# THE RELATION OF MICROORGANISMS TO DISEASES

**INFECTION:** A condition in which pathogenic microbes penetrate host defenses, enter tissues and multiply.

**MIXED INFECTION:** Several microbes grow simultaneously at the infection site.

**DISEASE:** Any deviation from health, disruption of a tissue or organ caused by microbes or their products.

## HOST DEFENSE.

These humeral defense are driven and produced by the immunologically specific cells. The sophisticated communication system that coordinated activity of all host defenses consists of chemicals produced by lymphocytes that are called **cytokines**. Cytokines also function as effector molecules for the cytotoxic lymphocytes. Another important humeral defense is the complement system, which consists of a cascade of enzymes that eventually result in a group of compounds ( C7-8-9) that are known collectively as the attack complex.

**CARRIER:** A Person or animal with asymptomatic infection that can be transmitted to another susceptible person or animal.

**NONPATHOGEN:** A microorganism that does not cause disease; may be part of the normal flora.

**OPPORTUNISTIC PATHOGEN:** An agent capable of causing disease only when the host's resistance is impaired (i.e., when the patient is "immunocompromised").

**PARASITIC BACTERIA:** Are those which live in or a living host.

**SAPROPHYTIC BACTERIA:** Are those which live freely in the soil and feed on decaying organic matter.

**COMMENSALS:** Are parasitic bacteria live on external or internal surfaces of the body without causing disease, these bacteria may even be beneficial to the host e.g. commensals of the gut digest polysaccharides and are source of certain vitamins, these bacterial flora also compete with pathogenic bacteria for nutrition thus inhibiting their growth.

**PATHOGENICITY:** refers to the ability of an organism to cause disease. Organisms that are capable of causing disease under the appropriate circumstances are called **pathogens. Virulence** usually refers to the degree of pathogenicity within a group or species of microorganisms. The virulence of a microorganism is not generally attributable to a single factor, but is dependent on several parameters that relate to the organism the host, and the dynamic interaction between them. This balance between the host and the "potential pathogen" is an area of increasing interest among microbiologists. In general, virulence encompasses two features of a pathogenic microorganism: its **infectivity** (i.e., the ability initiates an infection), and the **severity** of the condition produced. Highly virulent, moderately virulent, and/or avirulent strains may occur within a species or group of organisms that are generally considered to be pathogenic. Infection of the host by an organism is a necessary step in the production of disease. However, infection does not always cause disease. Colonization of a host with normal flora organisms is, in a broad sense, infection, and the colonization factors present ON the surfaces of normal flora organisms (e.g., fimbriae, lipoteichoic acids, capsules, and outer-membrane proteins) are operationally the same as those used by pathogenic microorganisms. Virulence can be measured by the designated as $LD_{50}$ or $ID_{50}$ : the $LD_{50}$ (50% lethal dose) is the number of organisms needed to kill half the hosts, and $ID_{50}$ (50% infectious dose) is the number needed to cause infection in half the hosts. These values are determined by inoculation of laboratory animals.

**Virulence depends on:**

**1-** Virulence factors (Adherence factors, Invasiveness, Toxin production).
**2-** Number of initial organisms.
**3-** Immune status.

**Table 5.2** Examples of surface virulence factors which interfere with host defences

| Organism | Virulence factor | Used in vaccine |
|---|---|---|
| Bacteria | | |
| *Streptococcus pneumoniae* | Polysaccharide capsule | Yes |
| *Streptococcus pyogenes* | M protein | No |
| *Staphylococcus aureus* | Protein A | No |
| *Neisseria meningitidis* | Polysaccharide capsule | Yes |
| *Haemophilus influenzae* | Polysaccharide capsule | Yes |
| *Klebsiella pneumoniae* | Polysaccharide capsule | No |
| *Escherichia coli* | Protein pili | No |
| *Salmonella typhi* | Polysaccharide capsule | No |
| *Mycobacterium tuberculosis* | Mycolic acid cell wall | No |
| Fungi | | |
| *Cryptococcus neoformans* | Capsule | No |

**STAGES OF PATHOGENICITY**

1-Transmission
2-Attachment (adhesion, adherence).
3-Colonization and multiplication of microorganism.
4-Avoidance of host defense mechanisms like phagocytosis.
5-Damage of host cells by:
A- Toxin production.
B- Invasiveness.
C- Both of them.

