Pathogenesis of bacterial infection

Assistant prof. Buroooj M.R. Al-aajem

Department of Microbiology

College of Medicine

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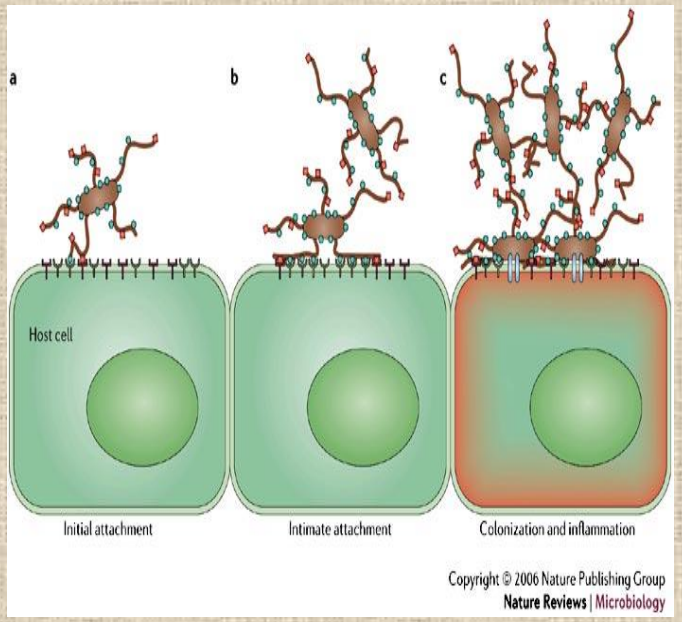
The pathogenesis of bacterial infection includes initiation of the infectious process and the mechanisms that lead to the development of signs and symptoms of disease.

Characteristics of bacteria that are pathogens include transmissibility, adherence to host cell, invasion of the host cell & tissues, toxigenicity, and ability to evade the host immune response.

Adherence (adhesion, attachment): The process by which bacteria stick to the surface of host cell. It is the major initial step in the infection process.

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

Invasion: The process whereby bacteria, animal parasites, fungi, and viruses enter host cell or tissues & spread in the body.



Infection: Multiplication of an infectious agent within the body. Multiplication of the normal flora in or on the body generally not considered an infection. Multiplication of pathogenic bacteria even if the person is asymptomatic is infection.

Nonpathogenic: A microorganism that does not cause disease (may be part of normal flora).

Opportunistic pathogen: An agent capable of causing disease only when the host resistance is impaired (immunocompromised patients).

Pathogen: A microorganism capable of causing disease.

Pathogenicity: The ability of an infectious agent to cause disease.

Toxigenicity: The ability of microorganism to produce toxin that contribute to the development of disease.

Virulence: The quantitative ability of an agent to cause disease. It involves adherence, invasion, and toxigenicity.

Pathogenesis of bacterial infection

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- **Identifying bacteria that cause disease:**

Human & animals have abundant normal flora that usually do not produce disease, but achieve a balance that ensure the survival, growth & propagation of both bacteria & host. Some bacteria that are important causes of disease are cultured commonly with the normal flora (*Str. Pneumonia, S. aureus*). Some bacteria that are clearly pathogenic (*Sal. typhi*) are present, but infection remains latent or subclinical & the host is a carrier of the bacteria. The host immune responses also should be considered when an organism is being investigated as the possible cause of a disease.

Pathogenesis of bacterial infection

Stages of Infection

The time between the exposure to an agent and the first appearance of clinical symptoms is called the **incubation period** and, although there are no symptoms, the organism may be causing substantial damage during this interval. it may followed by a period known as the **prodrome**, where non-specific signs and symptoms are noted, before the development of a specific symptom complex suggestive of a classical infectious disease such as pneumonia, meningitis or diarrhoea. Once the acute stage has passed, a period of **resolution** occurs, where the severity of the symptoms gradually decreases, and finally **convalescence** where the symptoms have largely disappeared.

The time course and severity of the disease depends upon the balance between the virulence of the infecting agent and the success with immune system combats the organism. Some infections may occur which are not sufficiently severe to produce clinical symptoms and these are **called asymptomatic** or **subclinical infections**. **Clinical infection** has a number of outcomes covering the spectrum between death and complete recovery.

Bacterial virulence factors

The term **chronic infection** In bacteriology, it is often used to describe the situation where a person continues to harbor a pathogenic organism but suffer no ill-effects themselves, examples being *S. typhi* in the gut and *C. diphtheriae* in the respiratory tract.

