

Pathology and Mechanisms of Pathogenicity (quicky version):

Pathology is the study of disease dealing with etiology, pathogenesis and the anatomical and physiological changes occurring within a host organism due to a particular disease process. As demonstrated by Koch's postulates, certain types of microorganisms are **etioloical** (disease-causing) agents, while others are not. Likewise, certain types of disease have very specific etiology, i.e., involve just one type of microorganism, while others involve various agents, or do not involve microorganisms at all. In microbiology we are most interested in **communicable diseases**, i.e., those caused by microorganisms that can be **transmitted directly** from one host to another, but we are also interested in those resulting from exposure to microorganisms or their toxins encountered in the environment, i.e., in association with non-living reservoirs and/or vehicles. We will not consider non-microbial diseases.

For study purposes then:

Pathology – Pathology is the study of disease that deals with:

- a) **Etiology** – the cause of the disease (type of pathogen involved)
- b) **Pathogenesis** – what the particular type of pathogen is doing inside the host
- c) **Symptoms** – the structural (anatomical) and functional (physiological) changes occurring within the body due to the activities of the pathogens.

As indicated earlier, immunity is resistance to or the ability to resist infection and disease, so infection and disease are not the same.

Infection – An infection is occurring when potential pathogens have colonized some part of the body, i.e., a region where these organisms are not normally found.

Disease – Disease is occurring when an infection results in negative changes to the overall health of the host organism.

Diseases may vary considerably in terms of duration and occurrence, and can be categorized as:

Acute disease – Acute diseases are those involving symptoms that develop rapidly but typically last a short period of time, e.g., the common cold or viral gastroenteritis.

Chronic disease – Chronic diseases are those involving symptoms that develop slowly and last a long time, e.g., mononucleosis, tuberculosis and leprosy.

Latent disease – Latent diseases involve pathogens capable of persisting within the body for long periods of time without causing disease symptoms, but still capable of doing so. All human herpesviruses are capable of causing latent disease, as are *Mycobacterium tuberculosis* and *Plasmodium falciparum*.

Diseases also vary with respect to the region of the body affected, and typically involve microorganisms with specific portals of entry (as described later). When pathogens or their products enter the bloodstream they may cause one or more of the following conditions:

Bacteremia – Bacteremia results when bacteria have gained access to the bloodstream, a region of the body where bacteria are not normally found. This can occur during dental or medical procedures, or may result from infection in other areas such as the urinary tract or intestine.

Septicemia – Septicemia is a more dangerous condition and involves bacteria in the bloodstream, reproducing there and causing disease or septic symptoms. Septicemia can also involve yeast-like fungi including *Candida* and *Cryptococcus*.

Toxemia – Toxemia can result from bacteria releasing toxins into the bloodstream, as can occur following infection with *Clostridium tetani* or *Corynebacterium diphtheriae*. Both types of bacteria tend to colonize small areas, but cause disease symptoms by releasing their toxins into the bloodstream.

Viremia – Viremia occurs where there are viruses in bloodstream. Depending on the type of virus involved, and whether viremia is primary or secondary, it may cause only mild symptoms or be deadly.

What about virulence?

As described earlier, one of the factors influencing the severity of epidemics is the **virulence of the microorganisms involved**. For this reason, it is useful to define virulence and consider the microbial features influencing it.

Although sometimes used interchangeably with pathogenicity, **virulence** refers to the degree of pathology caused by a particular type of microorganism. **Pathogenicity** is the ability of specific types of microorganisms to infect and cause disease symptoms in other organisms, i.e., cause harm. Many different types of microorganisms can be pathogens, including bacteria, fungi, algae, protozoa, and multicellular parasites; non-cellular entities including viruses, viroids and prions can also cause disease. None-the-less, interaction with a pathogenic microorganism does not always result in disease. Host organisms are equipped with a variety of immune mechanisms, and the eventual outcome of host-pathogen interactions are dependent on how effective these are when challenged by microorganisms. Microorganisms can be defined as being pathogenic (or not), but those recognized as pathogens may exhibit different levels of virulence depending on a variety of circumstances.

The virulence of a particular type of pathogen is variable, can change over time due to genetic alterations in microbial populations, and may be characterized by different symptoms in different host organisms. In general, the greater the virulence, the more likely it is that a particular type of microbe will cause disease.

The virulence of a particular type of pathogen can be expressed in terms of infectious dose, ID₅₀ and infective dose LD₅₀ as defined below.

Infectious dose (ID₅₀) – The infectious dose or ID₅₀ for a particular type of cellular pathogen is the concentration (cells/ml) required to infect 50% of a test population.

Lethal dose (LD₅₀) – The lethal dose or LD₅₀ is the concentration (cells/ml) of a particular type of cellular microorganism required to kill 50% of a test population.

