PATHOGENIC BACTERIOLOGY
MCB 303

Course Lecturer

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Pathogenic Bacteriology

1) Host parasite relationship
2) Koch's postulates
3) Pathogenic microorganisms and diseases
4) Methods of isolation of pathogens
5) Virulence, spectrum and symptoms of infection, treatment and control
6) Bacterial infections.

Koch's postulates

Koch's postulates are four criteria designed to establish a causal relationship between a causative microbe and a disease. The postulates were formulated by Robert Koch and Friedrich Loeffler in 1884 and refined and published by Koch in 1890. Koch applied the postulates to establish the etiology of anthrax and tuberculosis, but they have been generalized to other diseases.

The postulates

Koch's postulates are:

1. The microorganism must be found in abundance in all organisms suffering from the disease, but not in healthy organisms.
2. The microorganism must be isolated from a diseased organism and grown in pure culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

However, Koch abandoned the second part of the first postulate altogether when he discovered asymptomatic carriers of cholera and, later, of typhoid fever. Asymptomatic

carriers are now known to be a common feature of many infectious diseases, especially viruses such as polio, herpes simplex, HIV and hepatitis C. As a specific example, all doctors and virologists agree that poliovirus causes paralysis in just a few infected subjects, and the success of the polio vaccine in preventing disease supports the conviction that the poliovirus is the causative agent.

The third postulate specifies "should", not "must", because as Koch himself proved in regard to both tuberculosis and cholera, not all organisms exposed to an infectious agent will acquire the infection. Non-infection may be due to chance or to the host's immune system successfully repulsing the invading pathogen; acquired immunity, as from previous exposure or vaccination; or genetic immunity, as with the resistance to malaria conferred by possessing at least one sickle cell allele.

History

Koch's postulates were developed in the 19th century as general guidelines to identify pathogens that could be isolated with the techniques of the day. Even in Koch's time, it was recognized that some infectious agents were clearly responsible for disease even though they did not fulfill all of the postulates. Attempts to rigidly apply Koch's postulates to the diagnosis of viral diseases in the late 19th century, at a time when viruses could not be seen or isolated in culture, may have impeded the early development of the field of virology. Currently, a number of infectious agents are accepted as the cause of disease despite their not fulfilling all of Koch's postulates. Therefore, while Koch's postulates retain historical importance and continue to inform the approach to microbiologic diagnosis, fulfillment of all four postulates is not required to demonstrate causality.

Koch's postulates have also influenced scientists who examine microbial pathogenesis from a molecular point of view. In the 1980s, a molecular version of Koch's postulates was developed to guide the identification of microbial genes encoding virulence factors.

HOST PARASITE RELATIONSHIP

A larger organism that supports the survival and growth of a smaller organism is called the **HOST**.

A symbiotic relationship is an interaction between two organisms. *Symbiosis* often refers to the “living together” of organisms and it includes *commensalism, mutualism* and *parasitism*. This is an association between two living organisms. However, it is different from situations where organisms live on dead decaying organic matter and such organisms are referred to as *saprophytes*.

Parasites are those organisms that live on or within a host organism and are metabolically dependent on the host. Also any organism that causes diseases is a parasite.

Infections can be defined by the host-parasite relationship; several types of parasitism can be recognized. Two major levels of parasitism are well defined: the *ectoparasite* and *endoparasite*. When the parasite lives on the surface of the host it is an ectoparasite and when it lives internally it is an endoparasite. Some parasites live complex life cycles, they inhabit multiple hosts to complete this life cycle. The hosts are now determined by the stage at which the parasite lives in them. For example a "**Final host**" (**Primary or Definitive host**) is one in which the parasite either attains sexual maturity or reproduces. **Intermediate** host (**Secondary host**) is a host that serves as a temporary but essential environment for some stages of development. A paratenic host is a potential or substitute intermediate host that serves until the appropriate definitive host is reached, and in which no development of the parasite occurs; it may or may not be necessary to the completion of the parasite's life cycle. A "transfer host" is host used as a vehicle for reaching a final host but it is not necessary for the completion of the parasites life cycle. A "reservoir host" is a host infected with a parasitic organism that also serves as a source of infection for humans or another species.

The host-parasite relationship is complex and dynamic. When a parasite is growing and multiplying within or on a host, the host is said to have an infection.

An infectious disease is any change from a state of health in which part or all of the host body is not capable of carrying on its normal functions due to the presence of a parasite or its products.

