begins to accumulate. Sustained hyperuricemia can eventually lead to gouty arthritis of the central joints, or tissue damage to organs such as the kidneys. (Berkow 1992; Govan 1990, 814; Rubin and Farber 1990, 729-31)

The typical cause of hyperuricemia is the **impaired renal clearance of urate**, and thus gout is more common in patients that suffer from kidney diseases. Another clearly established cause of hyperuricemia is **increased purine synthesis**, seen in blood diseases such as lymphoma, leukemia, and hemolytic anemia, or diseases marked by excess cellular proliferation, such as psoriasis. There is also an autosomal-dominant inherited cause of hyperuricemia, either relating to a deficiency of hypoxanthine-guanine phosphoribosyltransferase or to an overactivity of phosphoribosylpyrophosphate synthetase. The former specifically is associated with a severe onset of gout and kidney disease at an early age. (Berkow 1992; Govan 1990, 814; Rubin and Farber 1990, 729-31)

Two environmental factors that appear to play an important role in gout are dietary purines and alcohol consumption. **Dietary purines** from protein catabolism is an important contributor to uric acid levels in the blood, with significant rises in uric acid often typically following the consumption of purine-rich foods (e.g. animal proteins, legumes, coffee). It appears that alcohol consumption functions synergistically to promote the formation of lactic acid in the liver, which blocks urate secretion by the kidney. (Berkow 1992; Govan 1990, 814; Rubin and Farber 1990, 729-31)

The signs and symptoms of acute gouty arthritis often begin without much warning, and can be precipitated by relatively minor events such as injuring a joint (such as the toe), an overindulgence in purine-rich foods and/or alcohol, or fatigue and stress. The pain typically affects only one joint, which becomes progressively more severe and is often excruciating, resembling an acute infection. The most common clinical manifestation is podagra, acute gouty arthritis in the metatarsophalangeal joint of the great toe, but is not limited to this, and may include other joints including the ankle, knee, wrist, and elbow. It polyarticular forms it is often
accompanied by ever, tachycardia, chills, malaise, and leukocytosis. In the initial stages of the disease the duration is limited, but with progressive inflammation the pain can be more or less chronic, eventually causing joint deformity. In many cases the condition is cyclical, with periods of remission and healing, interrupted by periods of exacerbation. (Berkow 1992; Govan 1990, 814; Rubin and Farber 1990, 729-31)

III. Muscular diseases

Myasthenia gravis

Myasthenia gravis (MG) is a comparatively rare, slowly evolving disease marked by periods of progressive muscle weakness. Skeletal muscle contraction is dependent upon the polarization of presynaptic neuron at a neuromuscular junction, and the synthesis and release of acetylcholine across the synaptic cleft. Myasthenia gravis is characterized by a defect in the action of acetylcholine, related to autoimmune factors, with antibodies directed against cell receptors for acetylcholine. In 90% of cases there are abnormalities in thymic function, including hyperplasia (~50%) or a thyoma (~40%). (Berkow 1992; Govan 1990, 784)

The disease is more common in women and usually develops by the age of 40, but can strike at any time. The initiating event leading to antibody production is unknown, but there are many speculations, including the theory of intestinal permeability. According to this theory, it is a permeable intestine that allows for the passage of bacteria such as E. coli into the bloodstream, causing the development of antibodies against bacterial receptors. Evidence has shown that these antibodies, originally formed against E. coli acetylcholine receptors may, in turn initiate an attack on human acetylcholine receptors (Stefansson et al 1985). Nutritional deficiencies have also been linked to MG, including as manganese, copper, zinc and other trace minerals, which may underlie thymic dysfunction (Boev et al 2002; Josephson 1961).

The most common early clinical presentation of MG is muscle weakness and fatigue of the face and neck muscles. More advanced signs and symptoms include ptosis (drooping of the eyelids) and diplopia (double-vision), with weakness of the limbs and difficulty breathing, and in some cases generalized
quadripareis. The clinical manifestations can fluctuate in intensity over a number of hours to days. (Berkow 1992; Govan 1990, 784)

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LESSON ELEVEN: Nervous system disease

Meningitis

Meningitis refers to the inflammation of the meninges, a series of membranes (dura mater, pia mater, arachnoid), that encloses the brain and spinal cord. Two forms are generally recognized: acute bacterial (purulent) meningitis and aseptic meningitis.

