

PATHOLOGIC PHYSIOLOGY

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Chapter One

INTRODUCTION

BASIC CONCEPTS

Subject Matter of Pathologic Physiology

Pathologic physiology is the science that deals with *functional disturbances in the diseased organism and establishes general regularities in the origin, onset, course and results of pathologic processes.*

Physiology furnishes the basic information on the normal functions of the organism as a whole, its different systems, organs and tissues. Pathologic physiology studies the vital activities of the diseased organism and may therefore be referred to as physiology of the diseased organism.

Pathologic physiology consists of two basic parts. The first part—general pathology—deals with the *concept of disease and pathologic processes, the theory of the causes and conditions of their origin (etiology) and the mechanisms of their onset (pathogenesis); it studies the general, standard reactions of the organism, i.e., various metabolic disorders, inflammations, neoplasia, fever, etc.*

The second part furnishes information on the regularities of the origin, onset and course of *dysfunction of the various systems—blood, hematopoietic, circulatory, respiratory, digestive, urinary, endocrine and nervous regulation—whatever the form of its manifestation.*

The objectives of pathologic physiology become clearer when compared with those of clinical investigation. Pathologic physiology discloses the causes and mechanisms of the onset of fever, while the clinic deals with definite forms of febrile diseases, mainly of infectious origin. Pathologic physiology studies the general regularities of the origin and development of the inflammatory processes, whereas the clinical sciences investigate separate diseases based on various forms of inflammation. The same applies to other pathologic processes—nutritional and metabolic disorders, neoplasia, etc.

Pathologic physiology gives the physician an insight into the essence of the disease, or pathologic process.

Experimental Pathology

Pathologic physiology utilises the information furnished by experimental pathology.

Production of experimental models or reproduction of human diseases in acute and, especially, chronic forms in animals helps to disclose the causes of diseases and the mechanisms of their onset, to gain an insight into the laws governing the development of functional disorders and restoration of functions.

Experimental observations have made it possible to solve such important problems of pathologic physiology as the causes and mechanisms of nutritional, metabolic and circulatory disorders, fever, many infectious diseases, hypertensive vascular disease, atherosclerosis, and endocrine disturbances; it has also helped to diagnose, prevent and treat them.

However, the information gained in experiments on animals cannot be mechanically applied to man. Unlike animals, man develops in a social environment and possesses a highly-organised nervous system.

The inadequate and one-sided information gained in experiments on animals is supplemented by clinical experimental studies of patients under different conditions of life and under certain physical and chemical influences. It is understood that these methods of investigation must under no circumstances do the organism any harm.

Connections with Other Medical Sciences

Pathologic physiology is closely linked with *biology*. Without a correct understanding of the basic laws governing animate nature it is impossible to gain an insight into pathologic phenomena. Biology has made possible an evolutionary phylo- and ontogenetic analysis of the complex pathologic processes in highly-organised animals. Modern progressive biology also plays an important role in the study of pathological heredity and constitution.

Pathologic physiology is most intimately connected with *normal physiology*. Knowledge of physiological regularities is an indispensable prerequisite for understanding pathologic processes. Moreover, pathologic physiology employs essentially the same methods of research as does normal physiology.

Pathologic physiology also utilises the information furnished by *pathologic anatomy* which studies the morphological changes occurring in the diseased organism and observed at different stages of the development of diseases. Both sciences supplement each other and together form the extensive branch of medical science known as *pathology*.*

* From the Greek words: *pathos*—suffering, disease, and *logos*—account.

All of the aforesaid concerning the objectives of pathologic physiology also indicates a necessity for its closest connection with the *clinic*. To disclose the causes and mechanisms of disease in man, the results of clinical observations must be studied under experimental conditions. On the other hand, the clinical aspects help to check on the generalisations made on the basis of experimental studies alone.

The experimental evidence is widely used to gain an insight into the causes and mechanisms of diseases. It makes it possible to exert purposive influence on the diseased organism and develop scientifically substantiated prophylactic and therapeutic measures.

HISTORICAL OUTLINE OF THE MAIN STAGES IN THE DEVELOPMENT OF PATHOLOGY

The modern concepts of pathology have formed as a result of the historical development of medicine, in the struggle between materialism and idealism.

Primitive man regarded disease as something extraneous, invading the organism from without. This view coincided with his ideas of natural phenomena as governed by some mysterious forces (primitive animism*).

The slave-owning epoch gave rise to elements of medicine which gradually developed on the basis of observations of the course of disease in animals and man. But the concepts of disease remained primitive for a long time and rested mainly on speculative, often fictitious ideas.

In keeping with the views of some ancient philosophers who regarded nature as consisting of four basic elements—water, fire, air and earth, Hippocrates (5th century B.C.), the father of medicine, believed the human organism to consist of four different fluids (*humours*)—blood, phlegm, yellow bile and black bile (*venous blood*). He held that a proper mixture of the fluids (*crasis*) ensured health, while diseases resulted from extraneous influences which caused these fluids to be improperly mixed or contaminated (so-called *dyscrasia*). Such was the *old humoral* explanation of the essence of diseases.

In addition to the humoral pathology there also existed a so-called *solid pathology* (*solidus*—hard) which arose on the basis of the teachings of Democritus (5th century B.C.). According to solid pathology, disease is a change in the density of the body and in the location of the solid constituents of the tissues, or, more correctly, by an alteration of the intervals between them as a result of the chaotic movement of atoms.

* From the Latin word *anima*—soul. *Animism*—the belief that all animals, inanimate objects and natural phenomena possess conscious souls.

The foregoing views of the ancient philosophers already contained elements of a materialist explanation of the essence of disease and enjoyed recognition for many centuries.

Along with these views there existed vitalistic concepts, according to which the fundamental principle of both health and disease was a soul, a "vital force". The development of the idealist concepts of disease rested on the philosophy of Plato and, in some measure, Aristotle (4th-3rd centuries B.C.).

The teaching of Galen, Roman physician (2nd century A.D.), was also essentially idealistic, although it contained a few materialist propositions. Like Hippocrates, Galen saw the cause of diseases in contamination of the humours, mainly the blood. At the same time he was one of the first experimenters to enrich medicine with new data on the anatomy and physiology of the different systems, particularly the physiology of the motorium and the nervous system.

During the dark ages the vitalistic views gained ascendancy in virtue of the increased influence of religion.

At the same time mention must be made of the remarkable Tajik scientist, philosopher and physician of the 10th-11th centuries—Ibn Sina, known in Europe as Avicenna. Contrary to the religious concepts of his time Ibn Sina tried to explain diseases from a materialist viewpoint, giving precedence to observation and experience and suggesting that the organism was influenced by environmental factors.

Modern science began to develop during the decline of feudalism and the transition to capitalism (Renaissance, and the 16th and 17th centuries). The advance in production contributed to the development of medicine, although the views of disease continued to be oversimplified.

For example, in the 16th century Paracelsus (1493-1541) elaborated a theory of chemical elements which, in his opinion, constituted the basis of the whole organic world. However, he considered a vital spirit to be the guiding principle of life and alterations in this spirit to be responsible for disease.

Two basic trends in medicine—*iatromechanical* and *iatrochemical* (*iatros*—physician)—took shape in the 17th century. The iatromechanics explained disease by the physical laws of statics and hydraulics. They represented the mechanistic view of the essence of disease. The iatrochemists ascribed disease to a change in the chemical composition of the body fluids, mainly the digestive juices and the blood. At the same time they attempted to account for diseases in the human organism by changes in a special vital force that was different from the known physical and chemical forces.

In the 16th and 17th centuries biology and medicine were already in possession of an appreciable amount of scientific and experi-

mental material as a result of the research conducted by outstanding scientists. For example, Vesalius (1514-1564) had made a deep study of human anatomy; Harvey (1578-1657) had discovered the mechanism of the circulation of the blood and thereby had laid the foundation of physiology as a science; Descartes (1596-1650) was the first to describe reflex reactions; Malpighi (1628-1694) had discovered capillary circulation and had described the blood cells.

Since the beginning of the 18th century the development of industry, the progress of chemistry and physics, and the achievements of the natural sciences, morphology and physiology in particular, led to an increasingly sharper struggle between materialism and idealism.

New views in pathology at first took shape on the basis of clinical observations of the course of diseases and of pathoanatomical studies of corpses (by autopsy) that established coarse deviations in the structure of the human body.

The pathologic changes discovered by anatomists in people who had died of particular diseases prompted them to study these changes in greater detail and to try to establish their connections with various diseases. The Italian anatomist and surgeon Morgagni (1682-1771) dealt with localisation and causes of diseases, while the French scientist Bichat (1771-1802) gave a fairly detailed description of pathoanatomical macroscopic changes in organs in their relation to certain functional disorders.

Thus, towards the end of the 18th century, along with the persisting old views of the nature of disease, there had accumulated extensive factual material which, added to the general development of natural science, formed a basis for a material solution of problems of physiology and pathology.

A decisive role in the development of the dialectical materialist view of nature in the second half of the 18th and the first half of the 19th centuries was played by three great discoveries, namely, the law of conservation of energy, the cell theory of the structure of organisms and the theory of evolutionary development of the organic world.

While maintaining their connections with the morphological sciences, physiology and pathology embarked in the 19th century on the path of independent development. At that time these sciences established close relations with the clinic and the foundations of pathologic physiology as an independent science were laid.

One of the originators of the physiological trend of studying disease was Claude Bernard (1813-1878), an outstanding French scientist. The works of this scientist led to a wide adoption of the experimental method in the studies not only of physiologic but also of pathologic phenomena. Bernard laid the foundation for modern experimental pathology. He demonstrated the glycogenic

function of the liver, the fat-splitting enzyne (lipase) in the pancreatic juice, and the role of the nervous system in the regulation of carbohydrate metabolism and heat production, etc. Studies of the dynamics of pathologic processes had become the main requirement of pathologic physiology.

At the same time Claude Bernard was not entirely free of idealist ideas in questions of physiology. For one thing, he never resorted to the evolutionary theory to explain the functions of the organism.

But the discovery of the cellular structure of plant and animal organisms had created prerequisites for the emergence of cellular pathology.

The prominent German pathologist R. Virchow (1821-1902) was the first to observe on the basis of the morphological structure of organs and tissues that not only the organs as a whole, but also the cells of which the tissues of these organs consist, change in disease. He began to explain every disease exclusively by the changes occurring in the cells and on this basis developed cellular pathology (1858), according to which any pathologic process is the sum total of the cellular changes. Virchow and his pupils and followers had studied and systematised extensive and valuable factual material about cellular phenomena underlying atrophy, hypertrophy, inflammation, tumours and other pathologic processes.

Cellular pathology was the result of long and very fruitful development of natural science. It was the first scientific theory endeavouring to explain the nature of disease from materialist positions. It superseded the theretofore existing abstract and not infrequently mystic concepts of the origin and onset of disease.

Subsequently, however, the propositions of cellular pathology met with serious objections which may be reduced to the following:

1. The view of the organism as a union of cells and of disease as a sum total of cellular changes had diverted pathologists from studying the organism as a whole and from those most complex interrelations which characterise any disease and are determined by the activities of the regulatory systems.

2. Cellular pathology developed a narrow organo-localistic trend, attaching the greatest importance to the analytical principle in studying disease; from the point of view of the adherents of cellular pathology any disease arising only as a result of the direct action of the pathogen on the tissue always has a definite localisation and is essentially a local process, whereas actually any local process always reflects the general state of the organism.

3. Although cellular pathology required that investigation of pathologic processes should disclose the dynamics of the changes

occurring in the cells, it actually developed mainly a static morphological approach and offered a descriptive picture of the pathologic processes; studies of pathologic processes on the basis of general and physical chemistry have shown that, to reveal the essence of pathologic processes, it is necessary to study not only the morphological cellular changes, but also the chemical, physicochemical and molecular phenomena taking place in the cell and its environment.

4. Cellular pathology equated (in excitability) the reactions of different tissues to the action of the stimulus and denied the specific role played by the nervous system, thereby denying the significance of the dysfunctions of the nervous system in the mechanism of pathologic processes.

5. Cellular pathology rejected the necessity of studying pathologic processes in the light of the historical development of organisms in their unity with the external environment; it was a slave to erroneous ideas of the autonomy and invariability of cells and was thus clearly hostile to Darwin's theory of evolution.

The development of bacteriology since the time of Pasteur's and Koch's discoveries (second half of the 19th century) had for a time diverted investigators from the studies of the macroorganism (toward the microorganism). However, the role of the macroorganism in the development of disease soon attracted greater attention again. A considerable contribution was made by the works of the outstanding Russian researcher I. I. Mechnikov (1845-1916), who demonstrated the importance of the organism in the reactions of infection and immunity.

Although the metaphysical assertions of cellular pathology were subject to fundamental objections from the very outset, cellular pathology continued for a long time to be the sole basis of pathology and medicine.

Owing to such pillars of Russian science as Sechenov, Botkin and Pavlov, Russian medicine very largely escaped in its development the one-sided and erroneous trend of cellular pathology.

Sechenov was the first to indicate the reflex nature of mental processes. His investigations of the functions of the central nervous system demonstrated the necessity of studying the organism as a whole in its reactions to the external environment.

Botkin recognised the paramount importance of the nervous system in the pathogenesis of disease and the necessity of an individual approach in the treatment of patients. These ideas were brilliantly substantiated and developed in Pavlov's teaching on higher nervous activity.

The dialectical materialist approach to the understanding of pathologic phenomena finally made it possible to overcome the erroneous views of cellular pathology and cellular physiology.

CONTRIBUTION OF PAVLOV'S TEACHING TO PATHOLOGIC PHYSIOLOGY

In all of his scientific work Pavlov (1849-1936) developed the idea of *nervism* by which he implied the physiologic trend that endeavoured to extend the influence of the nervous system to as many activities of the organism as possible.

As regards pathologic processes this means an attempt to disclose the mechanisms of their emergence from the point of view of the disturbances which occur in the interaction between the nervous system and the organism's environment (both external and internal).

Pavlov made an enormous contribution to various branches of general and pathologic physiology.

In his early studies of the circulation of the blood he discovered the influence of the accelerator and decelerator nerves on the metabolism and nutrition of the heart muscle both under normal and pathologic conditions. It was then, too, that he discovered the significance of the receptor zones of vascular walls in the operation of circulatory processes.

Pavlov's research in digestion contributed a new chapter to general and pathologic physiology. It demonstrated the leading role of the nervous system in the secretory and motor functions of the gastrointestinal tract and in the coordination of the digestive processes.

Lastly, by his most important investigations of higher nervous activity of animals and man he proved the paramount importance of the cerebral cortex and its connections with the subcortex in the functions of the organism. He based all higher nervous activity on the conditioned reflexes he had discovered. Since then it has been firmly established that the interrelations between the organism and its environment, both external and internal, are determined by unconditioned (inborn) reflexes and conditioned reflexes acquired during the individual's lifetime.

According to Pavlov, the activity of the cerebral cortex consisting in direct perception of objects and phenomena through the sense organs is designated as the first signal system. Moreover, human cortical activity is characterised by a specific aspect, namely, speech signalisation of environmental phenomena, which is designated as the second signal system and is inseparably linked with the first signal system. The theory of the two signal systems has shown their role in the regulation of man's activities in his interactions with the external environment and the significance of the word as a stimulus capable of exerting great influence on the patient.

As the nervous system differentiated in the process of evolution it became the regulatory system which reacts to stimuli in the

environment and transmits the stimulation to other systems and organs.

The theory of conditioned reflexes, based on objective methods of investigation, offered entirely new and extensive opportunities for studying the functions of the cerebral cortex. Thanks to this theory man's mental activity has become the object of scientific investigation based on the principle of determinism, i.e., causal determination of all phenomena.

The harmonious materialist teaching on higher nervous activity and the merging of the physiologic and the psychic struck a blow at the idealist concepts of psychophysical parallelism advocated by some foreign scientists, the concepts which in some form or other have also found reflection in their present-day views of disease and the patient.

Pavlov's teaching proved to be one of the most important natural science substantiations of the Marxist-Leninist theory of knowledge. This teaching disproved the metaphysical concepts of the autonomy of the cells and of strict localisation of pathological processes, which were superseded by the concept of the organism as a single whole and of disease as a process involving the whole organism.

By his extensive and penetrating research Pavlov was the first to introduce into general and pathologic physiology a *new method based on inseparable unity of analysis and synthesis*. Moreover, this research for the first time yielded experimental models of some chronic pathologic processes, which clearly explained the pathogenesis of a number of disorders of the secretory and motor function of the digestive glands and, especially, of pathologic states of man's higher nervous activity.

The principal propositions of Pavlov's teaching, as a new and progressive stage in the development of pathologic physiology, may be defined as follows:

1) the pathologic processes and their physiologic essence must be studied in the light of the reactions of the organism as a whole and in its unity with the external environment;

2) the pathologic processes with all their qualitative characteristics must be conceived as necessarily developing with the participation of the reflex activity of the nervous system, especially its higher parts;

3) the unity of analysis and synthesis must be observed in the studies of pathologic reactions through investigation of the role of the cerebral hemispheres which in the phylo- and ontogenesis subordinate the function of the lower parts of the nervous system;

4) the pathologic phenomena must be studied from the evolutionary point of view in order to disclose as broadly and deeply as possible the ways of their emergence, course and elimination.

While considering the nature of disease from the standpoint of

nervism and the integrity of the organism in its interaction with the external environment, the Pavlovian trend at the same time deems it necessary to study the disorders which occur in individual organs and tissues.

BRIEF OUTLINE OF THE DEVELOPMENT OF PATHOLOGIC PHYSIOLOGY IN RUSSIA

In the 18th century and during the first half of the 19th century pathologic physiology was taught in Moscow University as a mere branch of the clinic, normal physiology or pathologic anatomy. It was taught by prominent clinicians, including S. G. Zybelin, M. Y. Mudrov, I. Y. Dyadkovsky and K. V. Lebedev; the latter wrote the first Russian text-book of general pathology (*General Anthropopathology*, 1835).

General pathology together with normal physiology was read at Moscow University by the outstanding scientist A. M. Filomatitsky (1807-1849). He was the first in Russia ardently to advocate the experimental method in pathology. He conducted research in respiration, blood transfusion and neurophysiology and made important contributions to analgesia and general anesthesia.

In the 1870s pathologic physiology became an independent discipline although it continued to be read mainly by pathoanatomists and clinicians, in Moscow by A. I. Polunin (1820-1888), in Kiev by N. A. Khrzhonshchevsky (1836-1906) and in Kharkov by I. N. Obolensky, the latter organising a department of pathologic physiology in 1872. In most cases general pathology was taught in an abstract manner.

Only in 1874 did V. V. Pashutin (1845-1901), outstanding Russian pathophysiolist, pupil of I. M. Sechenov, organise, first at Kazan University and then at the Military Medical Academy in St. Petersburg (1879), an entirely independent department of general pathology with an experimental physiologic trend.

The separation of general pathology as an independent science played a very important part in its further development. Pashutin founded the first Russian school of pathophysiologists educated on principles of experimental pathology. The scientific endeavours of Pashutin and his school (M. P. Albitsky, N. G. Ushinsky, A. V. Reprev, Y. A. Kartashevsky, N. V. Vesylkin et al) were devoted to elaboration of the problems of starvation and metabolism. The studies conducted by Pashutin led him to the conclusion that there were additional factors of nutrition; he was thus a pioneer in the theory of vitamins. Moreover, he was the author of the first manual of pathologic physiology, which is in many respects still valuable today.

In Kharkov the Pashutin trend began to be developed in 1895 by A. V. Reprev (1853-1930) who investigated mainly problems of

endocrinology, neoplasia and the effect of roentgen rays. The studies of the disorders of endocrine and nervous regulation from the point of view of their participation in the pathogenesis of metabolic disturbances were continued by his pupils.

In addition to the Pashutin school, other schools of general pathology came into existence at the end of last century. For example, in Moscow A. B. Fokht (1848-1930) had concerned himself, since 1880, with questions of organopathology, the pathology of blood circulation in particular. Some eminent scientists belonged to the Moscow school; A. I. Talyantsev (1858-1929) conducted research in peripheral blood circulation, G. P. Sakharov (1873-1953)—in allergy and endocrinology, F. A. Andreyev (1879-1952)—in clinical death and resuscitation, V. V. Voronin and others—in inflammation.

V. V. Podvysotsky (1857-1913) developed general and experimental pathology since 1887, first in Kiev and then in Odessa, and is the author of a well-known manual of general pathology. The trend he had established played an important part in the studies of regeneration and neoplasia. I. G. Savchenko and L. A. Tarasevich (later—A. A. Bogomolets) who investigated problems of immunity belonged to his school. All these scientists were also greatly influenced by Mechnikov who had established a new trend in the theory of infection, immunity and inflammation, and was the first to employ in his studies the method of comparative pathologic investigation.

However, in prerevolutionary Russia pathologic physiology lacked the necessary conditions, material prerequisites and a proper methodology for extensive and successful development. The basic trends of pathologic physiology have made considerable progress only since the Great October Socialist Revolution. General pathology was transformed into pathologic physiology. This was done in order to define it more clearly as a science of physiology of the diseased organism, to distinguish the objectives of pathologic physiology from those of the kindred sciences, and to extend and deepen the study of the pathology of bodily systems, thereby bringing pathologic physiology closer to clinical medicine.

In addition to the old trends, new trends came into existence in pathologic physiology. In Saratov, and later in Moscow and mainly in Kiev, the eminent scientist and public figure A. A. Bogomolets (1881-1946) elaborated various problems of pathologic physiology, namely, the theory of reactivity in pathology in connection with endocrine regulation and the reaction of connective tissue, as well as questions of blood transfusion, neoplasia, etc. He founded a special institute in Kiev and his pupils continue working there in the same direction to date.

The pathologic physiology of metabolism was extensively and comprehensively developed by Y. S. London (1868-1939) at the

Leningrad Institute of Experimental Medicine. His unique polyfistular method, angiostomy and organostomy have made it possible to study digestion and metabolism in greater detail.

Questions of pathology of lipoid, especially cholesterol metabolism, mainly in connection with vascular pathology, were studied by S. S. Khalatov (1886-1951).

The activities of N. N. Anichkov and his pupils have made an important contribution to Soviet pathologic physiology. These scientists have conducted research in the pathogenesis of atherosclerosis, in circulatory pathology, the infectious process and other important problems of pathology.

Questions of participation of the nervous system in the onset of pathologic reactions and trophic disorders were elaborated in the works of A. D. Speransky, Pavlov's pupil. His studies have established certain fundamental propositions about the leading role of the nervous system in the onset of pathologic processes and have served as the basis for an original trend in the theory of pathogenesis.

In its further development on the basis of materialist philosophy and Pavlov's physiological teaching pathologic physiology has been making use of the achievements of modern physiology and biochemistry. Eliminating the shortcomings of the analytical trend of cellular pathology pathologic physiology has established even closer connections with the kindred biological sciences and the clinic. This has found its reflection in the numerous studies of pathophysiologists in problems of reactivity, shock, inflammation, blastomatous growth, circulatory disturbances, functions of the blood system, fever and nervous activity.

The problems most urgently requiring investigation today are those of cancer, hypertensive vascular disease and cardiovascular disorders.

