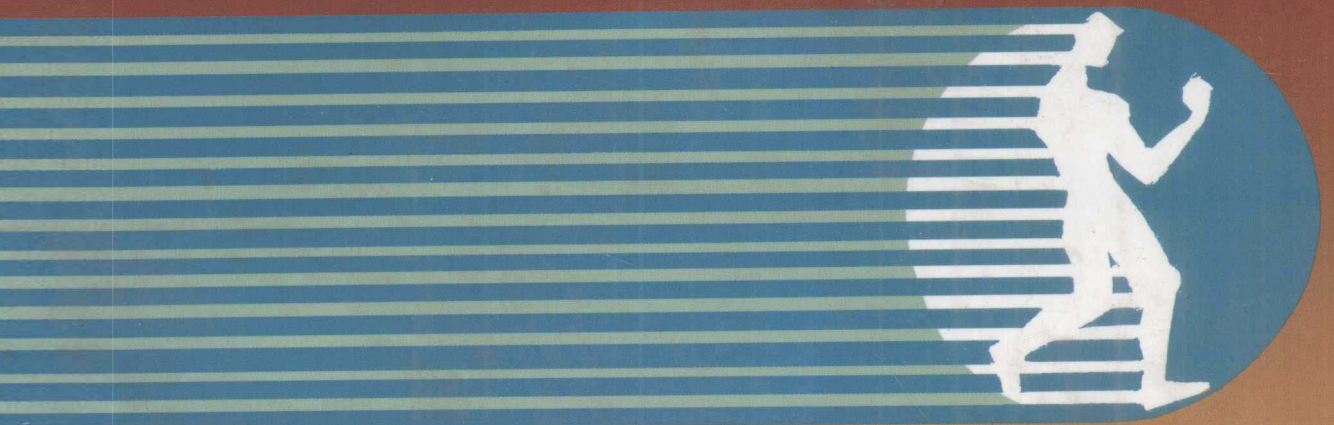


# CONTEMPORARY PATHOPHYSIOLOGY

(Second Edition)

CHIEF-EDITOR	KONG XIANSHOU
VICE-EDITOR	LI SHUNONG
REVIEWER	JACK O. KATZ



SHANGHAI MEDICAL UNIVERSITY PRESS

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## **CONTEMPORARY PATHOPHYSIOLOGY**

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## Preface

The first edition of CONTEMPORARY PATHOPHYSIOLOGY was published in 1993. Since then the new ideas and important discoveries in the field of pathophysiology have been appearing. In order to keep pace with the current advances in this field, it is necessary to have the first edition revised. In the second edition, although the organization and presentation of the materials remain the same in style as the first edition, most chapters were intensively revised or rewritten and a new chapter, i. e. the chapter of Multiple Organ Dysfunction Syndrome, has been added. The authors hope that the new edition would reflect the more important recent advances in pathophysiology, and it might serve to set up a proper link between the advanced basic medical sciences and clinical medicine.

Throughout the second edition, emphasis is laid on the pathogenesis of diseases, especially on the cellular and molecular mechanisms that underlie the development of diseases. In this edition, a plentitude of tables and figures are inserted which summarize the important information in the text and help the reader to master the related contents in this book. For the reader's further learning a number of references are listed at the end of each chapter, which cite some recent, well-written articles worthy of study or survey.

The original aim of writing this book is to present an overview of modern pathophysiology in the English language to Chinese readers. It can be used as a text or a reference book for a course of pathophysiology at medical college and medical university. In addition, this book is also valuable to senior medical students who enter the clinical practice, as well as to physicians who wish to get some up-to-date information of the principal areas of pathophysiology.

The editors wish to thank all the contributors for their contributions in creating this book, and is especially grateful to Dr. Jack O. Katz, Professor of University of London in England, who reviewed the manuscripts of the second edition and provided invaluable suggestions and comments regarding the overall presentation of this book.

There may be some insufficiencies in this second edition. The editors welcome and appreciate any comment, suggestion, and correction for this book.