Latency refers to a situation where an agent persists in a dormant, inactive form without causing damage, but which may reactivate to cause signs and symptoms of the disease, e.g. Latent or old TB, herpes simplex virus which causes the cold sores.

Virulent bacteria

The ability of bacteria to cause disease is described in terms of the number of infecting bacteria, the route of entry into the body, the effects of host defense mechanisms, and intrinsic characteristics of the bacteria called virulence factors. Host-mediated pathogenesis is often important because the host can respond aggressively to infection with the result that host defense mechanisms cause damage to host tissues. The virulence factors of bacteria are typically proteins or other molecules that are synthesized by enzymes. These proteins are coded for by genes in chromosomal DNA, or plasmids.

Bacterial virulence factors

- **Virulence factors:** are molecules expressed and secreted by pathogens (bacteria, viruses, fungi and protozoa) that enable them to achieve the following:

1. colonization of a niche in the host (this includes adhesion to cells)
2. Immunoevasion, evasion of the host's immune response
3. Immunosuppression, inhibition of the host's immune response
4. entry into and exit out of cells (if the pathogen is an intracellular one)
5. obtain nutrition from the host.

Virulence factors are very often responsible for causing disease in the host as they inhibit certain host functions. Pathogens possess a wide array of virulence factors. Some are intrinsic to the bacteria (e.g. capsules and endotoxin) whereas others are obtained from plasmids (e.g. some toxins).

A major group of virulence factors are bacterial **toxins**. These are divided into two groups: endotoxins and exotoxins. Lipopolysaccharide (LPS) is a prototypical example of an endotoxin, which is a component of the cell wall of Gram-negative bacteria.

Bacterial virulence factors

Exotoxins are actively secreted by some bacteria and have a wide range of affects including inhibition of certain biochemical pathways in the host. The two most potent exotoxins known to man are the tetanus toxin (tetanospasmin) secreted by *Clostridium tetani* and the botulinum toxin secreted by *Clostridium botulinum*. Exotoxins are also produced by a range of other bacteria including *Escherichia coli*; Vibrio cholerae (causative agent of cholera); *Clostridium perfringens* (causative agent of food poisoning as well as gas gangrene) and *Clostridium difficile* (causative agent of pseudomembranous colitis).

Another group of virulence factors possessed by bacteria are immunoglobulin (Ig) proteases. Igs are antibodies expressed and secreted by hosts in response to an infection. Some bacteria, such as *S. pyogenes* (causative agent of scarlet fever and many other conditions), are able to break down the host's Igs using proteases.

Bacterial virulence factors

Some bacteria, such as *Streptococcus pyogenes*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, produce a variety of enzymes which cause damage to host tissues. Enzymes include hyaluronidase, which breaks down the connective tissue component hyaluronic acid ; a range of proteases and lipases ; DNAses, which break down DNA, and hemolysins which break down a variety of host cells, including red blood cells.

Capsules, made of carbohydrate, form part of the outer structure of many bacterial cells including Klebsiella & *B. anthracis*, *St. pneumonia*. Capsules play important roles in immune evasion, as they inhibit phagocytosis, as well as protecting the bacteria while outside a host.

- Opportunistic pathogen: An agent capable of causing disease only when the host's resistance is impaired (ie, when the patient "immunocompromised").
Pathogen: A microorganism capable of causing disease.
- communicable infections, that is, are spread from host to host. If a disease is highly
communicable, the term "contagious" is applied.
- Superantigens: Protein toxins that activate the immune system by binding to major
histocompatibility complex (MHC) molecules and T-cell receptors (TCR) and stimulate large numbers of T cells to produce massive quantities of cytokines.
- Toxigenicity: The ability of a microorganism to produce a toxin that contributes to the development of disease. Epidemic :An infection if it occurs much more frequently than usual.
- pandemic : An infection if it has a worldwide distribution.
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An endemic infection is constantly present at a low level in a specific population.

- Inapparent or subclinical and can be detected only by demonstrating a rise in antibody titer or by isolating the organism.

Bacterial pathogenesis

Some infections result in a latent state, after which reactivation of the growth of the organism and recurrence of symptoms may occur. Certain other infections lead to a chronic carrier state, in which the organisms continue to grow with or without producing symptoms in the host.

- Colonization refers to the presence of a new organism that is neither a member of the normal flora nor the cause of symptoms.