All future achievements of the Soviet public health services in the fight for human health, longevity and reduction of mortality largely depend on the solution of these fundamental problems.

CONCEPT OF DISEASE

One of the most important problems of pathologic physiology is to elaborate a scientific definition of disease. A correct view of disease helps to establish the general regularities of its onset and development, which is in its turn necessary for prevention and treatment of diseases. It is difficult, however, to find a definition of disease that would take in all of its main features.

The concept of disease was modified at each stage of the development of pathology, in keeping with the level of knowledge.

Taking the main value of vital functions as the norm, scientists not infrequently defined disease as a deviation from normal (Sa-

muel et al). However, the limits of normalcy were set too arbitrarily. What is normal under some conditions may prove entirely abnormal under other conditions. For example, the absence of one kidney, gastrophtosis or altered sensitivity to certain foods or drugs do not manifest themselves under ordinary conditions but lead to disease under altered conditions of nutrition or work.

In this respect the definition of disease proposed by the founders of Russian clinical medicine S. P. Botkin and A. A. Ostroumov is more appropriate. These two scientists regarded disease as a complex process resulting from a disturbance in the relations between the organism and its external environment. Although this definition reflects one of the most important features characterising disease, it cannot, nevertheless, be considered adequate. In the first place it fails to take into account man's social being and his work, and, secondly, it does not fully explain the concept of the relations between the organism and the environment.

The external environment is understood mainly as atmospheric conditions, climate, light, sound, electric phenomena, infective agents, nutrition, etc. The effect of these and other factors is determined by the social conditions under which man lives and works. A correct view of the causes and mechanisms of various diseases in man can therefore be formed only by taking into consideration the factor of man's social being.

In the organism the physiologic processes are subject to the regulatory functions elaborated in the course of evolutionary development and adaptation to the external environment. Because of these regulatory functions the changes in the external environment do not, within certain limits, involve any appreciable deviations from the usual course of the vital processes. The ability of the organism to adapt itself to the variable conditions of the external environment and to maintain a relative constancy of its internal environment is ensured by the *physiologic regulation of functions*, associated with the state of health. The leading role in this regulation is played by the regulatory systems of the organism, by means of which a unity of the organism and its environment is established.

But the organism may be exposed to the action of excessively strong or unusual external stimuli, or its sensitivity to the usual stimuli in its environment may alter. In such cases the regulatory mechanisms are disturbed, new relations between the organism and its environment are established, and a new character of adaptations emerges.

In some cases the functional disorders can be so rapidly and fully eliminated that no disease develops. In other cases, however, the vital process operating under *new and unusual conditions of functional regulation* is disturbed and manifests itself in some form of *disease*. For example, man's skin tolerates a water temper-

ature of 37-40°C without any morbid phenomena, but immersion of the hand in water at 50-55°C for several minutes results in an inflammation characterised by disturbances in the structure, function and metabolism of the tissue, development of edema and other phenomena. Simultaneously with the injury to the tissue there develops a defence reaction in the form of altered permeability of the vessels and emigration of leukocytes with subsequent intensification of phagocytosis and multiplication of cells on the periphery of the inflammatory focus. Owing to its defence reaction, the organism adapts itself to the new conditions of existence and, in the end, the function and structure of the tissue are restored.

The neuroregulatory adaptation of functions under the action of unusual factors of the external environment can also be observed in an experiment in which the dog is bled from the femoral artery and its blood pressure is simultaneously measured (Fig. 1).

Loss of a small amount of blood (for example, about one-eighth of its total amount) does not usually affect the blood pressure and the latter remains normal. More intensive bloodletting (up to one-fourth or even one-third of the total mass of the blood) leads to a drop in blood pressure. After a while the pressure rises to normal again, as a result of the reflex functioning of compensatory mechanisms, i.e., constriction of the peripheral vessels, release of blood from the blood depots, intensification of the cardiac function and passage of tissue fluid into the blood stream. These compensatory mechanisms are stimulated by the protective physiological function of the central nervous system, which is an expression

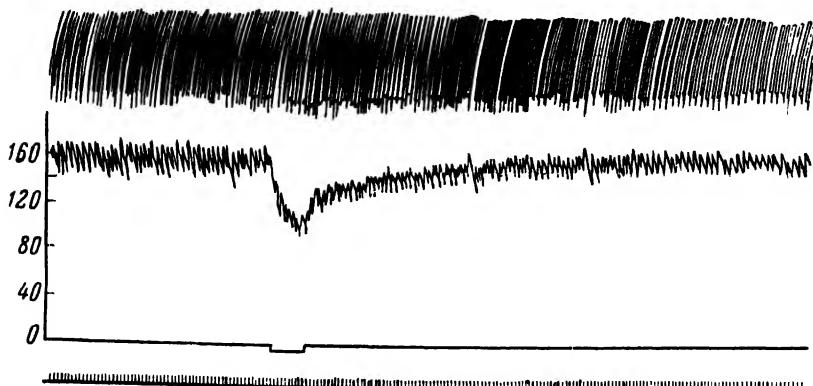


Fig. 1. Curves of blood pressure (lower) and respiration (upper) in acute venesection in the dog.

With one-third of the blood drained the blood pressure drops, but then gradually returns to normal owing to a regulatory adjustment of the following functions: constriction of the peripheral vessels, release of blood from the blood depots, intensified work of the heart and passage of tissue fluid into the blood stream. The mark on the zero line shows the time of venesection.
Time intervals—2 seconds.

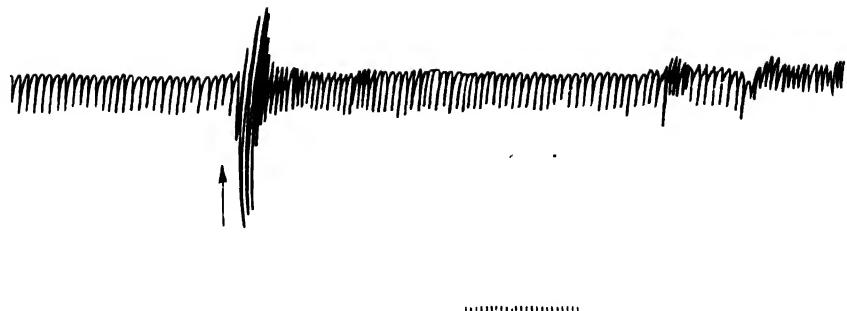


Fig. 2. Disturbance in the respiratory rhythm of the dog in acidosis. The acid-base balance is restored when the respiration is reflexly quickened and deepened. The arrow shows the moment of administration of 5 ml of a 10 per cent lactic acid solution into the femoral vein. Time intervals—5 seconds.

of the regulatory adaptation of the organism's functions to abnormal influences, in this case bloodletting. If half or more than half the total mass of the blood is lost, the blood pressure drops sharply, does not return to normal and the animal dies.

The same thing can be observed in another experiment: any shift in the reaction of the blood towards acidity or alkalinity involves a disturbance in the respiratory rhythm (Fig. 2). For example, injection of acid solutions into a vein disturbs the respiration, which becomes faster and deeper as a result of reflex, as well as direct, stimulation of the respiratory centre by the carbon dioxide displaced from the bicarbonates of the blood. The accelerated respiration increases the ventilation of the pulmonary alveoli, facilitates excretion of carbon dioxide and thereby preserves the normal reaction of the blood. Injection of alkalis is accompanied by a deceleration of the respiratory rhythm, diminished pulmonary ventilation and retention of carbon dioxide which is utilised for neutralising the excess of hydroxyl ions. Adjustment of the organism to a disturbed acid-base balance is possible only within certain limits, beyond which the concentration of H-ions in the blood is disturbed, the buffer properties of the blood are impaired and considerable disorders incompatible with the life of the animal develop.

It is not always possible to draw a clear line between physiologic and pathologic processes, between health and disease. Various, sometimes barely perceptible, transitions from one state to the other may take place. The very same pathogenic element may either harmfully affect or completely fail to affect the host depending on the conditions of the host's existence and its defence physiologic reactions. Pathologic physiology studies not only advanced pathologic processes, but also the transitional forms from health to disease. To recognise a given phenomenon as patholo-

gic, it is necessary to discover the regulatory disturbances which characterise disease and which are not observed in a healthy organism.

According to Pavlov, two closely associated phenomena must be distinguished in the picture of any disease—the injury and the organism's counteraction to the injury, or the "physiologic measures" against it, which in higher animals and man is effected by defence mechanisms based mainly on reflex activity of the nervous system and the functions of the other systems connected with it.

Often manifested as a complex of intensified or weakened physiologic processes the disease assumes a number of new qualitative aspects. *It is qualitatively a new process.* For example, the febrile process is conditioned by a quantitative disturbance in the ratio between heat loss and heat production, but the resultant fever is a specific process with specific features of metabolism and heat regulation. The peculiarities of heat regulation in a feverish patient are manifested, for example, in a lowered capacity for adjustment to variations in external temperature. At the height of fever it is easier to overcool or overheat the organism.

Hence, *disease is a complex, qualitatively new reaction of the organism to the action of the pathogenic agent, emerging as a result of disturbances in the organism's interaction with the external environment and characterised by a disturbance in the regulation of functions and adaptation, reduced capacity for work and socially useful activity.*

Any disease is associated with *injury to the organism and a response reaction to it in the form of defensive physiologic adjustments* which lead to restoration of functions; in higher animals and man these adjustments are ensured by the activity of the central nervous system.

Despite the complexity of the concept of disease the day-to-day practical experience of the physician enables him in most cases to distinguish the physiologic state from the pathologic.

The functional deviations characterising disease are for the most part studied by physiological and biochemical methods. In view of the unity of function and structure it is also necessary to study the morphological changes. However, these do not always occur or may not be detected, as is the case in functional diseases of the stomach or in various nervous disorders, as, for example, in neuroses.

Sensations of pain or discomfort are also characteristic of disease; these sensations impel the patient to seek medical advice. However, the patient does not always complain even when careful objective analysis reveals disorders of the regulatory processes; the state of compensated heart disease, the incipient stage of hypertensive vascular disease or the intervals between attacks of a disease (malaria) may serve as examples.

As a matter of fact, compensated heart disease produces no pain sensations, but is accompanied by dyspnea upon effort which in healthy people involves no noticeable disturbances in the respiratory rhythm. The incipient stage of hypertensive vascular disease objectively reveals elevated blood pressure, a change in the diastolic filling of the ventricles, etc., despite the absence of subjective complaints. The intervals with normal temperature (aprexia) between attacks of malaria cannot be regarded as a healthy state since these intervals are characterised by changes in the blood and enlargement of the spleen and liver.

The concept of disease includes the concepts of a *pathologic process* and *pathologic state*. The *pathologic process* is the organism's reaction to unusual stimulation and is based on a disturbed function, and, not infrequently, structure; the process does not as yet present a definite picture of disease (nosological* entity). From this point of view a pathologic process is a constituent of a complex of phenomena characterising a disease. For example, elevated arterial pressure in hypertensive vascular disease is one of the pathologic processes characteristic of this disease; the concept of hypertensive vascular disease includes, in addition to elevated arterial pressure, other changes in different organs and systems of the organism.

A *pathologic state* is characterised by weak development of the changes which have already occurred and is not infrequently one of the stages or a consequence of the pathologic process. For example, a transition of the pathologic process to a pathologic state is observed in the change of the active progressive form of pulmonary tuberculosis to the fibroid form. Endocarditis—inflammation of the lining membrane of the heart—may change to a pathologic state, namely, disease of the heart valves. However, a pathologic state is only relatively stable. A disturbance in the adaptation of the organism to its environment (for example, in cases of excessive functional load or infection) may lead to a change of a pathologic state to a pathologic process again.

PERIODS AND DURATION OF DISEASE

The following principal periods in the course of disease may be distinguished: 1) latent, 2) prodromal, 3) period of marked manifestations and 4) outcome.

The *latent period* lasts from the beginning of the action or entrance of the infective agent to the manifestation of the organism's reaction in the form of detectable morbid phenomena or symptoms. In infectious diseases this period is known as the *incubation period*. The latent period varies in duration from several minutes to several months and even years. It is apparently determined by

* From the Greek word *nosos*—disease.

the organism's reaction to the action of the causative agent, its ability to overcome the resultant disturbances by means of its defence mechanisms. Intoxication occurs almost instantly or within several minutes only after the action of powerful poisons.

Ascertainment of the latent period is of great practical importance for the prevention and treatment of the disease.

The *prodromal** period lasts from discovery of the first signs of the disease to its complete manifestation. For example, the onset of infectious diseases is often characterised by indefinite manifestations, such as general indisposition, sometimes chills, headache, inappetence, rise in temperature, etc.

The *period of marked manifestations* usually follows the prodromal period. It is the period of development of all the principal morbid phenomena. Some diseases, especially infectious diseases, run a rather definite course. For example, typhus usually lasts 13-16 days, measles—8-10 days. Other diseases, particularly chronic diseases, do not have a definite duration.

Diseases are divided according to their duration into *acute*, *subacute* and *chronic*. Acute diseases last a short time—from several days to 2-3 weeks, subacute—from 3 to 6 weeks; chronic diseases are not infrequently results of acute diseases and last more than 6 weeks. However, these periods cannot be definitely fixed. The duration of a disease depends on the characteristics of the infective agent and the intensity and duration of its action on the given organism, as well as on the properties of the infected organism.

Clinical cure may be followed by a *relapse*, i.e., recurrence of the disease, as is the case of recurrent endocarditis, erysipelas, etc. In addition to the persisting focus of infection, changes in the functional state of the central nervous system not infrequently play a part in the mechanism of occurrence of these relapses; these changes sometimes persist for a long period after convalescence and are the source of recurrence of the disease as a result of accidental, even weak, influences exerted on the organism.

Outcome of Disease. In some cases the disease ends in *restoration of functions and complete recovery*. However, complete restoration may only be imaginary. Thus, after infection the properties of the host alter just the same: the host acquires a state of immunity to the given infection (for example, smallpox, scarlet fever, typhoid fever) or, on the contrary, becomes more susceptible to it (for instance, erysipelas).

If the functional disturbances caused by the disease have not completely disappeared the *cure is incomplete*. Sometimes structural and functional changes persist; for example, the heart valves retain lesions after inflammation, or a joint remains immobile as a result of a tuberculous process in it.

* From the Greek word *prodromos*—running before.

If the organism cannot adjust itself to the altered conditions of existence, its adaptation mechanisms become exhausted, further vital activity becomes impossible, and the third possible outcome of the disease—*death*—ensues.

The direct cause of death is usually *cardiac arrest* which may be provoked by damage to the heart (for example, coronary thrombosis, heart failure) or to the cerebral centres which regulate the function of the cardiovascular system. Another cause of death is *respiratory arrest*. It is observed in paralysis of the respiratory centre in the medulla oblongata, for example, as a result of a hemorrhage or anemia, its compression by a tumour or intoxication with certain poisons (morphine, curare, cyanides).

Agony and Clinical Death. These conditions (terminal) are stages of dying and precede the onset of biological death.

The first to become extinguished in the process of dying is the function of the central nervous system. The extinction begins with cessation of the activity of the cerebral cortex followed successively by that of the interbrain, midbrain, medulla oblongata and the spinal cord, i.e., the older the parts of the central nervous system in their development the later they become extinguished.

Agony is characterised by disordered activity of the central nervous system and disturbances in all the vital functions of the organism—irregular and intermittent respiration, weakened heart action, relaxation of the sphincters, drop in temperature and, not infrequently, loss of consciousness. Agony precedes clinical death and may last from several hours to 2-3 days.

Clinical death is characterised by the deepest depression of the functions of the central nervous system. The metabolic processes are noticeably disturbed, the energy reserves become depleted, but the changes in the tissues are still reversible, for which reason restoration of the vital functions of the organism is sometimes possible during clinical death which lasts 5-6 minutes. But with the appearance of irreversible changes in the tissues, which first occur in the higher parts of the central nervous system, a state of biological or true death sets in.

To restore the vital functions of a dying organism, the heart is massaged, artificial respiration is administered and adrenalin is injected into the heart. A new method of a complex of measures aimed at restoring the vital functions of the organism has been elaborated and is now very successfully employed. It consists of intra-arterial pumping of blood with adrenalin and glucose in the direction of the heart and simultaneous administration of artificial respiration (V. A. Negovsky). The vital functions may be successfully restored during agony or clinical death (in severe shock, loss of blood, asphyxia, etc.). Resuscitation is impossible when death is the result of a severe and protracted disease with deep, irreparable damage to the vitally important organs such as the brain, heart and lungs.

Chapter Two

GENERAL ETIOLOGY AND GENERAL PATHOGENESIS

CONCEPT OF ETIOLOGY

*Etiology** is the science of the causes of disease and of the conditions under which disease arises. Establishment of general regularities of the origin of various diseases is one of the main objectives of general etiology; the study of the causes of various diseases is the aim of specific etiology.

The *specific, qualitative features of a pathologic process are determined by the cause which provoked it*. To treat and prevent various diseases, it is necessary to establish the relations between the cause and nature of the pathologic process.

Diseases may be caused by pathogenic agents which act on the organism from the external environment; in such cases the diseases are said to be provoked by *external (exogenic) factors*. The causes of diseases arising within the organism itself are referred to as *internal (endogenic) factors*.

However, in the etiology of pathologic processes the external and internal must not be opposed to each other. The external pathogenic factor cannot be considered in isolation from the internal properties of the organism. Acting on a living, reacting organism the external pathogenic agents cause disturbances in its internal environment, which may, in their turn, provoke a new pathologic process. For example, obesity caused by disturbances in nutrition may become the cause of circulatory disorders; a hemorrhage produced by injury may in its turn become the internal cause of an inflammatory reaction. The internal must thus be regarded as a result of the action of the external.

Pathogenic factors of the external environment are usually extraordinary or injurious stimuli (physical, chemical, infectious, etc.) which act on the organism from without. Unusual stimuli, which the organism never encountered before, or usual stimuli, in cases of their prolonged action, or the organism's increased sensitivity to them, for example, protein or certain other food substances, may

* From the Greek words: *aitia*—cause and *logos*—word.

also be pathogenic. The discovery of conditioned reflexes has extended the range of etiologic factors of disease by inclusion of numerous weak or indifferent stimuli which have become pathogenic through their repeated combination with unconditioned disease factors. Conditioned reflex attacks of bronchial asthma or coronary spasm occurring in patients under the influence of the situation in which they already suffered such attacks may be referred to as an example. Of special importance to man with his developed higher nervous activity are psychic factors of diseases causing disorders of the functions of the cerebral cortex, which influence all the other functions of the organism. Cases of neuroses developing as a result of psychic trauma which leads to overstrain of the stimulatory and inhibitory processes, or aggravation of a disease (diabetes, exophthalmic goitre, etc.) by hard emotional experiences have long been known.

Of the numerous external and internal factors affecting the body it is necessary in each concrete case to find the one which is the actual cause of the disease. Diseases are most frequently caused by factors in the external environment. The properties of the body proper usually play the part of the conditions which are conducive to the onset of the disease. For example, an infectious disease, say, typhoid fever, is caused by the invasion of the organism by a certain infective agent—typhoid bacillus (*Salmonella typhosa*). Without this microbe the aforesaid disease cannot develop. In this case the lowered resistance of the organism is but a condition for the onset of the infection.

Factors in the external environment may also serve as conditions for the onset of disease. For example, tuberculosis is caused by the tubercle bacillus (*Mycobacterium tuberculosis*). However, the onset, course and clinical manifestations of this disease depend on a number of other factors of the external environment, which serve as conditions conducive to its development; these factors include inadequate nutrition, poor housing, humid climate, etc. The conditions may be *favourable* and diminish the effect of the cause or, contrariwise, *unfavourable* and intensify its effect; in other words, the external conditions may raise or lower the resistance of the organism.

Experiments of infecting pigeons with anthrax may serve as experimental proof of the importance of external conditions. Pigeons, usually unsusceptible to anthrax, easily contract the disease if preliminarily subjected to starvation.

As regards human diseases, social conditions of existence are particularly important.

Thus the *etiology of a disease implies both the cause and entire complex of conditions under which the cause manifests its pathogenic effect on the organism*. However, the cause of a disease cannot always be disclosed. It often remains concealed from us (or we

confuse it with one of the intercurrent factors). The causes of most infectious diseases, diseases of a traumatic character, and metabolic disorders are well known, but our knowledge of the causes of tumours, many mental disorders and certain diseases of the cardiovascular system (for example, hypertensive vascular disease and coronary thrombosis) is still limited.

Criticism of Metaphysical Concepts of Etiology

The correct dialectic materialist concept of etiology was preceded by metaphysical conceptions of the causes of disease. With the development of bacteriology the discovery of the causes of a number of infectious diseases struck a crushing blow at the vitalistic conceptions of etiology of disease. But at the same time these achievements engendered the erroneous idea that penetration of the pathogenic agent or contact with it was alone enough to cause disease. This trend of etiology was named *monocausality*. It was essentially mechanistic because the cause was considered in its simple relation to the effect; the complexity of interrelations between the organism and its environment, the unity of the organism and the conditions of its existence were not taken into account.

The advocates of another trend—*conditionality*—reduce etiology to conditions whose aggregate they believe capable of causing disease.

The conditionalists try to prove that conditions alone suffice to produce disease. They are content with an external description of the agents taking part in the onset of the disease and are unable to single out the leading, determining factor and to establish its causal relation with the development of the given pathologic process.

It is well known that a mere penetration of tubercle bacilli into the organism is not enough for the onset and development of tuberculosis, since a certain part is also played by a number of conditions, namely, inadequate nutrition, poor housing conditions and preceding infections (measles, whooping cough, etc.). On this basis conditionalists draw the erroneous conclusion that there is no single causal factor in the onset of tuberculosis and that its development is determined by an aggregate of conditions. They completely disregard the fact that none of these conditions alone, nor all of them combined, can account for the specificity of the pathologic reaction arising in the organism only in response to the action of the tubercle bacillus. Knowledge of the cause of the disease makes it possible to gain an insight also into the conditions of its onset.

Conditionalists sever the external from the internal and, failing to uncover the objective regularities of pathologic phenomena, believe them to be unknowable. This reactionary trend disarms the physician in his prophylactic and therapeutic activity.

CONCEPT OF PATHOGENESIS

Pathogenesis is the science of the mechanisms of *production and development of disease*. It is most intimately connected with etiology.

Complete knowledge of the essence of diseases and their outcome depends on disclosure of their pathogenesis.

Main Mechanisms of Pathogenesis

Importance of Nervous and Neurohumoral Mechanisms in Pathogenesis

Modern concepts of the general pathogenesis rest on the theory of inseparable unity of the organism and its environment. The organism is adjusted to its environment by means of its nervous system which controls the functions, blood supply and metabolism of all its organs and tissues.

By acting on the organism of higher animals and man the pathogenic agent first *stimulates the nerve endings* (extero- or interoceptors) whose sensitivity is many times as high as the sensitivity threshold of the other tissue elements. The receptors are the initial link of reflex arcs by means of which the organism reacts to the pathologic influences exerted on it by its external or internal environment.