**TRANSMISSION** Most infections are acquired by transmission from external sources, i.e. they are **exogenous** in origin. Others are caused by members of the normal flora behaving as opportunist pathogens, i.e. they are **endogenous** in origin. Transmission can be by:

- inhalation- the airborne route
- ingestion - faecal contamination of food and water.
- Inoculation - by sexual contact, contaminated needles, skin contact, blood transfusions or biting insects.

There are four important portals (or gates) of pathogens (Table 5.1):

1- Skin.
2- Respiration.
3- Gastrointestinal tract.
4- Genitourinary tract.

**<u>Pathogenicity of the pathogens</u>**

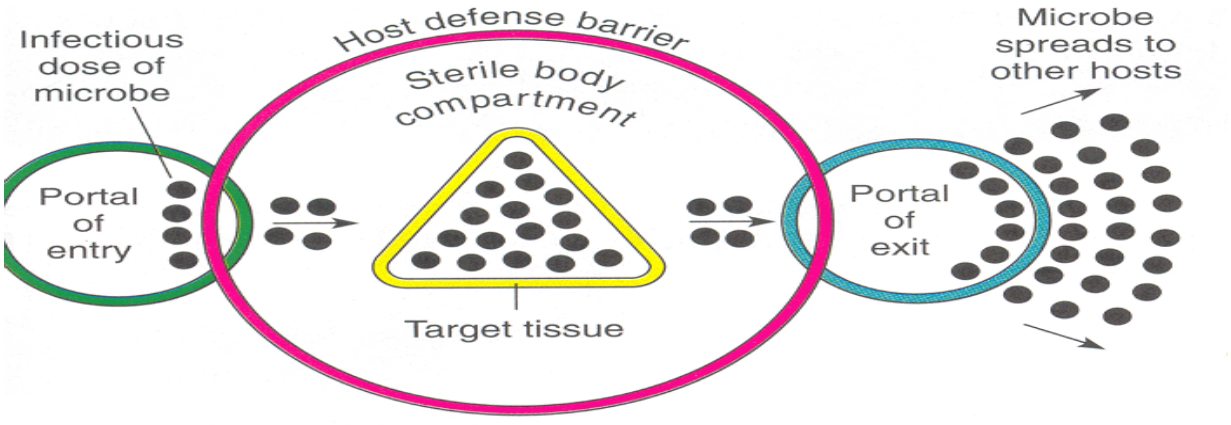


**Table 5.1** Portals of entry of some common pathogens

| Portal of entry | Pathogen | Disease |
|---|---|---|
| Skin | *Clostridium tetani* | Tetanus |
| | Hepatitis B virus | Hepatitis B |
| Respiratory tract | *Streptococcus pneumoniae* | Pneumonia |
| | *Neisseria meningitidis* | Meningitis |
| | *Haemophilus influenzae* | Meningitis |
| | *Mycobacterium tuberculosis* | Tuberculosis |
| | Influenza virus | Influenza |
| | Rhinovirus | Common cold |
| | Epstein–Barr virus | Infectious mononucleosis |
| Gastrointestinal tract | *Shigella dysenteriae* | Dysentery |
| | *Salmonella typhi* | Typhoid fever |
| | *Vibrio cholerae* | Cholera |
| | Hepatitis A virus | Infectious hepatitis |
| | Poliovirus | Poliomyelitis |
| Genital tract | *Neisseria gonorrhoeae* | Gonorrhoea |
| | *Treponema pallidum* | Syphilis |
| | Human immunodeficiency virus (HIV) | Acquired immune deficiency syndrome (AIDS) |
| | *Candida albicans* (fungus) | Vaginitis |