Bacterial meningitis
Several different bacteria can cause meningitis, but *Neisseria meningitidis* (meningococcus) and *Streptococcus pneumoniae* (pneumococcus) are the most common. Factors such as age, history of head trauma with leakage of CSF, as well as immune function (e.g. immunodeficiency) can aid in predicting the causative agent. (Berkow 1992, 1466)

Meningococci are found in the nasopharynx in about 5% of the population and are spread by respiratory droplets, but only a small fraction of carriers develop meningitis. Meningococcal meningitis occurs most often in very young children (< one year), or in epidemics among closed populations (e.g. military barracks) or in developing countries. In adults, pneumococcus is the most common cause of meningitis, most often in association with other risk factors such as alcoholism, EENT infections, head trauma, pneumonia, sickle cell disease, or spleen removal. (Berkow 1992, 1466; Rubin 2001, 213, 729)

Another organism involved in bacterial meningitis is the gram-negative *Haemophilus influenzae type b*, occurring more often in children between the ages of three months and three years, and rarely in adults with head trauma or immunodeficiency. *Escherichia coli* is another gram-negative pathogen in bacterial meningitis, usually developing in infants that haven’t developed resistance to gram-negative organisms. Other potential pathogens in bacterial meningitis include *Klebsiella*, *Enterobacter spp.*, *Staphylococcus* and *Listeria monocytogenes*, all of which are associated with immunodeficiency, head trauma, bacteremia, or surgical procedures. (Berkow 1992, 1466; Rubin 2001, 729)

Bacteria can reach the meninges by a number of routes depending upon the cause, including via the blood, local infection (e.g. sinusitis), or from the exposure of the CSF with the outside of the body, e.g. spinal trauma, surgery, etc.) Researchers have identified receptors for bacterial pili (filamentous projections) and other
surface components in the nasopharynx and choroid plexus, which facilitates invasion of the CSF. As the CSF has relatively low levels of antibodies, complement, and leukocytes, the infection develops unchecked, and only when it is more progressed does inflammation occur. Unfortunately, the immune response to these pathogens and the increasing exudate can damage cranial nerves and CSF pathways (causing hydrocephalus), and induces vasculitis and thrombophlebitis (causing ischemia). Inflammatory components of arachidonic acid metabolism and the cytokines generated by the exudate promote further damage cell membranes and disrupt the integrity of blood-brain barrier promoting edema of the brain and a rise in intracranial pressure. (Berkow 1992, 1466; Rubin 2001, 729-30)

If not caused by trauma or surgery, the typical signs and symptoms of bacterial meningitis include a prodromal respiratory illness or sore throat that precedes the fever, headache, stiff neck, and vomiting that characterize acute meningitis. Irritability, confusion, drowsiness seizure and coma may occur. If the infection continues unchecked the patient can die within 24 hours. (Berkow 1992, 1466-67; Rubin 2001, 729-30)

The most important clinical tests for meningitis includes an assessment for Brudzinski's sign, performed by flexing the neck of the supine patient forward until the chin touches the neck. Any pain or resistance, or flexion of the hips or knees suggests meningeal inflammation. Kernig’s sign involves flexing one of the patient’s legs at both the hip and knee, and then attempting to straighten the knee, noting any resistance of pain. Many patients will often experience some degree of resistance or discomfort, but in meningeal inflammation the pain and resistance is intense and bilateral. (Berkow 1992, 1467; Swash 1995, 327-28)

**Aseptic meningitis**

Aseptic meningitis refers to meningeal inflammation characterized by elevated leukocytes in the CSF (pleocytosis) and an absence of bacteria on examination and culture. It is a relatively common but rarely fatal condition usually caused by viral infections, drugs (e.g. chemotherapy, antibiotics, vaccines, NSAIDs), heavy metals (e.g. lead), and various diseases (e.g. stroke, multiple sclerosis, sarcoidosis, leukemia). Aseptic meningitis occurs in individuals of all ages and races, although it is more common in children, especially during summer, occurring up to three times more frequently in males than in females. (Berkow 1992, 1472-73)
The most common etiological agent in aseptic meningitis are viral infections, including the enteroviruses, herpes viruses, mumps virus, varicella virus, Epstein-Barr virus (infectious mononucleosis) and HIV. Enteroviruses such as the coxsackie viruses and echoviruses account for approximately half of the cases of aseptic meningitis. (Berkow 1992, 1473; Rubin 2001, 730)

The signs and symptoms of viral meningitis usually peak within three to six days after exposure, characterized headache, fever, stiff neck, photophobia, drowsiness, myalgia, malaise, chills, sore throat, abdominal pain, nausea, and vomiting. The specific diagnosis of the viral pathogen is elucidated by associated skin lesions such as the rash of varicella zoster, labial or genital lesions for HSV, or a mild maculopapular rash that typically occurs in the summer and fall months with the enteroviruses. Both Brudzinski's and Kernig's signs may be present. Unlike bacterial meningitis, viral meningitis is usually benign without any sequelae (Berkow 1992, 1473; Rubin 2001, 730)

Encephalitis and encephalomyelitis

The term encephalitis refers an acute inflammatory disease of the brain, whereas encephalomyelitis refers to inflammation of both the brain and spinal cord; in contrast, meningitis refers to the inflammation of the meninges and not the brain itself, although in many disorders there can be a considerable degree of overlap. The etiology of both encephalitis and encephalomyelitis is similar to meningitis, usually due to viral infection, but also includes hypersensitivity reactions caused by foreign proteins. Besides those already mentioned for meningitis, the encephalitides include the polio virus, rabies virus, arbor virus, western/eastern equine virus, St. Louis encephalitis and the measles virus. Diseases caused by proteins are related to the “infectious” prion diseases such as Creutzfeldt-Jakob disease. (Berkow 1992, 1472-73)