**Shanghai, 200032**  
**P. R. China**  
**January 1998**

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## PREFACE TO FIRST EDITION

Pathophysiology is the study of the underlying mechanisms by which diseases occur, and the study of the changes within the body that result from diseases. The mechanisms of diseases are concerned with the interplay of the pathogenic agents disrupting homeostasis and the body's response to maintain homeostasis. Much pathophysiologic knowledge has been applied in the understanding, diagnosis and treatment of diseases. Therefore, pathophysiology is one of the important preclinical sciences, on which the practice of clinical medicine is based. In medical school, lying at the juncture between the basic medical science courses and clinical medicine courses, pathophysiology is regarded as a critical one in the whole medical curriculum.

English has become a universal language in medical science and technology. In order to train Chinese medical students and readers to read pathophysiologic literatures in English, I wrote a teaching material of pathophysiology in English at Shanghai Medical University in 1988. This material has proved to be beneficial and has been well received by the Chinese students.

Since no formal suitable book of pathophysiology in English has been written by Chinese authors and published at home, I decide to compile a concise, readable and modern pathophysiology book in English to present to Chinese and foreign students, teachers, researchers, and physicians.

Recently there have been some exciting developments in the field of pathophysiology. Besides the general and important pathophysiologic knowledge, this book also includes the latest research results.

Organizationally, this book includes 18 chapters. Chapter 1 explains the general concept of diseases and the general etiology and pathogenesis of diseases. Chapters 2-12 deal with the fundamental pathological processes. Chapters 13-16 elucidate the pathophysiology of the critical systems and organs in diseased body. In view of the fact that heredity and immunity play important roles in many diseases, Chapter 17 and 18 are included to explain some basic principles of genetics and immunology related to diseases. Although the entire material is conceptually integrated, each chapter can stand on its own, thus allowing the instructor to have maximal flexibility in curriculum design. At the end of the book there is an appended glossary with Chinese interpretation for offering bilingual aid to readers.

This book, intended primarily for medical students, could be utilized in a variety of ways; as a textbook for pathophysiology course in "Medical English Class" or "Seven-Year Schooling Class"; as a recommended text for Chinese and foreign students who ask for supplementary

English material in the course; or as a reference for graduates and physicians who want to obtain a concise and update knowledge of the principles of this discipline that would enhance their understanding of disease processes. It is hoped that this book will be helpful to them while they use it for their respective purposes.

I wish to thank the contributors of this book for their sharing of knowledge and expertise in covering certain aspects of disease.

No doubt there are some shortcomings in this book because of the editor's and contributors' limited knowledge. Therefore, any comments and suggestions regarding this book are greatly appreciated.

**Shanghai 200032**  
**P.R. China**  
**January 1993**

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**Kong Xianshou(孔宪寿)**  
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# CONTENTS

## Chapter

1. Disease .....	1
2. Disorders of Water and Electrolyte Metabolism .....	11
2.1 Disorders of water metabolism .....	11
2.2 Disorders of sodium metabolism .....	19
2.3 Disorders of potassium metabolism .....	30
2.4 Disorders of magnesium metabolism .....	44
2.5 Disorders of calcium metabolism .....	50
2.6 Disorders of phosphorous metabolism .....	59
3. Acid-Base Disturbances .....	68
4. Edema .....	86
5. Hypoxia .....	97
6. Fever .....	115
7. Inflammatory Response .....	133
8. Stress .....	153
9. Disseminated Intravascular Coagulation .....	166
10. Shock .....	180
11. Neoplasia .....	204
12. Ischemia-Reperfusion Injury .....	239
13. Pathophysiology of Cardiovascular System .....	252
13.1 Coronary insufficiency .....	252
13.2 Arrhythmias .....	254
13.3 Heart failure .....	256
13.4 Hypertension .....	267
14. Pathophysiology of Respiratory System .....	277
14.1 Respiratory failure .....	278
14.2 Adult/ Acute respiratory distress syndrome ..	288
15. Pathophysiology of Liver .....	295
15.1 Hepatic encephalopathy .....	296
15.2 Hepatorenal syndrome .....	306
15.3 Jaundice .....	312
16. Pathophysiology of Kidney .....	323

16.1	Acute renal failure .....	324
16.2	Chronic renal failure .....	336
16.3	Uremia .....	348
17.	Genetics and Disease .....	356
18.	Immunity and Disease .....	366
19.	Multiple Organ Dysfunction Syndrome .....	383
<b>Glossary .....</b>		<b>405</b>



# CHAPTER 1

## DISEASE

By *Kong Xianshou*

Pathophysiology is the study of abnormalities or alterations in the body function and metabolism. Disordered function and metabolism are often due to diseases. The foundation for understanding the nature of diseases begins with pathophysiology.