The pathologic process may at first manifest itself in injury to the tissue at the point of application of the stimulus—mechanical, chemical, thermal, infectious, etc. The process gives rise to disturbances in metabolism and the structure of the tissue. These direct and limited disturbances, owing to the simultaneous stimulation of the receptors which send signals to the central nervous system, lead to a general reaction of the organism, based on the reflex mechanism, which can be observed, for example, in the experiment with the production of a burn. The action of a thermal agent applied to the surface of the body involves injury to the tissue and a simultaneous reflex elevation of arterial pressure, change in hemopoiesis and metabolism, disturbance in respiration, etc.

Pavlov observed the importance of reflex mechanisms in the pathogenesis of trophic disorders of the skin or oral mucosa. The disorders arose in dogs as a result of prolonged stimulation of the afferent nerves of the digestive tract caused by adhesions and scars sometimes developing in the abdominal cavity after production of fistulas.

As an illustration we can also mention the participation of the nervous system in the mechanisms of the phenomena sometimes involved in obstruction of a blood vessel (embolism), for example, obstruction of the vessels of pulmonary circulation. These phenom-

ena consist in a reflex spasm of the pulmonary and coronary arteries, a drop in general blood pressure and altered respiration. Severance of the reflex paths by surgical or pharmacological means diminishes these phenomena which in some measure are also due to local mechanical disturbances in the blood flow. By exerting certain influences on the nervous system it is also possible to delay the restoration of functions disturbed by the embolus.

Pathologic processes may arise *by the mechanism* of both *unconditioned* and *conditioned reflexes*. On repeated combination of the pathogenic factor with an indifferent stimulus the latter may also become the cause of the given disease which in this case develops by a conditioned reflex mechanism. For example, by administration of a physiologic saline solution it is possible to reproduce in dogs, by the conditioned reflex mechanism, intoxication with morphine, eserine, bulbocapnine and camphor. Pathologic conditioned reflexes sometimes underlie attacks of bronchial asthma, hay fever, eczematous lesions of the skin and other diseases.

In addition to reflex action, *pathogenic stimuli may affect the central nervous system directly*; these stimuli may be carbon dioxide accumulated in the blood or microbial toxins or toxic metabolites.

Depending on the etiological factor, the site of its action and properties of the organism, the pathogenesis of a disease may be connected with changes in the functions of various parts of the nervous system—from peripheral endings of afferent nerves to the cerebral cortex. Thus, respiratory disorders may arise in one case as a result of stimulation of the peripheral endings of the pulmonary branches of the vagi, in another—as a result of injury to the medulla oblongata or certain parts of the diencephalon, and in still another—as a result of a disturbed function of the cerebral cortex (for example, dyspnea during excitement or disturbance in higher nervous activity). The sugar in the blood may be increased experimentally by several methods: stimulation of the proximal end of the severed sciatic nerve, a puncture in the medulla oblongata, or intense emotional excitement. In other words, the pathologic process may be engendered in different parts of the organism. The sequence and degree of the functional disorder of the particular part of the nervous system are of certain importance in the character and rate of development of the given pathologic process. However, owing to reflex activity, the pathologic process in the end inevitably involves other divisions of the nervous system, parts of which are most intimately interconnected.

To elucidate the participation of the higher parts of the nervous system in the pathogenesis of a disease it is also important to study its basic regularities: typological properties, correlation of the processes of excitation and inhibition, phenomena of parabiosis (after Wedensky), dominant (Ukhtomsky), trace reactions, etc.

An important part in pathogenesis is played by *disturbances in the interrelations between the central nervous system and the internal environment of the organism*.

The dependence of the functions of the internal organs on the activity of the higher parts of the central nervous system was repeatedly observed by clinicians. On the one hand, we know about the effects of various emotional experiences on the heart action, respiration and digestion; for example, we know of cases of cardiac paralysis caused by distressing experiences, changes in the respiratory rhythm due to sudden fright, digestive disorders connected with mental depression and chronic lack of appetite. On the other hand, there are very well known examples of bodily afflictions overcome by positive emotions.

By his many years of studies of the cerebral cortex activity Pavlov demonstrated that the functions of the interpal organs, regulated by subcortical structures, also had their "cortical representation". For example, he observed a prolonged disturbance in the motor and secretory functions of the stomach of dogs as a result of disturbances in the functional state of the higher parts of the brain caused by a clash of the processes of excitation and inhibition. Disorders of higher nervous activity were also shown to play an important part in altering the functions of other internal organs—gastric secretion, bile secretion, blood pressure, excretion of urine, hematopoiesis. Other researchers have showed the possibility of forming conditioned reflexes involving the functions of the internal organs and the importance of interoception in these processes. They demonstrated the possibility of conditioned reflex polyuria (passage of an excessive quantity of urine) and anuria (arrest of urinary output), conditioned reflex bile secretion, contraction of the spleen, vasoconstriction and vasodilatation, changes in respiration, metabolism, etc. These studies formed the basis of the concept of feedback relations between the activity of the cerebral cortex and the function of the internal organs (corticovisceral relations, according to K. M. Bykov). The cerebral cortex not only regulates the internal environment of the organism, but in its turn is also under continuous influence of impulses coming from the periphery.

As soon as impulses from the extero- and interoceptors reach the cerebral cortex, the latter sets off a complex process of analysis and synthesis and creates the correlations between the processes of excitation and inhibition which determine the character of its influence on the functions of the internal organs. Disturbances in the normal relations between the cortex and subcortical region not infrequently underlie a number of diseases.

These data have shaped new conceptions of the role of the central nervous system in the pathogenesis of a number of diseases, for example, ulcers, hypertensive vascular disease, bronchial asthma and coronary insufficiency.

The influence of the higher parts of the central nervous system is exerted through its lower parts. The pathogenesis of diseases of the internal organs may also be primarily connected with disturbances in the functions of the subcortical region, particularly the region of the hypothalamus which contains the centres that regulate, by means of efferent neurons, the processes operating in the internal environment of the organism.

Humoral mechanisms, especially neuroendocrine and endocrine regulation, also constitute a very important link in the regulation of functions. Through their various functions endocrine glands determine, in close interaction with the nervous system, the reaction of the complex organism to the action of the stimulus. For example, disorders of urinary output may occur through subcortical vegetative centres and their connection with the posterior lobe of the hypophysis which secretes an antidiuretic hormone that influences water reabsorption in the kidneys.

With the evolutionary development of organisms the neuroendocrine relations assume increasing importance in pathologic reactions. The cortico-diencephalo-hypophyseal correlations and the hypophyseal-adrenal function closely connected with them play a particularly important role in higher animals and man. This system actively participates in the adaptability of the organism, in its nonspecific reactions to the action of any pathogenic stimulus.

In addition to the hormones produced by endocrine glands, tissue hormones may also take part in the pathogenesis of disease; these hormones, for example, active polypeptides and proteins, histamine, acetylcholine, serotonin are physiologically active substances. They may also participate in disturbing the regulation of functions, which is often discovered in pathologic processes.

Thus the mechanisms of pathologic processes are determined by the properties of the *pathogenic agent* as well as the *reaction of the organism*, its regulatory systems.

Significance of Effectors in Pathogenesis

For complete knowledge of the pathogenesis of diseases it is also necessary to study the changes occurring in the organs, tissues and cells. For example, disturbances in the small intestine are considered specific of cholera, in the large intestine—specific of dysentery, lobar affections of the lungs—specific of croupous pneumonia; bronchial asthma is manifested in spasms of small bronchi, ulcers—in lesions in the stomach or duodenum. Under pathologic conditions the pathologic processes proper, as well as the physiological defence processes, are manifested in the activity of various organs. Without consideration of the disturbances taking place in the organs and tissues, and all their characteristic interrelations with the regulatory systems, the concept of pathogenesis loses its concrete content.

While establishing interaction between parts of the organism the nervous system is itself most closely connected with the activity of the effectors which play an "executive" role. Located here are the endings of the efferent part of the reflex arcs along which impulses from the external and internal environments of the organism are received.

In addition to the endings of the efferent fibres, the effectors include receptors—the initial part of the reflex arcs. From the receptor apparatus of the organs the central nervous system receives signals pertaining to the state of the organism's internal environment.

The significance of the effectors in the mechanisms of pathologic reactions is also connected with the humoral properties of the tissue environment—tissue metabolism, particularly the enzymochemical and physicochemical processes, as well as the properties of protein structures which determine the effect of the perception of stimuli and the character of the response reactions to these stimuli. For example, stimulation of vasoconstrictor nerves running to inflamed tissue evokes, owing to changes in its physicochemical properties, a paradoxical effect—dilatation rather than constriction of the vessels. The participation of effectors in the mechanism of pathologic processes is particularly clearly observed when pathologic changes occur primarily as a result of direct damage to the tissues, for example, in trauma, burn, frostbite, and action of strong acids, alkalis or poisons.

Local and General Phenomena in Pathogenesis

Interrelation Between the Local and the General

Pathologic processes are never strictly localised. On the one hand, the character of their development is determined by the properties of the organism as a whole; on the other hand, once arising, these processes also affect, in their turn, the entire organism.

Such a local pathologic process as inflammation depends in its origin and development on the general condition of the organism and is a local expression of its general properties. For example, furunculosis is a local disease, but in actual fact it is often a result of nutritional and metabolic disorders and concomitant lowered immunity. Other diseases involving changes in the entire organism also produce local changes, such as functional and structural disturbances in some particular organ. Thus typhoid fever, although a disease of the entire organism, is characterised by peculiar changes in the small intestine. Atherosclerosis* which develops as a result

* Pathologic change in the walls of large vessels characterised by deposits of lipids (cholesterol and its esters) in the intima with subsequent excessive growth of connective tissue and induration of the walls.

of general metabolism disorders is marked by changes in the walls of large arteries. This is also true of gastric ulcers, diseases of the blood, renal diseases, etc.

An important part in establishing interrelations between the local and the general is played by the regulatory processes—nervous and humoral regulation of functions. This is evident from the fact that transection or stimulation of afferent or efferent nerves, i.e., disturbance of the function of the central nervous system, noticeably affects the interrelations between the local and the general and alters the development of pathologic processes, for example, the process of inflammation or metastasis (transfer) of tumour cells. Septic infection selectively affects the heart or kidneys, the gallbladder or several organs at once, depending, not only on the properties of the pathogenic agent, but also on the character of the reflex reactions which determine the functional state of these organs. The characteristics of the regulatory processes may account for the absence of parallelism between the extent of local disturbances and the general manifestations of the disease. This is not infrequently observed in cases of increased sensitivity of the organism to the pathogenic agent, for example, during an allergic state when an acute and stormy reaction arises at the site of contact between the tissue and the agent.

Thus, owing to the integrity of the organism and the interaction of its parts, *local processes must not be considered apart from the entire organism*. At the same time, originating in a particular part of the organism, at a certain stage of its development the pathologic process becomes the *starting point of new relations between the local and the general and affects the entire organism*. For example, an inflammatory focus evokes a general leukocytic reaction and visibly alters the sensitivity of the entire organism to foreign proteins and infectious agents.

The local and the general must be understood in their dialectical unity. Disclosure of these interrelations makes it possible to gain a deeper insight into the pathogenesis of disease and to understand that it is necessary to treat the diseased person rather than the disease.

Significance of the Site of Penetration of Pathogenic Agents

The gates of entrance of the pathogenic agents and the site of their initial effect play a very important part in pathogenesis. For example, penetration of gonococci to the urethral mucosa gives rise to gonorrhreal urethritis, whereas the action of the same microorganisms on the mucosa of the eye produces gonorrhreal conjunctivitis (blennorrhea). Subsequently these two processes greatly differ in their development.

In experiments in which the organism is acted upon with pharmacological substances (for example, adrenalin, acetylcholine, calcium, etc.) it is often possible to observe effects differing in intensity, duration or character when the same substance is administered at different sites. Of the factors that determine the mechanism of action of pathogenic stimuli an important part is apparently played by the anatomophysiological and biochemical properties of the organs and tissues, their functional state and characteristics of their receptor fields.

Pathologic processes predominantly affect particular organs, not only according to the portal of entry of the pathogenic agent, but also to the physiological peculiarities of the entire organism. For example, osteomyelitis (inflammation of bone marrow and bone) most frequently begins in the metaphyses of tubular bones. This is accounted for, not only by the characteristics of capillaries, but also by the regulation of the blood flow which provides an abundant blood supply to the given part of the bone where the best conditions are apparently created for contact of the tissue with the toxins or bacteria brought in by the blood flow.

Sometimes the effect of the etiologic factor is predominantly manifested in the parts of the organism which suffered injury. By damaging tissues, injuries produce nutritional and metabolic disorders in them, reduce the general resistance of the organism and facilitate the penetration and spread of the noxious agent in it. Thus, an injury to a lung may stimulate development of a purulent inflammation in it, an injury to the limbs—development of tuberculosis of bones.

Development and Periods of Diseases

The study of pathogenesis requires investigation of all stages in the development of pathologic phenomena, their succession and interconnections. For example, in tonsillitis, septic infection having penetrated into the organism from the focus in the tonsils may cause inflammation of the endocardium on the basis of which permanent changes in the heart valves often develop. These changes cause circulatory disorders in the heart itself. At first the organism and heart muscle surmount the obstacle to the work of the heart, but subsequently, the obstacle increases and gives rise to disturbances in the blood circulation accompanied by dilatation of the heart cavities and hemostasis in the veins of the systemic or pulmonary circulation. The hemostasis and metabolic disorders in cardiac patients give rise to edemas and disorders of the functions of various organs, including still greater cardiac disorders. Thus a vicious circle results. Consequently, the greatest importance in the mechanism of these phenomena must be attached to disturbances in the regulatory processes which determine the site, degree and character of the emerging changes, as well as the adjustment of the organ-

ism, particularly the circulatory apparatus, to the new obstacles in its activity.

Traumatic shock may serve as another example. Its cause—trauma—evokes overexcitation of the central nervous system and gives rise to deep functional disturbances in the cerebral cortex and subcortical centres. These result in disorders of the hemodynamics consisting in diminished vascular tone, circulatory disturbances, drop in blood pressure and, as a consequence, hypoxia which in its turn unfavourably affects the functional state of the central nervous system. As a matter of fact, the succession of causes and effects in the development of traumatic shock is still more complex because the damage to the tissues caused by the trauma itself becomes the cause of a number of subsequent phenomena, for example, blood loss and toxemia, which afterwards may in their turn become causes of disturbances in nervous activity.

The main pathologic process not infrequently leads to development of complications in the organs or systems. For example, scarlet fever may in its subsequent development give rise to severe affections of the kidneys.

Disclosure of the cause-and-effect relations is one of the most important objectives of pathogenesis because it helps to discover the main mechanism of the pathologic process and therefore to determine pathogenetic therapy.

Spread of Pathogenic Agents

To disclose the pathogenesis of diseases and understand their development it is also necessary to investigate the *spread of pathogenic agents in the organism* after their penetration into its internal environment. As a result of the spread of pathogenic agents the pathologic process may involve the adjacent and, not infrequently, distant organs and tissues.

The pathogenic agents may spread: a) by extension and contact, b) through the vascular (circulatory and lymphatic) system and c) through the nervous system.

The spread by extension occurs as a result of the action of the pathogenic agent, which affects one part of a tissue, on the adjacent normal part, for example, the spread of herpes over the skin or of infection along the urinary tract.

Closely resembling the aforescribed route of spread is the intracanalicular spread, for example, along bronchi or excretory gland ducts. Thus infected masses spreading along bronchi from some tuberculous focus in the lungs cause development of a pathologic process in other parts of the lungs.

The spread may also be a result of contact of an affected surface with a healthy surface. In inflammation of the gallbladder the inflammatory agent sometimes affects the serous coat of the stomach

causing its inflammation (perigastritis). In cancer of the lower lip the tumour cells may, as a result of contact, take root in the tissue of the upper lip.

Penetration of pathogenic agents (microbes, toxins and poisons, cells of malignant tumours, etc.) into the blood stream leads to their spread throughout the organism.

For example, after affecting the entire organism and weakening its defence mechanisms bacteria and toxins may at first gain entrance into the tissue fluid and then through the lymphatic vessels into the lymph nodes where they may be stopped or carried further by the lymph into the venous system. This route of spread through the lymphatic system is called *lymphogenic*.

In other cases bacteria and toxins penetrate, for example, together with emboli into the blood stream and are quickly transported by the latter; this route of spread by the circulatory system is known as *hematogenic*.

Microbial metabolites or tissue catabolites may spread from the focus of infection and cause general intoxication and a febrile process. Some infectious agents, for example, the rabies virus or tetanus toxin, which act selectively on nervous tissue, spread along nerve trunks.

The spread of pathogenic agents must not be conceived mechanically, as a phenomenon depending only on the direction of the vessels or nerves. Here we have a complicated biological process, i.e., a complex of unstable, continuously varying physiological states of the organism, particularly the environment into which the pathogenic principle gains entrance.

Restoration of Functions Impaired by Disease

The restoration of functions impaired by the pathogenic agent is inseparably connected with pathogenesis and underlies recovery.

The defensive functions of the organism manifest themselves variously: in production of immunity (in infectious diseases), in elimination of the pathogenic agent (for example, in the vomit, urine, feces, sweat, mucus), in healing of the tissue defect (in traumas and wounds), etc.

Compensatory reactions are one of the widespread forms of restoration of functions. These reactions include hypertrophy of the heart muscle in valvular diseases of the heart, replacement of one of the paired organs (in affection of a lung or kidney) or of one part of a single functioning system by another (in renal insufficiency—replacement of renal activity by the functions of the skin, lungs and intestines), restoration of blood pressure after bloodletting by constriction of peripheral arteries and contraction of the spleen, and a change in the correlations of antagonistic factors (increased activity of cholinesterase in cases of acetylcholine accumulation),

The defence reactions during the different stages in the development of disease are not equally strong and sometimes reach an intensity which may even prove harmful to the organism. For example, proliferation which is usually one of the defence mechanisms may be so intense as to prevent the repair of the damaged part of the tissue; fever which is conducive to elaboration of immunity becomes dangerous to the nervous and cardiovascular systems when the temperature rises too high; vomiting occurring in many forms of intoxication helps to rid the organism of toxic products, but intractable vomiting in toxemia of pregnancy may imperil life.

An important role in the defense physiologic reactions of the organism of higher animals and man is played by the higher divisions of the central nervous system, especially the cerebral hemispheres, the apparatus which adjusts and regulates all functions of the organism.

The *role of the central nervous system in the processes of restoration* of functions impaired by disease is particularly easy to observe in cases of deep anesthesia or cerebral trauma, which results in diminished efficiency of the organism and reduces the compensatory reactions in cases of inflammation; proliferation and regeneration of damaged tissue noticeably decrease; after a loss of blood the restoration of blood pressure is retarded; in disorders of cardiac activity hypertrophy of the heart muscle develops feebly and the blood circulation is impaired.

Studies in the physiology of the cerebral hemispheres have established the role of cortical inhibition as a defence reaction to exhaustion and great damage to or destruction of nerve cells. This inhibition is conducive to restoration of cortical activity and is, according to Pavlov, a safeguard. It often comes into play in the course of various pathologic processes as a defence reaction to noxious agents and the damage caused by them, for example, in cerebral anemia, various forms of poisoning and infectious diseases.

Production of defensive inhibition underlies the use of prolonged natural or artificial (induced by medication) sleep (if the latter closely resembles natural sleep). Prolonged sleep therapy is now indicated in some cases of traumatic shock, hypertensive vascular disease, ulcers, etc.

Chapter Three

SIGNIFICANCE OF THE EXTERNAL ENVIRONMENT IN THE ORIGIN OF DISEASE

Pathogenic effects may be produced on the organism by various extraordinary stimuli or factors of the external environment—physical, chemical, biological and psychic. Their pathogenicity varies and depends on the organism's external and internal environment. The pathogenic effects are produced under concrete social conditions of existence, which are of great, sometimes decisive, importance in the onset of disease.

PATHOGENIC PHYSICAL FACTORS

Mechanical Factors

These include injuries which vary in character, duration, intensity and point of application. Mechanical factors may be both of exogenous and endogenous origin, for example, pressure of a haemorrhage or growing tumour on the surrounding tissue.

There are *contusions* (inflicted by blunt instruments), *wounds* (made by cutting or pointed instruments), *gunshot wounds*, *sprains*, and *ruptures* of tissues and organs (for example, those caused by falls). Blunt instruments may *compress or crush the tissues*.

If the mechanical factor is an explosion, the air blast may severely *shake or jar the tissues* and disturb their physicochemical state, usually without involving coarse anatomic changes. *Concussion of the brain* may serve as an example of such injuries. Concussion of the brain is characterised by intense headache, sometimes unconsciousness and other phenomena on the part of the central nervous system. A blast affects the entire organism and may injure all organs and tissues.

Injuries caused by cutting or pointed instruments involve interruption of the continuity of the tissues and produce *incised*, *punctured* and other *wounds*. Wounds with lacerated edges heal with greater difficulty because of considerable destruction of the tissues.

The *results of mechanical injuries to the nervous system* are extraordinarily serious. Damage to the nervous system may result in pareses and paralyses.

Injuries to the osseous system are accompanied by dislocations, fractures or (in chronic cases) changes in the architecture of the ossaceous tissue.

Mechanical factors may cause *damage to internal organs*, for example, injuries to the heart, lungs, liver, etc.

An injury may cause a *hemorrhage*. Arterial, venous and capillary hemorrhages are distinguished, according to the nature of the vascular disturbances. Injuries to capillaries usually result in ecchymoses. Injuries to larger vessels bring about a loss of blood or produce hematomas.* Disruption of blood vessels during injury may allow air, fat and tissue elements to penetrate into them and subsequently obstruct the circulation in the organs and impair their functions.

Interruption of the continuity of tissues as a result of mechanical trauma is accompanied by an *inflammatory reaction*. The tensity of the inflammatory reaction depends on the extent and nature of the injury, the reactive properties of the organism and penetration of *infection into the wound*.

Prolonged, weak mechanical stimulation of a tissue sometimes causes *proliferation* (multiplication of cells), for example, on the skin or mucous membranes.

Traumatic Shock. A mechanical trauma is often characterised by general morbid phenomena.

Blows to the epigastric region, extensive wounds, fractures, or crushing of tissue may give rise to phenomena of traumatic shock.

Traumatic shock is a special state of the organism produced neuroreflexly by the action of an extraordinary stimulus and manifested in an acute circulatory disturbance with a sharp drop in blood pressure and depression of all important vital functions: nervous function, blood circulation, respiration, metabolism, etc. Traumatic shock may result in death.

Phenomena of traumatic shock may appear in man at the moment of injury or soon afterwards. More frequently, however, they develop within 4-6 hours and later. The pathogenesis of traumatic shock is based on *disturbances in the function of the central nervous system*.

Excessive stimulation of the extero- and interoceptors evokes strong excitation with subsequent transmarginal inhibition in the cerebral cortex.

Experimental observations of developed shock have shown diminished electrophysiological activity of the cortex and excitability of the vegetative centres (A. N. Gordienko).

* Hematoma—a collection of effused blood in a tissue.

