Testo consigliato: Kumar Abbas Fausto
Robbins e Cotran - Le basi patologiche delle malattie. Volume 1 - Patologia Generale.
Edizioni Elsevier Masson

- Elementi del processo patologico
- Danno, morte cellulare e adattamento: iperplasia, ipertrofia, atrofia e metaplasia.
- Malattie da accumulo di lipidi, proteine e glicogeno.
- Infiammazione cronica: caratteristiche, cause, cellule coinvolte. Infiammazione granulomatosa.
- Rinnovo e riparo dei tessuti: rigenerazione tissutale, riparazione mediante guarigione, cicatrizzazione e fibrosi. Guarigione delle ferite cutanee.
- Alterazioni emodinamiche, malattia tromboembolica, infarto e shock.
- Immunopatologia: HLA e malattie, reazioni di ipersensibilità, reazioni di rigetto dei trapianti, malattie autoimmuni, immunodeficienze primarie e secondarie.
- Diabete di tipo 1.
- Aterosclerosi.
- Amiloidosi.
- Malattie linfoproliferative dei globuli bianchi e linfonodi: proliferazioni reattive e neoplastiche.
Prerequisiti

- BIOCHIMICA
- ISTOLOGIA
- FISIOLOGIA
- ANATOMIA
- IMMUNOLOGIA
What is the Pathology

• Pathology is the *scientific study of disease*.
• In clinical practice and medical education, pathology also has a wider meaning: pathology constitutes a large body of scientific knowledge and investigative methods essential for the understanding and practice of modern medicine.
• Pathology embraces the *functional* and *structural* changes in disease, from the molecular level to the effects on the individual.
• Pathology is continually subject to change, revision and expansion as new scientific methods illuminate our knowledge of disease.
• The ultimate goal of pathology is the identification of the *causes* of disease, a fundamental objective leading to successful therapy and to disease prevention
• *Pathology is the foundation of medical science and practice. Without pathology, the practice of medicine would be reduced to myths and folklore.*
Subdivisions of clinical pathology

- Pathology is a vast subject with many ramifications. In practice, however, it has major subdivisions: histopathology: the investigation and diagnosis of disease from the examination of tissues
- cytopathology: the investigation and diagnosis of disease from the examination of isolated cells
- haematology: the study of disorders of the cellular and coagulable components of blood
- microbiology: the study of infectious diseases and the organisms responsible for them
- immunology: the study of the specific defence mechanisms of the body
- chemical pathology: the study and diagnosis of disease from the chemical changes in tissues and fluids
- genetics: the study of abnormal chromosomes and genes
- toxicology: the study of the effects of known or suspected poisons
- forensic pathology: the application of pathology to legal purposes (e.g. investigation of death in suspicious circumstances).
- These subdivisions are more important professionally (because each requires its own team of expert specialists) than educationally at the undergraduate level. The subject must be taught and learnt in an integrated manner, for the body and its diseases make no distinction between these professional subdivisions.
- In the systematic pathology, the normal structure and function of each organ is summarised, the pathological basis for clinical signs and symptoms is described, and the clinical implications of each disease are emphasised.
LEARNING PATHOLOGY

Pathology is best learnt in two stages:

• *general pathology*: the mechanisms and characteristics of the principal types of disease process (e.g. inflammation, tumours, degenerations)

• *systematic pathology*: the descriptions of specific diseases as they affect individual organs or organ systems (e.g. appendicitis, lung cancer, atheroma).
Building knowledge and understanding

• There are two apparent difficulties facing the new student of pathology: *language and process*.

• Pathology, like most branches of science and medicine, has its own vocabulary of special terms: these need to be learnt and understood not just because they are the language of pathology; they are also a major part of the language of clinical medicine.

• The student must not confuse the learning of the language with the learning of the mechanisms of disease and their effects on individual organs and patients. In this book, each important term will be clearly defined in the main text or the glossary or both. A logical and orderly way of thinking about diseases and their characteristics must be cultivated; for each disease entity the student should be able to list the chief characteristics:
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, prevalence and population distribution of a disease
Figure 2.1 Characteristics of disease. The relationship between aetiology, pathogenesis, morphological and functional manifestations, and complications and sequelae is exemplified by four diseases. A Skin abscess. B Lung cancer. C Cirrhosis. D Hypertension.
Aetiology

• The aetiology of a disease is its *cause*: the initiator of the subsequent events resulting in the patient's illness.