Any organism or agent that produces such a disease is also known as a pathogen. The ability to cause disease is called **pathogenicity**. A **primary pathogen** *is any organism that causes disease in a healthy host by direct interaction*. On the other hand, an **opportunistic pathogen** *refers to an organism that is part of the host's normal microbiota, but is able to cause disease when the host is immuno-compromised or when it has gained access to other tissue sites*[DO1].

A **latent state** *is a condition in which an infectious organism remains inactive and no symptom is present within the host cell*. However, the infectious organism is still present in the tissues of the host. **Latency** can be either intermittent latency or quiescent latency. In intermittent latency the infectious organism remains in the host for some weeks or years without causing the disease or symptoms only to be cyclically activated later.

In a quiescent latency the organism persists but remains inactive for long periods of time, usually for years.

The outcome of most host-parasite relationships is dependent on three main factors:

1) The number of microorganism infecting the host.
2) The degree of pathogenicity (or virulence) of the organism and
3) The host's defenses or degree of resistance

Virulence is the degree or intensity of pathogenicity. A lot of factors such as physical or chemical characteristics contribute to pathogenicity of a parasite. Individual characteristics that confer virulence are called **VIRULENCE FACTORS**. Examples of such factor include capsule, pili and toxins.

Virulence is determined by three characteristics of the pathogen (a) invasiveness (b) infectivity and (c) pathogenic potential.

Invasiveness *is the ability of the organism to spread to adjacent or other tissue*. Infectivity *is the ability of the organism to establish a focal point of infection*. Pathogenic potential *refers to the degree that the pathogen causes damage*. A major aspect of pathogen potential is toxigenicity. Toxigenicity *is the pathogen's ability to produce toxins, chemical substances that damage the host and produce disease*.

Virulence is often measured experimentally by determining the **LETHAL DOSE 50** (LD_{50}) or the **INFECTIOUS DOSE 50** (ID_{50}) the (LD_{50}) refers to number of organisms (pathogens) required to kill half (50%) of an experimental group of host within a specified time period while (ID_{50}) refers to the number of pathogens required to cause infection in half (50%) of the experimental group of host within a specified time period. Aside toxins causing diseases, diseases can often result from ***immunopathology*** a condition in which a host triggers exaggerated immunological responses upon a second exposure or chronic exposure to a microbial antigen. These hypersensitivity reactions damage the host even though the pathogen doesn't produce a toxin. Tuberculosis is a good example of this. Another form of immunopathology is called **MOLECULAR MIMICRY**. Molecular mimicry is a phenomenon that involves the auto-immune response. The immune system is triggered to attack the host tissues because it carries antigens that resembled those of the host. Streptococcal infections often cause rheumatic fever this way.

The table below shows the various types of infections associated with parasitic organisms.

S/N	TYPE	DEFINITION
1	Abscess	A localized infection with a collection of pus surrounded by an inflamed area
2	Acute	Short but severe
3	Bacteremia	Presence of viable bacteria in the blood

4	chronic	Persisting over a long time
5	covert	Subclinical, with no symptoms
6	cross	Transmitted between hosts infected with different organisms
7	Focal	Existing in circumscribed areas
8	fulminating	Infectious agent multiplying with great intensity
9	iatrogenic	Caused as a result of health care
10	latent	Persisting in tissues for long periods, during most of which there are no symptoms
11	localized	Restricted to a limited region or to one or more anatomical areas
12	Nosocomial	Developed during a stay at a hospital or other clinical care faculty.
13	opportunistic	Resulting from endogenous microbiota, especially when host resistance is very low
14	Overt	Symptomatic
15	Phytogenic	Caused by plant pathogens
16	polymicrobial	More than one organism present simultaneously
17	primary	First infection that often allows other organisms to invade host at that site
18	pyogenic	Resulting in pus formation
19	secondary	Caused by an organism following an initial or primary infection.
20	Sepsis	1) The condition resulting from the presence of bacteria or their toxins in blood or tissues, the presence of pathogens or their toxins in the blood or other tissues. 2) Systemic response to infection, this systemic

		response is manifested by two or more of the following conditions as a result of infection: ***Temperature***, >38^0 or <36^0 C; ***Heart rate***, >90 *beats per min*; ***Respiratory rate*** >20 ***breath per min,*** or $_{P}CO_2$ <32 mm hg;**,** ***Leucocyte count,*** **>12, 000** ***cells per ml***^{3} ***or*** >10% ***immature (band) forms***
21	septicemia	Blood poisoning associated with persistence of pathogenic organisms or their toxins in the blood
22	Septic shock	Sepsis with hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.
23	Severe sepsis	Sepsis associated with organ dysfunction hypoper fusion, or hypotension, hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status
24	Sporadic	Occurring only occasionally
25	Subclinical	No detectable symptoms or manifestations occurring (covert)
26	Systemic	Spread through the body
27	Toxemia	Condition arising from toxins in the blood
28	Zoonotic	Caused by a parasitic organism that is normally found in animals other than humans