Virulence

- is a quantitative measure of pathogenicity and is measured by the number of organisms required to cause disease. The 50% lethal dose (LD) is the number of organisms needed to kill half 50 the hosts, and the 50% infectious dose (ID) is the number needed to cause infection in half the 50 host

- The infectious dose of an organism required to cause disease varies greatly among the pathogenic bacteria. For example, *Shigella* and *Salmonella* both cause diarrhea by infecting the gastrointestinal tract, but the infectious dose of *Shigella* is less than 100 organisms, whereas the infectious dose of *Salmonella* is on the order of 100,000 organisms.

- The infectious dose of bacteria depends primarily on their virulence factors, for example, whether their pili allow them to adhere well to mucous membranes, whether they produce exotoxins or endotoxins, whether they possess capsule to protect them from phagocytosis, and whether they can survive various nonspecific host defenses such as acid in the stomach.

parasite. the term refers to the parasitic relationship of the bacteria to the host cells; that is, the presence of the bacteria is detrimental to the host cells. Bacteria that are human pathogens can be thought of, therefore, as parasites. Some bacterial pathogens are obligate intracellular parasites, e.g., *Chlamydia* and *Rickettsia,* because they can grow only within host cells. Many bacteria are facultative parasites because they can grow within cells, outside cells, or on bacteriologic media.

WHY DO PEOPLE GET INFECTIOUS DISEASES?

People get infectious diseases when microorganisms overpower our host defenses, that is, when the balance between the organism and the host shifts in favor of the organism. The organism or its products are then present in sufficient amount to induce various symptoms, such as fever and inflammation, which we interpret as those of an infectious disease. From the organism's perspective, the two critical determinants in overpowering the host are the number of organisms to which the host, or person, Exposed and the virulence of these organisms. Clearly, the greater the number of organisms, the greater is the likelihood of infection. It is important to realize, however, that a small number of highly virulent organisms can cause disease just as large number of less virulent organisms can. The virulence of an organism is 2determined by its ability to produce

various virulence factors . The production of specific virulence factors also determines what disease the bacteria cause. For example, a strain of *Escherichia coli* that produces one type of exotoxin causes watery (no bloody) diarrhea, whereas a different strain of *E. coli* that produces another type of exotoxin causes bloody diarrhea.

- Bacteria cause disease by two major mechanisms:
(1)toxin production

(2)invasion and inflammation.

- Toxins fall into two general categories: Exotoxins and endotoxins.

- Exotoxins are polypeptides released by the cell, whereas endotoxins are lipopolysaccharides (LPS), which form an integral part of the cell wall. Endotoxins occur only in gram-negative rods and cocci; are not actively released from the cell; and cause fever, shock, and other generalized symptoms. Both exotoxins and endotoxins by themselves can cause symptoms; the presence of the bacteria in the host is not required. Invasive bacteria, on the other hand, grow to large numbers locally and induce an inflammatory response consisting of erythema, edema, warmth, and pain.

STAGES OF BACTERIAL PATHOGENESIS •

Most bacterial infections are acquired from an external source, and for those, the stages of infection are as described below. Some bacterial infections are caused by members of the normal flora and, as such, are not transmitted directly prior to the onset of infection. A generalized sequence of the stages of infection is as follows:

1.Transmission from an external source into the portal of entry
2.Evasion of primary host defenses such as skin or stomach acid
3.Adherence to mucous membranes, usually by bacterial pili
4.Colonization by growth of the bacteria at the site of adherence
5. Disease symptoms caused by toxin production or invasion accompanied by inflammation
6. Host responses, both nonspecific and specific (immunity).
7.Progression or resolution of the disease.

Transmission •

An understanding of the mode of transmission of bacteria and other infectious agents is extremely important from a public health perspective, because interrupting the chain of transmission is an excellent way to prevent infectious diseases. The mode of transmission of many infectious diseases is"human-to-human," but infectious diseases are also transmitted from nonhuman sources such as soil, water, and animals.Fomites are inanimate objects, such as towels, that serve as a source of microorganisms that can cause infectious diseases.

