

Underwood: Chapter 2: The Characteristics, Classification and Incidence of Disease

What is Disease?

A disease is a condition in which the presence of an abnormality of the body causes a loss of normal health (dis-ease).

A disease is the clinical manifestation, through signs and symptoms, of an underlying abnormality.

Limits of Normality

Normal is virtually impossible to define as a single discrete state for any biological characteristic.

Most quantifiable biological characteristics are normally distributed, in statistical terms, about an average value. Normality has to be expressed as a numerical range, usually encompassed by two standard deviations (for a 'normally' distributed feature) either side of the mean.

A distinction must be drawn also between what is usual and what is normal. It is usual to find atheroma in an elderly individual - but is it normal?

Responses to the Environment

Adaptation

Disease: Failure of Adaptation

Characteristics of Disease

- *Aetiology*: the cause of a disease
- *Pathogenesis*: the mechanism causing the disease
- *Pathological and clinical manifestations*: the structural and functional features of the disease
- *Complications and Sequelae*: the secondary, systemic or remote consequences of a disease
- *Prognosis*: the anticipated course of the disease in terms of cure, remission, or fate of the patient
- *Epidemiology*: the incidence and population distribution of a disease.

Aetiology

The aetiology of a disease is its cause: the primary agent responsible for initiating the subsequent events resulting in the patient's illness. Environmental causes of diseases are called *pathogens*, though this term is used commonly only when referring to bacteria.

General categories of aetiological agents include:

- genetic abnormalities
- infective agents
- chemicals
- radiation
- mechanical trauma.

In the absence of any known cause, a disease is usually classified aetiologically as *primary, idiopathic, essential, spontaneous* or *cryptogenic*.

Identifying Causal Associations

A causal association is a marker for the risk of developing a disease, but it is not necessarily the actual cause of the disease.

Koch's Postulates

An infective cause for a disease is not usually regarded as proven until it fulfils the requirements of the postulates enunciated by Robert Koch (1843-1910), a German bacteriologist and Nobel prizewinner in 1905:

- the organism must be sufficiently abundant in every case to account for the disease
- the organism associated with the disease can be cultivated artificially in pure culture
- the cultivated organism produces the disease upon inoculation into another member of the same species
- antibodies to the organism appear during the course of the disease.

Pathogenesis

The pathogenesis of a disease is the *mechanism* through which the aetiology operates to produce the pathological and clinical manifestations.

Latent Intervals and Incubation Periods

Pathological and Clinical Manifestations

The aetiological agent acts through a pathogenetic pathway (mechanism) to produce the *manifestations* of disease, giving rise to clinical signs and symptoms and the pathological features or *lesions* to which the clinical signs and symptoms can be attributed.

Lesions

A lesion is the structural or functional abnormality responsible for ill health.

Pathognomonic Abnormalities

Pathognomonic features are restricted to a single disease, or disease category, and without them the diagnosis is impossible or uncertain.

Complications and Sequelae

Diseases may have *prolonged, secondary* or *distant* effects.

Prognosis

The prognosis forecasts the known or likely *course of the disease* and, therefore, the fate of the patient.

Remission and Relapse

Morbidity and Mortality

The *morbidity* of a disease is the sum of effects upon the patient.

The *mortality* of a disease is the probability that death will be the end result.

Causes of Disease

Diseases are caused by a variable interaction between *host* (including *genetic*) factors and *environmental* factors.

Ankylosing spondylitis is usually associated with the HLA-B27 tissue antigen.

Genetic Factors

Some diseases are due solely to a genetic defect, either inherited from parents or a spontaneous mutation. Others are due indirectly to a genetic factor that has a permissive effect, enabling an environmental agent to produce the disease.

All genes encode for biochemical events, but, as a general rule (with many exceptions), autosomal dominant disorders ultimately produce structural lesions and become manifest in adult life, whereas autosomal recessive disorders produce biochemical abnormalities which are evident in infancy or childhood.

Genetic Polymorphism

Within the human population there are many normal genetic variations or *polymorphisms*.

HLA Antigens

Clinical and experimental observations on the fate of organ transplants led to the discovery of genes known as the major histocompatibility complex (MHC). In humans, the MHC genes reside on chromosome 6 and are designated *HLA genes* (human leukocyte antigen genes). HLA genes are expressed on cell surfaces by the presence of substances referred to as 'antigens', not because they normally operate as antigens in the host that bears them, but because of their involvement in graft rejection.

