Unit Lecture 8

Human-Microbe Relationships

When a body comes in contact with a microbe a number of events can occur. The microbe can colonize the body (take up residence as part of normal flora), cause infection, be lost, or cause an allergy to develop. If an infection results, three outcomes are possible. The immune system may "cure" the body (results in immunity), the microbe may become entrenched and cause disease, or the body may develop a carrier state with the microbe. If infection progresses to disease, two outcomes are possible. The immune system may "cure" the body (results in immunity). Damaged tissue may lead to morbidity (tissue dysfunction). If damage is severe enough, mortality (death) may occur.

Our bodies are composed of 100 trillion cells. Only ten percent of those cells are human tissue cells. The rest are microbes, most of which are good cells, but some of which are bad. The relationships between man and microbe can be defined as follows:

- Independence: man and microbes exist together with no significant interaction.
- Mutualism: man and microbe both benefit from living together
- Commensalism: either man or microbe benefits from living together and neither helps nor harms the other significantly
- Parasitism: microbes live at the expense of the human host.
    - Ectoparasite: lives on the external surfaces of the body
    - Endoparasite: lives on the internal surfaces of the body or within the deeper tissues
    - Obligate parasite: requires coexistence with human host to survive
    - Opportunist: an organism which is normally a commensal becomes parasitic, usually because of environmental changes
    - Occasional parasite: rarely seen parasite

Normal flora is defined as organisms normally seen associated with humans' skin and mucous membranes. There can be a mutualistic or commensal relationship. Again, for every one human cell in or on our bodies there are ten bacterial cells. Normal flora serves the purpose of protecting the body against pathogenic organisms by occupying sites on the cells, thus preventing the pathogen from attaching. They also may stimulate or prime the immune system. For a list of normal flora by site, see Table 13.3 in the text.

A **pathogen** is defined as an organism that creates a disease state. Because of this one can say that there is a parasitic relationship. The main events in the historical background go back to Fracastoro, when in 1546 he suggested a "contagious" nature of disease. Koch in 1876 established the "postulates" to link microbes to disease. Below are listed Koch's postulates.

- Infectious organism must be found in all diseased individuals and absent in healthy ones.
- Organism must be isolated and grown in pure culture.
- Organisms from pure culture will cause disease when inoculated into healthy individuals.
- Same organisms must be recovered from laboratory-inoculated individuals.

For an organism to cause disease, three things must occur:

- The organism must become established in tissue. It's got to get into the body. Portal of entry is important. The two main portals of entry are the GI and respiratory systems. These systems contain some unique defenses that protect the body from infection. On the other hand, bacteria have developed some unique methods to hijack host cells and make them behave in a manner that is beneficial to the bacterium.
- The organism has to attach to the host otherwise it just passes out of the body. To attach, the organism may use fimbriae, pili, or flagella.
- The organism must survive the host defenses that are trying to destroy the foreign organism.

Virulence factors of microbes contribute to their pathogenicity or disease causing abilities. The number of organisms present in the inoculum plays a role in causing disease. For some organisms a small number of virulent organisms (e.g. tularemia) can cause disease whereas in another case, a large numbers of avirulent organisms (e.g. enteritis) may be needed to cause disease. In another situation it may take variable numbers of same organism depending on site and the immune status of the individual. The skin and mucous membranes are more resistant to some organisms but other exposed tissues have less resistance.

Bacterial toxins are chemicals which prevent normal metabolism of specific cells or groups of cells and results in disease or death of cell. The types of toxins an organism can produce include endotoxins (lipopolysaccharides from degenerating gram negative cell wall can cause Disseminated Intravascular Coagulation-DIC) and exotoxins (proteins secreted by living microbes). There are three types of exotoxins: cytotoxins which kill host cells, neurotoxins that interfere with nerve cell function and enterotoxins that affect the cells lining the GI tract. Some organisms produce hemolysins which destroy red blood cells but which can also be used to help classify organism. For example, alpha hemolysis causes a greening around the colony on a blood agar plate. Beta hemolysis is the complete destruction of red cells on a blood agar plate and gamma hemolysis produces no change or destruction of red cells. Other

toxins include leukocidin (destroys white blood cells), lecithinase (degrades collagen), coagulase (coagulates proteins), and hyaluronidase and streptokinase (spreading factors). Notice that a number of these are enzymes.