General motor and speech excitement, tachycardia, elevated blood pressure, dyspnea and increased metabolism are noted during the initial period of shock. Soon, however, (during the second period), the excitement is replaced by inhibition which radiates from the cortex to the subcortical region. At this time the phenomena most characteristic of traumatic shock are observed, namely, sharp diminution in reflex activity, reduced pain sensitivity, and not infrequently phasic states, for example, paradoxical and inhibitory reactions. Hemodynamic disorders develop inhibition of the vaso-motor and respiratory centres, dilatation of the peripheral vessels and a resultant drop in blood pressure, as well as a diminished volume of circulating blood and slower rate of the blood flow. Shallow, accelerated respiration and depression of the oxidative processes are observed.

The diminished metabolism is accompanied by an accumulation of incompletely oxidised metabolites which are toxic and in their turn depress the function of the central nervous system. A certain part in the mechanism of shock is also played by *intoxication* with some biologically active substances, namely, histamine, acetylcholine and adenine-nucleotides which, absorbed into the blood from crushed tissues, are conducive to a drop in blood pressure. The result is a vicious circle which aggravates the disorders of the vitally important functions (Fig. 3).

The mechanism of traumatic shock and subsequent restoration of the functions impaired by it also includes some hormones (of the

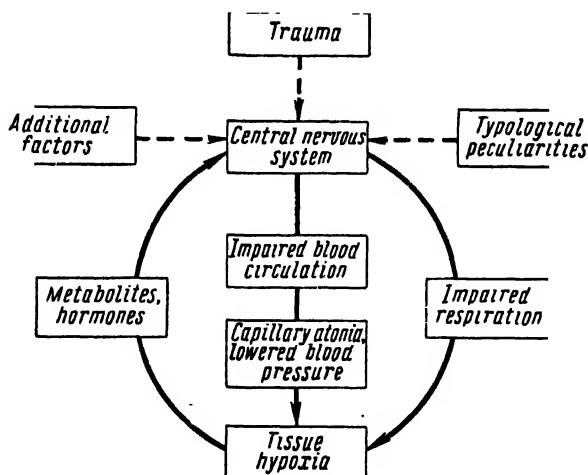


Fig. 3. Diagram showing onset of traumatic shock. The break in the arrow on top denotes a possible neuroreflex effect of the trauma on the central nervous system. The dotted arrows point at the conditions which play a part in the reaction of the nervous system to the trauma.

hypophysis and adrenals) which exert an influence on the function of the nervous system and other vitally important organs.

Administration of products of tissue proteolysis into the blood of a healthy animal produces a state which is similar to but not identical with shock. The development of shock is fostered by a number of additional factors, especially the character of the trauma (for example, injury to nerve trunks or vast crushing of tissue), blood loss, overstrain, starvation, overheating, overcooling, etc.

Kinetosis (Motion Sickness)

Kinetosis is a complex of pathologic processes emerging as a result of slight and continuously repeated concussions and accelerations which cause irregular movements and changes in the position of the body. The pathogenic effect of the concussions is observed when travelling by a ship (seasickness) or airplane (airsickness), and less frequently when riding in trains, automobiles, or rocking in swings. In kinetosis the disorders are manifested in disturbed functioning of the nervous system, especially in stimulation of the vestibular apparatus, which is transmitted to the centres of the vagi and the oculomotor nerves. The interoceptors of the internal organs, especially the stomach, are stimulated at the same time. This gives rise to general weakness, disturbances in neuromuscular coordinations, dizziness, nausea, vomiting, excessive sweating, slow heart action and drop in blood pressure. Seasickness usually does not affect children (because of the low excitability of their vestibular apparatus) or deaf-mutes. The significance of the stimulation of the vagi is confirmed by the fact that seasickness most frequently occurs in persons with an easily excitable vegetative nervous system and that the morbid manifestations of seasickness are suppressed by the action of atropine.

Acceleration is the time rate of change in velocity. The effect of accelerations depends on their magnitude, duration, direction and rate of increase, as well as on the functional state (endurance) of the organism.

The magnitude of acceleration is expressed in units represented by the symbol g . One unit equals 9.81 m/sec^2 , which corresponds to the acceleration of a freely falling body. The following accelerations are distinguished: *linear* (in changes in velocity of rectilinear motion), *centripetal* or *radial* (in curvilinear motion), and *angular* (in changes in angular velocity). The first two exert pressure on the body, while angular acceleration causes predominantly dizziness. An acceleration may be positive (craniocaudal), negative (caudocranial), or transverse, i.e., acting in an anteroposterior direction. Uniform linear positive acceleration is well tolerated by man even at high velocities.

Acceleration of 2-3 g lasting several seconds does not produce an

appreciable effect. Acceleration of 5-6 g for 3 seconds and longer causes respiratory difficulties, quickening of the pulse, a drop in blood pressure in the upper part of the body and a darkening of the field of vision; some cases may involve convulsive phenomena and unconsciousness. If the duration of linear acceleration is reduced to 1 second, the organism can tolerate even 10 g.

Negative acceleration affects the organism more intensely. Even at 1-2 g it may produce considerable congestion in the head, a rise in blood pressure, and disturbances in vision and in the functions of the higher divisions of the nervous system, which may persist for a long time after the flight. Great accelerations may give rise to cerebral hemorrhages and development of pulmonary edema. Transverse acceleration (even 6-8 g) is tolerated best. Brief radial acceleration is tolerated quite satisfactorily.

Prolonged acceleration (more than 5-6 g) causes fundamental functional disturbances.

The resistance of the organism to accelerations is diminished by fatigue, lack of sleep, consumption of alcoholic beverages, and weakened active inhibition in the cerebral cortex. Training increases the organism's tolerance of accelerations several fold. The main factors in the mechanism of the morbid effect of accelerations are changes occurring as a result of stimulation of the nervous system and disturbances in blood circulation. The accelerations give rise to disturbances in neuromuscular coordinations and vegetative functions, especially disturbances in redistribution of the blood with changes in blood pressure, disorders of vision due to stimulation of the nuclei of optic nerves and diminished blood supply to the retina. They also bring about compensatory phenomena: reflex vascular reactions from the region of the carotid sinus and the aortic arch, as well as reactions of the striated muscles, manifested in tension of the abdominal and leg muscles, which prevent the flow of blood to the vessels of the lower half of the body when the accelerations act in a craniocaudal direction.

It is very important to study the mechanisms of the effects of accelerations in order to increase the organism's endurance and to elaborate measures of prevention.

Acoustic Waves

Sound may prove pathogenic and cause an acoustic trauma only when excessively intense and acting for a very long period of time. The higher the amplitude of vibrations of the resonating body, the greater the mechanical pressure of the sound waves and the stronger the sensation of the sound. Even a single, unexpected, very intense sound (for example, a locomotive whistle or a shot) may suddenly produce a pain sensation and cause damage to the eardrum and the internal ear. In mice a strong and prolonged sound,

for example, a sharp electric bell, gives rise to disturbances in the activity of the central nervous system.

Especially harmful to the organism are *intense noises*, i.e., disorderly combinations of sounds of different pitch and frequency. The morbid effect of noises is the cause of neuropsychic disorders manifested in extreme fatigue, increased irritability, insomnia, headaches and diminished working capacity. Intense noises give rise to respiratory changes, increased intracranial pressure, impaired hearing and, in severer cases, auditory hallucinations and deafness. Repeated tiring effects of intense noises cause degenerative changes in the peripheral neuron of the auditory analyser and, in extreme cases, atrophy of the organ of Corti. That is why it is very important to control noise in the street, houses, transport and industry.

Considerable attention has also been attracted to the *morbid effect of ultrasound*, i.e., sound waves above the audible limit of 16,000-20,000 cycles per second. The ultrasonic waves are absorbed by the air, owing to which they lose a good deal of their energy.

Intense ultrasonic waves cause considerable changes in pressure in small spaces. They produce thermal and chemical effects manifested in accumulation of heat in the tissues, changes in the formed elements of the blood, an increase in blood viscosity and in the content of sugar and cholesterol in the blood. In severe cases metabolism appreciably diminishes, the enzymes become inactivated, the function and structure of cellular formalions are disturbed, and proteins coagulate.

Thermal Factors

Effects of Heat

Burn. Heat injures some portion of the body surface as a result of contact of the tissue with a heated body or the action of heat from a distance, for example, rays of the sun or radiations from heated objects. The degree and character of the developing disturbances depend on the method, duration and site of application of heat, as well as on the sensitivity of the affected part to it. Beginning at about 50°C the thermal factor (hot water, heated metal or glass, fire, etc.) causes injury to the surface of the body (burn). Contact of hot objects produces a greater effect than that of hot air of the same temperature. Long repeated action of relatively high temperatures on the oral mucosa, for example, frequent consumption of hot food, reduces the sensitivity of the mucosa to heat and results in a thickening of its epithelial layer.

Several degrees of burns are distinguished.

First degree burn is characterised by hyperemia and mild inflammation of the injured part. *Second degree burn* involves inflammation of an exudative character with formation of vesicles on the skin or mucous membrane. *Third degree burn* is accompanied by

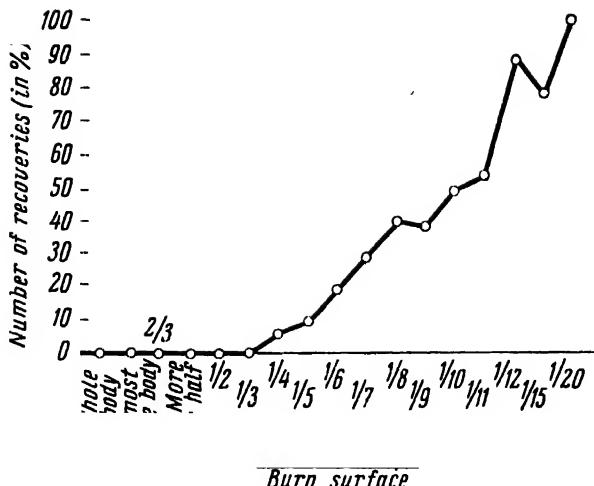


Fig. 4. Mortality and the number of recoveries depending on the extent of the burned body surface (Janelidze).

partial necrosis of tissue, its deciduation and formation of ulcers. *Fourth degree burn* results in charring of the tissue.

It is not always possible to draw a clear line between the degrees of burns. For example, simple hyperemia sometimes imperceptibly develops into an inflammatory and then into an exudative process.

The general changes in the organism resulting from burns depend on the degree of the burn and the size of the burned area.

The greater the burned surface of the body (Fig. 4) and the longer the action of the thermal stimulus, the more serious the consequence. The functional state of the organism is also very important.

Observations and experiments have shown that the organism perishes if one-third of the body surface is damaged (in second degree burns) and even less (in third and fourth degree burns). In cases of vast and severe burns death occurs instantaneously or within 2-3 days. Early death is due to the *burn shock*, i.e., sharp reflex depression and subsequent paralysis of the circulatory and respiratory centres. The general picture of a burn shows, in addition to disturbances in nervous activity, first a rise and then a drop in blood pressure, respiratory disorders, hemoconcentration due to the passage of plasma through the capillaries into the injured tissue, a relative increase in the erythrocyte count (sometimes 30-40 per cent), phenomena of hemolysis, accumulation of toxic products of tissue decomposition, a rise in body temperature, and development of infection which has gained entrance into the wound. In protracted cases the

kidneys are affected, urination is disturbed and anuria* sometimes develops.

General phenomena occurring in burns are due to accumulation in the organism of toxic products of tissue decomposition, which cause intoxication of the organism. In such cases the blood has a certain toxic effect, and phenomena characteristic of burns may be observed in experiment, not only in the animal which has sustained a burn, but also in another animal by artificially connecting their blood vessels.

However, in burns intoxication does not develop at once because absorption from the injured tissues into the blood stream is not appreciably disturbed; according to some sources, it is somewhat diminished (I. R. Petrov). That is why the mechanism of development of general phenomena in burns must be ascribed primarily to reflex influences from the burned parts of the body. The reflex influences are followed by absorption of the products of tissue decomposition, especially when the burned tissues become infected.

General action of heat on the organism may cause *overheating* (*hyperthermia*).

The more intense the heat loss, the more easily the organism tolerates rises in the surrounding temperature. Under conditions facilitating heat loss man can tolerate an external temperature of 50-60°C. Contrariwise, under conditions rendering heat loss difficult overheating occurs sooner, for example, in humid air or when physical work is done in warm clothes. In such cases overheating may take place at 30-35°C. Overheating is accompanied at first by excitation and then depression of the functions of the nervous system, general weakness, respiratory and circulatory disorders (accelerated respiration and tachycardia). Severe cases end in paralysis of the heart and death (for greater detail on hyperthermia and hypothermia see chapter on disturbances in thermoregulation).

Effects of Cold

Frostbite. The action of cold on some portion of the body surface causes a number of vascular and tissue disturbances which characterise frostbite. It gives rise to vascular spasm, a sensation of cold and pain. The skin turns pale and its temperature drops. Then the vessels dilate owing to paresis or paralysis of vasomotor nerves following the excitation. Sometimes the vessels dilate at once, as a reaction to intense cold. In such cases the vessels lose their tone and fill with blood, become more permeable, the blood somewhat concentrates and stasis develops. The fluid part of the blood passes from the capillaries into the injured tissue and produces edema.

* Anuria—arrest of urinary output.

Frostbite is divided into three stages, according to the intensity of the tissue changes—from erythema and a mild superficial inflammation to formation of vesicles and total destruction of the tissues. A drop in the temperature of the tissues to about -2°C leads to considerable diminution in oxygen consumption and then to necrosis and detachment of the affected part. The parts most commonly affected by frostbite are the tip of the nose, the ears, fingers, toes, hands and feet.

Some data indicate primary oxygen deficiency in the tissues regardless of circulatory disorders (I. A. Piontkovsky).

Frostbite is due, not only to the effects of cold and the duration of exposure to the cold, but also to concomitant atmospheric phenomena, for example, humidity and wind. Cold humid air, especially with a wind, considerably hastens the onset of frostbite. The state of the organism—decreased metabolism, fatigue, circulatory disturbances—is also very important. For example, a disturbance in circulation caused by tight clothing or footwear, limited mobility and exhaustion of the organism are conducive to development of frostbite. Under certain conditions, especially high humidity, frostbite may develop even at $7\text{--}8^{\circ}\text{C}$.

After one severe or several mild frostbites a chronic inflammation of the skin develops and is accompanied by appearance of purple macules and itching.

The *general effect of cold* on the organism is overcooling (hypothermia). Hypothermia develops as a result of a drop in external temperature and inability of the organism to regulate its own temperature. Increased heat loss and diminished heat production lower the organism's resistance to cold. Poor nutrition, inadequate clothing and decreased metabolism are conducive to development of hypothermia.

Hypothermia also results from prolonged exposure to a temperature even only $10\text{--}15^{\circ}\text{C}$ below normal body temperature. Prolonged hypothermia successively induces somnolence, diminished respiration, a certain fall in blood pressure, unconsciousness and, lastly, paralysis of the nervous centres. Hypothermia and even death may occur at -0.5°C .

Sudden cooling of separate parts of the body surface or of the whole body underlies *various chills*. Under certain conditions cooling reflexly produces first a spasm and then dilation of the vessels and a change in blood circulation. This lowers the resistance of the organism and facilitates the action of microbes. The vessels dilate in the cooled part of the body, and also in other, distal parts. For example, cooling of the lower limbs or the abdomen causes at first, a spasm of the vessels at the site of cooling and then a sudden dilation of the vessels in the mucosa of the air passages in the lungs with the result that their resistance to pathogenic microbes diminishes. Such disturbances resulting from cooling often lead to

appearance or aggravation of inflammatory processes (bronchitis, endocarditis, nephritis, arthritis, etc.). For example, sudden immersion of the dog's paws in water at 4°C may cause development of nephritis, a disease characterised by inflammation of the glomeruli. In experiments on rabbits involving their artificial sensitisation to protein it was discovered that rapid cooling of joints facilitated the appearance of an inflammatory process in them.

Effects of Radiant Energy

The organism may be exposed to the action of various forms of radiant energy. These include different parts of the spectrum of electromagnetic waves and fluxes of high-speed particles of matter (electrons, protons, etc.).

In the solar spectrum the eye is capable of perceiving only part of the waves, namely, those 0.4-0.75 μ long (visible light). The solar spectrum also has invisible rays: infrared rays with a wavelength of 0.75 and up to several dozen microns, and ultraviolet rays with a wavelength of 0.4-0.1 μ .

The *red and infrared rays* of the solar spectrum possess only a thermal effect. The action of the thermal rays is from the very outset accompanied by hyperemia of the skin. Owing to this the skin becomes, as it were, an ultrafilter barely permeable to ultraviolet rays. The inflammatory effect of infrared rays is connected with their thermal effect.

Ultraviolet rays possess mainly a chemical and a very mild ionising effect which depends on the intensity of irradiation, while the latter in its turn depends on the wave-length and duration of exposure to these rays, the angle of their incidence, the thickness of the atmospheric layer which in some measure or other blocks the rays, the degree of permeability of the tissues and the general reactivity of the organism. Ultraviolet rays (especially their short-wave part) produce erythema (*erythema solare*) accompanied by pain and not infrequently by subsequent development of an exudative inflammation. In photosensitive subjects these rays sometimes produce eczema (*eczema solare*). All these phenomena are particularly strongly pronounced at high altitudes, for example, in the mountains where the atmospheric layer is thinner.

The effect of ultraviolet rays on the body surface is manifested within a few (6-12) hours in a drop in blood pressure and change in metabolism, especially that of protein. An important part in the appearance of these phenomena is played by disturbances in vaso-motor regulation. Sometimes the reaction is from the very outset accompanied by proliferation of cells, which results in a thickening of the epidermis. Deposition of a pigment (melanin) in the skin is observed, the pigment most probably forming from phenylalanine

or tyrosine owing to the intensified activity of corresponding enzymes. A possibility of neoplastic development has been established in experiments involving prolonged exposure to ultraviolet rays.

In certain doses ultraviolet rays produce a favourable general effect on the organism partly because they kill bacteria and protozoa and cause destruction of toxins (for example, the diphtheria toxin).

The effect of ultraviolet rays sharply increases in the presence of photosensitising substances. These include fluorescent substances, like eosin, fluorescein, erythrosin and chlorophyll. Hematoporphyrin (one of the products of hemoglobin decomposition) also possesses a photosensitising property.

Photosensitisation is the combination of photosensitisers with molecular oxygen, forming peroxides and subsequently giving off atomic oxygen to the tissues. This results in intensification of the processes of oxidative decomposition in the tissues, decomposition of proteins in particular.

Intensive ultraviolet irradiation of a large body surface causes general circulatory disturbances, even shock and death.

Particularly important for the organism is the effect of *ionising radiation* which arises during radioactive decay and is capable, on absorption in any medium, of causing ionisation of neutral molecules and atoms.

There are various forms of ionising radiation which differ in physical properties and biological effect. The main ionising rays are: alpha (α), beta (β) and gamma (γ) rays. Moreover, during rapid decay of atomic nuclei a flux of neutrons (neutral particles) and protons (positive particles) is formed.

Alpha-particles, or nuclei of helium, and beta-particles, or electrons, released during transmutation of neutrons into protons, are characterised by relatively low penetrating power. They affect deeply located tissues only when radioactive substances penetrate inside the organism. Gamma-rays are a flux of photons emitted by the nucleus during transition from an excited to an unexcited state. They are characterised by weak ionising but considerable penetrating power. External irradiation with penetrating forms of radiant energy— γ -rays, hard roentgen rays and *neutrons*—usually affects the entire organism. Alpha-and beta-rays and *slow neutrons* possessing low penetrating power affect mainly the parts of the body surface which are exposed to them.

In an organism irradiated with large doses of roentgen rays or frequently exposed to them, the general disturbances comprising physiological, biological and immunological changes precede the local injury. Ionising rays are particularly damaging to young growing cells in the state of mitosis. Embryonal-type cells, for example, elements of myeloid tissue, the gonads and lymph nodes, are therefore the most sensitive to these rays. The harmful effect of

these rays on the eyes is manifested in atrophy of the ganglion cells of the retina. The action of roentgen rays on the skin may set off inflammatory phenomena, their intensity depending on the intensity and duration of the action of the radiant energy source. The effect is observed after a certain latent period (1-2 weeks).

Prolonged exposure of the skin to roentgen and γ -rays may cause formation of chronic ulcers and even a cancerous process (as happens to roentgenologists who fail to take necessary precautions).

Small doses of roentgen rays are used for therapeutic purposes during the stage of excessive growth, and multiplication of cells in skin and other diseases. The general pathogenic effect of roentgen and γ -rays is manifested in metabolic disturbances. Dystrophic changes in the tissues take place, and the enzyme systems, especially those taking part in the synthesis of nucleoproteins, are disturbed. Large doses of rays (more than 300 r for roentgen rays) sharply increase these disturbances and cause intoxication of the entire organism. A dose of 600 r is considered almost absolutely lethal for man.

Radiation Sickness

A general illness caused by the action of ionising radiation is known as the *radiation sickness*. It may be the result of *external* action of radiation, for example, roentgen irradiation, work with generators capable of producing ionising radiation, explosion of an atomic bomb or *internal* penetration of radioactive substances, such as radium, mesothorium and radioactive isotopes.

The severity of the radiation sickness depends on a number of factors, namely, the intensity or dose of radiation (capacity of the source, duration of the exposure, etc.), form of radiation (composition of rays acting on the organism), exposure of the entire organism or a limited part of it (in the latter case the pathogenic dose must be larger), individual sensitivity to ionising radiation, which varies within appreciable limits, and, lastly, the action of the source of radiation from without or from within (external or internal irradiation); in the latter case it is usually more limited.

Acute and chronic forms of the radiation sickness are distinguished. Acute radiation sickness results from exposure to large doses of radiation. *Four* (not strictly defined) *periods* are distinguished in the development of acute radiation sickness. The first, initial period (1-2 days) begins a few hours after irradiation. It is characterised by overexcitation of the nervous system, a state, as it were, of general intoxication, intense headache and dizziness, quickening of the pulse, dyspnea, and not infrequently nausea and vomiting, elevated temperature, and decrease in the lymphocytes of the blood (lymphopenia). Then the morbid phenomena disappear and the second, latent, period lasting up to 1-2 weeks begins. The

initial pathologic phenomena are absent. Only lymphopenia and thrombocytopenia may develop and the reticulocytes may diminish.

In severe cases of the radiation sickness the second period may not take place at all and the first period may be directly followed by the third period during which the main disturbances are most strongly pronounced. The temperature rises, headaches, nausea and vomiting develop, and signs of circulatory disturbances in the brain appear. The mucous membranes are inflamed and develop ulcerations, the function of the gastrointestinal tract is disturbed, metabolism is appreciably disordered and protein decomposition is observed. Hematopoiesis is depressed, the leukocyte count sharply decreases (leukopenia), thrombocytopenia is engendered, agranulocytosis sometimes occurs, progressive anemia develops and signs of bone marrow cachexia appear. The permeability of the vessels is impaired and hemorrhages into internal organs take place. The sputum, urine, feces and vomit are stained with blood.