Poliotherapy

Poliotherapy is a term that refers to the inflammation of the grey matter of the spinal cord from infection with one of three strains of the poliovirus (brunhilde, lancing or leon). The polio virus is a single-stranded RNA virus that is transmitted through the oral-fecal route, usually through the contamination of water. The incubation period is 5-35 days, with the viral particles initially replicating in the nasopharynx and gastrointestinal tract, then invading lymphatic tissues and subsequently spreading throughout the body via the blood. The virus then invades the nervous system,
and travels to the motor neurons in the anterior horn of the spinal cord, as well as the brainstem and sometimes the meninges. The infection promotes an inflammatory reaction within the motor neurons, leading to paralysis, the extent of which is dependent upon the number and severity of the lesions. (Rubin 2001, 731-32; Berkow 1992, 2182-83)

Before the 19th century poliomyelitis occurred sporadically, but during the 19th and 20th centuries poliomyelitis reached epidemic proportions, reaching its peak around the mid 1950s, well after the development and widespread institution of various polio vaccines – some researchers feel that the epidemic of polio was in large part caused by these vaccines, many of which used the live virus. Since the mid-1950’s the incidence of polio decreased dramatically, with only 8-10 cases reported every year. (Rubin 2001, 731-32; Berkow 1992, 2182-83)

The vast majority (90-95%) of poliomyelitis cases are asymptomatic, with children and the immunocompromised the most frequently displaying clinical indications of the disease. Typical symptoms include anorexia, vomiting, abdominal pain, fever and headache. Of these patients, fewer than 5% will go on to experience some degree of paralysis, typified by an asymmetric loss of muscle function of the major muscle groups. Complete paralysis is much less common. Muscle atrophy is generally observed several weeks after the beginning of symptoms, and recovery may be complete, partial, or nil. Of those that display paralytic signs, the mortality is between 5 and 25%, with death usually resulting from respiratory failure. Evidence has shown that severity of infection is associated with a previous tonsillectomy – during the polio epidemic in the mid-1950’s, such procedures were widely performed as a kind of “prophylaxis” (Rubin 2001, 731-32; Berkow 1992, 2182-83)

**Rabies**

Rabies is an acute infectious disease of the CNS, caused by a single-stranded RNA rhabdovirus. It is a disease of mammals, especially carnivores such as dogs, wolves and foxes, but bats, cattle, goats and pigs are potential reservoirs. The rabies virus is a neurotropic virus that is often present in the saliva of rabid animals, which transmit the infection by biting other animals or humans - transmission from infected saliva to a mucous membrane or skin abrasion is rare. The most common vector for the disease are rabid dogs. Although uncommon in developed countries due to vaccination programs, it is still relatively common in Latin America, Africa, and Asia. Besides dogs, the other most common
vector are infected wild animals such as bats. (Rubin 2001, 732-33; Berkow 1992, 205-06)

Upon infection the virus travels via the peripheral nerves to the spinal cord and the brain, where it multiplies. After a latency of between 10 days and one year, the virus continues through efferent nerves to the viscera and most notably the salivary glands. The presence of the virus in the spinal cord and brain stem promotes an inflammatory response, which can spill over into the cerebellum and hypothalamus. Infection of the CNS promotes the destruction of neurons in the brainstem, causing painful spasms of the throat and dysphagia. These signs and symptoms are usually accompanied by restlessness, malaise, and fever, which gradually increase to an uncontrollable excitement. Due to the progressive dysphagia the patient cannot drink despite being intensely thirsty, and death usually occurs from asphyxia, exhaustion, or generalized paralysis. While treatment of the symptomatic disease unavailable, suspected cases of infection are treated aggressively over a period of months with a series of vaccines, and is usually successful. (Rubin 2001, 732-33; Berkow 1992, 205-06)

Prion diseases
Prion diseases, or transmissable spongiform encephalopathies, are neurodegenerative diseases characterized by a slowly progressive ataxia (staggering gait) and dementia, as well as spongiform changes, or the development of holes or vacuoles in neurons and glia in the brain. At least four human spongiform encephalopathies that have been identified: Creutzfeldt-Jakob disease, Kuru, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia. At one time these conditions were referred to as slow viral diseases, but are now thought to be caused by a prion (PrP^Sc), a small proteinaceous infectious particle that can resist inactivation by normal procedures. A related protein called PrP^C is a normal constituent of many cells in the body, neurons in particular – in prion diseases it is believed that the infectious PrP^Sc causes the conversion of the normal PrP^C into PrP^Sc. The early diagnosis of prion diseases is difficult, most cases presenting with manifestations similar to other diseases such as Alzheimer's. (Rubin 2001, 735; Berkow 1992, 209-10; Wisniewski 2005)