Adherents such as fimbriae or flagella allow the microbe to attach to tissue. Capsules prevent the phagocytic action of WBC's. Some bacteria secrete molecules that change the host's cell membrane that allow the bacterium to attach, and in some cases penetrate the host cell. *E. coli* O157:H7, the agent of hemolytic uremic syndrome, and *Salmonella typhi* do just that. These secretion systems evolved not to sicken the host cell, but to protect the microbe from single-celled organisms in the soil.

Disease is any dysfunction of the body. Psychosomatic disease is a dysfunction of a psychic, emotional or mental origin and does not concern us. Organic disease is a dysfunction derived of substances from a living organism. A non-infectious disease is a dysfunction not capable of being caused by a parasitic organism; whereas an infectious disease is a dysfunction caused by a parasitic organism which invades and proliferates in a host. Those forms of infectious dysfunction may be due to toxicity (quality of being poisonous). When a toxin is toxin spread via bloodstream, a state of toxemia exists. Intoxication is due to ingestion of a preformed toxin, for example, Staphylococcal food poisoning. A change of a tissue to a less functionally active form is known as degeneration. Necrosis refers to death of a cell or group of cells which is in contact with living cells.

Factors relative to spread of infectious disease include:

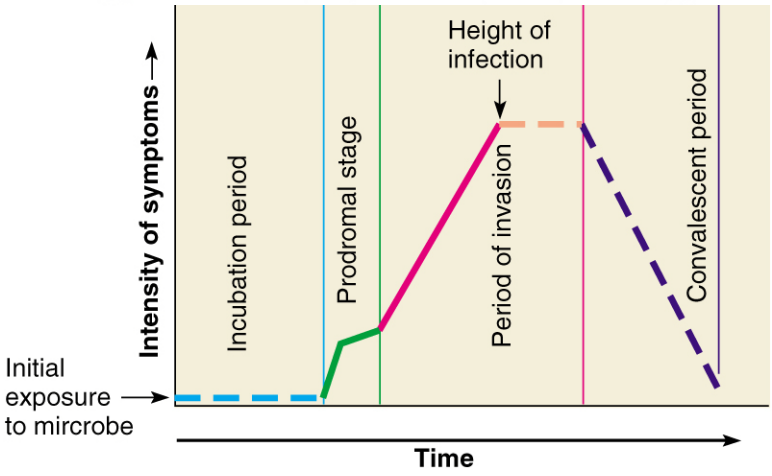
- Pathogenicity: ability of a microorganism to cause disease
- Virulence: degree of pathogenicity of an organism indicated by fatality rates or ability to invade the tissues of the host. True pathogens produce virulence factors that allow it to evade host defenses.
- Resistance: natural ability to ward off noxious agents (toxins, irritants, & pathogenic organisms).
- Susceptibility: state of being readily affected by noxious agents.
- Noncommunicable: not capable of being transmitted from one person to another.
- Communicable: capable of being transmitted directly or indirectly from one person to another.
- Contagious: capable of being transmitted easily and directly only from one person to another

The sources of infectious disease may originate outside the organism which becomes ill (**Exogenous**) or may originate from within the organism which becomes ill (**Endogenous**). The causes may be the loss of any of limiting factors from transplantation to a new environment. Examples of universal opportunists include *Staphylococcus, Streptococcus, Candida, and Pseudomonas*. A reservoir is: a place, animate or inanimate, of survival and

replication of organisms. A fomite is an inanimate object, other than food or water, involved in disease transmission.

During the course of an infectious disease signs and symptoms (See table in text) may be exhibited by the patient. A sign refers to any objective evidence of disease noted by the observer. **Signs** are observable and measurable. Examples of signs include fever, septicemia, microbes present, chest sounds, and skin eruptions. **Symptoms** are subjective evidence of disease. Symptoms are not measurable. They include chills, pain, nausea, malaise, chest tightness, and itching. A syndrome is a group of signs and symptoms that when taken together characterize a particular disease. For example, AIDS is characterized by malaise, loss of T-lymphocytes, diarrhea, weight loss, pneumonia, and infection with certain microbial diseases.