In order to succeed as virulent pathogens, microorganisms must be able to:

1. Gain access to host cells and tissues – This means the pathogen must be able to get past our first line of defense, i.e., skin and mucous membranes. Pathogens typically have a preferred **portal of entry** as determined by their ability to attach to and pass through cellular barriers. Different types of microorganisms cause infection in different regions of the body because they have receptors for and can bind with only certain types of cells.

Primary portals of entry involve mucous membranes, and include the respiratory tract, gastrointestinal tract, urinary tract, etc., but some types of pathogens have the ability to penetrate dry skin including *Treponema pallidum*, *Staphylococcus aureus*, and the larvae of *Schistosoma* and *Necator* (blood flukes and hookworms).

Some types of pathogens require the **parenteral route**, i.e., they can only enter the body with assistance, e.g., through a cut, bite, puncture wound, surgical procedure, etc. When introduced in this manner, many types of microorganisms not usually considered as pathogens can cause disease symptoms.

2. Avoid or damage the immune system – Microorganisms have developed a variety of mechanisms for avoiding immune cells, or for preventing damage usually caused by these cells. Some can cause damage to or kill immune cells; for example:

a) Capsules (glycocalyx) – Capsules allow bacteria to avoid being ingested by phagocytic WBCs apparently because the phagocytes do not recognize capsule materials as antigenic. Recall that *Streptococcus pneumoniae* strains are more pathogenic when they are capsule-formers.

A-proteins – Virulent strains of *Staphylococcus aureus* produce surface proteins called A-proteins that, like capsules, allow them to avoid phagocytes.

M-proteins – Virulent strains of *Streptococcus pyogenes* produce surface proteins called M-proteins that help them to avoid phagocytic WBCs.

b) Some microbes are consumed by phagocytes, but are not digested. Bacteria including *Salmonella enterica* ssp. *typhi* and *Mycobacterium tuberculosis* have this ability. The *Mycobacterium* cells apparently prevent digestion within phagocytic vesicles by preventing the transport of hydrogen ions into these vesicles. In both cases, the bacteria are not killed, but instead reproduce within phagocytes and are transported and dispersed by them.

Trypanosomes in certain developmental stages can also survive within WBCs.

- c) **Some bacteria produce leukocidins that kill WBCs** – Bacteria including *Staphylococcus aureus* and *Streptococcus pyogenes* produce leukocidins that kill phagocytic WBCs. In the case of *Staphylococcus aureus*, the leukocidin is an exotoxin called Panton-Valentine leukocidin. It causes the formation of pores in infected cell membranes, and is due to lysogenic conversion, i.e., is encoded by viral genes.
- d) **HIV kills T4 lymphocytes** – Recall that immune function overall is dependent on helper T-cell activity, because these cells stimulate the proliferation of other immune cells and activate phagocytes. Since HIV infects and kills T4 lymphocytes primarily, it has a devastating impact on the immune system.

3. Reproduce faster than body can eliminate them – Recall that bacterial growth is influenced by temperature requirements, gas requirements, pH requirements, osmotic pressure requirements, nutrient availability, and other factors. Mechanisms supporting normal body function often provide conditions ideal for the growth of microorganisms in terms of temperature, pH, osmotic pressure and nutrient requirements, but not all pathogens grow well in tissues supported by high levels of oxygen. In general, if microbial reproduction is slow, immune mechanisms will allow the body to eliminate them before disease symptoms develop, but if reproduction is rapid and goes unchecked, disease is likely to occur.

4. Cause damage to the host – Many types of microorganisms live commensally in various regions of the body without causing any type of disease symptoms, while others cause disease. Generally, those causing disease symptoms are those capable of causing damage.

Substances involved in disease processes can be divided into two categories, **enzymes** and **toxins** (though distinguishing these is sometimes difficult). For this class, those substances with names ending in *ase* will be considered as enzymes, and include:

- a) **Bacterial Kinase** – Bacterial kinase is an enzyme that causes the breakdown of fibrin, a material involved in blood clotting and produced during inflammation to prevent the spread of microorganisms from an area of trauma into surrounding tissues. **Streptokinase**, produced by *Streptococcus pyogenes* is used clinically to degrade fibrin clots during acute myocardial infarction and cases of stroke, but is effective only if applied quickly.
- b) **Hyaluronidase** – Hyaluronidase is an enzyme that breaks down hyaluronic acid, a material typically found between tissue cells, and which serves as a sort of intercellular “cement”, i.e., helps to hold cells together. Degradation of this material increases the invasiveness of bacteria.
- c) **Coagulase** – Coagulase is an enzyme that coagulates blood plasma, and is commonly produced by *Staphylococcus aureus*. This may aid pathogens to avoid phagocytes by causing plasma to form into a solid, gel-like substance.