### Concept of Disease

Health and disease are relative concepts. The World Health Organization (WHO) defines health as complete physical, mental, and social well-being and not merely the absence of disease. Health implies a person's ability to do what he deems as worthwhile, and conducts his life as he wishes.

#### **1. Disease Is An Abnormal State of the Body**

Disease represents an abnormal state which distorts normal life process. Disease is a deviation from or interruption of the normal structure, function or metabolism of any part organ, or system of the body which is manifested by a characteristic group of symptoms and signs whose etiology, pathogenesis, and prognosis may be known or uncertain. By means of a variety of clinical and laboratory tests it is possible to measure certain values of normalcy or deviation. In the health state, a certain value is consistently within normal limits. Deviations from this range are usually considered abnormality which often appears in diseases.

#### **2. Disease Is A Disordered State of the Body**

Physiologically, all cells in the body need optimal amounts of oxygen, water, electrolytes and nutrients for their continuing survival, and also an environment which affords a balanced supply of these substances and excretion of waste product. This balance is defined as homeostasis. Homeostasis also refers to the body's tendency to maintain a steady normal state in the face of continual environmental variation. The physiologic and metabolic parameters of the body are constantly regulated to remain within normal ranges. Thus homeostasis can be more accurately defined as a dynamic, steady body state, representing the net effect of all the turnover (synthesis and breakdown) reactions. Maintenance of internal homeostasis is an essential feature of a

normal body. In disease, control of the homeostatic balance fails and imbalances prevail. When homeostasis is disrupted, cells, tissues, organs, systems, or the whole body can not function normally. Disease can therefore be viewed as a disturbance of homeostasis, which is disrupted by processes that interfere with the functions of homeostatic sensors, regulatory centers, or effectors.

### **3. Disease Is A Incapacitating State of the Body**

Disease may be manifested by perceptions of discomfort, deformity, disability, or frank injury. Discomfort is a general unpleasant feeling, which prevents people from doing what they intend to do. Disability is analogous to illness because it represents an incapacitating disorder. A crucial aspect with regard to disease is that of bodily upset or disorder. These lead to failure in certain system or systems that prevents the human body from working properly.

In summary, disease is defined as an abnormal life process under the action of certain cause and condition, with disturbances of function, metabolism and structure in the body which are manifested by a series of symptoms and signs. Disease represents a struggle taking place in the body, a fight between the agents or forces that tend to disrupt body functioning and the defending forces or mechanisms of the body that attempt to maintain or restore normal function, and the outcome of disease is determined by the issue of this struggle. From a practical viewpoint, disease is a pattern of response of human body to injurious agents, and is described as a situation which has characteristic signs and symptoms.

## **Etiology of Disease**

Etiology is the study of the factors that cause diseases. According to their different roles in the development of disease, these factors are classified into etiological factors, predisposing factors, and precipitating factors.

### **Etiological Factors**

Among the etiological factors, a wide range of extrinsic factors in the environment and intrinsic factors in the body must be considered.

#### **Extrinsic Factors**

(1) *Biological agents* Biological agents are the cause of infective diseases. These agents range from submicroscopic viruses to larger parasites, including bacteria, fungi, rickettsia, spirochete, etc. . They are able to replicate themselves within the body and thus can continue to produce their injurious effects. Biological agents cause cell injury through diverse mechanisms: viruses enter the cells and disrupt the intracellular environment; certain bacteria elaborate exotoxins that interfere with cellular production of ATP; and other bacteria such as the gram-negative bacilli release endotoxins that cause profound cell and blood vessel changes. Still other microorganisms produce their effects via inflammatory or immune mechanisms.