Classic Stages of Clinical Infections



The **incubation period** is the time between implantation of a disease agent and its clinical manifestations. Illness is the time of pronounced deviation from the normal, healthy state. During the **prodromal stage** the first appearance of a symptom or symptoms indicates the onset of illness. In the **Period of Invasion**, the microbes multiply in high numbers and cause the severest symptoms. This period is often marked by fever and a specific symptom or symptoms that may be used to identify an illness. At the acme (height of infection) or crisis there exists a turning point for good or bad. In the **convalescent** or decline period, the patient's strength and health return, symptoms subside, lesions, if present, subside or become secondary, a scab (crust of a superficial sore) and scars (connective tissues formed in the healing of a wound) form. The fever is lysed. If the infection results in death, the infection is referred to as terminal.

Primary lesions can present in different ways:

- Erythema: a rosy rash
- Macule: a discolored spot not raised above the surface of the skin
- Papule: a small, circumscribed, solid elevation of the skin
- Wheal: a flat, edematous, spongy elevation of the skin
- Vesicle: a small, fluid-filled elevation of epithelium
- Pustule: a small, pus-filled elevation of epithelium

Exudates present: specific gravity >1.015

- Any substance deposited in or on the tissues that contains cellular debris
- Serous: containing serum; “no” clotting proteins
- Fibrinous: containing fibrin; all blood protein
- Sanguineous: containing blood; all blood cells
- Purulent: containing pus
- Catarrhal: containing mucus
- Serosanguineous: containing serum and blood
- Fibrinopurulent: containing fibrin and pus

Terminology of infectious disease in individuals

- Local: restricted to one spot
- Focal: a beginning local infection that spreads from that site
- Systemic: affecting the body as a whole
- Chronic: continuing for a long time
- Acute: of short duration but usually generally severe
- Subacute: don’t come on as acute and don’t last as long as chronic infections
- Primary: first in time, place or importance
- Secondary: second in time, place or importance
- Mixed: showing two or more organisms simultaneously causing one type of infection
- Asymptomatic: not showing symptoms
- Latent: potential, not yet manifest
- Nosocomial: those infections acquired in a health care setting
- Bacteremia: bacteria in the blood
- Septicemia: pathogenic bacteria and their toxins in the blood
- Sapremia: non-pathogenic bacteria in the blood (may, however, produce toxins when in the blood and become a septicemia)
- Abscess: an anaerobic, hollow site filled with debris
- Pyemia: general septicemia with secondary foci of suppuration and abscess
- Toxemia: toxins absorbed into blood from a localized source of infection

Portals of entry/exit refer to how an organism usually associated with system enters and exits the infected individual. Remember, what is the meaning of life? Is it advantageous for an organism to be a quick, efficient killer or one that causes a slow, chronic type disease (establishes a parasitic relationship that lasts a long time)?

- Diseases of the GI Tract enter via mouth and exit via anus.
- Diseases of the respiratory tract enter and exit via the nose or mouth.
- Diseases of the GU tract usually enter and exit via genitals. Some UTI are of a hematogenous source (from the blood stream).
- Diseases of the skin enter and exit from the skin.

- Systemic diseases occur in areas restricted from environment by skin or mucous membranes. They usually have variable, but predictable, portals.

Transmission of microbes occurs in a variety of ways. Direct transmission involves surface-to-surface contact, contact with body fluids, and congenital (vertical) transfer from mom to fetus. Direct transmission usually involves parasites with little ability to adapt to conditions away from human host. Direct transmission may also involve animate vectors, a reservoir host (where the organism resides), carriers, mechanical vectors (not necessary to life cycle of organism), biological vectors (actively participates in an organism's life cycle) or human carriers (which can be asymptomatic or passive). Indirect transmission involves inanimate vectors, such as food, water or other beverages, or air. A fomite is an inanimate vector other than food, water or air. These parasites have a greater ability to survive away from human host. Examples included spore and cyst formers, an organism that produces a capsule, has a slow rate of metabolism, frequently mutates, and has a saprophytic existence.

Factors of host that impact on the transmission of microbes to a host involve the host's resistance to the microbe, the genetic factors of the host (some races or individuals are more likely to fight off a certain microbe than others), the host's current health and diet, the host's vaccination status and age. Host susceptibility is the limiting factor in the spread of infectious disease.

Epidemiology determines the factors influencing causation, frequency, and distribution of disease in a community. There is a set terminology of infectious disease in a populace.

- **Sporadic**: occurring only occasionally
- **Endemic**: low in incidence but constantly present in a geographic area
- **Epidemic**: attacking higher than normal number of people at the same time and spreading rapidly
- **Pandemic**: widespread epidemic
- **Prevalence**: total number of cases
- **Incidence**: number of new cases
- **Morbidity**: general health of the population
- **Mortality**: death rates

Role of the epidemiologist is involved in surveillance of reportable diseases. They are statistic keepers and investigators of when and where outbreaks start.