## ADHERENCE TO HOST SURFACES.

Adherence is the first step in the infection. Unless organisms have the ability to stick or adhere to host surfaces they will be unable to cause infection. Some bacteria and fungi have specialized structures or produce substances that facilitate their attachment to the surface of human cells or prostheses (e.g. dentures, artificial heart valves), thereby enhancing their ability to colonize and cause disease. These adherence mechanisms are critical for organisms that attach to mucous membranes; mutants that lack these mechanisms are often non-pathogenic(e.g. the hair-like pili of *Neisseria gonorrhoeae* and *Escherichia coli* mediate their attachment to the urinary tract epithelium; the extracellular polysaccharides of *Streptococcus mutans* help it adhere to enamel surfaces). Simple attachment is mediated through a receptor on the host cell surface, and an adhesin on the bacterial one. Some may be species or even strain specific, while other exhibit tissue tropism i.e. *Streptococcus mutans* will colonize teeth, but not the tongue epithelium.

### Adherence factors.

**1**-Fimbriae: Are the most common adhesion molecules e.g. *Neisseria gonorrhoeae* and *E coli* mediate the attachment to cell surfaces.

**2**-Filamentous haemagglutinin of *Bordetell pertusis*.

**3**-Exopolysaccarides.Present on the surface of some-gram positive bacteria are also involving in adhesions.

**4**- Flagella act as adhesion *in Vibrio cholerae* and *Campylobacter jejani*.

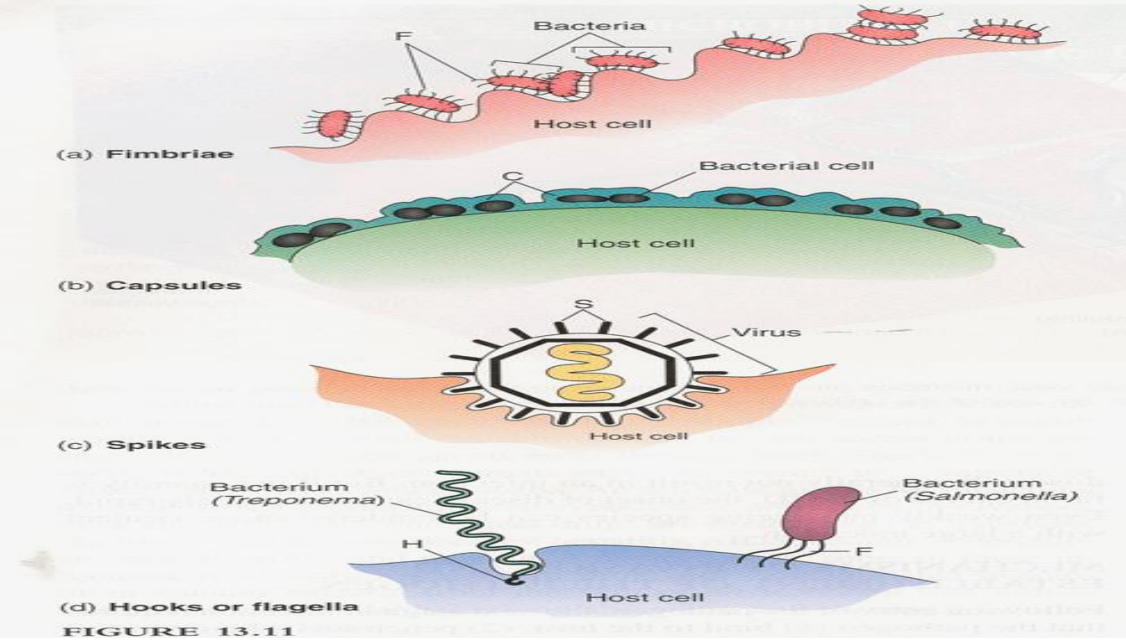
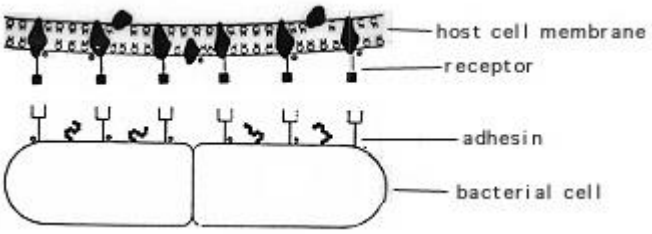


FIGURE 13.11

**Specific adherence** involves permanent formation of many specific lock-and-key bonds between complementary molecules on each cell surface. Complementary receptor and adhesin molecules must be accessible and arranged in such a way that many bonds form over the area of contact between the two cells. Once the bonds are formed, attachment under physiological conditions becomes virtually irreversible.