• Diseases are caused by a variable interaction between *host* (e.g. genetic) and *environmental* factors. Environmental causes of diseases are called *pathogens*, although this term is used commonly only when referring to *bacteria*; bacteria capable of causing disease are pathogenic bacteria and those that are harmless are non-pathogenic.

• General categories of aetiological agents include:
  – genetic abnormalities
  – infective agents, e.g. bacteria, viruses, fungi, parasites
  – chemicals
  – radiation
  – mechanical trauma.
Aetiology

• *multifactorial aetiology.*
• Some diseases are due to a combination of causes, such as genetic factors and infective agents
• *risk factors*
• Sometimes the aetiology of a disease is unknown, but the disease is observed to occur more commonly in people with certain constitutional traits, occupations, habits or habitats;
• *permissive effect*
• Other risk factors may facilitate the development of a disease in that individual: examples include malnutrition, which favours infections.

In each instance the precise initial cause awaits discovery.

• *Some agents can cause more than one disease* depending on the circumstances; for example, ionising radiation can cause either rapid deterioration leading to death, scarring of tissues, or tumours.
Identification of the causes of disease

• In terms of causation, diseases may be:
  – entirely genetic
  – multifactorial (genetic and environmental interplay)
  – entirely environmental.

• Most common diseases have an entirely environmental cause, but genetic influences in disease susceptibility are being increasingly discovered, and *many diseases with no previously known cause are being shown to be due to genetic abnormalities*; this is the reward of applying the principles of clinical genetics and the new techniques of molecular biology to the study of human disease.

  *The extent to which a disease is due to genetic or environmental causes can often be deduced from some of its main features or its association with host factors.*

• Features pointing to a significant *genetic contribution* to the occurrence of a disease include a *high incidence in particular families or races*, or an *association with an inherited characteristic* (e.g. gender, blood groups, histocompatibility haplotypes).

• Diseases associated with particular occupations or geographic regions tend to have an *environmental basis*; the most abundant environmental causes of disease are microbes (bacteria, viruses, fungi, etc.).
Probability of disease

The relationship between the quantity of causal agent and the probability that disease will result is not always simply linear

- For example, many infections result only if a sufficient dose of micro-organisms has been transmitted; the body's defence mechanisms have to be overcome before disease results.

- Some agents capable of causing disease, such as alcohol, are actually beneficial in small doses; those who abstain from alcohol have a slightly higher risk of premature death from ischaemic heart disease.
Relationships between the amount of a causal agent and the probability of disease.

- Many diseases are the *predictable* consequence of exposure to the initiating cause; *host factors make relatively little contribution.*
  - This is particularly true of physical injury: the immediate results of mechanical trauma or radiation injury are dose-related; the outcome can be predicted from the strength of the injurious agent.

A Physical agents.
For example, the risk of traumatic injury to a pedestrian increases in proportion to the kinetic energy of the motor vehicle.
Relationships between the amount of a causal agent and the probability of disease.

- Other diseases are the probable consequence of exposure to causative factors, but they are not inevitable.
- This is exemplified by infections with potentially harmful bacteria: the outcome can be influenced by various host factors such as nutritional status, genetic influences and pre-existing immunity.

B Infectious agents.
Many infectious diseases result only if sufficient numbers of the micro-organism (e.g. bacteria, virus) are transmitted; smaller numbers are capable of being eliminated by the non-immune and immune defences.
Relationships between the amount of a causal agent and the probability of disease.

C Allergens.
In sensitised (i.e. allergic) individuals, minute amounts of an allergen will provoke a severe anaphylactic reaction.
Relationships between the amount of a causal agent and the probability of disease.

D J-shaped curve.
Best exemplified by alcohol, of which small doses (c. 1-2 units per day) reduce the risk of premature death from ischaemic heart disease, but larger doses progressively increase the risk of cirrhosis.
Diseases that predispose to others

Some diseases predispose patients to the risk of developing other diseases.

- Diseases associated with an increased risk of cancer are designated premalignant conditions;
- hepatic cirrhosis predisposes to hepatocellular carcinoma
- ulcerative colitis predisposes to carcinoma of the large intestine.

The histologically identifiable antecedent lesion from which the cancers directly develop is designated the premalignant lesion.