Non-specific Body Defenses

What's a body to do? How can it defend itself from the onslaught of microbes? The body produces certain factors which limit growth of microbes. The tissue may contain limited moisture (microbes require water to survive),

be at a pH where the microbe cannot reproduce (pH of the stomach is <2). The mucous membranes trap microbes because of the mucous it produces and then removes it by ciliary action of certain types of epithelial cells. Mucous can also contain secretory substances (IgA). The washing action of fluids (urination, crying) removes organisms. The body can prevent microbes from reaching sites where they could cause disease by filtering the organisms out before they get to those sites. Lastly, the presence of other microbes can prevent the occupation of that cellular site by pathogenic organisms.

A non-specific body defense is any defense that protects against a variety of invaders. Whereas a specific body defense is defense directed against a single kind of invader of the body. Specific body defense involves the formation of antibodies and will be covered later.

The **first line of defense** involves both mechanical factors and chemical factors. A continuous tissue layer (the skin and mucous membranes) serves as a barrier to invading microbes. Genetic barriers also play a role in the first line of defense. Mechanisms such as filtering by hairs, blinking, coughing and sneezing, ciliary and washing action are all mechanical actions the body performs to protect against invasion by microbes. Chemical factors in the first line of defense include the production of mucus/mucin, an acidic pH, bile salts, and nutritional factors. Those that are primarily antimicrobial are lysozyme (found in tears and perspiration breaks apart bacterial cells (esp. Gram-pos)).

The **second line of defense** takes over if the first line has been penetrated. Phagocytic cells and a chemical system are the found in the second line of defense. Fixed phagocytes or fixed macrophages comprise the basic cells of the reticulo-endothelial system (RES). They sit in prominent locations such as the spleen, liver (Kupffer cells), lymph nodes, bone marrow, lung (Dust cells), nervous tissue (Microglia), and connective tissue (Histiocytes). Circulating phagocytes or wandering macrophages are also known as Monocytes. Microphages include the neutrophils (PMN's) and eosinophils. Phagocytes digest the invading microbe and then eliminate the remnants from the cell. Natural killer (NK) cells are lymphocytes that secrete toxins onto infected cell surfaces or a neoplasm. All of these cells have specific functions.

A couple of the chemicals the body produces are interferon, which is produced to prevent viral replication, and complement (a series of twenty plasma proteins that interact in sequence). The compliment cascade is normally initiated by reaction of antigen with antibody. C3b is called "opsonin". Opsonin coats invading antigens enabling phagocytosis. The membrane attack complex (C5-C9) is called "cytolysin". Cytolysin coats invading cells and pokes holes through the cell wall which destroys cell. Two complements are called "anaphylotoxins" (C3a, CC4a, and C5a). Anaphylotoxins bring about histamine release from platelets, basophils and

mast cells. Histamine causes vasodilation & increased capillary permeability. This is manifest by inflammation.

In the inflammatory response the "cardinal signs" include redness (rubor), heat (calor), swelling (tumor), and pain (dolar).

Chemotaxis, also stimulated by anaphylotoxins, summons WBC's to the site of infection. Properdin, a plasma protein, stimulates the "alternate pathway" of complement cascade. It is initiated by cell wall polysaccharides or endotoxins. It has same results as normal pathway of cascade.

Prostaglandins are localized tissue hormones that have many functions. They increase capillary permeability for inflammation and cause the pain of inflammation. Interleukins (cytokines, leukotrienes) are produced by WBC's for communication. There are over one hundred kinds.

Fever (body temperature >37^{o}C) or pyrexia is a common mechanism associated with invasion of microbes. Fever is stimulated by presence of foreign or abnormal protein. This protein affects the thermoregulator of the hypothalamus. The source of unrecognized proteins is exogenous pyrogens, viral infections, pyogenic bacterial infections, endotoxins from Gram-negative bacteria, eukaryotic infections, allergies, endogenous pyrogens, destroyed phagocytes, and tumor cells. Other organic causes include neural disorders and endocrine disorders. Lastly, fevers may be of an unknown origin (FUO). Side effects of fever include malaise, body aches, and tiredness.

The primary concept to remember about first and second lines of defense is that they are nonspecific. The Immune system will attack any foreign antigen that it detects and will move to destroy it.