Modes of transmission. •

1.Human to human : •

A. Direct contact Gonorrhea Intimate contact: e.g., sexual, or passage through birth canal.

B. No direct contact (Dysentery) Fecal–oral: e.g., excreted in human feces, then ingested in food or water.

C. Transplacental :Congenital syphilis Bacteria cross the placenta and infect the fetus.

D. Blood-borne Syphilis Transfused blood or intravenous drug use can transmit.

2. Nonhuman to human •

1. Soil source :Tetanus Spores in soil enter wound in skin.

2. Water source :Legionnaire's disease Bacteria in water aerosol are inhaled into lungs.

3. Animal source:

A. Directly Cat-scratch fever Bacteria enter in cat scratch

B. Via insect vector: Lyme disease Bacteria enter in tick bite

A. Excreta Via animal: hemolytic–uremic syndrome ,*E. coli;Bacteria in cattle feces are ingested in undercooked* hamburger.

B. Fomite source : Staphylococcal skin infection; Bacteria on an object, e.g., a towel, are transferred onto skin.

vertical transmission. •
The three modes by which organisms are transmitted vertically are across the
placenta, within the birth canal during birth, and via breast milk. Horizontal transmission, by contrast, is person-to-person transmission that is not from mother to offspring. Portals of entry

1. Respiratory tract:
- Streptococcus pneumonia(Pneumonia).
- Neisseria meningitides (Meningitis).
- Haemophilus influenza (Meningitis).
- Mycobacterium tuberculosis (Tuberculosis).

2. Gastrointestinal tract:
- Shigella dysenteriae (Dysentery).
- Salmonella typhi (Typhoid fever).
- Vibrio cholera (Cholera).

3. Skin:
- Clostridium tetani (Tetanus).
- Rikettsia rickettsia(Rocky Mountain spotted fever).

4. Genital tract:
- Neisseria gonorrhoeae (Gonorrhea).
- Treponema pallidum (Syphilis).
- Chlamydia trachomatis(Urethritis)

BACTERIAL VIRULENCE FACTORS •

1. Adherence to Cell Surfaces

Certain bacteria have specialized structures, e.g.,pili, or produce substances, e.g., capsules or glycocalyces, that allow them to adhere to the surface of human cells, thereby enhancing their ability to cause disease. These adherence mechanisms are essential for organisms that attach to mucous membranes; mutants that lack these mechanisms are often nonpathogenic. For example, the pili of *Neisseria gonorrhoeae* and *E. coli* mediate the attachment of the organisms to the urinary tract epithelium, and the glycocalyx of *Staphylococcus epidermidis* and certain viridans streptococci allow the organisms to adhere strongly to the endothelium of heart valves. The various molecules that mediate adherence to cell surfaces are called adhesions. The matrix formed by these adhesins forms a coating called a *biofilm.*

Foreign bodies, such as artificial heart valves and artificial joints, predispose to infections. Bacteria can adhere to these surfaces, but phagocytes adhere poorly owing to the absence of selectins and other binding proteins on the artificial surface .

Some strains of *E. coli* and *Salmonella* have surface proteins called curli, which mediate binding of the bacteria to endothelium and to extracellular proteins such as fibronectin. Curli also interact with serum proteins such as factor XII, a component of the coagulation cascade. Curli, therefore, are thought to play a role in the production of the thrombi seen in the disseminated intravascular coagulation (DIC) associated with sepsis caused by these bacteria.

2. Invasion, Inflammation, & Intracellular Survival •

Invasion is the term commonly used to describe the entry of bacteria into host cells, implying an active role for the organisms and a passive role for the hostcells. **One of the two main mechanisms by which bacteria cause disease is invasion of tissue followed by inflammation**. 3. Enzymes Several enzymes secreted by invasive bacteria play a role in pathogenesis. Among the most prominent are •

1. collagenase and hyaluronidase, which degrade collagen and hyaluronic acid, respectively, thereby allowing the bacteria to spread through subcutaneous tissue; they are especially important in cellulitis caused by *Streptococcus pyogenes.*

2. coagulase, which is produced by Staphylococcus aureus and accelerates the • formation of a fibrin clot from its precursor, fibrinogen (this clot may protect the bacteria from phagocytosis by walling off the infected area and by coating the organisms with a layer of fibrin).

3. Immunoglobulin A (IgA) protease, which degrades IgA, allowing the • organism to adhere to mucous membranes, and is produced chiefly by N. gonorrhoeae, Haemophilus influenzae, and Streptococcus pneumonia.

4. leukocidins, which can destroy both neutrophilic leukocytes and macrophages •

5. Many hemolytic streptococci produce streptokinase (fibrinolysin), a substance that activates a proteolytic enzyme of plasma. This enzyme is then able to dissolve coagulated plasma and probably aids in the rapid spread of streptococci through tissues. Streptokinase has been used in treatment of acute myocardial infarction to dissolve fibrin clots.