HLA antigens are grouped into two classes:

- Class I antigens are expressed on the surface of all nucleated cells. In all diploid cells there are pairs of allelic genes at each of three loci: these genes are known as A, B and C. The normal role of class I antigens is to enable cytotoxic T-lymphocytes to recognise and eliminate virus-infected cells.

- Class II antigens are expressed on the surface of those cells that interact with T-lymphocytes by physical contact, such as antigen-presenting cells (i.e., Langerhans' cells). The pairs of allelic genes at each of three loci are known as Dp, DQ, and DR. The normal role of class II antigens is the initiation of immune responses.

Diseases may be associated with HLA antigens because:

- some infective micro-organisms bear antigens similar to those of the patient's HLA antigens and thereby escape immune recognition and elimination.

- the immune response to an antigen on an infective micro-organism cross-reacts with one of the patient's HLA antigens, thus causing tissue damage

- the gene predisposing to a disease is closely linked (genetic linkage) to a particular HLA antigen.

Examples of diseases associated with HLA antigens

Eczema, asthma	A23	Environmental antigen
Ankylosing spondylitis	B27	In c. 90% cases
Coeliac disease	DR3 B8	Gluten sensitivity
Graves' disease	DR3 B8	Due to LATS globulin
Hashimoto's thyroiditis	DR5	Aberrant HLA class II expression on thyroid epithelium
IDDM	DR3 DR4 DR8	Viral injury to beta-islets
Rheumatic disease	DR4	Autoimmune disease

Autoimmune Disease

Autoimmune diseases are most frequently associated with specific HLA antigens. The combination of HLA-DR3 and HLA-B8 is particularly strong in this regard, but it must be emphasised that it is present in only a minority of patients with autoimmune disease. Normally, HLA class II antigens are not expressed on epithelial cells. However, in organs affected by autoimmune disease, the target cells for immune destruction are often found to express class II antigens. This expression enables their immune recognition and facilitates their destruction.

Blood Groups

A few diseases show a weaker and indirect association with blood groups. This association may be due to genetic linkage; the blood group determinant gene may lie close to the gene directly involved in the pathogenesis of the disease.

Examples:

- duodenal ulceration and group O
- gastric carcinoma and group A.

Gender and Disease

Gender, like any other genetic attribute of an individual, may be directly or indirectly associated with disease. Haemophilia is an inherited X-linked recessive disorder of blood coagulation. It is transmitted by females to their male children. Haemophilia is rare in females because they have two X chromosomes, only one of which is likely to be defective. If the mother is a haemophilia carrier, half of her male children will have the disease.

Some diseases show a predilection for one of the sexes. For example, autoimmune diseases (i.e., rheumatoid disease, SLE) are generally more common in females than in males; the reason for this is unclear. Atheroma and its consequences tends to affect males earlier than females, but after menopause the female incidence catches up with that in males. Females are more prone to osteoporosis.

Racial Differences

The cystic fibrosis gene is carried by 1:20 Caucasians, whereas this gene is rare in Negroes and Asians. Conversely, the gene causing sickle-cell anaemia is more common in Negroes than in any other race.

Environmental Factors

Infective Agents

The main classes of infective agents are: bacteria, viruses, yeasts and fungi and parasites. In addition there is some evidence for the existence of infectious proteins (called *prions*) as a possible cause of neurodegenerative disease, in particular the rare Jakob-Creutzfeldt disease.

Bacteria

Normally-present bacteria are called *commensals*.

Bacteria usually cause disease through the production of enzymes and toxins that injure host tissues. They may also cause tissue damage indirectly by prompting a defensive reaction in excess of that justified by their innate capacity to injure. For example, most of the tissue destruction seen in pulmonary tuberculosis is due to the body's reaction to the causative bacterium rather than to any bacterial enzymes or toxins.

The harmful effects (pathogenicity) of bacteria are mediated by:

- pili and adhesins
- toxins
- aggressins
- undesirable consequences of immune responses.

Bacterial Pili and Adhesins

Pili, or *fimbriae*, are slender processes on the surface of some bacteria. They are coated with recognition molecules called *adhesins*. They serve two functions:

- sexual interaction between bacteria: sex pili
- adhesion to body surfaces: adhesion pili.