BACTERIAL PATHOGENESIS

The steps for infection by pathogenic bacteria usually include the following:

1) Maintain a source and/or reservoir
2) Initial transport to and entry into the host
3) Adhere to colonize, and or invade host cells or tissue.
4) Evade host defense mechanisms.
5) Multiply (grow) or complete the life cycle on or in the host or the host cells
6) Damage the host
7) Leave the host and return to the reservoir or enter a new host.

1.0 Maintain a Source and/or Reservoir

If the source or reservoir of the infection can be eliminated or controlled, the infectious disease cycle itself will be interrupted and transmission of the pathogen will be prevented.

A **source** is the location from which the pathogen is immediately transmitted to the host, either directly through the environment or indirectly through an intermediate agent. The source can be either animate (e.g. humans or animals) or inanimate (e.g. water, soil or food). The **period of infectivity** is the time during which the source or infections is disseminating the pathogen.

The reservoir is the site or natural environmental location in which the pathogen normally resides it is also the site from which a source acquires the pathogen and or where direct infection of the host can occur. Thus a reservoirs also can be animate or inanimate.

Human beings are usually the most important reservoirs and are called carrier. A carrier is an infected individual who is a potential source of infection for others. Four types of carriers are recognized.

1) An acute carrier is an individual who has an overt clinical case of the disease.
2) A convalescent carrier is an individual who has recovered from the infectious disease but continues to harbor large numbers of the pathogen
3) A healthy carrier is an individual who harbors the pathogen but is not ill.
4) An incubatory carrier is an individual who is incubating the pathogen in larger numbers but is not ill.

Convalescent, healthy and incubatory carriers may harbor the pathogen for only a brief period say for hours, days or weeks. In this case they are called CASUAL, ACUTE OR TRANSIENT CARRIERS.

However, if they harbor the pathogen for long period say for months, years or life they are called CHRONIC CARRIERS.

Animal diseases that can be transmitted to humans are called ZOONOSES, this animals can serve as reservoirs.

2.0 Transport of the Bacterial Pathogen to the Host[DO2]

The major mean of transporting bacterial pathogen to the host is by direct contact through coughing, sneezing, body contact etc. The indirect transporting of pathogen to the host include soil, water and food. Other means of transporting include arthropod vectors and fomites (inanimate objects that harbor and transmit pathogens).

3.0 Attachment and Colonization by the Bacterial Pathogens.

Colonization is the establishment of a site of microbial reproduction on or within a host. It does not necessarily result in tissue invasion or damage. Colonization depends on the ability of bacteria to survive in the new (host) environment and to compete successfully with the host's normal microbiota for essential nutrients. Specialized structures that allow bacteria to compete for surface attachment sites also are necessary for colonization. Bacterial pathogens adhere with a high degree of specificity to particular tissues. Adherence structures such as pili and fimbriae are specialized adhesion molecules on the bacterium's cell surface that bind to complementary receptor sites on the host cell surface facilitating bacterial attachment to host cells. They are one type of virulence factor. Virulence factors are bacterial produce or structural components (e.g. capsule, and adhesins) that contribute to virulence or pathogenicity.

4.0. Invasion of Host Tissues.

Entry into host cells and tissues is a specialized strategy used by many bacterial pathogens for survival and multiplication. Pathogen often actively penetrate the host's mucous membranes and epithelium after attachment to the epithelial surface. This may be accomplished through production of lytic substances that alter the host tissue by (1) attacking the extracellular matrix and basement membrane of integuments and intestinal linings (2) degrading carbohydrate protein complexes between cells or on the cell surface (the glycocalyx) or (3) disrupting the cell surface.