6. Hemolysins they dissolve red blood cells. •

Pathogenicity Islands •

The genes that encode many virulence factors in bacteria are clustered in pathogenicity islands on the bacterial chromosome. For example, in many bacteria, the genes encoding adhesions, invasions, and exotoxins are adjacent to each other on these islands. Nonpathogenic variants of these bacteria do not have these pathogenicity islands. After bacteria have colonized and multiplied at the portal of entry, they may invade the bloodstream and spread to other parts of the body. Receptors for the bacteria on the surface of cells determine, in large part, the organs affected.

4. Antiphagocytic Factors: •

In addition to these enzymes, several virulence factors contribute to invasiveness by limiting the ability of the host defense mechanisms, especially phagocytosis, to operate effectively:

1. The most important of these antiphagocytic factors is the capsule external to the cell wall • of several important pathogens such as S. pneumonia and Neisseria meningitidis. The polysaccharide capsule prevents the phagocyte from adhering to the bacteria; anticapsular antibodies allow more effective phagocytosis to occur (a process called opsonization).

2. A second group of antiphagocytic factors are the cell wall proteins of the • gram-positive cocci, such as the M protein of the group A streptococci (S. pyogenes) and protein A of S. aureus. The M protein is antiphagocytic, and protein A binds to IgG and prevents the activation of complement.
Bacteria can cause two types of inflammation:pyogenic pyogenic (pus- producing) inflammation And granulomatous(*Mycobacterium tuberculosis)*.

7. Intracellular Pathogenicity •

Some bacteria (eg, M tuberculosis, Listeria monocytogenes, Brucella species, and Legionella species) live and grow in the hostile environment within
polymorphonuclear cells, macrophages, or monocytes The bacteria accomplish this feat by several mechanisms:

- they may avoid entry into phagolysosomes and live within the cytosol of the phagocyte; •
- they may prevent phagosome–lysosome fusion and live within the phagosome.
- they may be resistant to lysosomal enzymes and survive within the phagolysosome.

8. Antigenic Heterogeneity •

The surface structures of bacteria (and of many other microorganisms) have considerable antigenic heterogeneity .Often these antigens are used as part of a serologic classification system for the bacteria(salmonella and V cholerae)
The antigenic type of the bacteria may be a marker for virulence.

9. Bacterial Secretion Systems •

Bacterial secretion systems are important in the pathogenesis of infection and are essential for the interaction of bacteria with the eukaryotic cells of the host
The gram-negative bacteria have cell walls with cytoplasmic membranes and outer membranes; a thin layer of peptidoglycan is present. Gram positive bacteria have a cytoplasmic membrane and a very thick layer of peptidoglycan
Some gram-negative bacteria and some gram-positive bacteria have capsules as well. The complexity and rigidity of the cell wall structures necessitate mechanisms for the translocation of proteins across the membranes. These secretion systems are involved in cellular functions such as the transport of7

proteins that make pili or flagella and in the secretion of enzymes or toxins into the extracellular environment.

10. The Requirement for Iron •
The ability of a microbial pathogen to efficiently obtain iron from the host environment is critical to its ability to cause disease. Iron availability affects the virulence of many pathogens(P aeruginosa and Listeria monocytogenes).

11. The Role of Bacterial Biofilms •
biofilm is an aggregate of interactive bacteria attached to a solid surface or to each other and encased in an exopolysaccharide matrix. A single species of bacteria may be involved or more than one species may coaggregate to form a biofilm. The bacteria in the exopolysaccharide matrix may be protected from the host's immune mechanisms Some of the bacteria within the biofilm show marked resistance to antimicrobials Biofilms are important in human infections that are persistent and difficult to treat Staphylococcus epidermidis and S aureus infections of central venous catheters, eye infections such as that occur with contact lenses and intraocular lenses, in dental plaque, and in prosthetic joint infections.

12. Toxin Production •
The second major mechanism by which bacteria cause disease is the production of toxins. A comparison of the main features of exotoxins and endotoxins is shown in Table 1.