**COLONIZATION AND INVASION:**

For many pathogenic bacteria, the initial interaction with host tissues occurs at a mucosal surface and colonization-the establishment of a stable population of bacteria in the host-normally requires adhesion to the mucosal cell surface. This allows the establishment of a focus of infection that may remain localized or may subsequently spread to other tissues.

**INVASION. I**s the process whereby bacteria, parasites, fungi, and viruses enter host cells or tissues and spread in the body. Cell invasion confers the ability to avoid humoral host defence mechanisms and potentially provides a nich in nutrients and devoid of competition from other bacteria. Examples of bacteria that are able to invade and survive within host cells include Mycobacteria and

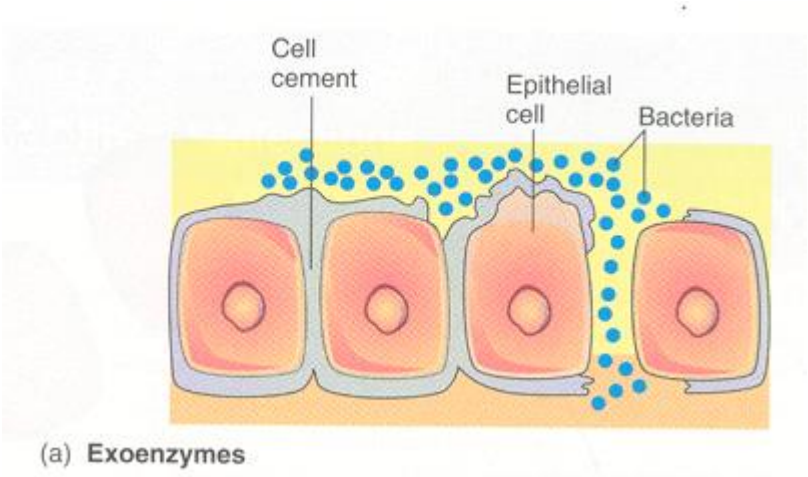
those of the genera *Salmonella,. Shigella, Escherichia, Yersinia, Legionella, Listeria. Campylobacter,* and *Neisseriae.* Many intracellular pathogens use normal phagocytic entry mechanisms to gain access.

## AGGRESSINS

In order to survive and multiply within the host, many organisms produce a variety of substances that allow them to avoid or circumvent host defense mechanisms. These substances, termed aggressins, include capsules and extracellular slime substances, surface proteins and carbohydrates, enzymes, toxins, and other small molecules. The capsular structures of some bacteria enable the organisms to avoid phagocytosis by preventing interaction between the bacterial cell surface and phagocytic cells or by concealing bacterial cell-surface components that would otherwise interact with phagocytic cells or complement and lead to their ingestion. Specific antibodies directed against capsular lowing opsonization, encapsulated bacteria are readily and rapidly ingested and killed by phagocytic cells. Some organisms produce capsules that are structurally similar to host tissues and, therefore, are not recognized as foreign by immunosurveillance. In this manner, such organisms can evade host defenses. For example, the capsules of *E. coli.* Organisms that possess capsules mat behave as aggressins include S. *aureus, S. pneumoniae, N. meningitidis, H. influenzas* type b, *K. pneumoniae* .

## INVASIVENESS

This is the ability to invade tissues, multiply and spread rapidly. Invasiveness of bacteria plays a critical role in pathogenesis; this property is dependent upon secreted bacterial enzymes. Most are enzymes, affecting physical barriers like tissue matrices and cell membranes. In this way, the bacterium can quickly spread through intercellular spaces.