At times a bacterium can penetrate the epithelia surface by passive mechanisms not related to the pathogen itself. Examples include:
(1) Small breaks, lesions, or ulcers in a mucous membrane that permit initial entry (2) Wounds, abrasions, or burns on the skin's surface
(3) Arthropod vectors that create small wound while feeding,

(4) Tissue damage caused by other organisms: (e.g. a dog bite) and
(5) Existing eucaryotic internalization pathways (e.g. endocytosis and phagocytosis).

Once under the mucus membrane, the bacterial pathogen may penetrate to deeper tissues and continue disseminating throughout the body of the host. One way the pathogen accomplishes this is by producing specific structures and / or enzymes that promote spreading. These products represent other types of virulence factors. Bacteria may also enter the small terminal lymphatic capillaries that surround epithelial cells. These capillaries merge into large lymphatic vessels that eventually drain into the circulatory system. Once the circulatory system is reached, the bacteria have access to all organs and systems of the host.

Bacterial invasiveness varies greatly among pathogen. For example ***Clostridium tetani*** (cause of tetanus) produces a variety of virulence factors but is considered noninvasive. ***Bacillus anthracis*** (cause of anthrax) and ***Yersinia pestis*** (cause of plague) also produce substantial virulence factors and are highly invasive.

5.0 Growth and Multiplication of the Bacterial Pathogen

For bacterial pathogen to grow and multiply appropriate environment such as pH, temperature and redox potential within the host must be available. Those areas of the host's body that provide these appropriate conditions will promote the growth and multiplication of the bacterial pathogen and allow it to produce infection.

Some bacteria are able to grow and multiply within various cell of a host. Organisms with this ability to live intracellularly are subdivided into two

groups. (a) **Facultative Intracellular Pathogen**: are those organisms that can reside within the cells of the host or in the environment. An example of a facultative intracellular pathogen is ***Brucella abortus*** which is capable of growth and replication within macrophages, neutrophils, and trophoblast cells.

(b) **Obligate Intracellular Pathogen**: are incapable of growth and multiplication outside a host cell. Example of this include rickettsias and viruses.

6.0 Leaving the Host

The last determinant of a successful bacterial pathogen is the ability to leave the host and enter either a new host or a reservoir unless a successful escape occurs, the disease cycle will be interrupted and the microorganism will not be perpetuated. Most bacteria employ passive escape mechanisms. Passive escape occurs when a pathogen or its progeny leave the host in feaces, urine, droplets, saliva or desquamated cells.

Table: Bacterial Adherence Factors that Play a Role in Infectious Diseases.

S/N	ADHERENCE FACTOR	DESCRIPTION
1	Fimbriae	Filamentous structure that help attach bacteria to other bacteria or to solid surfaces
2	Glycocalyx or capsule	A layer of exopolysaccharide fibers with a distinct outer margin that surrounds many cells it inhibits phagocytosis and aids in adherence; when the layer is well organized and not easily washed off it is called a capsule.

3	Pili	Filamentous structure that bind prokaryotes together for the transfer of genetic material
4	S layer	The outermost regularly structured layer of cell envelopes of some bacteria that may promote adherence to surfaces
5	Slime layer	A bacterial film that is less compact than a capsule and removed easily.
6	Teichoic and lipoteichoic acids	Cell wall components in gram-positive bacteria that aid in adhesion

TOXIN-MEDIATED PATHOGENESIS

In some diseases the symptoms are caused by an Exotoxin: *a specific protein toxin which is released by the pathogen and which affects specific site(s) in the body*; some of these proteins are phage-encoded (e.g cholera toxin, diphtheria toxin) and some are plasmid-encoded (e.g. anthrax toxin).

(a) CHOLERA

Part of the symptoms of cholera involves vomiting and a profuse diarrhea which eventually becomes virtually water. The pathogen (certain strains of vibrio cholera) multiplies in the gut and forms a type of exotoxin called ENTEROTOXIN (cholera toxin, CT). the cholera toxin (CT) acts on mucosal cells in the small intestine, stimulating the enzyme adenylate cyclase leading to increase in intracellular levels of cyclic AMP (cAMP) (also known as adenosine 3',5'-cyclic monophosphate). The cAMP also stimulates the secretion of chloride ions into the gut lumen. Probably as a related effect, there is also a net loss of HCO_3^- outflow of water to the gut gives rise to the characteristic rice- water stools of cholera.

Infections by strains of *V. cholerae* which do not synthesize CT may give rise to (less severe) symptoms as a result of other toxins (the zot and Ace toxins) encoded by the pathogen.