GRAM-POSITIVE BACTERIA

The exotoxins produced by gram-positive bacteria have several different mechanism of action and produce different clinical effect

1. Diphtheria toxin, produced by Corynebacterium diphtheriae, inhibits protein synthesis by ADP-ribosylation of EF-2.

2. Tetanus toxin, produced by Clostridium tetani, is a neurotoxin that prevents release of the inhibitory neurotransmitter glycin

3. Botulinum toxin, produced by Clostridium botulinum,is a neurotoxin that blocks the release of acetylcholine at the synapse, producing a flaccid paralysis.

4. Two exotoxins are produced by Clostridium difficile, both of which are involved in the pathogenesis of pseudomembranous colitis. Exotoxin A is an enterotoxin that causes watery diarrhea. Exotoxin B is a cytotoxin that damages the colonic mucosa and causes pseudomembranes to form.

5. Multiple toxins are produced by Clostridium perfringens and other species of clostridia that cause gas gangrene. The best characterized is the alpha toxin, which is a lecithinase that hydrolyzes lecithin in the cell membrane, resulting n destruction of the membrane and widespread cell death.

6. Three exotoxins are produced by Bacillus anthracis, the agent of anthrax: edema factor, lethal factor, and protective antigen. Protective antigen binds to a cell surface receptor and forms pores in the human cell membrane that allow edema factor and lethal factor to enter the cell.

7. TSST is a superantigen produced primarily by certain strains of S. aureus but also by certain strains of S. pyogenes. TSST binds directly to class II major histocompatibility (MHC) proteins on the surface of antigen-presenting cells (macrophages) without intracellular processing.

8. Staphylococcal enterotoxin is also a superantigen but, because it is ingested, acts locally on the lymphoid cells lining the small intestine.

9. Exfoliatin is a protease produced by S. aureus that causes scalded skin syndrome. Exfoliatin cleaves desmoglein, a protein in the desmosomes of the skin, resulting in the detachment of the superficial layers of the skin. Exfoliatin is also called epidermolytic toxin.

GRAM-NEGATIVE BACTERIA •

The exotoxins produced by gram-negative bacteria also have several different :mechanisms of action and produce different clinical effects

1. The heat-labile enterotoxin produced by *E. coli* causes watery, nonbloody diarrhea by stimulating adenylate cyclase activity in cells in the small intestine.

In addition to the labile toxin, there is a heat-stable toxin, which is a polypeptide that is not inactivated by boiling for 30 minutes. The heat-stable toxin affects cyclic guanosine monophosphate (GMP) rather than cyclic AMP. It stimulates guanylate cyclase and thus increases the concentration of cyclic GMP, which inhibits the reabsorption of sodium ions and causes diarrhea.

2. Verotoxin is an exotoxin produced by strains of *E. coli* with the O157:H7 serotype. These enterohemorrhagic strains cause bloody diarrhea. the toxin inactivates protein synthesis by removing adenine from a specific site on the 28S rRNA in the large subunit of the human ribosome. The enterotoxin produced by Shigella (Shiga toxin).

When verotoxin (Shiga-like toxin) enters the bloodstream, it can cause hemolytic–uremic syndrome (HUS).

3. The enterotoxins produced by V. cholerae, the agent of cholera and Bacillus cereus, a cause of diarrhea, act in a manner similar to that of the heat-labile toxin of E. coli.

4. Pertussis toxin, produced by B. pertussis, the cause of whooping cough, is an exotoxin that catalyzes the transfer of ADP-ribose from NAD to an inhibitory G protein. Inactivation of this inhibitory regulator has two effects: one is in the

stimulation of adenylate cyclase activity and a consequent increase in the amount of cyclic AMP within the affected cells.

TYPICAL STAGES OF AN INFECTIOUS DISEASE •

A typical acute infectious disease has four stages: •
1.The incubation period, which is the time between the acquisition of the organism (or toxin) and the beginning of symptoms (this time varies from hours to days to weeks, depending on the organism)

2. The prodrome period, during which nonspecific symptoms such as fever, malaise, and loss of appetite occur •

3.The specific-illness period, during which the overt characteristic signs and symptoms of the disease occur •
4. The recovery period, during which the illness abates and the patient returns to the healthy state After the recovery period, some individuals become chronic carriers of the organisms and may shed them while remaining clinically well. Others may develop a latent infection, which can recur either in the same form as the primary infection or manifesting different signs and symptoms. Although many infections cause symptoms, many others are subclinical; that is, the individual remains asymptomatic infections although infected with the organism. In subclinical infections and after the recovery period is over, the presence of antibodies is often used to determine that an infection has occurred.