Creutzfeldt-Jakob disease (CJD) is a rare, slowly progressive disease of the CNS, characterized by progressive dementia and myoclonus (muscle spasm). The disease occurs worldwide, and can be sporadic, iatrogenic, infectious or familial. Sporadic CJD is linked to the spontaneous mutation of PrP^C to PrP^Sc, and is typically found in patients in their early 60’s. Iatrogenic CJD is linked to the transmission of infectious prions via certain medical
procedures such as organ transplants, blood transfusions, infected brain electrodes and the use of growth hormone prepared from cadavers. Infectious CJD is acquired by eating the meat and especially the neural tissue of animals suffering from spongiform encephalopathies (e.g. sheep, cattle, deer, elk, etc.), and has an average onset of 29 years. The familial form of CJD is related to an autosomal dominant trait linked to mutations in the PRNP gene, and usually occurs in patients in the mid to late 40’s. (Wisniewski 2005; Rubin 2001, 735-36)

The recent epidemic in Great Britain of bovine spongiform encephalopathy (BSE, or “mad-cow” disease) is believed to be the result of cattle being fed sheep parts from animals suffering from scrapie, a spongiform encephalopathy found in sheep. As cattle are herbivores and typically don’t choose to eat their fellow ruminants and browsers, this recent phenomena has arisen as the result of big agri-business attempting to maximize profits and eliminate the problem of waste disposal. Recent cases of this infectious Creutzfeldt-Jakob disease in humans, called new variant CJD (nvCJD), have been linked to eating BSE-infected beef. The clinical manifestations and pathology of nvCJD are very similar to those of kuru, discussed below. Infection occurs from eating animal products contaminated with PrPSc, which passes from the gut into lymphoid tissues where it replicates and infects PrPC. The infectious prions then spread to the brain via peripheral nerves and/or by hematogenous routes. (Wisniewski 2005; Rubin 2001, 735-36)

The signs and symptoms of CJD disease are gradual, presenting with memory loss that slowly progresses over weeks to months. In 10 to 20% of cases however, the onset occurs within days with little or no prodromal stage. In these cases, the first symptom is usually an episode of vertigo, blurred vision, or diplopia that rapidly deteriorates within days, followed by increasing mental deficits, fatigue and insomnia. As the condition progresses myclonus is a common clinical feature, usually appearing within the first six months of the disease. Dementia follows, and death typically occurs within two years. (Wisniewski 2005; Rubin 2001, 735-36)

Kuru
Kuru is a prion disease similar to CJD that was once very common among the Fore peoples of the New Guinea highlands. The etiology was related to the practice of women and children eating the body parts and especially the brain of departed family members. Its unclear how this tradition evolved, but since measures have been taken to discourage the practice the disease
Multiple sclerosis

Multiple sclerosis (MS) is a slowly progressive disease of the CNS characterized by numerous patches of demyelination in the white matter of the brain and spinal cord. These neural lesions result in a number of different neurologic symptoms and signs, and usually follows a course of remission and exacerbation. It is the most common CNS disorder among young adults in the developed world, affecting 1 in 1000 people, primarily in temperate climates. There is a familial incidence with certain HLA allotypes (e.g. HLA-DR2) suggesting a genetic susceptibility. Women have twice the prevalence as men, with a typical onset by about the age of 30 – the acquisition of the disease in childhood and in the elderly is rare. (Rubin 2001, 737; Berkow 1992, 1488)

The hallmark of MS is the development of plaques of demyelination that are disseminated throughout the white matter of the CNS, with the destruction of the oligodendroglia and perivascular inflammation. Plaques are of variable size but typically no more than 2 cm in diameter, frequently manifesting in the optic nerves, brainstem and spinal cord. As a result, the initial onset of the disease is often characterized by blurred vision or a loss of vision in one eye (relating to lesions of the optic nerve), double vision or vertigo (brainstem), or weakness and/or numbness in the lower limbs (spinal cord). Signs and symptoms typically follow a course of remission and recurring exacerbations, and can range from mild weakness and muscle fatigability, incontinence, emotional irritability, paralysis, visual defects and dementia. Death usually occurs with respiratory paralysis or urinary tract infection. Exposure to excess heat, such as warm weather, a hot bath, sauna, etc. may worsen the symptoms and signs. (Berkow 1992, 1488; Rubin 2001, 737-38)

The causes of MS are unclear, and many theories have been suggested, much of which implicates immune dysfunction. Some experimental and epidemiological evidence suggests the role of immunological cross tolerance, in which antigens are directed against self-tissues, which could be mediated by a variety of etiological agents, including viruses (Tejada-Simon et al 2003) or dietary components, the latter of which has been demonstrated in other conditions such as rheumatoid arthritis and diabetes mellitus. In both cases, injury to the epithelium of the digestive tract may
allow for the passage of both microbial and dietary antigens into the blood stream, initiating a hypersensitivity reaction resulting in neural inflammation.

Geographically, MS has three primary areas of frequency. High frequency areas, which is a prevalence of more than 30 per 100,000, include most of Europe, Israel, Canada, the northern US, southeastern Australia, New Zealand, and easternmost Russia. Medium frequency areas include the southern US, most of Australia, South Africa, the southern Mediterranean basin, Russia into Siberia, the Ukraine and parts of Latin America. Prevalence rates under 5 per 100,000 are found in the rest of Asia, Africa and northern South America. Migrants from high to lower risk areas retain the MS risk of their birthplace only if they are at least age 15 at migration. Those from low to high increase their risk even beyond that of the natives, with susceptibility extending from about age 11 to 45. Thus MS is ordinarily acquired in early adolescence with a lengthy latency before symptom onset (Kurtzke 2000).