Following ingestion of *V.cholera*, colonization of the small intestine and the development of the disease depend on two main virulence factors: 1) appendages which mediate adhesion to the mucosal surface that is also referred to as "toxin co-regulated pili" (TCP) and (ii) cholera toxin (CT). The genes for CT and TCP are coordinately (jointly) regulated by transcriptional regulator proteins ($T_{ox}R$, $T_{ox}S$ and $T_{ox}T$) which apparently promote CT and TCP expression when receiving environmental signals within the intestinal tract.

(b) **BOTULISM**

Botulism involves muscle paralysis, and death may result for example from mechanical (muscular) failure of the respiratory system. The pathogen (strains of *Clostridium botulinum*) forms a type of exotoxin a NEUROTOXIN *which acts on nerve muscle junctions, inhibiting the release of acetylcholine and (hence) inhibiting nervous stimulation of the muscles*. Disease can result from the ingestion of preformed toxin usually in toxin contaminated foods such as cooked meats, sausage, and improperly canned vegetable that is, the pathogen itself need not be ingested.

(c) TETANUS

Tetanus (lockjaw) involves uncontrollable contractions of the skeletal muscles often leading to death by asphyxia or exhaustion. The disease develops e.g. when deep, anaerobic wounds are contaminated with the pathogen, *Clostridium tetani. C. tetani* produces a neurotoxin

(tetanospasmin) which acts on certain cells (interneurones) in the central nervous system, by inhibiting the releases of a neurotransmitter (glycine) from these cells, tetanospasmin permits the simultaneous contraction of both muscles in a protagonist-antagonist pair producing spastic (rigid) paralysis.

Similarities between Botulinum Toxin and Tetanospasmin.

Although both give different clinical symptoms, both toxins bind to nerve cells (b) both are taken up by the cells (internalized) (c) both produce their effects by acting as enzymes (zinc-endopeptidase) which cleave specific proteins in the nerve cells, thereby inhibiting the normal release of neurotransmitter substances.

(d) **STAPHYLOCOCCAL FOOD POISONING.**

Staphylococcal food poisoning: due to the effects of enterotoxins produced by several species of *Staphyloccocus* (mainly *S. aureus*). There are five distinct types of toxin (types A-E) which characteristically cause vomiting and often diarrhea, shortly after contaminated food is eaten. The mode of action of the toxins is not known.

(e) **Shiga toxin and shiga-like toxins (verotoxins)**.

These enterotoxins formed by some strains of *Shigella* and by EHEC (enterohemorrhagic *E. coli*) respectively have similar mechanisms. They bind to sites in the gut and are taken up by receptor-mediated endocytosis. Apparently, the toxins affect protein synthesis and e.g. inhibit the absorption of Nacl; however, the mechanism responsible for the fluid loss in dysentery remains unclear but may involve tissue

damage/inflammation, the toxin serving tend to exacerbate the symptoms e.g. by causing vascular damage and (thus) promoting the formation of blood stool etc.

PATHOGENESIS INVOLVING OTHER BACTERIAL PRODUCTS.

AGGRESSINS are products which can promote the invasiveness of a pathogen. For example, certain bacteria, including *Streptococcus pyogenes* and most coagulase-positive staphylococci produce HYALURONATE LYASE (spreading factor): an enzyme which cleaves hyaluronic acid, a component of the intercellular cement in animal tissues, in at least some cases this enzyme may assist bacterial penetration of an infected site. Another example is STREPTOKINASE. Bacterial products can also contribute to pathogenesis in a more mechanical way as for example in cystic fibrosis

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an inheritable disease involving defective transmembrane transport of chloride. The lungs are typically congested with thick, dehydrated mucus and may become infected with organisms such as mycobacteria, *Burkholderia cepacia* and *Pseudomonas aeruginosa* can produce a viscous slime (alginate) that inhibits phagocytosis and promotes congestion leading to poor prognosis. High levels of salt (Nacl) on CF airway epithelia may permit bacterial colonization by inhibiting normal antibacterial activity.

Most strains of *P. aeruginosa* have genes for alginate, but strains isolated from the general environment typically do not express these genes, in CF patients, however, conditions in the lung seem to select for mucoid (i.e. alginate producing) strains.