Adhesion pili are the means by which bacteria stick to body surfaces. Pili are a feature predominantly of Gram-negative bacteria (i.e., enterobacteria causing gastrointestinal infections, neisseriae causing meningitis and genital infections). A few Gram-positive bacteria

also possess pili, notably beta-haemolytic streptococci, enabling them to adhere to the pharyngeal mucosa.

Host factors rendering some individuals more susceptible to certain types of infection include polymorphisms of the glycoproteins on cell surfaces to which the adhesin-coated pili stick. These include blood group substances.

Bacterial Toxins

- exotoxins
- endotoxins.

Exotoxins. These are enzymes secreted by bacteria and have local or remote effects:

- pseudomembranous colitis due to *Clostridium difficile*
- neuropathy and cardiomyopathy due to *Corynebacterium diphtheriae*
- tetanus due to tetanospasmin produced by *Clostridium tetani*
- scalded skin syndrome due to *Staphylococcus aureus*
- diarrhoea due to activation of cyclic AMP by *Vibrio cholerae*.

The genes directing the synthesis of exotoxins are usually an intrinsic part of the bacterial genome. In a few instances, however, bacteria acquire the gene in the form of a *plasmid*, a loop of DNA that can convey genetic information from one bacterium to another; this is also a mechanism by which bacteria can acquire resistance to an antibiotic. Genes encoding for exotoxins can also be transmitted by *phages*: these are viruses that affect bacteria. The toxin produced by *Corynebacterium diphtheriae* is encoded on a gene conveyed to the bacterium by a phage; strains of this and other organisms synthesising exotoxins are known as *toxigenic*.

Occasionally, disease results from the ingestion of preformed toxins; this is the mechanism in some cases of food poisoning. A typical, but fortunately rare, example is botulism due to contamination of food with a neurotoxin from *Clostridium botulinum*. Toxins acting upon the gut are often referred to as *enterotoxins*.

Endotoxins. These are lipopolysaccharides from the cell walls of Gram-negative bacteria (i.e., *Escherichia coli*). The most potent is lipid A, a powerful activator of:

- the complement cascade - causing inflammatory damage
- the coagulation cascade - causing disseminated intravascular coagulation
- interleukin 1 (IL-1) release from leukocytes - causing fever.

When the effects are severe, in an overwhelming infection, the patient is said to suffer from *endotoxic shock*. The patient is feverish and hypotensive; cardiac and renal failure may ensue. Disseminated intravascular coagulation may be evinced by bruising and prolonged bleeding from venepuncture sites, as well as more serious internal manifestations. Bilateral adrenal haemorrhage, particularly associated with overwhelming meningococcal infection (Waterhouse-Friderichsen syndrome), is a dramatic consequence of endotoxic shock.

Aggressins

These are bacterial enzymes with predominantly local effects, altering the tissue environment in a way that favours the growth and spread of the organism. In this way, aggressins inhibit or counteract host resistance. Examples include:

- *coagulase* from *Staphylococcus aureus* - inducing coagulation of fibrinogen to create a barrier between the focus of infection and the inflammatory reaction

- *streptokinase* from *Streptococcus pyogenes* - digesting fibrin to enable the organism to spread within the tissue

- *collagenase* and *hyaluronidase* - digesting connective tissue substances, thus facilitating the invasion of the organism into the host tissues.

Some bacterial enzymes have brought great benefits to medicine, notably the restriction enzymes (endonucleases) that are used to break DNA at specific points into smaller fragments prior to electrophoretic separation, and streptokinase used to dissolve thrombi in patients with blood vessel thrombosis.

Undesirable Consequences of Immune Responses

Bacteria can indirectly cause tissue injury by inducing an immune response that harms the host.

Immune responses can harm host tissues by three possible mechanisms:

- *immune-complex formation*. Soluble antigens from the bacteria combine with host antibody to form insoluble immune complexes in the patient's blood. These complexes can usually be removed by phagocytic cells lining the vascular sinusoids of the liver and spleen, causing no further harm. However, under certain conditions the complexes can become entrapped in the walls of blood vessels, notably the glomeruli of the kidney (causing glomerulonephritis), and capillaries in the skin (causing cutaneous vasculitis). Post-streptococcal glomerulonephritis is a good example of this phenomenon.