Some diseases predispose to others because they have a permissive effect, allowing environmental agents that are not normally pathogenic to cause disease.

The case of immunodeficiencies

- opportunistic infections in patients with impaired defence mechanisms resulting in infection by organisms not normally harmful (i.e. non-pathogenic) to humans.

Patients with leukaemia or the acquired immune deficiency syndrome (AIDS), organ transplant recipients, or other patients treated with cytotoxic drugs or steroids, are susceptible to infections such as pneumonia due to Aspergillus fungi, cytomegalovirus or Pneumocystis carinii
Causes and agents of disease

• It is argued that a distinction should be made between the cause and the agent of a disease; for example, tuberculosis IS CAUSED, arguably, not by the tubercle bacillus (Mycobacterium tuberculosis) but by poverty, social deprivation and malnutrition-the tubercle bacillus is 'merely' the AGENT OF THE DISEASE;

• the underlying cause is adverse socioeconomic factors.

There is, in fact, incontrovertible evidence that the decline in incidence of many serious infectious diseases is attributable substantially to improvements in hygiene, sanitation and general nutrition rather than to immunisation programmes or specific antimicrobial therapy. Such arguments are of relevance here only to emphasise that the socio-economic status of a country or individual may influence the prevalence of the environmental factor or the host susceptibility to it.

Causes and agents are conveniently embraced by the term aetiology.
Causal association

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

• The stronger the causal association, the more likely it is to be the aetiology of the disease.

Causal associations become more powerful if:
• they are plausible, supported by experimental evidence
• the presence of the disease is associated with prior exposure to the putative cause
• the risk of the disease is proportional to the level of exposure to the putative cause
• removal of the putative cause lessens the risk of the disease.
Lung cancer is more common in smokers than in non-smokers

- tobacco yields carcinogenic chemicals; the risk of lung cancer is proportional to cigarette consumption;
- population groups that have reduced their cigarette consumption (e.g. doctors) show a commensurate reduction in their rate of lung cancer.

Causal associations may be neither exclusive nor absolute

- For example, because some heavy cigarette smokers never develop lung cancer, smoking cannot alone be regarded as a sufficient cause; other factors are required.
- Conversely, because some non-smokers develop lung cancer, smoking cannot be regarded as a necessary cause; other causative factors must exist.
Causal associations tend to be strongest with infections.

Syphilis, a venereal disease, is always due to infection by the spirochaete *Treponema pallidum*;

There is no other possible cause for syphilis; syphilis is the only disease caused by *Treponema pallidum*.

HOWEVER
Koch's postulates

An infective (e.g. bacterial, viral) cause for a disease is not usually regarded as proven until it satisfies the criteria enunciated by Robert Koch (1843-1910), a German bacteriologist and Nobel prizewinner in 1905.

The criteria requiring satisfaction are:

1. The organism must be sufficiently abundant in every case to account for the disease.
2. The organism associated with the disease can be cultivated artificially in pure culture.
3. The cultivated organism produces the disease upon inoculation into another member of the same species.
4. The organism must be isolated from experimentally infected host +
5. (Antibodies to the organism appear during the course of the disease).
**Pathogenesis**

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

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- Groups of aetiological agents often cause disease by acting through the same common pathway of events.
Pathogenesis

• Examples of pathogeneses of disease include:

  • degeneration: a deterioration of cells or tissues in response to, or failure of adaptation to, a variety of agents
  • inflammation: a response to many micro-organisms and other harmful agents causing tissue injury
  • carcinogenesis: the mechanism by which cancer-causing agents result in the development of tumours
  • immune reactions: undesirable effects of the body's immune system.

These pathways of disease development constitute our knowledge of general pathology.
Latent intervals and incubation periods

Few aetiological agents cause signs and symptoms immediately after exposure.

- In the context of carcinogenesis, this time period is referred to as the *latent interval*; it is often two or three decades.
- In infectious disorders (due to bacteria, viruses, etc.), the period between exposure and the development of disease is called the *incubation period*; it is often measured in days or weeks, and each infectious agent is usually associated with a characteristic incubation period.