PATHOGENESIS INVOLVING DESTRUCTION OF HOST CELLS OR TISSUES

1) TYPHOID

   Typhoid, caused by *Salmonella typhi*, involves e.g. intestinal symptoms and systemic illness. After ingestion, the organisms penetrate the ileal mucosa, entering the bloodstream (via the lymph system) and multiplying e.g. in the liver, gall bladder and spleen. The intestine can be secondarily invaded from the gall bladder. Intestinal inflammation can be so intense that it causes local necrosis (death) of tissue (with formation of typhoid ulcers) and may cause perforation and haemorrhage.

2) Dysentery (dysentery)

   Dysentery is caused by *Shigella* spp, EHEC (Entorohaemorrhagic *E. coli* also called verocytoxic (VTEC) and EIEC (Enteroinvasive *E. coli*). *Shigella* and EIEC invade and spread among the host mucosal cells by the same mechanism. The bacteria invade and destroy mucosal cells in the ileum/colon. The spread of bacteria within and between these host cells requires the presence of a plasmid encoded protein (Vir G) in the bacterial outer membrane. Within the cytoplasm of an invaded intestinal cell, VirG induces the host cell to deposit actin filaments on the bacterial surface; ongoing deposition seems to propel the bacterium through the host cells cytoplasm thus facilitating the spread of these bacteria through the tissues. Another outer membrane protein (OmpT) a protease which cleaves (and inactivates) Vir G appears to occur in most strains of *E. coli* but is absent in EIEC and *Shigella* spp the absence of OmpT seems to be necessary for the invasive properties of these pathogens

Oroya Fever

Oroya fever, which occurs in parts of south America, involves e.g. fever and anaemia, the cause agent, *Bartonella bacilliformis* is transmitted via the "bites" of sand flies. *B. bacilliformis* grows in and on erythrocytes (red blood cells) and in the endothelia cells of the host, bacterial growth leads to the destruction of erythrocytes etc. and leads to associated symptoms.

OTHER FORMS OF PATHOGENESIS

1) Endotoxic shock (septic shock)

The endotoxins of gram-negative bacteria have been regarded as macromoleular complexes containing certain elements of the cell envelope

a) Lipopolysaccharides (LPS)
b) Proteins
c) Phospholipids

The toxic component of LPS is lipid A

The often fatal condition ENDOTOXIC SHOCK appears to involve the activity of blood-borne endotoxins (following lysis of gram negative bacteria). Endotoxins act on macrophages and other cells of the immune system, stimulating the secretion of certain physiologically potent agents (cytokines) such as interleukin-I (IL-I) and tumour necrosis factor (TNF); these cytokines can recruit others, resulting in the classical symptoms of shock (e.g a fall in blood pressure) and the blocking of blood vessels by white blood cells. Death may occur as a consequence of the progressive failure of the body's functions.

A vaccine, consisting of anti-endotoxin monoclonal antibodies, has been tried unsuccessfully.

2) *Helicobacter pylori* ASSOCIATED INTESTINAL DISEASE

Helicobacter pylori has been casually connected with e.g. gastritis and peptic ulcer disease, although the detail of pathogenesis are not fully understood However, it has been found that lipopolysaccharides from *H. pylori* include antigens identical to the lewis x and lewis y antigens which occur e.g. in human gastric mucosa, and this has suggested the possibility that anti-lipopolysaccharide antibodies which may promote autoimmune inflammation by binding to mucosal lewis antigens.

3) **THE JARISCH HERXEIMER REACTION**

This potentially fatal reaction may follow the first effective dose of an antimicrobial agent given to combat disease caused by certain bacterial (particularly spirochaetes) or protozoa. Symptoms, which include an initial rise in temperature, are associated with a cascade of cytokines (e.g. TNF. IL-6, IL8) that are presumed to be responsible for at least some of the pathophysiological events; the mechanism of the sudden release of cytokines is not understood yet.