(2) *Chemical agents* Chemical agents are numerous and can cause injury to cell membrane and other cell structures; block enzymatic pathways; cause coagulation of cell proteins;

and disrupt the osmotic and ionic balance of the cell. Corrosive chemicals such as strong acids and alkalis can destroy cells at the site of contact. Still other types of chemicals are selective in their sites of action, for example, carbon monoxide has a special affinity for the hemoglobin molecules.

(3) *Physical agents* Physical agents include mechanical injuries, extremes of temperature, electricity, and radiation. Mechanical injuries may disrupt the soft tissues, and injure bones, causing trauma and fracture. Extremes of heat and cold damage the cell, its organelles, and its enzyme systems. A high temperature produces tissue burns. Heat stroke may be caused by direct exposure to the sun or other objects of high temperature, but freezing crystallizes the cytoplasmic contents. Further, extreme cold may cause frostbite. The result varies from blistering to necrosis of tissues. Electrical injuries are mainly caused by heat generated from the electrical current that passes through tissues. Radiation injury includes the effects of ultraviolet radiation and ionizing radiation (X rays and gamma rays). All cells are susceptible to ionizing radiation, but the degree of susceptibility varies. Rapidly proliferating cells of the bone marrow and the gastrointestinal epithelium are more susceptible than other cells to the effects of ionizing radiation. Pressure of the atmosphere becomes too low when a person passes too rapidly from a high to a normal atmospheric pressure, the dissolved air is released from the blood forming bubbles in the small arteries resulting in tissue damages. The condition is known as caisson disease. Effects of decreased atmospheric pressure may occur at altitudes over 10 000 m. The gases in the body cavities expand, causing marked discomfort, and gas bubbles are released in the blood and cause air embolism, with the result similar to that of caisson disease.

(4) *Nutritional imbalance* Nutrients from the external environment are necessary because they provide not only the materials for growth and maintenance of body constituents but also the energy to carry out metabolic processes. Either nutritional excesses or deficiencies predispose cells to injury. Obesity, and diets high in lipids and carbohydrates, predispose a person to obese disease, atherosclerosis and diabetes. Obesity is a major problem in many countries. The most common nutritional deficiency is the lack in certain constituents in the diet, e. g., deficiencies of vitamins, calcium, and trace elements. Iron deficiency anemia, scurvy, beriberi, and pellagra are examples of injury caused by deficits in specific vitamins or minerals. The protein and calorie deficiencies that occur with starvation cause widespread tissue damage. Oxygen is vital to normal cellular metabolism. Therefore, oxygen must be constantly and adequately supplied to the body tissues. If the oxygen supply is insufficient or interrupted, it will lead to cell injury. Water intake and water loss must be balanced in order to keep the volume and constitution of the body fluid constant and thus to maintain homeostasis. Water deficit or water excess can be induced by alterations in distribution of body water or in body fluid volume.

### **Intrinsic Factors**

(1) *Immunological factors* Although the immune response is a normal protective mechanism, it may cause disease when the response is deficient (immunodeficiency disease), or in-

appropriately strong (allergy or hypersensitivity), or misdirected (autoimmune disease).

(2) *Genetic factor* Genetic derangements may fall into chromosomal disorders, including numerical and structural abnormalities, single gene disorders and polygenic disorders. Genetic disorders are apparent at birth or shortly thereafter, and they are transmitted by defective genes. Hemophilia, sickle cell anemia, and colorblindness are examples of genetic disorders. Many other diseases have been linked with the types of human leukocyte antigen (HLA) complex.

(3) *Congenital factors* In some cases, nongenetic disorders are of a developmental nature. It results from abnormal embryonic development but no specific genetic alteration is known to be responsible. Congenital birth defects, mental or physical, may be due to a developmental error resulting from maternal infection during pregnancy. The fetus is usually susceptible to a variety of influences during intrauterine life, not only infectious diseases but also diet and drug-taking of the mother may affect the development of the fetus. Some congenital malformations are thus referred to as developmental anomaly.