(a) **Exoenzymes**

## A few examples are:

● **a hemolysin** called **listeriolysin O**: Which intercalates into the membrane of the vacuole and causes the formation of pores. *Listeria monocytogenes* then enters the cytoplasm of the cell, where it continues to grow, thereby escaping the toxic environment with the phagolysosome

● **catalase and superoxide dismutase:** Secretes by *S. aureus* which inhibit organism destruction by the myeloperoxidase system of phagocytic cells.

●**Streptokinase** and **staphylokinase :**Elaborate from Group A streptococci and staphylococci that hydrolyze fibrin clots , which also facilitate the spread of organisms in the tissues.

• **Collagenase :** It breaks down collagen fibers & promote spread of infection.

•**Hyaluranidase:** It split hyaluric acid, a constituent of the cement substance of connective tissue. It help spread of infection.

• **Coagulase**: Produced by *Staphylococcus aureus,* accelerates the formation of a fibrin clot (from fibrinogen). It helps protect the organisms from phagocytosis by walling off the infected area and by coating the organisms with a fibrin layer.

• **Immunoglobulin A (IgA) protease** :Degrades protective IgA on mucosal surfaces, allowing organisms such as *N gonorrhoeae, Haemophilus injluenzae* and *Streptococcus pneumoniae* to adhere to mucous membranes.

• **Leukocidins** :Can destroy both neutrophilic leukocytes and macrophagcs; the periodontopathic organism *Actinobacillus actinomycetemcomitans* possesses this enzyme. The mutants that do not secrete the enzyme are less virulent

## TOXIGENICITY

Toxin is a protein or conjugated protein produced by some pathogenic bacteria that is highly poisonous for other living organism and the ability of microorganism to produce a toxin that contributes to the development of disease called **toxigenicity.** Toxin production or toxigenicity is another major mediator of bacterial disease. Toxins are of two categories: endotoxins and exotoxins. Their main features are shown in Table 5.3.

### Toxin production

***Endotoxins***

Endotoxins are the cell wall lipopolysaccharides of Gram-negative bacteria (both cocci and bacilli) and are not actively released from the cell. *(Note:* thus, by definition, Gram-positive organisms do not possess endotoxins.) Endotoxins cause fever, shock and other generalized symptoms.

It is an outer membrane chemical moiety consisting of three sections:

**1**-A toxic lipid (Lipid A) anchored in the outer membrane,

**2**-An immunogenic polysaccharide core, and

**3-**An antigenic O-linked series of oligosaccharides at the extracellular surface. Endotoxins are toxic to most mammals, and can be lethal if encountered in too high a dose.

***Exotoxins***

Both Gram-positive and Gram-negative bacteria secrete exotoxins, whereas endotoxin is an integral component of the cell wall of Gram-negative organisms. Exotoxins in particular can cause disease in distant parts of the body as a result of diffusion or carriage of the toxin via systemic routes (e.g. tetanus bacillus infecting a lesion in the foot produces an exotoxin which causes 'lockjaw' or spasm of masseter muscles on the face).

Bacterial exotoxins can be broadly categorized as:

- neurotoxins
- enterotoxins
- miscellaneous exotoxins.

***Neurotoxins.*** Tetanus toxin, diphtheria toxin and botulinum toxin are all neurotoxins and their action is mediated via neuronal pathways.

***Enterotoxins***. These toxins act on the gut mucosa and cause gastrointestinal disturbances.

*Escherichia coli* enterotoxin is of two types: one heat-labile and one heat-stable.

***Miscellaneous exotoxins***. An array of exotoxins is produced by *Clostridium perfringens* and other species of clostridia that cause gas gangrene. These include the a-toxin (a phospholipase that hydrolyses lecithin, present in all eukaryotic cell membranes).