In radiation sickness affections of the central nervous system are observed very early and include disturbances in the intensity, mobility and balance of the excitatory and inhibitory processes, depression of reflex activity, neurovascular and neurotrophic disorders (especially of the skin) in the form of alopecia and ulcerations, and dysfunction of the hypophysis, adrenals and gonads.

In cases of a favourable course of the disease the fourth period—gradual restoration of the functions impaired by the sickness—begins within 2-3 weeks. Although irritability and fatigability persist, the nervous system shows some improvement, the temperature drops and hematopoiesis is restored. Sometimes the disease takes a protracted course and becomes chronic.

Chronic radiation sickness may also result from prolonged and repeated exposure to small doses of ionising radiation. It is characterised by disorders of the functions of the nervous system and, especially, disturbances in hematopoiesis. The first to be observed is a decrease in leukocytes and thrombocytes; after a temporary compensation of these phenomena deeper changes in the blood—leukopenia and appearance of megalocytes, megaloblasts and myelocytes—occur. Eventually ionising radiations may have a cancerogenic effect and cause disturbances in the chromosomes of the germ cells.

The *mechanism of action* of ionising radiation on the organism has not as yet been completely uncovered. Most investigators attach the main importance to ionisation of water molecules in the organism, when so-called free H, OH and HO₂ radicals are the first to form. Separation of an electron from a molecule of water produces an H₂O⁺ ion and at some distance an ejected electron which joins another molecule and creates an H₂O⁻ ion. Both these ions dissociate, free HO and H radicals forming as a result. The latter either directly or through a chain of secondary transmutations

(formation of HO_2 , H_2O_2) lead to disturbances predominantly in the enzyme systems taking part in nuclein metabolism. The synthesis of nucleoproteins in the tissues is disturbed, the nuclei are destroyed and the cells die.

The ability of ionising radiation to suppress the division of nuclei has been used in the treatment of tumours and other neoplasms on the skin and mucous membranes by small doses of radiant energy.

According to P. D. Gorizontov, the pathogenesis of radiation affections is very complex; in addition to the direct influence on the tissue, there are also early disturbances in nervous and endocrine regulations, as well as the humoral disorders in the form of toxemia, i.e., accumulation of toxic substances in the blood.

Latterly biology and medicine have come to use artificial radioactive substances, for example, radioactive isotopes of iodine, phosphorus, potassium, sodium, iron, manganese, etc. Because of their radiant property even the most negligible amounts of radioactive isotopes (so-called tracer atoms) can be easily detected in the organism by sensitive instruments (Geiger counter, etc.).

Experimenters and clinicians use radioactive isotopes to elucidate a number of most important questions, for example, localisation of biologically active substances and the ways of their transformation in the organism, nutrition, intermediate metabolism and secretion; they also use them to study the mechanism of a number of pathological processes, such as disturbances in the rate of the blood flow and in the functional state of the thyroid.

Effects of Electric Energy

The organism experiences the harmful influence of electric energy either through exposure to discharges of atmospheric electricity or through accidental contact with electric current.

The phenomena resulting from contact with electric current depend on a number of conditions, the most important of which are the properties of the current and the functional state of the organism. The properties of electric current are determined by the character of the current (direct or alternating), its tension and strength, direction and duration of its action. Direct current acts faster than alternating current, but the latter is more dangerous than the former at a relatively low tension and low frequency because tissue offer less resistance to alternating than to direct current. Alternating current of 100-150 V produces a strong effect and sometime proves fatal. Up to 500 V alternating current is more dangerous than direct current of the same voltage. Above 500 V direct current becomes more dangerous than alternating current. Alternating current with a frequency of 40-60 cps is the most dangerous to life. Increase in the frequency diminishes the harmful effects of the

current. High-frequency currents are not dangerous and are even used for therapeutic purposes (for example, d'Arsonval current).

The strength of a current is expressed in the ratio of the tension of the current to the resistance offered by the tissues. At the same tension the strength is the greater, the lower the resistance of the tissues. The harmful influence of current will be much greater when exerted on moist skin, whereas dry human skin offers greater resistance to electric current. An important part in the resistance to electric current is also played by the area of tissue surface contacting the electrodes.

Very significant is the *direction of the current* through particular organs. The animal which tolerates the passage of current through its head dies if one of the electrodes is applied to a forepaw and the other to the hindpaw, i.e., if the same current is directed through the heart. Electric current injuries, especially if the current is grounded often give rise to cardiac arrhythmia, ventricular fibrillation and then cardiac arrest in the diastole. The action of current is particularly dangerous in the beginning of diastole.

Lastly, the extent of the disturbances caused by electric current is also dependent on the *duration of its action*. It is well known that current even of high voltage and great strength is not fatal if it acts less than 0.1 second.

Sensitivity to electric current differs in different species of animals and even in individuals of the same species. The functional state of the organism, especially of its nervous system, plays an important part in this respect; the more excitable the nervous system, the more intense its reaction during the passage of current. Very strong electric current also acts directly on tissues.

The *general effects of electric current* on the organism include (depending on its strength) headache, nausea, not infrequently acceleration of the cardiac rhythm and respiration, a rise and subsequent slight drop in blood pressure, paralysis of nerves and muscles, edema and dropsy (Fig. 5).

By stimulating the nervous system the action of strong current (100 mA and stronger) at first causes a rise in blood pressure and dyspnea. These are followed by inhibition of the central nervous system, which is accompanied by a considerable drop in blood pressure, weakening and even temporary arrest of respiration, clouded consciousness and sometimes unconsciousness. Such a state may manifest itself as "sham death", but with timely aid it is often possible to restore the vital functions. Electric shock may cause convulsions, respiratory paralysis and complete cardiac arrest.

In addition to general phenomena, the *action of electric shock on the body surface* usually produces a *burn* which not infrequently is shaped like the conductor which made contact with the body. Wounds resembling those resulting from a gunshot are formed at the sites of entrance and exit of the current. In some cases necrosis

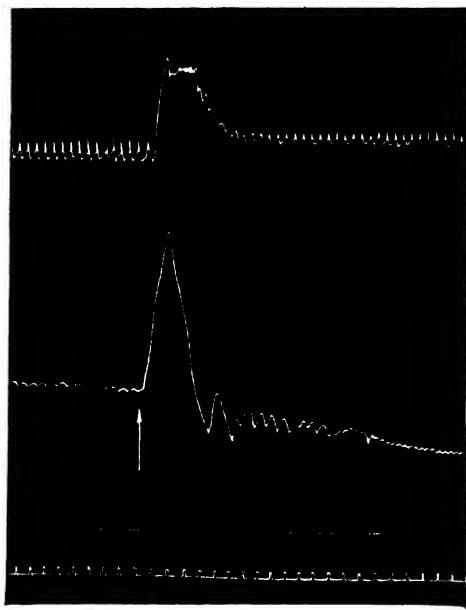


Fig. 5. Experiment on the rabbit subjected to an electric shock (75 V).
Upper curve—disturbed respiration; lower curve—drop in arterial pressure.

of the affected portions of the skin and underlying tissue is observed; it develops some time after the action of the electric current.

The *mechanism of the action of electric current* apparently has three aspects: electrolytic, electrothermal and electromechanical. Electrolysis may account for the biochemical and colloidal changes produced by electric current in the tissues. The electrothermal effect is conditioned by the conversion of electric energy into thermal energy with a resultant burn, while the electromechanical effect is expressed in the conversion of electric energy into mechanical energy which causes structural injuries, i.e., damage to the tissue.

An ultra-high-frequency alternating electric field (*short and ultra-short waves*—metre, decimetre and centimetre) also produces a biological effect. The latter is determined by the heat liberated as a result of absorption of part of the energy by the tissues, and by the peculiar stimulation possibly produced by the chemical effect unconnected with the effect of heat. The high-frequency field increases protein metabolism and phagocytosis and produces a bactericidal effect. Under experimental conditions high-tension decimetre and centimetre waves caused disorders of the function of the nervous system with subsequent circulatory disturbances and even the animals' death. In medicine low-tension ultra-short waves are used for therapeutic purposes in various inflammatory processes.

Effects of Altered Atmospheric Pressure

Changes in the organism are observed in cases of both lowered and elevated atmospheric pressure beginning at an altitude of 4,000 m.

Lowered atmospheric pressure is injurious to the organism because of lowered partial oxygen pressure in the inhaled air. At an altitude of 5,000 m arterial blood contains about 70 per cent of the normal amount of oxygen. A number of pathologic signs may be observed at this altitude, these signs increasing as the partial oxygen pressure drops. At an altitude of 6,000 m, when the blood contains 65 per cent of the normal amount of oxygen, the signs of disease are strongly pronounced.

The disease developing as a result of lowered atmospheric pressure affects persons climbing high mountains (mountain sickness) or pilots flying at high altitudes without oxygen masks (altitude sickness).

Lowered atmospheric pressure gives rise to various functional disorders: fatigue, dizziness, headaches, tinnitus, dyspnea, tachycardia, diminished conditioned reflex activity and metabolic disturbances (Fig. 6).

Prolonged staying at an altitude of 7,000-8,000 m usually results in unconsciousness and even death. All the aforementioned phenomena are conditioned by oxygen deficiency in the organism and are intensified by the increased oxygen requirements connected with muscular work (for example, mountain climbing) and increased rate of ascent. The state of the organism—its endurance, typological characteristics of the nervous system, rate of adjustment, etc.—is particularly important.

The action of rarefied air on the organism develops a number of adaptive phenomena—reflex acceleration of respiration and increase in pulmonary ventilation, acceleration of the blood flow, contraction of the spleen and stimulation of the hematopoietic apparatus,

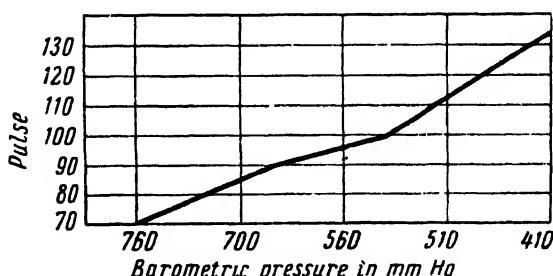


Fig. 6. Quickening of the pulse caused by lowered barometric pressure (V. V. Pashutin).

which is accompanied by increase in the erythrocytes of the blood and of its oxygen capacity.

Elevated atmospheric pressure also produces pathologic phenomena in the organism (for example, in deep-sea diving or caisson work). As a result of the increase in atmospheric pressure the partial pressure of oxygen and other gases forming part of the atmospheric air rises. Signs of the morbid effect of elevated atmospheric pressure may appear already after a few hours' stay under a pressure of 2-3 atmospheres, i.e., at a depth of 10-20 m under water. In such cases the pulse and respiration slow down, the blood pressure rises and the internal organs overfill with blood; severer cases are characterised by marked inhibition of the central nervous system, general convulsions and unconsciousness. In cases of rapid return from elevated to normal atmospheric pressure (which causes decompression) the gases formerly dissolved in the blood, mainly nitrogen, are liberated in the form of bubbles and often obstruct small vessels (caisson disease). At the same time pains in the muscles and joints develop, the skin itches, respiration and circulation are disturbed; severe cases are accompanied by paryses, convulsions and unconsciousness. Owing to resorption of the gases these phenomena often disappear.

CHEMICAL FACTORS

Chemical substances may produce various effects and often cause *poisoning*. Poisoning may result from substances gaining entrance into the organism from without—*exogenous poisons*—and those formed within the organism—*endogenous poisons*. Poisoning with endogenous substances—metabolites and products of tissue decomposition—is called *auto intoxication* (self-poisoning). Auto intoxication may develop as a result of dysfunction of excretory organs, abnormal processes of absorption from the intestines, and metabolic disorders, for example, in infectious diseases, diabetes mellitus, liver pathology, etc.

The poisonous effects of a chemical substance depend on the dose of the substance, method of its administration, and resistance of the organism. Depending on the dose, the same chemical substance may produce therapeutic or toxic effects, or even prove lethal. Age and individual characteristics of the organism, the functional state of its regulatory systems in particular, very largely determine the severity of the poisoning.

Substances administered through the gastrointestinal tract produce a lesser effect than when injected subcutaneously or into the blood because from the intestines they pass into the liver where they are completely or partly detoxicated.

Toxic substances comprise *inorganic and organic poisons*. The inorganic poisons include acids, alkalis, salts of lead, mercury, ar-

senic and copper, chlorine, iodine and bromine; the organic poisons include alcohol, ether, chloroform, phenol and cyanide compounds, etc. Among the organic poisons there are substances of *vegetable* origin (alkaloids, glucosides) and *animal* origin (snake venom, cantharidin, animal alkaloids, ptomaines and products of putrefaction).

The toxic effects of poisons are manifested in disturbances of various functions, on which basis the following distinctions are usually made: chemical substances producing a general toxic effect (cyanide compounds, narcotics), affecting the blood (potassium chlorate, pyrogallol, carbon monoxide), affecting the liver (tolylendiamine, phlorhizin, carbon tetrachloride), asphyxiating (chlorine, phosgene), affecting the nervous system (strychnine, arsenic), etc. But once inside the organism all of them affect the nervous system which is particularly sensitive to many poisons. On entering the tissues a poison, in addition to affecting the enzyme systems, may stimulate the receptors of various parts of the organism, especially those of the carotid sinus and aortic areas.

Repeated administration of chemical substances, especially poisons, not infrequently results in *habituation* which may be explained by gradually diminishing permeability of the surface of the skin and mucous membranes (for example, as regards arsenic), faster destruction of the poison (as in the case of alcohol or morphine) or elaboration of defense physiologic reactions producing antidotes (as against abrin or ricin) and faster and more intense excretion of poisons by the excretory apparatus (for instance, atropine) or reduced tissue sensitivity to the poisons. In other cases of repeated poisoning an increased sensitivity to the poisons may be observed, as is the case in allergic states. However, increased sensitivity, for example, to strychnine, digitalis, mercury and lead, in cases of their repeated administration may also be due to accumulation of poison in the organism, especially when the poison is excreted slowly because of disturbances in the excretory apparatus and barrier functions of the organism.

NUTRITIONAL DISORDERS AS A PATHOGENIC FACTOR

Underfeeding, malnutrition, overseeding, vitamin deficiency, lack or excess of salts and an altered composition of the water are causes of, or, more frequently, are conducive to appearance and development of disease.

BIOLOGICAL FACTORS (living pathogenes)

Concept of Infection. Infection implies implantation of pathogenic microbes in the organism and their interaction with the latter under certain conditions of the external environment. The reaction

of the host to the effect of the pathogenic microbes underlies the infectious process.

The infectious process is determined by the infective agent (micro-organism), the host (macroorganism in which the infective agent carries on its vital activities) and the external environment which influences the properties of both the host and the infective agent.

The causative agents of the infectious process are pathogenic microbes and filtrable viruses. The latter produce a number of diseases (measles, rubella, influenza, poliomyelitis, smallpox, etc.) and are apparently capable of penetrating even through intact skin and mucous membranes. Not all microbes cause infectious diseases. For example, the microorganisms living on the skin and mucous membranes (so-called saprophytes) are usually harmless.

Pathogenicity (the capacity to produce disease) is the main property of the causative agents of infectious diseases. Some nonpathogenic microbes may, under certain conditions, acquire this property. For example, in cases of general exhaustion of the host saprophytes sometimes become pathogenic. On the other hand, man may be a carrier of a pathogenic microbe without contracting the disease. For example, pathogenic diphtheria bacilli or meningococci may be found in some people, although these people do not contract diphtheria or meningitis. They are so-called carriers. This is accounted for by the properties of the pathogenic microbe and the resistance of the host.

To produce an infectious disease the microbe must be *virulent*, i.e., must be able to produce a toxic effect. The virulence of a microbe also depends on the properties of both the microbe and the host. Microbes become more virulent when passing through a susceptible animal organism. For instance, streptococci grow much more virulent by repeated passage through the organism of the rabbit.

Microbes also become more virulent by producing aggressins and antipeptolytic enzymes, which suppress the immune properties of the host, and the spreading factor which increases the permeability of tissues. The latter is the enzyme known as hyaluronidase which causes the breakdown of hyaluronic acid, a constituent of connective tissue.

In other cases the passage of microbes through a nonsusceptible organism reduces their virulence.

Cultivation in artificial media (with addition of immune serums) also reduces their virulence.

The changes in the properties of microbes under the influence of environmental factors leading to their attenuation may be used for practical purposes, for example, in preparation of attenuated vaccines.

Infective agents gain entrance into the host from the external environment.

Portals of Entry. These are the gates through which microbes gain entrance into the host with air, foodstuffs and water, by contact with a patient or through bites of insects. The portals of entry are the respiratory tract, gastrointestinal tract, injured skin, mucous membranes, tonsils, excretory gland ducts, etc. They play an important part in the development of infectious diseases. For example, the *Vibrio comma*, causative agent of cholera, enters the organism through the mouth but cannot penetrate through the skin; gonococci act only through the mucosa of the urogenital tract or the eyes. Even for the microbes which have several routes of penetration the portal of entry plays an important part in the onset and development of disease. For example, anthrax bacilli are less virulent when entering through the skin than when penetrating through the lungs or intestines.

Portals of entry are not only the point of penetration, spread and multiplication of microbes, but also a vast reflexogenic zone. On coming in contact with the receptor apparatus of the affected tissue the infective agent or toxin is capable of evoking reflex reactions. The participation of the nervous system in the mechanism of the infectious process is also evident from the fact that infectious diseases are usually marked by diminution and even disappearance of conditioned reflexes, development of protective inhibition and even phasic phenomena, and clinically—apathy, somnolence and sometimes delirium. Experimentally it is sometimes possible, by numerous nonspecific influences (for example, trauma) exerted on the nervous system, to hasten the infection of an animal and the development of an infectious process in it.

Spread of Infection. While affecting the organism as a whole, the infective agents also produce characteristic pathologic changes in various organs, for example, in cases of gonorrhea, pneumonia or typhoid fever.

From the infected focus microbes may penetrate into other organs and tissues where they establish secondary foci. The transfer of pyogenic cocci accompanied by development of purulent processes (*pyemia*) in different parts of the body may be mentioned as an example. Infective agents may invade the blood (*bacteremia*) and, by spreading throughout the organism, simultaneously affect many organs (*septic phenomena*).

The harmful effects of pathogenic microbes consist in their *toxicogenicity*. Some bacteria poison the organism by elaborating toxic substances (*exotoxins*) which easily diffuse from the bacterial bodies, are absorbed and invade the entire organism (so-called bacterial intoxication), for example in tetanus or diphtheria. In other cases there is a bacterial infection proper, causing the organism to react to the effect of the bacteria themselves (for instance,

in anthrax). However, it is not always possible to draw a clear line between the two forms of toxigenicity.

Lastly, toxins may be liberated from bacterial bodies during destruction of bacteria—so-called *endotoxins* (for example, the endotoxins of typhoid fever or cholera).

Exo- and endotoxins are specific products of the vital activities of microbes.

Products of decomposition of microbial bodies, for example, bacterioproteins, enzymes, products of cellular metabolism and decomposition of the tissues of the host subjected to the poisonous effects of the infectious elements (for instance, ptomaines) must be regarded as nonspecific substances which poison the organism during the infectious process. All the aforementioned substances, especially those of microbial origin, cause intoxication of the organism with various consequences.

There are different ways of elimination of microbes from the organism. Microbes are most frequently eliminated through the intestines (mainly in intestinal infections). The microbes which have gained entrance into the blood are often eliminated in the urine (for example, in typhoid fever), in the milk (in general septic diseases), and in the saliva and phlegm (in respiratory diseases).

Infectious diseases may also be produced by filtrable viruses. Viruses multiply in the tissues and form inclusions, for instance, Negri bodies in the cells of the hippocampus in rabies. Measles, rubella, poliomyelitis, influenza, smallpox and a number of other diseases are also of viral origin.

Parasites as Pathogens. Parasitic diseases must also be regarded as diseases caused by biological factors. These diseases are caused by both animal (protozoa, worms, arthropods) and vegetable parasites (fungi). Parasitic diseases result from infestation of the organism with parasites through the digestive tract with food (for example, *Trichinella*, *Echinococcus*) or through vectors (for instance, the malarial plasmodium is transmitted through mosquito bites).

Parasitic protozoa cause protozoan diseases, for example, malaria and amebic dysentery. Parasitic worms—helminths—produce diseases referred to as helminthiases. Helminthiases are caused by flat worms (broad tapeworm, echinococcus, etc.) and round worms (ascaris, pinworm, etc.). The parasitic arthropods include one of the mites—the causative agent of scabies, as well as lice, crab lice, fleas, etc., which are vectors of certain infective agents.

The sting of scorpions and bees also causes morbid phenomena, such as edema, and tissue necrosis; the effect of their venoms on the central nervous system is manifested in nausea, vomiting and intense dyspnea (to the point of paralysis of the respiratory centre). Compounds of the type of histamine, acetylcholine and enzymes are apparently the active principle of these venoms whose contact

with the plasma gives rise to active polypeptides, for example, bradykinene.

Fungi may cause skin diseases (ringworm, favus, blastomycosis, etc.) and diseases of the internal organs (actinomycosis).

MENTAL INFLUENCES AS A POSSIBLE PATHOGENIC FACTOR

Overstraining of higher nervous activity and a clash between the processes of excitation and inhibition in the cerebral cortex caused by difficult external conditions may lead to changes in the functional relations between the cortex and the subcortex. The resultant vegetative disturbances include dysfunctions of various organs, for example, the respiratory and cardiac dysfunctions, a rise in blood pressure, spasm of the coronary vessels and intensification of the motor function of the intestines.

The verbal stimulus may also be a pathogenic factor in man.

It is well known that by verbal suggestion it is possible to disturb the usual course of physiologic processes—slow down or accelerate cardiac activity, constrict and dilate vessels, alter gastric secretion, increase metabolism and even develop an inflammatory process.

A verbal stimulus may evoke various emotions (fear, fright) and even a state of psychic trauma which considerably affects somatic functions. Such diseases as diabetes, exophthalmic goitre, etc., may develop on this basis. Moreover, psychic trauma may hasten the manifestation or aggravate the course of a disease already in progress.

Careless use of words by a physician may sometimes produce psychic trauma in the patient and thereby provoke diseases—so-called *iatrogenic diseases* (from the Greek—*iatros*, physician, and *genesthai*, to be produced). Attentive and tactful treatment of a patient very favourably influences the patient and helps to restore the functions impaired by disease.

SOCIAL FACTORS IN THE OCCURRENCE AND CONTROL OF DISEASE

Unfavourable living and working conditions are conducive to disease. Economic crises and unemployment, chronic overstrain and physical exhaustion, undernourishment and mental depression are causes of premature wearing out of the organism and lowered resistance to disease.

In the past wars were responsible for an enormous increase in diseases, so-called wartime diseases—infectious, traumatic, psychogenic, etc.

As a result of the Great October Socialist Revolution the social conditions in the Soviet Union have radically changed. Exploitation

of man by man has been abolished, crises and unemployment are a thing of the past, and the standards of living and culture are continuously rising.

Unlike the former wars, during the Second World War the infectious disease incidence was low both at the battle and home fronts. Proper organisation of the medical services and medical care ensured the return of the majority (more than 70 per cent) of the sick and wounded to the ranks.