(4) *Psychological factors* Anxiety, strong or persistent psychological stimulation or stress may lead to mental illness and may be related to some diseases such as hypertension, peptic ulcer, coronary heart disease, and depression.

Not all those who are exposed to harmful agents become ill. Whether or not a person becomes ill is also influenced by precipitating factors and predisposing factors. Of course, when the etiological factor is very potent, the precipitating factors and predisposing factors will be less significant in determining the illness onset.

### **Predisposing Factors**

A predisposing factor refers to the factor that influences the susceptibility or resistance to certain disease of the body. It includes the body's genetic constitution, physiological make up, as well as various psychological characteristics.

(1) *Genetic constitution* The groups of red blood cell antigens and white blood cell antigens (human leukocyte antigens, HLA) may influence the development of some diseases. More recently, association between particular normal genetic types and particular diseases has been discovered, e.g., the blood group A is associated with an increased incidence of gastric cancer. The most striking association is of HLA B27 with ankylosing spondylitis (AS); 90 percent of AS subjects possess HLA B27. The sum of the genetic and environmental constituents makes a person more or less likely to develop diseases. A person with weak or less significant risk genes is unlikely to manifest the disorder unless exposed to very adverse environmental conditions.

(2) *Physiological make up* The structural states and functions of critical body systems may alter the resistance to illness. Every organism has a surface membrane that forms a barrier between the internal and external environments. Disruption of the surface membrane will provide a pathway for noxious elements to enter the body. The body has many protective reflexes. Maintenance of homeostasis involves various forms of reflex adjustment by the organism in response to actual disturbances in the internal environment.

(3) *Psychological characteristics* Some people do not suffer from illness in spite of major life changes because their psychological constitution apparently insulates them from the effects of stressful life experiences. Psychological defenses may prevent stress effects from causing a physiological response. In other words, it appears that if a person has adequate psychological defence makeup, then that person will have little or no response to social stressors.

### **Precipitating Factors**

A precipitating factor refers to the factors that intensify the roles of etiological factors through a change in condition that promotes the development of disease and influences the timing of illness onset.

(1) *Nature conditions* Weather condition and geographical environment may influence the illness onset. For example, the common cold is caused by a virus, and one is most apt to develop a cold if he has been exposed to cold weather. The development of some epidemical diseases is closely related with the geographical environment in which these diseases are easier to occur.

(2) *Body condition* The illness onset will be influenced by the existing body condition. For example, a person may be predisposed to some diseases if he is in a status of physical or mental fatigue or anxiety. As another example, a person may be predisposed to myocardial infarction if he has a high serum cholesterol level and hypertension.

(3) *Social condition* It is generally recognized that social factors may influence a person's health status. The social factors include labour and hygiene condition, social events or stress, etc. . Poor labour and hygiene conditions are apt to induce some occupational diseases and certain infectious diseases. Social life events involve a significant change in a person's mood and life pattern. Mood changes can bring about physiological changes mediated by the central nervous system. Any of these factors is in itself not usually sufficient to cause disease, but could influence the frequency or severity of illness.

In summary, the presence of specific etiological and predisposing factors together determine the disease occurrence, and the precipitating factors influence the illness onset. Although a disease agent (e.g., trauma, infection, exposure to physical and chemical irritants) can affect more than one organ, and a number of disease agents can affect the same organ (e.g., lungs). It is important to recognize that most disease states do not have a single cause. Rather, many diseases are multifactorial in origin. This is particularly true of diseases such as cancer, heart disease, and diabetes.

## **Adaptation and Compensation**

Human body is able to withstand, to a considerable extent, exposure to a variety of harmful agents while maintaining its internal environment within narrow confines of what is termed "normal". This capability of adjusting to environmental conditions is called "adaptation", and the process of providing functional alteration with a balancing effect for some tissue loss or some

function lacking in the body is called “compensation”.