*During time intervals the pathogenesis of the disease is being enacted, culminating in the development of pathological and clinical manifestations that cause the patient to seek medical help.*
Structural and functional manifestations

• The aetiological agent (cause) acts through a pathogenetic pathway (mechanism) to produce the *manifestations* of disease, giving rise to *clinical signs and symptoms* (e.g. weight loss, shortness of breath) and the *abnormal features or lesions* (e.g. carcinoma of the lung) to which the clinical signs and symptoms can be attributed.

• The pathological manifestations may require biochemical methods for their detection and, therefore, should not be thought of as only those structural abnormalities evident to the unaided eye or by microscopy.

• The biochemical changes in the tissues and the blood are, in some instances, more important than the structural changes, many of which may appear relatively late in the course of the disease.
Structural manifestations

• space-occupying lesions (e.g. tumours) destroying, displacing or compressing adjacent healthy tissues
• deposition of an excessive or abnormal material in an organ (e.g. amyloid)
• abnormally sited tissue (e.g. tumours, heterotopias) as a result of invasion, metastasis or developmental abnormality
• loss of healthy tissue from a surface (e.g. ulceration) or from within a solid organ (e.g. infarction)
• obstruction to normal flow within a tube (e.g. asthma, vascular occlusion)
• rupture of a hollow viscus (e.g. aneurysm, intestinal perforation).
Functional manifestations

- excessive secretion of a cell product (e.g. nasal mucus in the common cold, hormones having remote effects)
- insufficient secretion of a cell product (e.g. insulin lack in diabetes mellitus)
- impaired nerve conduction
- impaired contractility of a muscular structure.
What makes patients feel ill?

The 'feeling' of illness is usually due to one or a combination of common symptoms:

- pain
- fever
- nausea
- malaise.

Other specific expressions of illness help to focus attention, diagnostically and therapeutically, on a particular organ or body system

- altered bowel habit (diarrhoea or constipation)
- abnormal swellings
- shortness of breath
- skin rash (which may or may not itch).
Lesions

• A lesion is the structural or functional abnormality responsible for ill health.
• In a patient with myocardial infarction, the infarct or patch of dead heart muscle is the lesion; this lesion is in turn a consequence of another lesion—occlusion of the supplying coronary artery by a thrombus (coronary artery thrombosis).

A lesion may be purely biochemical, such as a defect in haemoglobin synthesis in a patient with a haemoglobinopathy.

• Not all diseases have overtly visible lesions associated with them, despite profound consequences for the patient; schizophrenia and depressive illness yield nothing visibly abnormal in the brain using conventional methods.
NOMENCLATURE OF DISEASE

- Uniform nomenclature facilitates communication and enables accurate epidemiological studies.

- Many standard conventions are used to derive names of diseases.

- Eponymous names commemorate, for example, the discoverer or signify ignorance of cause or mechanism.

- Syndromes are defined by the aggregate of signs and symptoms.
Primary and secondary

The words primary and secondary are used in two different ways in the nomenclature of disease: they may be used to describe the causation of a disease.

• PRIMARY means that the disease is without evident antecedent cause. Other words which have the same meaning in this context are essential, idiopathic and cryptogenic.
  – Thus, primary hypertension is defined as abnormally high blood pressure without apparent cause.

• SECONDARY means that the disease represents a complication or manifestation of some underlying lesion.
  – Thus, secondary hypertension is defined as abnormally high blood pressure as a consequence of some other lesion (e.g. renal artery stenosis).

• The words primary and secondary may be used to distinguish between the initial and subsequent stages of a disease, most commonly in cancer. The primary tumour is the initial tumour from which cancer cells disseminate to cause secondary tumours elsewhere in the body.
Acute and chronic are terms used to describe the *dynamics* of a disease.

- Acute conditions have a rapid onset, often but not always followed by a rapid resolution.

- Chronic conditions may follow an acute initial episode, but often are of insidious onset, and have a prolonged course lasting months or years.

- Subacute, a term not often used now, is intermediate between acute and chronic.

These terms are most often used to qualify the nature of an inflammatory process. They can be used to describe the dynamics of any disease. The words may be used by patients to describe some symptoms, e.g. an 'acute' pain being sharp or severe.
Benign and malignant are emotive terms used to classify certain diseases according to their likely outcome.

- **Benign tumours** remain localised to the tissue of origin and are very rarely lethal unless they compress some vital structure (e.g. brain), whereas

- **Malignant tumours** invade and spread from their origin and are commonly lethal.