**Table 5.3** Comparison of main features of exotoxins and endotoxins

| Property | Exotoxin | Endotoxin |
|---|---|---|
| Source | Some species of some Gram-positive and Gram-negative bacteria | Cell walls of Gram-negative bacteria |
| Origin | Secreted from cell | Cell wall constituent |
| Chemistry | Polypeptide | Lipopolysaccharide |
| Toxicity | High (fatal dose of the order of 1 μg) | Low (fatal dose in the order of hundreds of micrograms) |
| Clinical effects | Variable | Fever, shock |
| Antigenicity | Induces high-titre antibodies called antitoxins | Poorly antigenic |
| Vaccines | Toxoids used as vaccines | No toxoids formed and no vaccine available |
| Heat stability | Most are thermolabile (destroyed rapidly at 60°C) | Thermostable at 100°C for 1 h |
| Typical diseases | Cholera, tetanus, diphtheria | Sepsis by Gram-negative rods, endotoxic shock |

**ANTIPHAGOCYTIC (Survival Inside of Phagocytes )**

Many bacteria pathogens are rapidly killed once they are ingested by polymorphonuclear cells or macrophages. Some pathogens evade phagocytosis or leukocyte microbicidal mechanisms by adsorbing normal host components to their surfaces. For example, *Staph..aureus* has surface protein A. Other pathogens have surface factors that impede phagocytosis, e.g., *Streptococcus pneumoniae, N meningitidis;*and many other bacteria have polysaccharide capsules. *S pyogenes* (group A streptococci) have M protein, *N gonorrhoeae*(gonococci) have pili. Most of these antiphagpcytic surface structures show much antigenic heterogeneity. For example, there are more than 80 pneunococcal capsular polysaccharide types and more than 60 M protein types of group A *streptococci*. Antibodies against one type of the antiphagocytic factor (e.g., capsular polysaccharide, M protein) protect the host from disease caused by bacteria of that type but not from those with other antigenic types of the same factor. A few bacteria (e.g., *capnocytophaga and bordetella*) produce soluble factors or toxins inhibit chemotaxis by leukocytes and thus evade phagocytosis by a different mechanism. Bacteria that can resist killing and survive or multiply inside of phagocytes are considered intracellular parasites. The environment of the phagocyte may be a protective one, protecting the bacteria during the early stages of infection or until they develop a full complement of virulence factors. The intracellular environment guards the bacteria against the activities of extracellular bactericides, antibodies, drugs, etc.