- *immune cross-reactions*. The host tissue of some individuals have antigenic similarities to some bacteria. The defensive antibody response to some bacteria can, therefore, cross-react with normal tissue antigens; rheumatic fever is a good example.

- *cell-mediated immunity*. The degree of tissue destruction seen in tuberculosis is not attributable to the organism itself but to the host's immune reaction to the organisms. Without much host immunity, *Mycobacterium tuberculosis* induces the formation of small granulomas that can become widely disseminated and thus be fatal. In the presence of host immunity, if the organism gains a foothold, it induces a severely destructive tissue reaction in which the organisms are extremely sparse.

Viruses

Viruses are submicroscopic infectious particles consisting of a nucleic acid and a protein coat.

Viruses can survive outside cells, but they always require the biochemical machinery of cells for their multiplication. Viruses show more evidence of tissue specificity than do bacteria. The ability to infect a cell type depends upon the virus binding to a substance on the cell surface; for example, HIV selectively infects a subpopulation of T-lymphocytes expressing the CD4 (CD = cluster differentiation antigen) substance on their surface.

The possible pathological effects of viruses are:

- acute tissue damage exciting an immediate inflammatory response
- slow virus infections causing chronic tissue damage
- transformation of cells to form tumours.

Slow virus infections are a known or postulated cause of several neurodegenerative disorders.

Viruses can produce tissue injury by a variety of mechanisms:

- *direct cytopathic effect*. Cells harbouring viruses may be damaged by their presence. This effect can often be demonstrated in cell cultures where, after incubation with the virus, a cytopathic effect is observed: the cells swell and die. This effect is mediated by injury to the cell membranes, causing fatal ionic equilibration with respect to the extracellular electrolyte concentrations. An example of a directly cytopathic virus is hepatitis A virus.

- *induction of immune response*. Some viruses do not harm cells directly but cause new antigens to appear on the cell surface. These new virus-associated antigens are recognised as foreign by the host's immune system and the virus-infected cells are destroyed. A consequence of this phenomenon is that, if the immune response is weak or non-existent, the virus-infected cells are not harmed. This situation may benefit the patient because their infected cells are not destroyed, but on the other hand the patient becomes an asymptomatic and apparently healthy carrier of the virus, capable of infecting other people. A good example is hepatitis B virus.

- *incorporation of viral genes into the host genome*. This phenomenon underlies the ability of some viruses to induce tumours. Genes of DNA viruses can become directly

incorporated into the host genome, but the genes of RNA viruses require the action of reverse transcriptase enzymes to produce a DNA transcript that can be inserted. RNA viruses with reverse transcriptase activity are called *retroviruses*.

Yeasts and Fungi

They cause *mycoses*. The usual tissue reaction to yeasts and fungi is inflammation, often characterised by the presence of granulomas and sometimes also eosinophils.

Parasites

They are nucleated unicellular or multicellular living organisms deriving sustenance from their hosts.

Parasites are the most heterogenous group of infectious agents. Due to their requirement for particular environmental conditions and, in some instances, other hosts for their life-cycle, parasitic infections are generally more common in the tropics.

Parasites are subdivided into:

- *protozoa*: unicellular organisms
- *helminths*: worms (roundworms, tapeworms and flukes).

Parasites, particularly helminths, have complex and exotic life-cycles requiring more than one host. Furthermore, within one host there may be successive involvement of more than one organ. Humans may either be *definitive hosts* or *inadvertent intermediate hosts*.

The tissue reactions to parasites are extremely variable. If an inflammatory reaction is prompted, it is often characterised by the presence of eosinophils and granulomas. Two parasites are associated with an increased risk of tumours: *Schistosoma haematobium* is associated with bladder cancer, and *Clonorchis sinensis* is associated with bile duct cancer.

Chemical Agents as a Cause of Disease

The study of environmental chemicals causing disease is *toxicology*.

Corrosive Effects

Strong acids and alkalis have a direct corrosive effect on tissues. They cause digestion or denaturation of proteins, and thus damage the structural integrity of the tissue. Powerful oxidising agents have a similar effect.

Metabolic Effects

Alcohol causes drowsiness and impaired mentation, liver damage, pancreatitis, etc.