Researchers have demonstrated that MS is five times more common in temperate climates than in the tropics. Auer et al recently demonstrated a striking, near sinusoidal annual variation in the number of active magnetic resonance imaging lesions in 53 multiple sclerosis (MS) patients (2000). These results suggest a seasonal fluctuation in MS disease activity. Some researchers have suggested that that vitamin D supply, which fluctuates with seasonal UV light exposure, is the primary environmental factor involved in MS (Ashton et al 2000). Moreover, circulating 25-hydroxyvitamin D [25(OH)D] also shows a near sinusoidal annual fluctuation at higher latitudes (Maxwell 1994). A vitamin deficiency has been implicated in the etiology of MS by epidemiological, experimental and immunological data (Hayes et al 1997).

Dietary fat has also been shown to play an important in MS. One study examined fat consumption in 150 MS patients from 1949 to 1984. In those patients whose daily fat consumption was less than 20.1 g (average 17 g), only 31% died and deterioration was slight. A daily intake of greater than 20 g (average of either 25 or 41 g) however, was attended by serious disability and deaths of 79% and 81%, respectively (Swank and Grimsgaard 1988). Although a low fat diet has been shown to make a difference in MS, it appears the type of fat consumed may play a significant role. Epidemiologic studies performed on the relation between the mortality rates from multiple sclerosis demonstrated that a high saturated fatty acid
intake is positively with multiple sclerosis mortality, whereas a high unsaturated fatty acid intake was negatively correlated with multiple sclerosis mortality (Esparza et al 1995). Some kinds of animal fats however, may be worse than others, such as pork (Nanji and Narod 1986). Researchers have determined that fat consumption plays an important role in myelogenesis (Di Biase and Salvati 1997) and that supplementation with fish oils has been shown to reduce the severity of MS attacks, and can improve clinical outcome in patients with newly diagnosed MS (Nordvik et al 2000).

Numerous other nutritional factors have been observed in MS, including deficiencies of B vitamins, vitamin E, calcium, magnesium, copper, selenium and zinc (Werbach 1996; Johnson 2000).

**Parkinson’s disease**

**Parkinson's disease (PD),** also known as **paralysis agitans** and **Parkinsonism,** is a progressive disorder of the CNS that typically affects older adults around the age of 60, prevalent in 1% of the population over the age of 55. The disease results in the widespread destruction of the areas of the basal ganglia that send dopamine secreting nerve fibers to the caudate nucleus and putamen. With the destruction of dopaminergic neurons the caudate nucleus and putamen become overly agitated, sending excitatory signals to the corticospinal motor system, leading to excitation and muscular rigidity. The high feedback gains without the inhibitory control of dopamine leads to tremor at a fixed rate of 3 to 6 cycles per second. In addition to the loss of dopaminergic neurons in the basal ganglia, other dopamine, monoamine and non-monoamine neurons may be destroyed in other parts of the brain. Diminished levels of norepinepherine, GABA (gamma amino butyric acid), GAD (glutamic acid decarboxylase, which acts on glutamic acid to produce GABA), serotonin, substance P, enkephalin, cholecystokinin and somatostatin have been observed in patients with PD. Reduced levels of homovanillic acid, a metabolite of dopamine, has been observed in the cerebrospinal fluid of PD patients, and is diagnostic marker. (Rubin 2001, 739-740; Berkow 1992, 1496-97)

PD is characterized by rigidity of the musculature, involuntary tremors and an inability to initiate movement (akinesia). Motor performance is impaired and the patient will have great difficulty in performing everyday activities such as shaving, brushing the
teeth, eating with utensils, buttoning shirts and opening door handles. As the disease progresses, handwriting becomes illegible, walking difficult and speaking unintelligible. Rigidity of the facial muscles can give the face a mask-like appearance, characterized by a wide, unblinking stare, an open mouth and uncontrolled drooling. (Rubin 2001, 739-740; Berkow 1992, 1496-97)

The cause of PD is unknown, although many have speculated that it may be the result of environmental toxins. Epidemiological and experimental data suggests the potential involvement of specific agents that acts as neurotoxicants (e.g. pesticides) in the pathogenesis of nigrostriatal degeneration (Di Monte et al 2002). In one epidemiological study an increased risk for PD appeared to be associated with occupational exposure to Mn, Fe and Al, especially when the duration of exposure is longer than 30 years (Zayed et al 1990). These studies in support of PD as a post-industrial disease however is in contrast with a disease described in ancient Indian medical texts called kampavata, that very much resembles PD (Manyam 1990). There is increasing amount of evidence to suggest that the pathogenesis of PD relates to oxidative stress and a reduced ability to deal with it, primarily in the mitochondria of the dopaminergic neurons of the substantia nigra.