Soviet medicine is based on a system of planned and scientifically substantiated prophylactic and therapeutic measures. Morbidity and mortality have sharply decreased and life expectancy has considerably increased.

Chapter Four

SIGNIFICANCE OF THE ORGANISM'S GENERAL PROPERTIES AND OF ITS INTERACTION WITH THE ENVIRONMENT IN THE ORIGIN OF DISEASE

ROLE OF HEREDITY IN PATHOLOGY

Concept of Heredity. Heredity is the property of living organisms to develop, under certain conditions of existence, the traits and characteristics of their parents or more remote ancestors. It ensures the continuity of generations and is inseparably connected with reproduction.

According to Charles Darwin, the heredity of any species (breed or variety) is formed over a long period of time in the process of evolutionary development and interaction of the organism with the environment, and is characterised by great *stability* or conservatism. In the course of its historical development the organism has become adapted to the conditions of existence. The individuals of any biological species therefore require definite conditions for life and development and in a definite manner react to these conditions.

The hereditary nature of an organism is not invariable. Heredity is inseparably connected with variability.

Under altered conditions of existence the hereditary properties of an organism may develop in a different manner and under some conditions the changes may be deep enough to alter the very type of heredity.

Material Basis of Heredity. New facts have of late come to light concerning the biochemical and molecular basis of heredity. The most important substrate for the transmission of hereditary characters (genetic information) is a bundle of very long molecules of desoxyribonucleic acid (DNA) organised in the chromosomes. DNA plays the role of a specific organiser of protein synthesis in the cell, or of a "matrix" which through ribonucleic acid (RNA) determines the amino acid composition and arrangement of various amino acids in the protein molecule. The genetic code by means of which the genetic information is transmitted to the cytoplasm was deciphered but very recently. Changes in DNA may alter the molecular, structural, antigenic and enzymatic properties of protein. From the biochemical point of view the hereditary properties trans-

mitted through the nuclei of the ova and sperms are formed under the regulatory influence of DNA and depend on the arrangement of four nucleotides—purine and pyrimidine derivatives (adenine, guanine, thymine and cytosine)—in its molecule. Each DNA molecule consists of two polydeoxyribonucleotide chains spirally wound about a common axis. Heredity is associated with biological replication of DNA, i.e., reproduction of its own kind. Independently or in combination with protein, DNA produces a certain intermediate complex consisting of RNA and protein. This complex in its turn influences the synthesis of definite proteins by the ribosomes of the cytoplasm and conditions the specific surface configuration of the protein molecules and their enzymatic properties.

Hereditary failure of a protein of a specific structure to be synthesised, or a change in the structure of the protein enzyme may cause a block of some stage of the biosynthesis with resultant pathological changes.

Changes in the type of metabolism underlie the changes in the hereditary nature of an organism.

Changes in the basic biochemical structure and in the type of metabolism with possible resultant changes in heredity are observed in various organisms.

For example, by growing tubercle bacilli under definite conditions it is possible sharply to reduce their virulence, while preserving their ability to produce immunity. By becoming fixed in the successive generations this property plays an important role in the production of living BCG vaccines used to obtain immunity against tuberculosis. The antibiotic properties of microbes can also be strengthened by prolonged growing of microbes in a modified nutrient medium.

The role of nucleic acids in the transmission of hereditary characteristics was shown by other experiments. It was found possible to transmit to a nonpathogenic race of pneumococci, through heredity, the property of toxicity by means of desoxyribonucleic acid isolated from a killed culture of a pathogenic pneumococcus. Transformation is widespread among bacteria. Analogous phenomena were discovered in experiments with certain viruses in which the hereditary information is altered by means of nucleic acid isolated from cultures of other viruses.

Malignant neoplastic growth is apparently also based on a defect in the structure of DNA of the cell, which leads to transmission of its malignancy to filial cells.

Various observations of animals confirm the possibility of modifying the hereditary basis of the organism by altering the metabolism.

The following experiments were recently performed. Over a certain period of their development ducks of one breed were injected nucleic substances isolated from the blood of ducks of

another breed. The injections not only produced deep biochemical changes in the experimental birds but also modified a number of characteristics (beak, colouring) in their progeny, i.e., altered their heredity.

However, the altered properties of an organism are not always transmitted through heredity. They are reproduced in the progeny only if some of the changes in the *type of metabolism are fixed in the reproductive cells*.

The organism and its hereditary nature are formed only *in the process of its individual development* on the basis of its constant interaction with the external environment, i.e., the conditions of its existence, without which the organism is unthinkable.

This concept of heredity extends our ideas concerning effective methods of altering it.

By changing the conditions of existence and development (nutrition, biochemical regimen, temperature, radiation and other factors in their aggregate) it is possible to effect changes in the type of metabolism and in a number of cases to modify the hereditary predisposition. This method of modifying heredity has long been widely used in agriculture to produce new species of plants and animals by crossing, breeding and selection.

From the point of view of modern genetics heredity, which is the result of a most complicated process of development, cannot be reduced to invariability of a special hereditary substance. Deviations in heredity are inseparably connected with the organism's metabolism and the conditions of its existence. This viewpoint has found complete confirmation in the studies of the role played by desoxyribonucleic acids and their complexes with proteins in the development of hereditary characteristics. Changes in hereditary properties (mutations) occur under the influence of changes in the structure of DNA and the protein or enzyme formed with its participation. This is attested by the results of the investigations of hereditary variations under the influences of extraordinary agents, such as ionising radiation, ultraviolet rays and certain potent chemicals.

Diseases Conditioned by Heredity. Knowledge of heredity and its variability is necessary to uncover the causes of a number of diseases. Medical genetics, i.e., the theory of the hereditary basis of human diseases, has developed into an important division of pathology. It is not diseases as entities, that are usually inherited, but only the properties which predispose the organism to particular diseases or reduce its resistance and under certain conditions of the external environment make the onset of disease possible.

The conditions under which the hereditary possibility of disease is realised vary. In some cases, for example, in certain forms of obesity or gout, the underlying causes are irregular nutrition and an improper work regimen. Development of a congenital dislocation

of the femur requires a trauma. A predisposition to epilepsy is not infrequently realised as a result of a birth trauma or of infection. In other cases the hereditary predisposition to disease is scarcely dependent on changes in the environment, or the conditions under which the predisposition is realised are still unknown as, for example, in hemophilia which is characterised by impaired blood coagulation. Lastly, a hereditary predisposition to disease may be manifested under normal environmental conditions, as in deaf-mutism, colour blindness, hemolytic jaundice, and developmental defects (polydactyly, brachydactyly, talipes, etc.).

Investigations of pathologic heredity must aim at disclosing the interaction between the genotype and the external environment, and, as regards man, also the social environment. Transmission of pathologic characteristics through heredity is studied by analysis of numerical relationships existing between the healthy and sick members of one family or genus (established by questioning). Investigation of uniovular twins which may prove to be carriers of an identical hereditary predisposition, is also very helpful.

A predisposition to hereditary diseases may be transmitted as a *dominant characteristic*, i.e., directly from parents to offspring if at least one of the parents has the particular disease.

The diseases inherited as dominant characteristics include anomalies of the osseous system (brachydactyly, achondroplasia, congenital bone fragility), certain forms of retinitis pigmentosa, hereditary cerebellar ataxia, a number of metabolic anomalies (xanthomatosis, pentosuria, lipomatosis), a form of hemolytic anemia, etc.

Diseases may also be inherited as a *recessive characteristic*. The offspring of two apparently healthy individuals carrying suppressed (recessive) rudiments of a disease may develop the disease. Diseases often appear in such manner in collateral relatives, while the parents who have transmitted the particular disease are well and the sick relatives married to healthy people have healthy children. Diseases transmitted through heredity as recessive characteristics are most commonly observed in children born of closely related parents.

The diseases transmitted as recessive characteristics include albinism, microcephaly, congenital deaf-mutism, certain metabolic disorders, such as alkapturia, severe cystinuria, fructosuria, etc.

Pathologic hereditary characteristics may be sex-linked, in which case the development of the pathologic characteristic is due to the influence of one of the sex chromosomes. Some hereditary diseases, for example, nyctalopia, hemophilia and colour blindness, manifest themselves only in individuals of one sex, usually only males.

The diseases conditioned by heredity must be distinguished from pathologic phenomena arising as a result of influences exerted on the fetus during its intrauterine development, for instance, infection of the fetus with syphilis through the placenta, intoxication of the

fetus with alcohol, transplacental transmission of certain characteristics of the maternal blood, as inherited thrombocytopenic purpura, and intrauterine deformation of the fetus. The latter may be caused by changes in the egg membranes, diminution in amniotic fluid or pressure on the gravid uterus. These pathologic phenomena are called *congenital* and are diseases acquired in utero.

The following properties of an organism must thus be distinguished: 1) hereditary, i.e., transmitted through the parents' sex cells, 2) congenital, i.e., arising during intrauterine development, and 3) acquired in the course of life. The first ones are the most permanent.

As a whole hereditary nature forms under the influence of long-existing conditions of life, in continuous interaction of the organism with the external environment. This offers to medicine extensive opportunities, by altering the external environment, to prevent diseases in whose pathogenesis a certain part is played by hereditary factors.

The concept of hereditary predisposition to tuberculosis has proved erroneous since, according to available data, the tuberculosis of the mother causes no disturbances in the child that may lead to its reduced resistance precisely to tuberculous infection. If the child suffers from any disturbances, the latter are of a nonspecific character and arise under various unfavourable conditions of the external environment, which in equal measure harmfully affect the nutrition and metabolism of both mother and the fetus.

It is now possible by means of an appropriate general regimen to exert a favourable influence on the metabolism of patients affected with gout, diabetes and obesity in whose pathogenesis the hereditary factor also plays a certain role.

Disclosure of the essence of the biochemical, molecular disturbances underlying the diseases conditioned by heredity is a particularly important prerequisite for revealing the mechanisms of these diseases and for exerting purposeful influences on the affected organism.

Changes in the hereditary basis most commonly disturb or block a certain stage of metabolism.

Biochemical research has helped to gain a deeper insight into the pathogenesis of a hereditary disease called sickle-cell anemia; this condition is due to a disturbance in the structure of the hemoglobin molecule, with one of the nearly 300 amino acids supplanted by another. This atypical sickle-cell (S) hemoglobin characteristic of sickling erythrocytes differs from normal adult (A) hemoglobin in that the sixth place of the B chain, instead of the glutamic acid carrying a negative charge, is occupied by valine, a neutral amino acid, the molecules of reduced hemoglobin losing their charge and capacity for mutual repulsion and as a result acquiring an abnormal structure in a deoxygenated medium.

The pathogenesis of hereditary hemolytic jaundice is apparently based on the absence or diminished activity of glucuronidase, the enzyme that participates in combining bilirubin with glucuronic acid without which normal transformation of this pigment is impossible.

It was long believed that the principal role in the development of pernicious anemia was played by inherited embryonal megloblastic hematopoiesis. It was finally shown, however, that pernicious anemia is due to a deficiency of a special antianemia factor which regulates erythropoiesis. The antianemia factor is essentially vitamin B₁₂ which is ingested with food and is absorbed in the intestines with the aid of the intrinsic factor of albuminous nature produced by the stomach. This has clarified the role not only of the internal conditions, but also of the extrinsic factor in the origin of pernicious anemia, and the possibility of curing it by parenteral administration of vitamin B₁₂.

Hereditary galactosuria in infants results from suppression of the activity of galactotransferase, an enzyme helping in the assimilation of galactose by the liver. This disease can be prevented by a diet which contains no galactose.

Hereditary disturbances in tryptophan metabolism can be diminished by administration of large doses of vitamin B₆ which acts as a coenzyme in tryptophan metabolism.

Hereditary phenylketonuria is due to a blocking of the synthesis of tyrosine from phenylalanine with a resultant excessive accumulation of phenylalanine which is responsible for mental retardation in children. It has been possible to restore such children to normalcy by exclusion of phenylalanine from their food.

The foregoing examples show that the discovery of similar pathologic phenomena in parents and children and the inclusion of these phenomena in the group of hereditary diseases do not as yet constitute a disclosure of their essence, their etiology and pathogenesis. A concrete analysis of the causes of each disease and the conditions under which it arises is necessary; the patient's case history, including the deviations in his metabolism, on the molecular level if possible, and the character of his reactions to the factors in his surroundings, must be carefully examined. This makes possible a better insight into the essence of diseases considered to be hereditary and offers extensive prospects for their prevention and treatment.

This approach to the study of hereditary diseases renders the concept of their total incurability untenable.

The agencies capable of altering hereditarily conditioned morbidity include nutritional factors (for example, vitamins and hormones), the climate, working conditions, physical exercise, etc., which in the aggregate favourably affect the human organism. Special attention in preventing hereditary diseases must be devoted to protecting the organism from factors capable of producing

mutations, mainly ionising radiation which may lead to development of cancer. Surgical intervention helps to eliminate already formed hereditary defects such as talipes, congenital dislocation of the femur, harelip, polydactyly, etc.

In pathology, as in biology, the materialist understanding of the role of heredity resolutely opposes the erroneous concepts of invariability of the hereditary nature of diseases.

Underestimation of the role of the external environment and metabolism in the manifestation of hereditary properties, and denial of the possibility of controlling the hereditary predisposition to disease lead to the fallacious recognition of the insuperable stability and fatal role of the hereditary factor as a cause of disease.

The advocates of this viewpoint often erroneously conclude that the invariable hereditary factors play the decisive role in human pathology. The concepts of invariability of the genotype and genotypical inequality of people are used to divide people into biologically unequal groups, into "higher" and "lower" races. However, these views propounded by the advocates of so-called eugenics, racial hygiene and racial theory are unscientific in their very essence.

SIGNIFICANCE OF THE CONSTITUTION IN PATHOLOGY

Concept of Constitution

Constitution implies the aggregate of all sufficiently stable functional and morphological characteristics of an organism, which determine the specificity of its reactions to external agents and are formed on the basis of heredity and acquired properties in interaction with the external environment, primarily the social environment in the case of man.

Great importance was attached to constitutional properties even in antiquity. Hippocrates held that the constitution was determined by a mixture of body fluids (humours) and that disease resulted from their improper mixture. He distinguished good, bad, strong, weak, dry and moist constitutions according to the state of the humoral environment and divided people into sanguine (energetic and lively), choleric (impetuous), melancholic (reticent and unsociable) and phlegmatic (inert) according to temperament.

Cellular pathology with its anatomic localistic principle tended to ignore the significance of the organism as a whole in origination of disease and the very concept of constitution. Another factor indirectly conducive to this was the development of bacteriology and the underestimation—characteristic of the time—of the significance of the host in the etiology and pathogenesis of diseases. The problem of constitution was only later subjected to deeper study.

Today there is no agreement on the essence of constitution as yet. There are two diametrically opposed trends in understanding constitution.

Representatives of one trend understand constitution as an aggregate of stable and only inherited properties. They hold that constitution remains unchanged all through a person's life and is the cause of most of the diseases. This view is a result of their concept of heredity, according to which nature is invariable. The adherents of this trend disregard the role of the environment in changing heredity. The definition that "constitution is the somatic fate of the organism", which always predetermines the origination of disease, ignores the significance of the external environment in the formation of man's constitution.

The representatives of the other trend understand constitution as the complex of the organism's properties formed in the process of its development in interaction with the conditions of its existence. They believe that the *organism's constitution is not something invariable and fixed* either in the organism's individual (ontogenetic) or historical (phylogenetic) development. Prolonged influence of external factors leads to the appearance of qualitatively new and stable properties which in some cases are fixed in the progeny and determine man's reactions to physiologic and pathologic factors. For a correct evaluation of the significance of constitution the organism must be viewed not as a sum of the properties of its organs, tissues or cells, but as a single whole in its inseparable unity with its environment, in all its individuality at the moment of its affection.

Classification of Constitutions

Many attempts have been made to establish definite types of constitutions according to similarities of the various properties of the organism. Measurements of the body and its parts (somatometry) were most frequently used as criteria. Some observations showed certain types of body build to correspond to certain functional properties.

Thus one of the widespread classifications of constitutions (Sigaud) establishes the following four principal types according to characteristics of body build: 1) respiratory type—long thorax, acute epigastric angle, long neck, relatively small abdomen, developed maxillary and frontal sinuses, and hexagonally-shaped face; 2) muscular type—broad and high shoulder girdle, developed chest, developed muscles, medium epigastric angle, and square face; 3) digestive type—well developed lower third of the face, protruding jaw, short neck, broad chest, and well developed abdomen and obtuse epigastric angle; 4) cerebral type—delicate slim physique, large skull, well developed frontal part of the face, and short limbs.

In addition to classifications according to body build, there have been several more attempts to distinguish constitutions in accordance with the organism's functional properties, the peculiarities of muscle tone, metabolism, nutrition or vegetative functions. The constitutions established by various researchers according to these characteristics usually fit into the three following principal types with certain variations in the different classifications: 1) hyposthenic, hypotonic and asthenic types (correspond to Sigaud respiratory and cerebral types); 2) normosthenic, normotonic and athletic types (correspond to the muscular type); 3) hypersthenic, hypertonic and pyknic types (correspond to the digestive type).

A predisposition to particular diseases was frequently ascribed without sufficient reason to each of the foregoing types, for example, a predisposition to respiratory diseases was ascribed to people of the respiratory and asthenic types, metabolic diseases—to people of the digestive or pyknic type. Some investigators (Kretschmer) ascribed to the types they distinguished (asthenic, pyknic and athletic) predispositions to various mental diseases. But this view is erroneous because it is based on observations of mental patients.

The basic flaw of these classifications is that they are all schematic and one-sided. In most cases they are predominantly of a descriptive character and fail to take into account the continuous interaction of the organism with the external environment. They do not always permit of determining with certainty the character of man's possible reaction to a particular pathogenic agent. Moreover, the constitution of most people is mixed and does not fit into any definite type; this is particularly true of women and children.

It is very important to note that an individual's constitution may vary with the conditions of his life. Observations have shown, for example, that the physique of a person, who as a child belonged to the hyposthenic or asthenic type but for a long time did physical work or systematically went in for sports, gradually changes and manifests features characteristic of a normosthenic or athletic type. This shows that certain external factors acting over a long period of time may alter the manifestations of a constitution, its functional and even morphological characteristics.

Attempts have also been made to classify constitutions according to properties of certain systems, for example, the endocrine glands or vegetative nervous system.

Types of people were at different times distinguished according to the properties of endocrine glands, i.e., by an increase or decrease in certain incretory functions, for example, hypo- or hyperthyroid constitutions, hypo- and hyperpituitary, etc. However, there are no reasons to consider the constitution of an organism exclusively from the standpoint of the functional characteristics of the endocrine glands because the latter closely interact with the nervous system.

Human constitutions were also distinguished according to peculiarities of the vegetative functions, i.e., with the tone of either the sympathetic or parasympathetic nervous systems predominating (sympathicotonic and vagotonic types). But this classification was likewise based on a one-sided and erroneous concept of the self-sufficiency of each division of the vegetative nervous system and the direct antagonism between them.

Significance of Types of Higher Nervous Activity in the Theory of Constitution. The teaching on higher nervous activity and the role of the cerebral hemispheres in the regulation of all functions of the organism has made it possible to overcome the one-sided views of constitution and its significance for pathology and the clinic and to elaborate a classification of types of nervous system.

A type of higher nervous activity is a complex of inborn traits and characteristics acquired by the organism in the course of its individual development under the continuous influences of the external environment. Each type is characterised by certain features of higher nervous activity such as: 1) strength of the basic nervous processes—excitation and inhibition—which determines the efficiency of the nervous system, 2) balance between the two processes, and 3) mobility of these processes, i.e., ready reaction to stimulation and rapid transition from inhibition to excitation and vice versa. These features ensure the organism's adjustment to the conditions of its existence.

Pavlov distinguished weak and strong types of nervous system in accordance with the strength of the nervous processes—excitation and inhibition. Strong animals are divided into equilibrated and unequilibrated, according to the balance between the basic nervous processes in the cerebral cortex. The equilibrated animals are in their turn divided into lively (mobile) and calm (inert), according to the mobility of the cortical processes.

Thus the following principal types of nervous system may be distinguished according to the manifestations of nervous activity: 1) weak type characterised by weakness of the stimulatory and inhibitory processes with relative predominance of inhibition over excitation; 2) strong, equilibrated, mobile type with equally strongly developed processes of excitation and inhibition, and capable of resisting pathogenic stimuli; 3) strong, unequilibrated, excitable ("impetuous") type with excitatory and inhibitory reactions out of proportion to the stimulation, a type in which both processes are strong but the process of excitation predominates; 4) calm, phlegmatic type with a well balanced and somewhat inert nervous system, capable of great endurance and easily adjusting itself to its environment. The aforesaid types correspond to the melancholic, sanguine, choleric and phlegmatic temperaments. There are also a number of intermediate typological variants.

For the clinic the problem of types of nervous system is of paramount importance because its solution would allow a correct evaluation of the role of constitution in the pathogenesis of disease and would offer a possibility of exerting purposeful influences on the affected organism.

Attempts at elaborating a working scheme for classifying types of nervous system in man in accordance with Pavlov's classification principles based on experimental studies of higher nervous activity in animals have been repeatedly made. The problem is extremely complex, however, and these attempts have not as yet succeeded.

Concept of Diathesis*

The concept of constitution is tied in with that of diathesis. Diathesis usually implies a morbid state of the organism characterised by its abnormal reactions to the action of usual stimuli. The clinic often endeavours to distinguish different forms of diatheses according to the organism's susceptibility to certain groups of diseases.

The following diatheses are thus distinguished: exudative diathesis with frequent inflammatory reactions and eczematous eruptions on the skin; neuroarthritic diathesis with sluggish metabolism, endocrine disturbances and joint affections; spasmophilic diathesis with increased nervous excitability and tendency to convulsions; asthenic diathesis with adynamia and diminished vascular tone; hemorrhagic diathesis with a tendency to hemorrhages. There are also other forms.

Certain scientists identify diatheses with hereditary predispositions for certain diseases. However, such concepts are ungrounded since various external factors influencing the organism during intra- and extrauterine life may play a certain part in the origination of diatheses. The prolonged influences exerted on the mother and fetus by infections, intoxications, altered nutrition, and climatic conditions are particularly important. It is sometimes possible to diminish or entirely eliminate the manifestations of diatheses by prophylactic and therapeutic measures.

THE ORGANISM'S REACTIVITY AND ITS SIGNIFICANCE IN PATHOLOGY

Concept of the Organism's Reactivity

The organism's reactivity is its ability to respond in a definite manner to the action of ordinary and pathogenic stimuli and is a very important aspect of the organism's adaptation—developed in the course of its evolution—to the external environment. In addition

From the Greek, meaning predisposition.

to general (i.e., specific) reactive properties, there are also individual reactive properties.

Reactivity underlies the organism's ability to resist influences of pathogenic agents. Thus, not all people are equally susceptible to the same infection. The course of an infectious disease depends on the organism's reactivity and therefore runs differently in different people. The same thing is observed in other pathologic processes. For example, all other things being equal, wounds heal differently in different people. In cases of higher reactivity wounds heal relatively fast, whereas in cases of low reactivity they heal slowly. To understand the pathogenesis of diseases and be able to exert purposeful influences on the affected organism, it is very important to study reactivity and its changes.