The mechanisms of adaptation and compensation can make rapid or gradual adjustment and mobilize body reserves to reverse or ameliorate changes in the internal or external environment so as to maintain homeostasis and preserve the integrity of the organism. Adaptation and compensation of the body are essential because sometimes minute changes in the internal environment can be lethal. For example, the normal range of blood pH is between 7.35 and 7.45, yet even small deviations from these values can cause death. As a whole, however, human beings are rather limited in their ability to adapt to or compensate for environmental changes. Furthermore, not all people have the same capacity to adapt or compensate. Examples of compensation are: if one kidney fails, the other enlarges to meet the needs of the body and compensate for the defective one; Heart muscle hypertrophies when it is required to do extra pumping action due to the defective valve that is either too narrow or too wide.

Adaptation and compensation are affected by a number of factors including the age, coexisting disease and function states of the critical systems.

### **1. Effects of age**

Adaptative capacity is decreased with extremes of age. For example, the infant has difficulty in concentrating urine due to the immaturity of renal tubular structures and is less able than an adult to tolerate decreased water intake or excessive water loss.

### **2. Effects of pre-existing diseases in the body**

Persons with co- or pre-existing diseases are less able to adapt to stress. For example, the person with pre-existing heart disease is difficult to adapt to some stresses that require recruitment of cardiovascular response.

### **3. Effects of the function of critical systems**

The function and response of the critical systems are important in adaptation of the body. For example, the increase in heart rate that accompanies a febrile illness is a type of temporary response designed to deliver additional oxygen to the tissues since the elevated temperature increases the metabolic needs of the tissues. On the other hand, hypertrophy of the left ventricle is a long-term adaptive response that occurs in a person with chronic hypertension.

Adaptation is most efficient when the changes that occur in body function are gradual rather than sudden. It is possible, for instance, to lose a liter of blood through chronic gastrointestinal bleeding over a period of a week without developing signs of shock. However, a sudden hemorrhage that cause the loss of an equal amount of blood is easy to cause hypotension or shock.

In summary, disease is usually manifested by an alteration in body functions. It is this alteration in function and the body's attempt to compensate for the altered functions that causes the signs and symptoms associated with a specific disease state.

## Pathogenesis of Disease

Pathogenesis of disease refers to the mechanisms of development or evolution of the disease. Pathogenesis studies how the primary pathogenic agent can cause the disease in the body. The basic mechanisms of diseases include the neural, humoral, cellular, and molecular mechanisms. The general aspects of pathogenesis in the disease are the disruption of homeostasis, the body's responses to damage and anti-damage activities, and the reversal of cause-result sequence in the disease process.

### 1. Disruption of homeostasis

The term "homeostasis" denotes the maintenance of constant conditions in the internal environment of the body. The maintenance of homeostasis is necessary for optimum functioning of the body. If homeostasis is disrupted by a variety of harmful agents, the body cannot function optimally, and illness may result.

### 2. Damage and anti-damage

When a variety of harmful agents attacks and injures the body, the latter usually induces an anti-damage response in an attempt to restore the normal status. For example, when tissue is traumatized, injured, or becomes infected, blood flow increases to the damaged site. This is vital because the blood carries cells that are specialized to remove harmful substances and cellular debris. Other cells in the blood produce antibodies against invading organisms that cause diseases.

### 3. Reversal of roles of cause and result

In the evolution of a disease, the cause of the disease can produce a result, and this result can also become another cause in the evolution process of disease. For example, during chronic hypoxia the bone marrow produces more erythrocytes to carry and release more oxygen to the tissues. However, the high red blood cell counts result in a secondary disease——polycythemia, in which the blood viscosity is high and therefore thrombi in vessels may be formed.

## Manifestation of Disease

Disease is an unhealthy state of a body part or the whole body. Disease always manifests itself by signs and symptoms. A certain disease usually has characteristic signs and symptoms. Signs are objective evidence of disease observed on physical examination, such as abnormal pulse or respiratory rate, fever, and pallor; whereas symptoms are indications of disease perceived by the patient, such as pain, dizziness, and itching. The abnormal tissue structure or function is referred to as a lesion. Signs and symptoms may be related to the primary disorder, or they may represent the body's attempt to compensate for the altered function caused by the pathologic condition. Some nonspecific signs and symptoms, such as fever, headache, malaise and

anorexia, are commonly associated with many diseases. A syndrome is a set of signs and symptoms that occur together and are characteristic of a specific disease state. Two examples of syndrome are the syndrome of inappropriate antidiuretic hormone (SIADH), described in chapter 2 and the acute or adult respiratory distress syndrome (ARDS) in chapter 14. Another example is Down's syndrome with concurrent signs: very prominent mental retardation, enlarged, protruding tongue, and a characteristic appearance of the eyes.