Pathogenesis of some diseases caused by *Escherichia coli*

GROUP	DISEASE
EIEC Enteroinvasive *E.coli*	Usually food born. The pathogen adheres to, invades and destroys epithelia cells in the ileum/colon, causing dysentery at least some virulence factors are plasmid encoded. The pathogen can also cause a watery diarrhea, at least one plasmid encoded enterotoxin is formed
EHEC Enterohaemorrhagic *E. coli* (EHEC) or	Usually food-borne. Minimum infective dose apparently <100 cells. The pathogen forms one or both of two phage-encoded toxins whose activity closely resembles that of the toxin

Verotoxigenic *E.coli* (VTEC)	Of *Shigella dysenteriae* type I and II (SLTI, SLTII) or VTI and VT2, respectively. Symptoms range from mild diarrhoea to severe, bloody diarhoea (haemorrhagic colitis). Possibly reflecting differing responses to the toxins from different parts of the gut. Particularly in children, infection can result in haemolysis.
ETEC Enterotoxigenic *E. coli*	Usually food and/or water borne. ETEC is a common cause of traveller's diarrhea and of diarrhea in children in the developing countries. The pathogen has plasmid-encoded fimbriae e.g. the so-called COLONIZATION FACTORS (CFI) CFI and CFII with which it adheres specifically to the epithelium of the small intestine. These adherence factor are equally referred to as CFAI and CFAII. ETEC forms heat-stable toxins (STI, STII) and heat labile toxins (LTI, LTII). STI binds to the brush border and activates host intracelullar mechanisms, resulting in stimulation of CL^- secretion and/or inhibition of Nacl absorption leading to watery diarrhoea. LTI resemble cholera toxin in its activity LTII rarely occurs in a human host.
EPEC Enteropathogenic *E.coli*	Food and/or water borne. The pathogen adheres to epithelium in the small intestine brush border microvilli; interaction between EPEC and epithelia cells is a multi-stage process. Diarrhea, mainly in infants, may result partly from reduction in absorption due to loss of microvilli.

EAggEC/EAEC Enteroaggregative *E. coli*	Strains in this group cause persistent diarrhoea in children, particularly in developing countries. The pathogen forms toxins and adhesins, but the mechanism of pathogenesis is not known. Strains of EAggEC may be characterized in vitro by the "aggregative" pattern of adherence to (mammalian) HEP-2 cells.

THE BODY'S DEFENCES

There are two major ways by which the body defend itself against microbial agents, these are (a) constitutive defences and (b) adaptive response.

(a) **Consitutive defences.**

Constitutive defences are non-specific defence mechanisms which are typically operative all the time.

(i) A good example of constitutive defence is the **skin**. To most bacteria, it is a hostile environment, where water in scarce and sites are occupied by well adapted to skin microflora, some of which produce antibacterial fatty acids from lipids secreted by the sebaceous glands.

(ii) Another constitutive defence is mucous membranes. The secretions which bath these tissues actively discourage the establishment of a pathogen, both by their mechanical flushing action and by their antibacterial substances.

For example tears contain an enzyme called LYSOZYME in addition to these, these surfaces contain microflora with which any pathogen must compete with if it is to become established.

When a pathogen penetrates the outer defence, it is immediately faced with the inner defences within the tissues and circulatory systems, certain specialized cells (phagocytes) engulf and destroy particles of "foreign" matter-including many types of microorganism these scavenging cells (which include e.g. macrophage) can usually prevent the establishment of a pathogen in the (nutrient-rich) tissues of the body.

If the pathogen persist it may cause inflammation, reddening, swelling, warmth and pain at the affected site. Although inflammation can be caused by other agents such as host and chemical irritants. Inflammation remains one of the body's generalized reaction to pathogens. During inflammation there in an increase in the outflow of plasma from small blood vessels into the affected tissue thereby increasing the pathogen to antimicrobial factors present in normal plasma.

(iii) Complement

Complement is a form of constitutive defence. Normal plasma contains complement. A complement is a number of different proteins which in the presence of certain types of molecule, undergo a "cascade" of reactions involving sequential activation. On activation various component of the system carry out specific physiological functions.

Activation of the complement system can be triggered in various ways, the type of trigger determines which of two pathways are followed for example, the lipopolysaccharide (LPS) of a gram-negative bacterium can trigger the alternative pathway. Activation by a gram-negative bacterium can have several consequences for example, the binding of component

C3b makes the cell more susceptible to phagocytosis by macrophages moreover, if components C5b-9(the membrane attack complex) bind to cell surface they can form a hole in the outer membrane which, in some cases, can lead to cell lysis (immune cytolysis). Lysis resulted not from the breaching of the outer membrane but from the opportunity that this provide for lysozyme to reach peptidoglycan, thus, a potential gram-negative pathogen (such as *Haemophilus influenza*) on the conjunctiva would be at risk of lysis since the fluid which bath the eye contains both lysozyme and complement is thus an early, rapid and potent form of non-specific defense.