- **Benign hypertension** is relatively mild elevation of blood pressure that develops gradually and causes insidious injury to the organs of the body. This situation contrasts with

- **malignant hypertension**, in which the blood pressure rises rapidly and causes severe symptoms and tissue injury (e.g. headaches, blindness, renal failure, cerebral haemorrhage).
Pre and suffix

Prefixes

• *ana-*-, meaning absence (e.g. anaphylaxis)
• *dys-*-, meaning disordered (e.g. dysplasia)
• *hyper-*-, meaning an excess over normal (e.g. hyperthyroidism)
• *hypo-*-, meaning a deficiency below normal (e.g. hypothyroidism)
• *meta-*-, meaning a change from one state to another (e.g. metaplasia)
• *neo-*-, meaning new (e.g. neoplasia).

Suffixes

• *-itis*, meaning an inflammatory process (e.g. appendicitis)
• *-oma*, meaning a tumour (e.g. carcinoma)
• *-osis*, meaning state or condition, not necessarily pathological (e.g. osteoarthritis)
• *-oid*, meaning bearing a resemblance to (e.g. rheumatoid disease)
• *-penia*, meaning lack of (e.g. thrombocytopenia)
• *-cytosis*, meaning increased number of cells, usually in blood (e.g. leukocytosis)
• *-ectasis*, meaning dilatation (e.g. bronchiectasis)
• *-plasia*, meaning a disorder of growth (e.g. hyperplasia)
• *-opathy*, meaning an abnormal state lacking specific characteristics (e.g. lymphadenopathy).
Eponymous names

An eponymous disease or lesion is named after a person or place associated with it. Eponymous names are used commonly either when the nature or cause of the disease or lesion is unknown, or when long-term usage has resulted in the name becoming part of the language of medicine, or to commemorate the person who first described the condition.

Examples:
- Graves' disease: primary thyrotoxicosis
- Paget's disease of the nipple: infiltration of the skin of the nipple by cells from a cancer in the underlying breast tissue
- Crohn's disease: a chronic inflammatory disease of the gut affecting most commonly the terminal ileum and causing narrowing of the lumen
- Hodgkin's disease: a neoplasm of lymph nodes characterised by the presence of Reed-Sternberg cells
- Reed-Sternberg cells: large cells with bilobed nuclei and prominent nucleoli which are virtually diagnostic of Hodgkin's disease.
A syndrome is an aggregate of signs and symptoms or a combination of lesions without which the disease cannot be recognised or diagnosed.

Syndromes often have eponymous titles.

Examples include:

- **Cushing's syndrome:**
  - hyperactivity of the adrenal cortex resulting in obesity, hirsutism, hypertension, etc. (Cushing's disease is this syndrome resulting specifically from a pituitary tumour secreting ACTH)

- **nephrotic syndrome:**
  - albuminuria, hypoalbuminaemia and oedema;
  - this syndrome can result from a variety of glomerular and other renal disorders.
Danno cellulare: cause
Figure 1-1 Stages in the cellular response to stress and injurious stimuli.
Figure 1-2 The relationships between normal, adapted, reversibly injured, and dead myocardial cells. The cellular adaptation depicted here is hypertrophy, and the type of cell death is ischemic necrosis. In reversibly injured myocardium, generally effects are only functional, without any readily apparent gross or even microscopic changes. In the example of myocardial hypertrophy, the left ventricular wall is more than 2 cm in thickness (normal is 1 to 1.5 cm). In the specimen showing necrosis, the transmural light area in the posterolateral left ventricle represents an acute myocardial infarction. All three transverse sections have been stained with triphenyltetrazolium chloride, an enzyme substrate that colors viable myocardium magenta. Failure to stain is due to enzyme leakage after cell death.
Figure 1-3 Physiologic hypertrophy of the uterus during pregnancy. A, Gross appearance of a normal uterus (right) and a gravid uterus (removed for postpartum bleeding) (left). B, Small spindle-shaped uterine smooth muscle cells from a normal uterus (left) compared with large plump cells in gravid uterus (right).
Figure 1-4 Changes in the expression of selected genes and proteins during myocardial hypertrophy.
Figure 1-6 Metaplasia. A, Schematic diagram of columnar to squamous metaplasia. B, Metaplastic transformation of esophageal stratified squamous epithelium (left) to mature columnar epithelium (so-called Barrett metaplasia).
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