The diagnosis of a disease is based on many factors, including the signs, symptoms, and often, laboratory findings. A physician can make use of these kinds of information to get a diagnosis.

## Course of Disease

The course of a disease varies. Disease processes are often classified as acute and chronic. An acute disease has a relatively sudden onset and short term. A chronic disease lasts for a long period of time. Sometimes chronic disease processes begin with an acute phase and become prolonged when the body's defenses are unable to entirely overcome the causative agent. The symptoms of a chronic disease at times subside, during a period known as "remission"; they may recur in all their severity in a period of "exacerbation". A "relapse" at times occurs when a disease returns weeks or months after its apparent cessation. Certain diseases, leukemia and ulcerative colitis, for example, are characterized by periods of remission and exacerbation.

Generally, a disease often proceed through the following stages:

### **1. Latent period** (incubation period in infectious diseases)

The interval occurring between exposure of a tissue or body to an injurious agent and the first appearance of signs and symptoms is termed the latent period.

### **2. Prodromal period**

This period refers to the appearance of the signs and symptoms indicating the onset of a disease. The prodromal symptoms are often nonspecific.

### **3. Manifest illness period**

In this period, the disease reaches its full intensity, and signs and symptoms attain their greatest severity.

### **4. Resultant period**

This period is the stage of either recovery or exacerbation. Of the two the latter leads to lasting damage or disability, or to death.

## Outcome of Disease

An important aspect of any disease is its outcome. There are generally three kinds of outcome of disease.

### **1. Complete recovery**



This is the best outcome of a disease. In complete recovery, the alteration of the function, metabolism and structure of the body which appeared in the disease are perfectly restored, and the signs and symptoms of this disease disappear entirely.

## **2. Incomplete recovery**

The main symptoms are absent but some pathological changes are still present in the body. It is brought about by the compensatory response to maintain a relatively normal life activity, e.g., some patients with heart failure whose main symptoms and signs might disappear after treatment, but the cardiac valvular lesion may remain. The result of an incompletely cured disease is called the sequela. The permanent damage to the heart valve after rheumatic fever is an example of sequela, as is the paralysis after polio.

## **3. Death**

Traditionally, cessation of heart-beats is used as the criterion of death of a body. As is well known, the stopped or ineffective heart-beats may often be restored by prompt medical attempts, e.g., converting the fibrillation, or using other measures to reestablish normal rhythm. Today the accepted definition of death is brain death. Death can be judged to have occurred if all the activity of central nervous system has stopped. This is indicated by a complete lack of response to any stimuli, regardless of intensity. The electroencephalogram (EEG) is of value in confirming the cessation of the activity of central nervous system. A consistently flat EEG is taken as an indication that an irreversible cessation of all the activity of central nervous system has occurred.

The World Health Organization (WHO) has specified four criteria of brain death.

(1) *Irreversible coma and cerebral unresponsivity* It implies the complete lack of cerebral response to any form of external excitation—a state which is generally referred to as unresponsive coma.

(2) *Absence of cephalic reflexes and dilated pupils* The reflexes mediated by the cranial nerves are important indicators of the integrity of the brainstem, and their absence is an essential part of brain death. It includes the absence of pupillary reflex, corneal reflex, oculocardiac reflex, and dilated pupils.

(3) *Absence of vital functions* The absence of the vital functions of heart action and spontaneous respiration has traditionally been considered as the cardinal manifestation of death.

(4) *Absence of any electrical activity of the brain* Linear EEG may appear even when stimulated. This is called electrocerebral silence of brain.

In summary, Disease manifests itself by signs and symptoms that are objective and subjective indications of its presence. Diagnosis is based on these, together with medical histories, physical examinations, and laboratory findings. The most suitable treatment is then prescribed.