An organism's reactivity is usually judged by its metabolism, functional mobility and excitability of its nervous system, vascular reaction, chronaxy, etc.

Disclosure of the mechanisms underlying the organism's reaction to pathogenic agents under various conditions of their action on the organism is one of the most important problems of pathology.

The progressive trend in studying reactivity has formed in opposition to the narrowly localistic principles of cellular pathology which erroneously considered general reactivity a sum of the reactive properties of individual cells, tissues and organs.

Mechnikov was the first to stimulate by his research an interest in reactivity. His investigations of reactivity at the different stages of evolution of organisms demonstrated how gradually their reactivity developed in the struggle against microbes, the causative agents of disease.

It has been well known since Mechnikov's time that reactivity to inflammatory agents grows more complex with the development of organisms and differentiation of their nervous systems. For example, in cold-blooded animals (amphibians and fish) inflammation is less clearly marked than it is in warm-blooded animals.

The same thing is observed in experiments aimed at developing increased sensitivity to protein. In warm-blooded animals it develops relatively easily, whereas cold-blooded animals either react to protein very feebly or do not react at all (N. N. Sirotinin).

Significance of the Higher Parts of the Nervous System in the Organism's Reactivity

As an organism and its nervous system develop, the organism's reactivity or sensitivity to a number of toxic substances increases and its defence reactions alter. For example, a lizard very well tolerates such doses of diphtheria toxin as would be enough to kill several hundred mice. Similar results have also been obtained in ontogenesis. For instance, the peculiar reactivity of infants, espe-

cially their tendency toward digestive and metabolic disorders, is due to the insufficient functional maturity of the cerebral hemispheres. Despite certain exceptions, these data indicate the great importance of the higher parts of the nervous system in the organism's reactivity. It has also been established that in hibernating animals the reactions to the influences of various noxious agents, for example, inflammatory or infectious, sharply diminish during hibernation in consequence of the prolonged inhibition of the central nervous system. The reactivity of decerebrated animals to the action of various stimuli, for instance, alcohol, morphine and thyroxin, is noticeably altered. Decerebrated animals possess less resistance to infection.

Subjection of animals to prolonged deep sleep or narcosis which, as is well known, primarily affects the higher parts of the central nervous system also alters their reactivity to protein, various toxic substances, extreme heat or cold, and hypoxia (V. S. Galkin).

Clinical observations have likewise shown that the course of a disease is considerably altered by excitation and inhibition occurring in the cerebral cortex. Thus, if inhibitory processes predominate in the cerebral cortex, the reactivity to stimuli noticeably diminishes.

The theory of conditioned reflexes offers new and very extensive opportunities to investigate the functions of the brain and the significance of higher nervous activity in the organism's reactivity and its equilibration with the external environment.

The discovery of the regularities of higher nervous activity facilitates the solution of problems concerning the mechanisms of diseases and pathologic processes.

The *changes in reflex reactions* which essentially determine the organism's reactivity and its role in the functional deviations of systems, organs and tissues, are very important.

Studies in conditioned reflexes and types of higher nervous activity have established the pathogenic importance of the complex *regularities of cortical activity* (phenomena of induction, concentration and irradiation of excitation and inhibition, and processes of defensive inhibition) in the disturbances in reactivity and adjustment of the organism to its external environment. For example, hypofunction of the cerebral cortex (in experimental neuroses, severe trauma and overstrain of the nervous system) causes a disturbance in reactivity with the result that both weak and strong stimuli produce an equal effect, or weak stimuli begin to act as strong ones and vice versa, or else negative stimuli act as positive ones and positive stimuli produce a diminished or zero effect.

The state of higher nervous activity is thus an important factor in raising or lowering the organism's resistance to the action of any stimuli, including pathogenic stimuli.

In this connection it is necessary to note the effect of psychic trauma and hard emotional experiences on the pathogenesis and

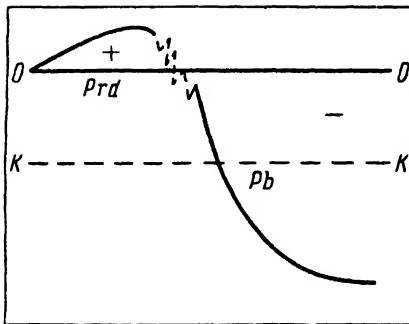


Fig. 7. Variations in the potential of a parabiotic part. The preparation is the frog's sciatic nerve. P_{rd} - prodromal (electropositive) phase of parabiosis. This is followed by a transitional phase of variations in the parabiotic current. The electronegative phase of parabiosis is the last to occur. When the negative potential of the parabiotic part reaches the critical level ($K-K'$), conductivity and excitability of part P_b completely cease (N. Y. Wedensky).

course of such diseases as, for example, disorders of carbohydrate metabolism, disturbances in thyroid function (exophthalmic goiter), changes in the functions of the gastrointestinal tract, and a stable rise in blood pressure (hypertensive vascular disease).

The significance of the nervous system in the organism's reactivity has also been demonstrated by studies in the nature of excitation and inhibition. N. Y. Wedensky was the first to observe the depressing effect produced on the nervous system by stimuli of great strength and frequency, so-called pessimum of stimulation. A qualitatively different form of propagation and transmission of the wave of excitation—phenomenon of parabiosis—arises at the point of application of the stimulus to the nerve. In a state of developing parabiosis the nerve exhibits an altered reaction to the stimulus.

The theory of parabiosis (Wedensky) shows the importance of the initial functional state, the functional mobility or lability of the central and peripheral nervous systems (any other living substrate to a lesser extent) in the origination of qualitatively different forms of transmission of the wave of excitation.

Any stimulus, whatever its characteristics, may, under conditions of altered functional mobility of the nervous system, produce a phasic effect on the excitability of this system, i.e., at first decrease the excitability (electropositive depression of nervous functions) and then increase it (period of variations in the electric potential), and again sharply and for a long time depress it—electronegative, increasing depression of nervous functions (Fig. 7).

The transition from an active state of a nerve to a parabiotic state is accompanied by a successive appearance of several intermediate phases which determine the response reaction: 1) provisional or

equalising phase during which both strong and weak stimuli produce an equal effect; 2) paradoxical phase during which weak stimuli are productive of a greater effect than are strong stimuli; 3) inhibitory phase during which both weak and strong stimuli cease to evoke a response reaction. Restoration of a function goes successively through all these phases, only in the reverse order.

Investigations of the lability of nervous structures are fundamentally important for the understanding of reactivity since they show that a *stimulus of the same strength may, depending on the reactive properties of the nervous system, evoke different reactions on the part of the whole organism*.

Parabiotic phenomena have been discovered in the development of some basic pathologic processes, for example, traumatic shock which is based on overexcitation of the central nervous system with its subsequent inhibition, anaphylaxis and allergic phenomena which will be discussed below.

As regards the other changes in the activity of the central nervous system, on which the organism's reactivity may depend, mention should be made of the role played by the dominant focus and trace reactions. A. A. Ukhtomsky has demonstrated the dominant importance of the focus of stable excitation in the character or reflex reactions.

One of the experiments most convincingly showing the importance of the dominant is that in the dog with a replete rectum stimulation of the cortical centres of the forelimbs does not evoke a motor reaction but leads to rapid defecation. The reason for this is that from the intestines the nervous impulses travel to the central nervous system where they create a focus of excitation. Under the given conditions the process of excitation during stimulation of the cortical centres of the forelimbs is, as it were, "drawn" to the formerly excited, dominant focus and reinforces the process of excitation operating there, thereby hastening the defecation. In this case a process of inhibition develops in other centres of the cortex, the cortical centres of the forelimbs in particular. After defecation the excitation of the entire cortex is restored.

Recognition of the dominant, as a general principle of the work of nerve centres, helps to understand the mechanisms of a number of pathologic processes. For example, some investigators account for attacks of stenocardia, a disease based on spasm of the coronary vessels, by appearance in the cerebral cortex of a pathologic dominant focus connected with the coronary vessels. The existence of such a focus conditions, as it were, the attraction to it of extraneous stimuli if they reach the cerebral cortex. In such cases any emotional experience or overstrain of higher nervous activity may become a stimulus for attacks of stenocardia.

The studies which have shown that the *nervous system retains traces of stimuli once applied* also indicate that a focus of inert excitation or pathologic dominant may develop in the central nervous system. Under certain conditions the excited centre continues

to play the role of a dominant factor with respect to the other centres even after the influx of adequate nervous impulses from the initial peripheral source has ceased. This phenomenon is typical of any living substrate but in the course of evolution it has become the leading characteristic of the nervous system.

In a general biological sense the ability of the central nervous system to retain traces of former stimulations is necessary for the organism because it facilitates consolidation of useful properties. However, influences of pathogenic agents may also result in consolidation of unusual reactions in the central nervous system.

In some cases the recurrence of already extinct pathologic processes is apparently based on a trace stimulation or an "after-effect" phenomenon. On repeated action of various types of stimuli the developing nervous excitation spreading all through the nervous system is drawn, as it were, to the parts which retain a trace of former stimulation. This finds its concrete expression in the organism's altered reaction.

The phenomena of tetanus produced in the dog by action of tetanus toxin on its nervous system and then eliminated may reappear if the organism is subjected to the traumatic influences of factors which bear no direct relation to the etiology of tetanus ("second stroke", according to Speransky).

As an example of such reactions mention may be made of a number of clinical observations, particularly concerning the recurrence of certain eczematous changes in the skin as a result of influences not directly related to the cause of this disease. Another example is that of the recurrence—under the influence of psychic trauma—of cholelithiasis symptoms in a patient after excision of the gall-bladder together with the calculi and after apparent recovery.

Role of the Lower Parts of the Nervous System in the Organism's Reactivity

The influence of higher nervous activity on the mechanism of reactivity is exerted through the lower parts of the nervous system.

Disturbances in the activity of the lower parts of the nervous system may in some measure or other alter reactivity. This is evident from clinical and experimental data. For example, injury to the tuber cinereum produced by a foreign body, tumour or inflammatory infiltrate is accompanied by alterations in reactivity manifested in diminished resistance of the organism to infection and development of trophic disorders. It has also been established experimentally that trauma to the diencephalon impairs the resistance to infection and disturbs the thermal reaction of the organism to the effects of heat and cold. Transection of the spinal cord in pigeons reduces their resistance to anthrax.

There is a great deal of evidence proving the importance of the

vegetative nervous system in the mechanism of reactivity. For example, stimulation of the parasympathetic nervous system increases the production of antibodies, while stimulation of sympathetic nerves intensifies the reaction of phagocytosis. Removal of the sympathetic chain in the abdominal cavity of animals results in lowered resistance of the organism to infection, decreased protective function of connective tissue and diminished general adaptation of the organism to temperature variations in the external environment.

Significance of Humoral Factors in Reactivity

Humoral factors—mediators, hormones and other physiologically active substances—also play an important part in the organism's reactivity.

On entering the organism's internal environment they affect the organism's reactivity. In pathology certain physiologically active substances are liberated and accumulated in the organism in accordance with the processes of excitation and inhibition operating in the nervous system. These substances are, in the first place, cholinergic and adrenergic substances which stimulate the effectors and take part in the complex chain of reflex processes; for example, cholinergic reactions prevail in cases of ulcers and bronchial asthma, while adrenergic reactions predominate in spontaneous gangrene and hypertensive vascular disease.

Walter B. Cannon established the significance of the sympathico-adrenal system in the organism's adjustments to the changing conditions in its surroundings (homeostasis); the reactions of the sympathico-adrenal system are evident when the organism is acted upon by various pathogenic stimuli, for example, in cases of traumas or excessive cooling. Thermoregulation, redistribution of the blood and increased glycogenolysis in cases of diminished sugar in the blood cannot be normally effected during dysfunction of the sympathetic nervous system.

Disturbances in the organism's reactivity arise in connection with endocrine disorders; for example, the resistance of the organism to certain infections diminishes in hypothyroidism and in insufficiency of the islets of Langerhans.

Considerable attention is now attracted by Selye's hypothesis of the role played by the hypophyseal and adrenocortical hormones in the organism's physiological stress. According to his views, the organism responds to pathogenic stimuli (infection, cold, trauma, starvation) with a general, nonspecific adaptation syndrome which consists of three stages: 1) alarm reaction or mobilisation with phases of shock and countershock, or defence, 2) stage of resistance characterised by restoration of the disturbed equilibrium, and 3) stage of exhaustion in cases of prolonged overexposure to pathogenic stimuli to which the resistance can no longer be maintained and

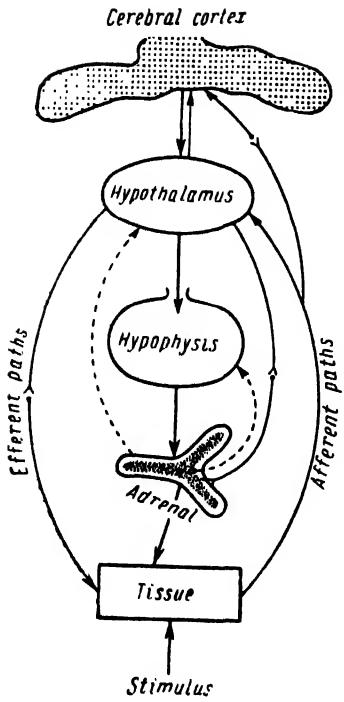


Fig. 8. Diagram showing participation of neural and endocrine factors (hypophysis and adrenals) in the reactivity of the organism.

corticoid hormones, mainly glucocorticoids. General adaptation phenomena are discovered in lesions of the kidneys (nephrosclerosis), rheumatism, allergic diseases, inflammation, etc. Corresponding hormones are now being used in the clinic for the therapy of diseases regarded as adaptation diseases.

However, the role of the other hormones and the neural factor in the joint reaction of the anterior lobe of the hypophysis and the adrenal cortex to the stimuli, as well as in the formation of the adaptation syndrome, has remained underestimated; and yet, according to available information, the hypophysis is but part of the more complex cortico-diencephalo-hypo-physeal system which influences the reactive properties of the normal, as well as the diseased organism (Fig. 8).

The influence of the nervous and neuroendocrine systems on the organism's reactivity is realised by numerous effectors of the organism's internal environment. A *disturbance in the specific activity*

the adaptation has been lost. The adaptation syndrome develops because of the reaction to stimuli of the anterior lobe of the hypophysis and the function of the adrenal cortex which is under its control. The changes in the adrenal secretion of glucocorticoids and mineralocorticoids are conducive to disturbances in reactivity and to origination of a number of diseases which have been given the designation of *adaptation diseases*; thus diminished secretion of glucocorticoids and an excess of mineralocorticoids are contributive to development of hypertension, malignant nephrosclerosis, periarteritis, polyarthritis. The somatotropic hormone of the hypophysis and the mineralocorticoids (especially desoxycorticosterone) intensify inflammatory reactions, while the adrenocorticotrophic hormone and glucocorticoids (cortisone and dehydrocortisone) depress them. It has been established that the alarm reaction evoked by the action of stimuli, for example cooling, produces an anti-inflammatory effect on the organism in virtue of the increased secretion of glucocorticoids.

General adaptation phenomena are discovered in lesions of the kidneys (nephrosclerosis), rheumatism, allergic diseases, inflammation, etc. Corresponding hormones are now being used in the clinic for the therapy of diseases regarded as adaptation diseases.

The influence of the nervous and neuroendocrine systems on the organism's reactivity is realised by numerous effectors of the organism's internal environment. A *disturbance in the specific activity*

of the organs and tissues therefore also finds reflection in the organism's reaction to the effects of pathogenic agents.

Significance of Age in Reactivity

Some diseases, for example, rickets, scarlet fever, diphtheria, rubella, whooping cough and poliomyelitis, affect only or predominantly the young. Intestinal diseases are often observed in early childhood. Children adjust themselves with greater difficulty to considerable fluctuations in the surrounding temperature. The newborn hardly ever contract such diseases whose onset is possible only on a definite level of development of the child's organism. For example, the newborn do not yield to croupous pneumonia, scarlet fever and measles. Such insusceptibility of the newborn to children's infections is in some measure accounted for by the level of development of the regulatory systems, but possibly also by the presence of antibodies transmitted to them by the mother and as yet not excreted from the organism.

Malignant tumours most frequently occur in elderly people. Characteristic of old age are atherosclerosis and a sluggish course of pathologic reactions, for example, inflammation, regeneration and fever. At this age, because of lowered reactivity, infectious diseases usually run a severe course and people are particularly susceptible to purulent diseases, influenza and pneumonia.

Effect of External Factors on Reactivity

By constantly acting on the organism the factors of the external environment affect its reactivity. Reactivity varies with nutrition, environmental temperature, effects of poisonous substances, radiant energy and, particularly, social conditions.

One-sided nutrition and various forms of starvation noticeably weaken the organism's reaction to pathogenic agents. The organism's resistance to infections diminishes in cases where the food is deficient in vitamins. In tuberculosis and rheumatism the organism's vitamin C reserves decrease and administration of this vitamin favourably affects the course of these diseases. Protein starvation weakens inflammatory reactions and greatly reduces the organism's resistance to infections, for example, abscesses, typhus and typhoid fever.

Overheating and overcooling of the organism produce a reflex reorganisation of its reactivity to all stimuli. For example, sudden cooling resulting in a cold reduces man's resistance to influenza and pneumonia. Experimental cooling of chickens makes them susceptible to anthrax which normally does not affect them. Overheating lowers the sensitivity of sensitised guinea pigs to foreign protein.

Poisoning with war gases, alcohol, carbon monoxide, mercury, lead and hydrocyanic acid reduces the processes of inhibition in the cerebral cortex and the organism's resistance to pathogenic agents. For example, pigeons poisoned with alcohol become readily susceptible to anthrax. Chronic alcoholism perceptibly weakens man's general reactivity.

Radiant energy, in the form of ultraviolet rays, in some doses increases the organism's resistance to infections and in others lowers it. The organism's reactivity is particularly harmfully affected by prolonged exposure to roentgen and gamma rays.

According to available information, the organism's reactivity is also affected by other factors (atmospheric pressure, trauma). This goes to show that the organism's reactivity varies with environmental conditions and that the environment can be used to exert purposeful influences on it.

IMMUNITY

Immunity or insusceptibility is the condition of a living organism whereby it resists the harmful action of infectious agents and their toxins. It also develops with respect to various foreign substances mainly of a protein nature. Immunity forms part of the concept of reactivity and is considered one of its basic manifestations.

Defence Mechanisms

In penetrating into the organism of the host microbes encounter obstacles primarily on the part of the anatomophysiological non-specific defence mechanisms (so-called barrier functions), which have developed in the process of evolution and the organism's adjustment to its environment. *External* and *internal* defence mechanisms are distinguished. The former include the skin with its adnexa, and the mucous membranes with the glands imbedded in them. Impairment of these mechanisms facilitates penetration of infectious agents into the organism.

The skin is impermeable to most of the microbes; it is covered with stratified cornifying epithelium which serves as a mechanical barrier to their penetration. Gradual desquamation of the superficial layer of the skin helps in eliminating the microbes. Infectious agents, especially streptococci, anthrax and plague bacilli, easily penetrate into the organism through damaged skin.

Bacteria can also gain entrance into the organism through the openings of the excretory ducts of sweat and sebaceous glands, which is confirmed by experiments with rubbing bacteria into intact skin.

At the same time the sweat and sebaceous glands play an important part in the barrier function of the skin. The substances secreted

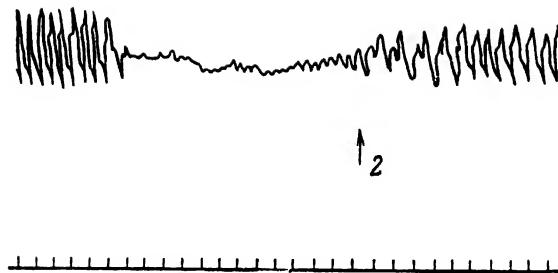


Fig. 9. Defence reaction in the rabbit. Reflex slowing of the respiratory rate and respiratory arrest upon inhalation of ammonia.

1—beginning of inhalation, 2—cessation of inhalation.

by these glands on the surface of the skin wash off the microbes and prevent infectious agents from penetrating into the organism.

The skin also has bactericidal properties with respect to many pathogens, for example, the hemolytic streptococcus and the colon and typhoid fever bacilli. The bactericidal properties of the skin are due to the acidity of the sweat, the composition of the secretion of the sebaceous glands and the secretion of antiseptic metabolites, for example, certain lipids.

An important part in the defensive function of the skin is played by its innervation; disturbances in innervation impair the sensitivity of the skin, increase its permeability, alter its metabolism and, as a result, reduce its resistance.

The conjunctiva and the *mucous membranes* lining the nasopharynx and the respiratory, digestive and urogenital tracts prevent the entrance of microbes by their low permeability. Their barrier function is enhanced by the secretions of their glands, which eliminates foreign bodies, including microbes, mechanically. The mucous membranes of the respiratory tract are covered with ciliated epithelium, its cilia vibrating in the direction of the nasopharynx and thus expelling dust particles and microbes to the exterior. The motor reflexes of a defensive nature—changes in respiration, sneezing and coughing (Fig. 9)—are likewise of considerable importance.

Lastly, the secretion of the mucous membranes also has a bactericidal effect. The tears, sputum and saliva contain lysozyme which dissolves certain species of microbes, for example, saprophytes, meningococci and comma bacilli. Lysozyme is apparently not the only bactericidal secretion of the mucous membranes.

Gastric juice possesses considerable sterilising action; it kills comma bacilli and weakens the effect of diphtheria toxin. The intestinal juice also produces a bactericidal effect. The intestinal mucosa contains mucopolysaccharide which depresses certain neurotropic

viruses. The defensive function of the intestinal mucosa is also promoted by the presence of a constant flora, for example, the colon bacillus which is an antagonist of the typhoid fever and dysentery bacilli, the streptococcus and staphylococcus. Döderlein's bacillus in the vagina prevents invasion of streptococci.

In this connection mention must be made of the bactericidal action of a number of substances contained in plant juices and filtrates of cultures of certain microorganisms. These substances known as antibiotics have found wide application in medical practice; they include pyocyanin, gramicidin, streptomycin and, especially, penicillin which is very effective in coccal infections.

The barrier role of the mucous membranes is regulated by the activity of the nervous system. Thus in disturbances of its function, for example, during intense inhibition in the central nervous system, the upper respiratory mucosa becomes more permeable to strepto- and pneumococci. This also occurs in colds since they are based on changes in reflex activity which entail increased permeability of the mucous membranes.

An inflammatory process produced by microbes in the skin or mucous membranes may play the role of a defence mechanism. Vascular disturbances, increase in leukocytes and intensification of their phagocytic activity (engulfing and digesting microbes) in inflammation prevent the spread of infection, while the exudate formed in the process may remove and partly neutralise bacteria and toxins. Such elimination of microbes and toxins by the organism is particularly noticeable when the exudate has an outlet to the exterior.