- d) **Collagenase** – Collagenase is an enzyme that breaks down collagen, a major component of dense connective tissue. Cells capable of degrading collagen also have increased invasiveness.
- e) **DNase and Lecithinase** – DNase and lecithinase are enzymes capable of breaking down DNA and lecithin respectively. The ability of cells to produce these enzymes is useful in diagnostic testing.

Bacterial toxins can be divided into two broad categories, **exotoxins** and **endotoxins** based on whether they are released by living cells or are components of cells, and released when the cells are killed.

Exotoxins – Exotoxins are proteins released by living bacterial cells, and often encoded by viral genes, i.e., acquired from bacteriophages through lysogeny. Only some strains exhibit toxin production because it is a characteristic acquired through lysogenic conversion. Exotoxins typically interact with specific targets (receptors on cell surfaces) and initiate specific reactions associated with those targets. Some examples of exotoxins include the following:

- a) **Leukocidin** – Leukocidins are toxins that kill leukocytes or WBCs. As described earlier, the Pantan-Valentine leukocidin of *Staphylococcus aureus* causes the formation of pores in infected cell membranes, resulting in cell death. Other types of bacteria form leukocidins, including *Streptococcus pyogenes*.
- b) **Hemolysins** – Hemolysins are toxins that kill erythrocytes or RBCs, and are produced by multiple types of bacteria. Some pathogens produce more than one type, for example, *Staphylococcus aureus* can form two hemolysins designated as α -hemolysin and β -hemolysin, while two types formed by *Streptococcus pyogenes* are designated as streptolysin-o and streptolysin-s.
- c) **Pyrogenic toxin superantigens (PTSAgs)** – The pyrogenic toxin superantigens produced by *Staphylococcus aureus* are responsible for both staphylococcal food poisoning and the symptoms of toxic shock syndrome. Staphylococcal toxins associated with food poisoning are sometimes called enterotoxins because they cause gastrointestinal symptoms, specifically vomiting and diarrhea typically within 1-3 hours after ingestion.

Superantigens stimulate the activity of large numbers of T cells, resulting in excessive cytokine release and massive immune reactions not specific to any antigen. The release of cytokine (primarily tumor necrosis factor), can trigger inflammatory activity resulting in circulatory shock.

- d) **Clostridium toxins** – Bacteria in the genus *Clostridium* can produce the potent exotoxins responsible for tetanus and botulism.

Tetanus also known as lock-jaw is a condition involving spastic contraction of skeletal muscles body-wide. In some cases the force exerted by contracting muscles can cause teeth and/or bones to be broken. The toxin responsible is called **tetanospasmin**, and **acts on inhibitory neurons**, blocking the release of gamma-aminobutyric acid (GABA) and glycine, **inhibitory neurotransmitter substances**. Without inhibitory signals present, excitatory responses trigger uncontrolled contractions.

Botulism toxins cause the flaccid paralysis of skeletal muscle, by **blocking the release of the excitatory neurotransmitter acetylcholine** from **excitatory motor neurons**. Since external respiration (breathing) is dependent on skeletal muscle activity (contraction of the diaphragm and intercostal muscles), the ingestion of botulism toxin is often lethal. Botox, initially used to control muscle spasms, is now used extensively to eliminate smiles. ☺

An interesting feature of these *Clostridium* toxins is their similarity in structure. Although tetanospasmin typically causes tetanus, and botulism toxins typically cause flaccid paralysis, the two can sometimes cause opposing symptoms and their amino acid sequences are very similar.

- e) **Enterotoxins** – Enterotoxins are secreted by a variety of different types of bacteria within the gastrointestinal system, including *Escherichia coli*, *Vibrio cholerae* and *Shigella dysenteriae*. These toxins act on intestinal epithelial cells causing changes in membrane function. In the case of cholera, the toxin triggers cyclic-AMP production resulting in secretion of Na^+ , K^+ , Cl^- and HCO_3^- ions into the large intestinal lumen, causing water to follow. The result is watery diarrhea and severe dehydration within the body due to fluid loss.
- f) **Toxins inhibiting protein synthesis** – The exotoxins of *Corynebacterium diphtheriae* and *Pseudomonas aeruginosa* act in a similar manner to block translation, ultimately causing cell death by preventing protein synthesis.

Endotoxins – Endotoxins are non-protein cellular components released typically when the cells forming them are killed. They are much less specific than are exotoxins with respect to both targets and actions. The lipopolysaccharide (LPS) associated with the outer membrane of Gram-negative cell walls is one example and when released, may cause a variety of symptoms including elevated temperature, circulatory malfunction, general malaise and circulatory shock. Endotoxins interact with Toll-like receptors (TLRs) found on a variety of cells including monocytes/macrophages, B-lymphocytes, mast cells and epithelial cells. Cellular responses to endotoxins include release of cytokines (triggering inflammation), apoptosis (cell death), or release of interferons.