Secondary PD can be drug induced by antipsychotic drugs (e.g. haloperidol) that are dopamine antagonists. The chronic use of resperine, an alkaloid from Rauwolfia serpentina, leads to dopamine depletion and can precipitate secondary PD as well. Researchers have found an increased prevalence of PD in patients born during an influenza pandemic. Only 5% of patients with PD have a family history of the condition. (Rubin 2001, 739-740; Berkow 1992, 1496-97)

Huntington’s disease

Huntington’s disease (HD) is an autosomal dominant disorder characterized by involuntary movements of all parts of the body, progressive intellectual deterioration, and often severe emotional disturbance. It usually begins in middle age, between 35 to 50 years, affecting both sexes equally. It is a disease that primarily affects whites of northwestern European ancestry, and is notably rare in Africa and Asia. (Rubin 2001, 740-41)

Researchers have discovered an HD gene on chromosome 4 that codes for a protein called huntingtin (htt), that is synthesized from an expanded and unstable trinucleotide (cytosine-adenosine-
guanosine, CAG) repeat (Rubin 2001, 741). It has been recently demonstrated that this mutant protein disrupts the mitochondria of nerve cells in the brain. Panov et al found that the mitochondria from blood cells of people with HD have a lower membrane potential than normal, and cannot take up calcium as efficiently as normal mitochondria. Mitochondrial degeneration is thought to be the underlying cause for the atrophy of the caudate nucleus, and decreased levels of the neurotransmitters GABA and substance P (Panov et al 2002).

Some researchers have postulated that abnormal metabolism of tryptophan or quinolinic acid underlies the mechanism that causes brain damage in Huntington's disease, and case histories have been reported where a low tryptophan diet was associated with an unexpectedly good outcome (Pascoe 1993). Other researchers report that individuals with HD are prone to abnormalities of carbohydrate metabolism, with results from the analysis of family data indicating that HD affected relatives of an HD patient with diabetes are 7 times as likely to have diabetes over the patient's non-HD relatives (Farrer 1985).

The symptoms and signs of HD develop slowly, with dementia and other psychiatric disturbances that range from apathy and irritability to full-blown bipolar or a schizophreniform disorder. These features typically precede or are simultaneous with chorea, including flicking movements of the extremities, a lilting gait, the inability to sustain motor activities, and other clinical features such as such as tongue protrusion, facial grimacing, ataxia, and dystonia. Patients ultimately lose the capacity to care for themselves, and walking becomes impossible, swallowing difficult, and dementia profound. At the end stage of the disorder most patients require institutionalization. (Rubin 2001, 2001)

**Amyotrophic lateral sclerosis**

**Amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease)** is a degenerative disease of motor neurons that results in a progressive weakness and wasting of the extremities, and eventual impairment of the respiratory muscles. It is named after the famous baseball player that suffered from the disease in a very public way. The cause is unknown, and has an incidence of 1 in 100,000 people, peaking in the 5th decade of life, with a greater tendency in men. Only 5% of cases are familial, and are linked to a mutant gene on chromosome 21. (Rubin 2001, 742)
The dysfunction of ALS is initially noted most often in the hands, with muscle wasting and painful cramping. The feet are another common site, but in some cases the presentation is random and progression is asymmetric. In progressed conditions there are visible fasciculations without limb movement, followed by a total disability of the musculo-skeletal system – however, sensory systems, voluntary eye movements and urinary sphincters remain functional. Most (50%) patients die within 3 years of onset, with 20% living up to 5 years, and 10% reaching 10 years. In rare cases a patient can live up to 30 years or more. (Rubin 2001, 742; Berkow 1992, 1513)

One recent study has shown that combining the supplement creatine and the antibiotic minocycline significantly slows disease progression, and prolongs survival in a mouse model of ALS. The combined treatment was significantly more effective than either compound administered alone (Zhang et al 2003).

Alzheimer’s disease

**Alzheimer's disease (AD)** is a degenerative condition of the brain that destroys memory, disrupts personality and accelerates death. The disease was first described in 1907 by Dr. Alois Alzheimer, who had a 51-year-old female patient suffering from a severe form of dementia. Upon autopsy, he noticed the deposition "of a peculiar substance in the cerebral cortex," which has since been determined to be a 40 amino acid long protein fragment called amyloid beta-protein. Alzheimer's disease affects more than 4 million people in the US, with an estimated 250,000 new cases every year. (Rubin 2001, 742-43; Berkow 1992, 1403; Roberts 1996)

The tendency to develop AD is probably multifactoral rather than a case of simple genetics or infection: in the case of familial prevalence, this may or may not be genetic, but rather, evidence of similar predisposing factors. Above all, AD appears to be a 20th century disease, resulting from the combined effect of dietary and environmental changes with genetic and immunological factors.