Membrane Effects

Mutagenic Effects

Chemical agents or their metabolites that bind to or alter DNA can result in genetic alterations (i.e., base substitutions) called *mutations*. *Mutagens*:

- can affect embryogenesis, leading to congenital malformations - *teratogenic agents*.
- may be *carcinogenic*.

Allergic Factors

Large molecules (i.e., peptides and proteins) may induce immune responses if the body's immune system recognises them as foreign substances. Very small molecules are unlikely to be antigenic, but they may act as *haptens*.

Physical Agents as a Cause of Disease

Mechanical Injury

Mechanical injury to tissues is called *trauma*.

Thermal Injury

The body is more tolerant of reductions in body temperature than of increases. Recovery from hypothermia is usually possible unless the body temperature has fallen below 28 °C.

Increased body temperature is known as *pyrexia*. In infections, it is usually mediated by the action of interleukins on the hypothalamus. Above 40 °C enzyme systems are severely disturbed, with severe metabolic consequences.

Radiation Injury

Ionising Radiation

- at high doses, immediate clinical effects due to tissue damage from the production of free radicals
- injury to rapidly dividing cell populations
- inflammatory reactions leading to scarring of tissues due to the induction of fibrosis
- neoplasia.

Non-Ionising Radiation

UV, particularly UVB, is harmful to the skin:

- skin tumours (melanoma)
- dermal elastosis.

Nomenclature of Disease

Primary and Secondary

Acute and Chronic

Benign or Malignant

Principles of Disease Classification

General Classification of Disease

- congenital
 - genetic
 - non-genetic
- acquired
 - inflammatory
 - vascular
 - growth disorders
 - injury and repair
 - metabolic and degenerative disorders.

Congenital Diseases

Occur in approximately 5% of births in the UK. They comprise:

- malformations in 3.5%
- single gene defects in 1%
- chromosome aberrations in 0.5%.

Common malformations include congenital heart defects, spina bifida and limb deformities. Single gene defects include phenylketonuria and cystic fibrosis. Chromosomal aberrations are Turner's (XO) and Down's syndrome. The risk of chromosomal abnormalities increase with maternal age: for example, the risk of Down's syndrome, the commonest chromosome abnormality, is estimated at 1 in 1500 for a 25-year-old mother, rising to 1 in 30 at the age of 45 years.

An example of a genetic defect is cystic fibrosis, which is a disorder of cell membrane transport inherited as an autosomal recessive abnormality from parental genes.

Acquired Diseases

Inflammatory Diseases

Inflammation is a physiological response of living tissues to injury.

Vascular Disorders

Growth Disorders

Injury and Repair

Metabolic and Degenerative Disorders

Iatrogenic Diseases

Adverse Drug Reactions

- dose-dependent or predictable (type A)
- unpredictable (type B).

Epidemiology

Epidemiology is the study of the incidence of disease. It also concerns the identification of the causes and modes of acquisition of diseases. It involves the recording and analysis of data about diseases in groups of people rather than the individual person only.

Disease Incidence, Prevalence, Remission and Mortality Rates

Those are numerical data about the impact of a disease on a population:

- *the incidence rate* is the number of new cases of the disease occurring in a population of defined size during a defined period
- *the prevalence rate* is the number of cases of the disease to be found in a defined population at a stated time

- *the remission rate* is the proportion of cases of the disease that recover

- *the mortality rate* is the number or percentage of deaths from a disease in a defined population.

Migrant populations are especially useful to epidemiologists, enabling them to separate the effects of genetic (racial) factors and the environment (i.e., diet).

Data Capture

If a disease does not have a fatal outcome, mortality data will severely underestimate its incidence.

Geographic Variations

Historical Changes in Disease Incidence and Mortality

Socio-Economic Factors

A particularly sensitive and widely used indicator of the socio-economically related health of a population is the *infant mortality rate*.

Occupational Factors

Hospital and Community Contrasts

Common Causes of Death

Death is inevitable. In developed countries, it is estimated that a newborn infant has a 1 in 3 chance of ultimately dying in adult life of ischaemic heart disease, and a 1 in 5 chance of ultimately dying of cancer. In some famine-ridden countries, newborn infants have similar probabilities of dying from diarrhoeal diseases and malnutrition in childhood.