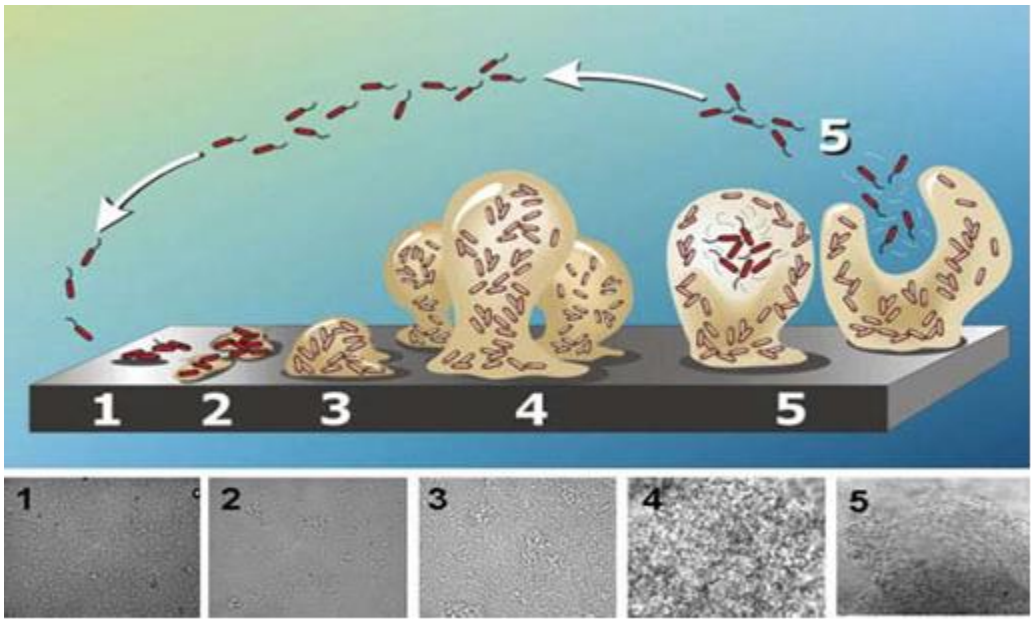
**The role of bacterial biofilms**

A biofilm is an aggregate of interactive bacteria attached to a solid surface or to each other and encased in an exopolysaccharide matrix. This is distinct from planktonic or free- living bacterial growth, in which interactions of the microorganisms do not occur. Biofilms form a slimy coat on surfaces and throughout nature. Single species may coaggregate to form a biofilm. Fungi-including yeasts are occasionally involved.

**Biofilms are:**

- -formed when microbes adhere to a surface
- -each microbe secretes glycocalyx allowing other microbes to adhere; large mass is formed
- the biofilm is resistant to disinfectants and antibiotics (outer layer protects inner layers)-problem for catheters and surgical implants: serves as chronic reservoir.

Biofilms are important in human infections that are persistent and difficult to treat. A few examples include *Staphylococcus epidermidis* and *Staphylococcus aureus* infections of centralvenous catheters, eye infections such as occur with contact lenses and intraocular lenses, in dental plaque, and with *Pseudomonas aeroginosa* airway infections in cystic fibrosis patients.




**Pathogenesis of viral infection**

As obligate intracellular parasites, viruses require effective mechanisms of transmission, adherence and cellular penetration to establish infection. Many viruses have specific preferences for certain host tissues (e.g. rhinoviruses for the upper respiratory epithelium and human immunodeficiency virus (HIV) for CD4 T lymphocytes). Viruses can spread by lysis of the primary infected cell and secondary viraemia, or by formation of bridges (syncytia) between cells.

Human cells need not be destroyed. Viral penetration of the host cell cytoplasmic membrane without cell rupture is a complex process in which the virus may use cell surface molecules to subvert normal membrane and cytoskeletal functions.

Viruses can be continually formed at the cell surface or the genome can even be integrated into the host cell's own genome. The long-term survival of viruses within human cells as obligate intracellular parasites places them beyond the reach of immune defenses. Some viruses integrate into the host cell genome to produce a latent state. Viral damage is caused by the cytotoxic effects of the virus or by host immune attack. Mechanisms of late-stage viral damage include autoimmune, immune-complex or neoplastic disease.

**Pathogenesis of fungal infection**

Fungal disease, particularly its life-threatening extreme, is relatively rare despite the many species of fungi present in the environment and on the human body surface. Most fungal infections appear to require a breach in host defenses in order to become established. Yeasts often cause mucosal inflammation following alteration of either vaginal or gastrointestinal flora. Dermatophytic fungi cause

a variety of skin conditions but rarely cause more invasive disease in immunocompetent patients because they are restricted to the skin. There is no good evidence for the involvement of toxins in fungal disease. Most damage is probably caused by the host response.

**Pathogenesis of parasitic infections**

Protozoal and helminth infections have a complex pathogenesis, which is best understood by referring to the parasite's life cycle. Some protozoal and helminth infections require transmission by a disease vector. The vector is often an arthropod. The development of disease depends on a three-way relationship between microorganism, vector and human victim in these infections. The ecology of the vector (sometimes known as the 'intermediate host') is critical to the long-term survival of the parasite within a human population. In developed countries, parasitic infections are most common in international travellers, the sexually active, immunocompromised patients and poor people. The application of novel molecular parasitology techniques has provided new insights into the mechanisms of parasite disease.

**Opportunist infections**

If an organism is capable of causing disease in an apparently healthy individual, it is clearly aggressively pathogenic. If it is normally incapable of causing disease but can do so only when the human body is compromised in some way, it is said to be opportunist. Opportunist infections are of particular importance in hospital patients and in people whose immune systems are depressed by drugs or infection, particularly by HIV.

**References:-**

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