The clinical features of AD include dementia, disturbances in comprehension and language, as well as several other behavioral clues. Dementia refers to an impaired ability to pursue one's occupation and social activities. This may include confusion, difficulty in memory recall, difficult speech, altered judgment and impaired abstract thinking. There may also be a feeling of "not
being oneself," a loss of interest in favourite pastimes, diminished creativity and a diminished ability to express affection. Language disturbances include the inability to find the correct word or the use of "filler" words in conversation, circumlocation (talking around the subject), an inability to express one's thoughts in a written form or comprehend the written word, and difficulties in performing everyday physical tasks such as dialing the telephone or unlocking the door. Concomitant behaviours may include a deterioration of personal hygiene, inappropriate dress, a loss of social graces, losing and misplacing items, repeated traffic accidents, irritability, stubbornness, suspiciousness, a short attention span, an inability to perform simple instructions and an obsessive attention to trivial matters. The diagnosis of probable Alzheimer's disease (PAD) occurs when other possible causes of the above clinical features have been ruled out. This includes multi-infarct disease, Parkinson's, depression, alcoholic dementia, hypothyroidism, adverse reactions to pharmaceuticals, vitamin B12 deficiency, hydrocephalus (increased CSF in the brain's ventricles) and infections such as syphilis. (Rubin 2001, 742-43; Berkow 1992, 1403; Roberts 1996)

There are characteristic changes to the morphology of selective brain structures in AD, specifically of the hippocampus and cerebral cortex, which can be detected by MRI (multiple resonance imaging). The characteristic findings in AD are amyloid plaques, neurofibrillary tangles and the loss of nerve cells and synapses. Amyloid plaques are spherical structures that have a central core of beta-amyloid and varying degrees of inorganic aluminum. The number of these plaques directly corresponds with the severity of the disease. Beta-amyloid is cleaved from a much larger protein called amyloid precursor protein (APP), which is encoded on the 21st human chromosome, which in Down's syndrome is triplicated (trisomy 21). The production of beta-amyloid is not limited to the brain however, but also occurs in the walls of peripheral blood vessels. Thus, the gradual production and accumulation of amyloid plaques may occur well before neuronal degeneration in the brain: thus, AD may begin in early adulthood. The enzyme which cleaves APP has a genetic determinant and current research is focused on finding substances that block the activity of this enzyme. Neurofibrillary tangles are the twisted ends of dead nerve cells, and although not specific to AD, large quantities of them have been correlated with severe dementia. These tangles slow down nerve transmission and impair cellular function. There is a significant loss of brain cells and nerve synapses in AD, within the cerebral cortex and subcortical structures, the major suppliers of acetylcholine, norepinepherine and serotonin that serve the higher
cortical centres. (Rubin 2001, 742-43; Berkow 1992, 1403; Roberts 1996)

In cases of AD a marked depletion of acetylcholine has been noted in an area of the brain called the nucleus basalis of Maynard, in contrast to other neurotransmitters such as dopamine and GABA which remain normal. This has lead to the theory that AD is a degenerative nerve cell disorder that targets cholinergic neurons. Acetylcholine is a neurotransmitter that binds with M1 muscarinic receptors to evoke changes in that tissue, and is quickly broken down by acetyl cholinesterase. It has been suggested that there may be a deficiency of acetyl-L-carnitine, which provides acetyl groups for the production of acetylcholine. (Rubin 2001, 742-43; Berkow 1992, 1403; Roberts 1996; Mitchell 1996)

The average adult brain requires 112 grams of glucose to maintain proper brain function and impaired glucose levels can alter brain cells, initiate the induction of a neurotoxin called glutamate and cause dramatic alterations in the synthesis and metabolism of acetylcholine. The areas of the brain that seem to be highly vulnerable to glucose deprivation are the same regions of the brain that are affected by AD. Reactive hypoglycemia, caused by the overconsumption of refined carbohydrates, the usage of exogenous insulin in the absence of dietary precautions, calorie restriction, as well as the chronic usage of caffeine, alcohol and tobacco, are all possible cause of impaired glucose metabolism in the brain. (Roberts 1996; Mitchell 1996)

Reduction in the levels of brain oxygen, necessary for the production of ATP in oxidative phosphorylation, may affect various neurotransmitters, acetylcholine and nerve growth factor and is another possible contributing factor in AD. Factors that limit brain O2 include smoking, lung and heart disease, anesthesia, air travel, excessive sleep, poor breathing habits, migraine related brain blood vessel spasm and cerebral atherosclerosis. The latter of these factors may be caused by chronic states of hyperinsulinemia. (Roberts 1996; Mitchell 1996)

Certain food additives have been implicated in the development of AD, such as MSG and aspartame (NutraSweet®). Increased concentrations of glutamate and aspartate have been found in the CSF of AD patients. When MSG was tested on young experimental animals it lead to the rapid destruction of brain cells, leading it to be banned in baby foods. Aspartame consists of 50% phenylalanine, 40% aspartic acid and 10% methyl ester. Upon entering the stomach the methyl ester is transformed in free methyl
alcohol, which in small amounts can cause blindness, permanent neurological damage and even death. There is increasing evidence that mutation involving a single amino acid may be the cause of the production of amyloid precursor protein (APP). In a family with three generations of early onset autosomal dominant AD, DNA sequencing revealed the substitution of phenylalanine for valine in the transmembrane domain of APP. Excessive amounts of D-aspartate and other stereoisomers have been found in the neurofibrillar tangles of AD patients, as well as in the amyloid plaques. (Roberts 1996)

A substantial amount of evidence has indicated that aluminum plays a role in Alzheimer's disease. As much as four times the amount of aluminum as normal has been found in the brain of AD patients. Aluminum is known to interfere with essential enzymes needed to metabolize glucose for ATP production, cause the destruction of the blood brain barrier and transform L-aspartic acid into the neurotoxic D-aspartic acid. (Roberts 1996)

Demographic studies have found a greater preponderance of AD in women, possibly due to a higher incidence of excessive sugar consumption, fad dieting (causing reactive hypoglycemia), and greater longevity. On average, men have a higher metabolic activity in the temporal and limbic regions of the brain than women, which may confer a preventative benefit. (Roberts 1996)

Epilepsy

Epilepsy is a brain disorder characterized by short, recurrent, periodic attacks of motor, sensory or psychological malfunction. These attacks, called epileptic seizures, are caused by the abnormal, synchronous electrical discharge of millions of neurons in the brain, perhaps resulting from abnormal reverberating circuits. The incidence of seizure disorders is about 2%, with about 0.5% of those suffering from epilepsy on a regular basis. At least four types of epileptic seizures have been identified: grand mal, temporal lobe, focal and petit mal. Grand mal (tonic-clonic seizure) is characterized by generalized involuntary muscular contraction and cessation of respiration followed by tonic and clonic spasms of the muscles. EEG recordings indicate a high voltage synchronous discharge that occurs over the entire cortex on both sides of the brain, originating in the basal regions of the brain that drive the cortex. The reticular activating system may be temporarily depressed so that the person loses consciousness. The teeth may be clenched, the tongue may be bitten and control of
bowel and bladder may be lost. After the seizure consciousness shortly returns and breathing begins with noisy respirations. The person may feel sleepy, fall asleep or experience confusion and has no memory of the episode upon awakening. The prodromal symptoms of grand mal may include auras, as well as unusual odours and sounds. (Berkow 1992, 1439)

**Temporal lobe (psychomotor seizure)** is characterized by psychic symptoms (visual or auditory hallucination, déjá vu), loss of judgment and autonomic behaviour, and abnormal activity. Typically, there are no apparent convulsions, but there may be a loss of consciousness or amnesia for the episode. During the seizure the patient may appear drowsy, intoxicated, violent or commit asocial behaviours, but other activities such as driving a car or eating remain unaffected. Psychic symptoms may be accompanied by chest pain, transient respiratory arrest, tachycardia, abnormal taste and/or smell sensations, and GI disturbances. EEG readings during a psychomotor attack show a low frequency rectangular wave with a frequency of between 2 and 4 Hz, superimposed with 14 Hz waves. (Berkow 1992, 1439-40)

**Focal epilepsy** can involve almost any region of the brain, resulting from localized lesions such as a tumor or damaged neural tissue, or from congenitally deranged circuitry. Such lesions can promote the rapid discharge of local neurons, and when this electrical activity passes a threshold of about 1000 Hz, it begins to spreads to adjacent cortical regions, as slow as a few millimeters per second to as fast as a few centimeters per second. When such a wave progresses over the motor cortex, it often causes a progressive series of muscular contractions throughout the body, while the person remain conscious. It may begin in the fingers and toes and progress upwards, or it may begin in the mouth region and progress downward to the legs. This particular manifestation of progressive muscular contraction is called **Jacksonian epilepsy**. (Berkow 1992, 1437-40)

**Petit mal (absence seizure)** is characterized by a sudden momentary loss of consciousness (10-15 seconds), occasionally accompanied by myoclonus of the neck or upper extremities, slight symmetric twitching of the face or a loss of muscle tone. EEG recordings in petit mal show a characteristic spike and dome pattern. (Berkow 1992, 1438-40)

Brain samples from epileptic foci of experimental animals have been shown to have abnormally low concentrations of GABA and abnormally high levels of glutamate. Physiologically, the role of
glutamate is excitatory, promoting neuronal firing in the cerebellum and depolarization in the cerebral cortex. GABA, on the other hand, inhibits cerebral firing. Administration of glutamate in experimental animals has been shown to induce epileptic seizures. Thus, excessive amounts of glutamate may be a mechanism of seizure. Seizures are believed to stop because of neuronal fatigue, and the active initiation of inhibitory neurons. (Cooper 1996)

Epileptic seizures are known to be initiated by strong emotional stimuli, alkalosis caused by hyperventilation, drugs (e.g. metrazol, insulin), fever, loud noises and flashing lights. Other possible causes of epilepsy include severe head injuries (even in gestation), atherosclerosis, brain tumors or abscesses, intracranial infection, drug abuse, cerebral ischemia, exposure to rapid fire images common to some kinds of television programming and video games, food allergies, and Leaky-Gut syndrome.

Many epileptics report an unusual odor prior to seizure, which may or may not be present in the environment. Neural pathways from the basal ganglia and many other brain regions extend into the olfactory bulb, and thus odor may be a trigger or a symptom for seizure. Some clinicians have speculated that it may be possible to prevent seizures by anticonvulsant essential oils such as Aniseed, Celery seed and Lavender. Some kinds of essential oils are reported to initiate seizures, such as Artemisia spp., and should be avoided.
References