An inflammatory process not only detoxicates and eliminates the noxious agent by means of the exudate, but also isolates it by forming a granulation wall and a connective tissue capsule. The focus of injury is not infrequently calcified. This occurs, for example, in tuberculosis, when the focus of pulmonary infection is calcified, or in organisation of the exudate in the pleura and the abdominal cavity.

On penetrating through the skin or mucous membranes microbes encounter the *internal* defence mechanisms. These include: a) the lymph nodes which can retain microbes in the tissue of the lymph nodules and participate in the elaboration of specific immunity; b) the reticuloendothelial elements of various organs (spleen, bone marrow, liver, etc.) which participate in retaining and digesting microbes; c) the liver in which microbes are retained and eliminated with the bile and toxic substances are detoxicated by the formation of paired glucuronic and ethersulfuric acids; d) the kidneys which eliminate toxic substances and certain microbes from the organism (for example, bacteriuria in typhoid fever); e) the so-called hematogenous or cerebrospinal barrier (meninges, ependyma of the cerebral ventricles, choroid plexus and vascular endothelium of the

brain) which regulates and maintains the constancy of the chemical composition and other properties of the internal cerebral environment; f) lastly, the biochemical and physicochemical properties of tissues which impede the development and vital activities of infectious agents, and affect the degree of permeability of cell membranes, and the intensity and character of tissue metabolism; for example, the bactericidal properties of tissue extracts and serum noticeably diminish in an environment deficient in oxygen.

In evaluating the defence function of the barriers it is necessary to take into account not only the distinguishing features of each barrier, but also their interaction, for example, the ability of the kidneys in some cases of intoxication to replace the detoxicating function of the liver, or the increased excretory function of the skin and lungs in cases of renal affection. This interaction is apparently effected by the activity of the systems which regulate all of the organism's defence functions.

Particularly important, however, is the organism's ability to resist the action on pathogenic microbes and toxins by means of specific immune reactions.

The serum contains *antibodies* which participate in the reactions of specific immunity (see below) and certain nonspecific substances which possess bactericidal properties, for example, *properdin* (an euglobulin which acts in the presence of a complement and magnesium ions).

Types of Immunity

Immunity is referred to as *native* when the insusceptibility of a given species of animal or of man to a particular infection is an in-born property. Man's insusceptibility to cattle plague or the insusceptibility of animals to gonorrhea and leprosy may serve as examples of such immunity.

Native immunity may be not only specific, but also *individual*. Daily observations show that not all people are equally immune to the same infectious diseases.

Native immunity is usually noted for its stability, although it may alter as a result of various influences exerted on the organism by factors of the external environment and consequent changes in the organism's immunobiological properties. For example, the frog which is insusceptible to tetanus and cholera yields to them when placed in a thermostat. Chickens, although insusceptible to anthrax, may contract this disease if cooled from 41-42 to 37°C.

The immunity is called *acquired* if the organism's insusceptibility has originated in the course of its life. The immunity acquired as a result of an infectious disease is known as *naturally acquired immunity*. For example, a person who has survived smallpox usually becomes insusceptible to this disease. People who have survived measles are insusceptible to this disease for a number of years. The

duration of acquired immunity varies and depends on the character of the disease, properties of the organism and environmental conditions. Acquired immunity may be unstable to diphtheria, cholera and typhoid fever; it is temporary or does not develop at all to influenza and, especially, to rheumatism.

Immunity acquired as a result of immunisation with bacterial preparations (vaccines) or administration of immune serums, i.e., taken from vaccinated animals or those who have survived the particular disease, is called *artificially acquired immunity*. Acquired immunity may be *active* or *passive*.

Immunity is *active* when the organism itself has elaborated it as a result of disease or inoculation with a vaccine prepared from attenuated or killed microbes (for example, in smallpox or typhus vaccination).

The organism may become insusceptible to infection as a result of administration of immune serums. In such cases the acquired immunity is called *passive*. Thus, passive immunity for purposes of prophylaxis or treatment may be produced to diphtheria and tetanus by administration of corresponding serums from immunised horses (antidiphtheritic and antitetanic serums). Passive immunity manifests itself very quickly but is unstable.

Cellular Phenomena in Immune Reactions

Mechnikov explained immunity by intracellular digestion of substances foreign to the organism—microbes, toxins, particles of cell elements, products of tissue decomposition, etc. He named the ability of the cells to engulf and digest the substances penetrating into them *phagocytosis*, while the theory thus explaining the organism's insusceptibility is known as the *phagocytic theory* (1883).

Mechnikov's phagocytic theory was the result of many years of observations of the insusceptibility of animals at different stages of their evolution. Phagocytic phenomena may be observed in inflammatory exudates artificially produced by injections of vaccines in the abdominal cavity of experimental animals.

A suspension of staphylococci or streptococci is injected in the abdominal cavity of an animal, say, a guinea pig. Already 30 minutes later the content (exudate) of the abdominal cavity is extracted by means of a thin glass tube and a fine smear is made on a slide. Phagocytic phenomena may be observed in stained preparations under the microscope. Phagocytosis manifests itself not only with respect to microbes but also to foreign red blood cells, particles of India ink, etc.

Phagocytic ability is possessed by polymorphonuclear and large mononuclear blood cells (monocytes). The former have been named *macrophages* and the latter—*microphages*.

Macrophages easily ingest the causative agents of acute infec-

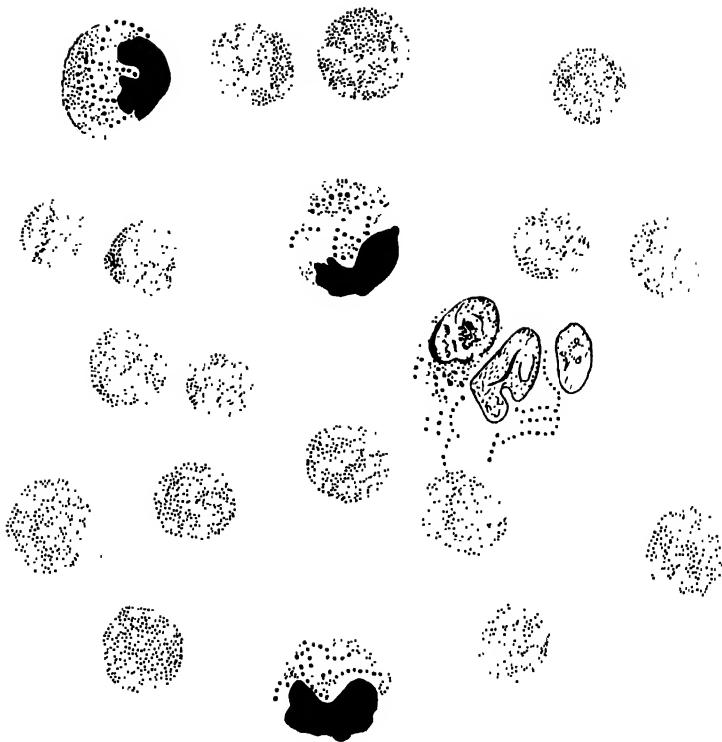


Fig. 10. Phagocytosis of streptococci by leukocytes.

tions—strepto- and staphylococci (Fig. 10), pneumococci, typhus, dysentery and comma bacilli.

Macrophages phagocytose mainly microbes capable of producing chronic infections (for example, leprosy and tuberculosis), as well as particles of moribund cells and products of decomposition. Four phases of phagocytosis are distinguished.

Phagocytosis proper is preceded by the *approach* of leukocytes to the substances (in infections—to microbes, products of their vital activity or products of tissue decomposition), i.e., the phagocytes approach the object of phagocytosis. This ability of the leukocytes to be attracted toward chemical substances is known as *chemotaxis*.

The approach is followed by *adhesion* (contact) of the object to the phagocyte and *engulfing* of the object by the phagocyte. This function is based on physicochemical processes which effect a change (diminution) in the surface tension in the phagocyte.

Lastly comes *intracellular digestion*, the microbes being enzymatically digested in the protoplasm of the leukocyte.

Phagocytes digest the engulfed microbes by means of enzymes—cytases. Microphages have mainly proteolytic (protein-converting) and macrophages—lipolytic (fat-splitting) enzymes.

There is a connection between phagocytosis and native immunity in that the infected animal, for example, the dog infected with anthrax survives, if it has appreciable phagocytosis and the ability to digest microbes gaining entrance from without, or it dies in the struggle against infection. The increase in the leukocyte count in the blood (leukocytosis) in a number of infections is also one of the proofs of the role of leukocytes in elaboration of immune properties.

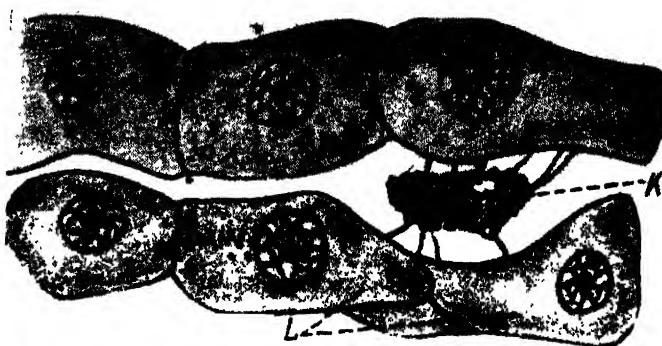
Immunisation is accompanied by increased phagocytosis. The following experiment may serve as an example: 1 ml of a suspension of a two-week-old typhoid fever culture is injected into the abdominal cavities of two groups of guinea pigs. Twenty-four hours prior to this one of these groups is immunised with antityphoid-fever serum. Four hours later the exudate is removed from the abdominal cavities of both groups of animals. The exudate of the nonimmunised animals shows feeble phagocytosis, whereas in the exudate of the immunised animals phagocytosis is very strongly pronounced.

However, the phagocytic reaction of the leukocytes is not always an index of the organism's immune properties with respect to infection. There are cases in which the phagocytic reaction and the immune properties fail to correspond.

Mechnikov was the first to observe in certain organs cells possessing phagocytic properties. He qualified the reticular cells of the splenic pulp, the lymph nodes, certain endothelial cells, neuroglial cells and a number of other elements of connective tissue as macrophages.

Following Mechnikov, V. K. Vysokovich (1886) discovered, in experiments with intravenous administration of bacterial emulsions to animals, the ability of endothelial cells of the splenic sinuses, liver and bone marrow to ingest microbes.

Subsequent observations conducted on the basis of Mechnikov's theory showed that fixed macrophages are capable of ingesting electronegative colloids, including microbes. This function is possessed mainly by the macrophages of certain internal organs, for example, the Kupffer cells of the liver (Fig. 11), the reticular and endothelial cells of the spleen, bone marrow, lymph nodes and adrenal cortex, the histiocytes or wandering cells at rest—the so-called reticuloendothelial system (Aschoff and Landau). The importance of the reticuloendothelial or macrophagal system in immune reactions is evident from the following observations. Removal of the spleen abounding in reticuloendothelial cells lowers the organism's resistance to infection. Introduction of colloid substances into the blood, leading to overloading of these cells (so-called block) also often reduces the resistance of the organism to infection. Moreover, it has been discovered that the macrophagal



*Fig. 11. Liver taken from the rat after intravenous injection of India ink.
K--Kupffer cells; L--liver cells (from Best and Taylor).*

system participates in the processes of ingestion and metabolism of lipoids (for example, cholesterol), in the formation of hemoglobin derivatives, bilirubin in particular, and in ingestion of colloid substances of albuminous origin. All these data have made it possible to ascertain the participation of this system in immune reactions and in metabolism, especially in the processes of fat-lipoid and iron metabolism.

According to latest information, lymphocytes and plasma cells which are producers of immune bodies take a big part in immune reactions. The function of plasma cells has been demonstrated by the isotope method.

Thus, all the cells of mesenchymal origin perform many functions, mainly trophic (participation in processes of metabolism and nutrition) and defensive (phagocytosis and formation of antibodies). They take an active part in processes of inflammation and regeneration. According to Bogomolets, they also play an important part in the organism's resistance to development of malignant tumours.

Humoral Phenomena in Immune Reactions

Studies of the immune reactions have made it possible to uncover the significance of a number of humoral processes in the elaboration of immunity.

Antigens. *Antigens are substances which stimulate production of antibodies in the organism or react with them.*

The antigens include microbes, toxins, foreign erythrocytes and any substances of albuminous nature foreign to the given organism, as well as certain hormones and enzymes (pepsin, trypsin, etc.). Antigenic properties are also possessed by some substances of nonalbuminous nature, for example, highly polymerised polysaccha-

rides and liposaccharides which in themselves are not antigens but may play the role of *hapton*s, i.e., possess the ability of combining with proteins and acquiring the properties of true antigens. A hapten may react with an antibody formed after administration of a true antigen independently, without protein. To produce immunity antigens must be administered *parenterally*, i.e., other than by the digestive tract, directly into the blood or subcutaneously.

Classic antigens have a relatively high molecular weight; for example, the molecular weight of the serum globulin of the horse is 167,000, diphtheria toxin—74,000, egg albumin—44,000.

Owing to the relatively large molecule and the peculiarities of their surface antigens affect the structure of the surface of the globulin from which antibodies are formed. However, the molecular weight does not alone determine the properties of an antigen. There are macromolecular substances which are very weak antigens (hemoglobin, gelatin).

Endogenous proteins, i.e., the proteins of the organism itself, may become antigens—*autoantigens*—only as a result of changes in their specific properties, for example, in cases of denaturation.

The *specificity of an antigen* is dependent on the nature and spatial arrangement of the polypeptide chains and various atom groups on the surface of its molecule. The antigenic specificity of a protein may be changed by addition of relatively simple polypeptides and other chemical compounds, for example, various azo compounds or radicals—acetyl, sulfate, nitrate and arsenic. The chemical compounds determining antigenic specificity are called the determinative groups of the given antigen.

The period of the antigen's retention in the organism also determines its antigenic properties. To increase the effect of immunisation, the antigen is sometimes administered in combination with substances conducive to its retention in the organism, for example, it is administered in oil or together with calcium chloride, which causes coagulation of tissue proteins.

After gaining entrance into the organism the antigen begins gradually to disappear from the blood. Most of the known true antigens are retained in the blood for no more than 2-3 weeks. Some of them disappear sooner, as, for example, egg albumen which is retained in the blood only for a few hours.

Experiments conducted with stained or labelled antigens have shown that from the blood the antigens pass into the organs (liver, spleen, bone marrow and lymph nodes) in which antibodies are produced. In these organs the antigen is retained for months, but its concentration diminishes because it is gradually destroyed and excreted from the organism.

Antibodies. *An antibody is a specifically modified gamma globulin which appears in the blood as a result of parenteral administration of an antigen and selectively reacts with it.*

Types of antibodies and their reactions with antigens: 1) *antitoxins*, 2) *agglutinins* and *precipitins*, and 3) *lysins* (bacterio- and cytolysins) and *opsonins*. Antitoxins neutralise the toxic effect of corresponding antigens; for example, antidiphtheric serum containing the requisite antitoxin prevents and cures diphtheria. Agglutinins and precipitins cause antigens to adhere to one another or precipitate them thus aiding in their phagocytosis and elimination from the organism. The third type of antibodies dissolve antigens by peptisation (lysins) or make them more accessible to phagocytosis by altering the surface of microorganisms (opsonins).

Like antigens, antibodies are specific.

Complement which is a complex of proteins of the blood serum with fermentlike action in reaction of antigens with complement-fixing antibodies is also an important factor in immune reactions. The action of complement is nonspecific. Its activity may be established by its lytic action, for example, in bacteriolysis or hemolysis, although in these cases it is also necessary to take account of other active chemical and physicochemical factors. The capacity of complement to be fixed by the antigen-antibody complex is utilised for serologic tests of fixation or deviation of complement.

The number of antibodies formed increases during immunisation but does not always correspond to the degree of immunity. The presence of a small number of antibodies in the blood is sometimes associated with stable immunity, for example, in smallpox. The lack of correspondence between the content of antibodies and the degree of immunity shows that formation of antibodies does not exhaust all the complex biological phenomena which enable the organism to resist the effect of infectious agents. The physical and chemical properties of the blood and tissues are also important (for example, the presence of bactericidal euglobulin—properdin—in the serum, the reaction of the environment, and metabolism, especially of protein).

Antibodies may, either alone or in combination with antigens, also serve to produce other phenomena. For example, protein precipitates and clumps of microbes formed during agglutination and precipitation may evoke a shock reaction by affecting vascular receptors and the central nervous system (agglutination shock). The same thing is possible in lysis of microbes or animal cells.

Some General Regularities in the Formation of Antibodies. Antibodies are formed in organs which produce blood proteins—the liver, spleen, bone marrow, lymph nodes and sites of accumulation of macrophages. In addition to the reticuloendothelial cells, lymphocytes and, especially, plasmacytes (in the spleen, bone marrow and lymph nodes in particular) take part in forming antibodies. A proof of the importance of the plasmacytes is that during immunisation of animals (for example, in vaccination of rabbits with pneumococ-

ci) the spleen acquires additional plasmacytes. Moreover, a parallelism between plasmacyte proliferation and formation of antibodies in the lymph nodes has been established.

Antibodies are not produced immediately after penetration of antigens into the organism. A certain, latent period must elapse (3-5 days) before the effect of antigens becomes manifest. The content (titre) of antibodies usually increases for 1-2 weeks and then gradually decreases and reaches its level in nonimmunised animals. On readministration of antigens the titre of antibodies increases to a greater extent than after the first administration. For successful immunisation of animals and man antigen is therefore administered repeatedly at very definite intervals, the period of increase in the content of antibodies in the blood not infrequently being preceded by a certain decrease as a result of antigen fixation of antibodies in the blood (*negative phase of immunity*).

Antigen-antibody Reaction. The studies of humoral phenomena of immunity have given rise to a number of hypotheses attempting to explain the mechanism of production of antibodies.

Antibodies are serum globulins and are formed as peculiar products of a synthesis of globulins modified under the influence of an antigen. The molecule of such a globulin differs from that of normal globulin by a special configuration of some parts of its surface.

According to modern views, the formation of antibodies is based on colloid-chemical processes. On gaining entrance into the organism the antigen apparently disturbs the equilibrium of its colloids and causes a certain regrouping of their molecules. The interaction of the antigen and antibody must in such cases be regarded as adaptation of the organism's colloids (which are in a certain state) to the antigen. The various manifestations of the immune reactions and the specificity of the immunity are apparently dependent not on the multiplicity of antibodies, but on the physicochemical properties of the antigen reacting with a single antibody.

Great importance in the formation of antibodies is also attached to chemical reactions. Any antigen includes at least two components — a high molecular substance of colloidal nature, i.e., native protein, and a so-called determinative group which determines its specificity. The determinative group consists of the amino acids and specific polysaccharides arranged on the surface of the colloid protein (globule). The specificity of antigens is determined not only by the quality and quantity of the determinative groups, but also by their spatial arrangement.

According to one of the hypotheses (advanced by Pauling), the globulins which go to form antibodies consist of the main stable polypeptide chain with semistable ends of amino acids. In the presence of an antigen these ends change their configuration under the influence of the polar groups of the antigen's determinant in accordance with the spatial arrangement of these groups on the

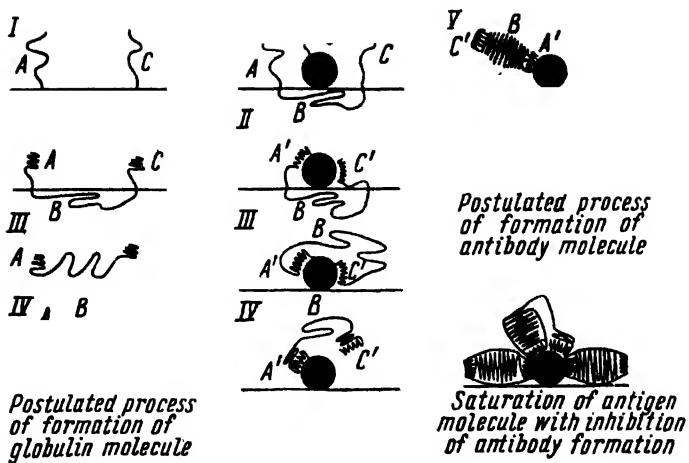


Fig. 12. Four hypothetical stages in the formation of a molecule of normal serum globulin (left), and six stages in the formation of an antibody molecule as the result of interaction of the globulin chain with an antigen molecule. Also shown (lower right) is an antigen molecule surrounded by attached antibody molecules, or parts of molecules, and thus inhibited from further antibody formation (Pauling).

antigen's surface and become, as it were, its stereochemical reflection. The antigen and antibody merge as a result of the mutual attraction of their polar groups which carry opposite charges (Fig. 12).

This hypothesis is now accepted in principle by the majority of scientists, but it is one-sided since it does not embrace the multiformity of processes operating in the organism. With the uncovering of the structure of proteins more mechanisms of production of immune bodies and antigen-antibody reactions will be discovered. Moreover, the study of immunity must be conducted from broader physiological positions.

Role of the Nervous and Endocrine Systems in Immune Reactions

In the course of evolutionary development, as the nervous system of animals differentiated, the latter developed a capacity to react to microbes and toxins and improved the mechanisms of immunity production.

A number of factors prove the regulating role of the *nervous system* in the development of immunity.

Lesions in the central nervous system resulting from cuts, traumas, poisons and narcotics exert a certain influence on phagocytosis and formation of immune bodies.

Another important proof of our concept of the nervous mechanisms of immunity is the possibility of producing immunity by conditioned reflexes. A heated culture of anthrax bacilli or a suspension of a killed staphylococcus culture was administered into the abdominal cavity of guinea pigs; each such administration was combined with a conditioned stimulus, for example, application of a metal plate heated to 50°C to the animal's abdomen. After 15-20 such combinations application of the conditioned stimulus alone caused the appearance in the abdominal cavity of an exudate analogous to the one formed by the action of the unconditioned stimulus—the antigen; the experiments simultaneously established a conditioned reflex change in the titre of the antibodies (S. I. Mettalnikov). Analogous results were obtained by other researchers in experiments not only on guinea pigs, but also on rabbits when all rules for elaborating conditioned reflexes were observed. The possibility of influencing immunity by conditioned reflexes has thus become the question of the day and requires further study.

There are also other observations. Deep inhibition and intense depression of functional mobility in the central nervous system in some animals during winter hibernation and in animals in a state of narcotic sleep reduce the production of antibodies, the phagocytic reaction of leukocytes and the general reactivity of the organism to stimuli, including infectious agents and toxins. Lastly, the role of the central nervous system in immune reactions has been demonstrated in experiments with intracerebral and subarachnoid administration of antigens. The effectiveness of such inoculation is often manifested sooner and to a greater extent than in administration of antigens subcutaneously or into the blood.

The central nervous system regulates immunity through the vegetative nerves. For example, stimulation of parasympathetic nerves depresses the phagocytic reaction of the leukocytes, whereas stimulation of sympathetic nerves stimulates it. Although the results of the experiments with various influences on the vegetative division of the nervous system have often been contradictory, on the whole they have established the fact of its influence on the immune properties of the organism.

Some researchers explain the formation of immune bodies by influences exerted on the nervous receptors by antigens gaining entrance into the organism. Transection of the afferent nerves of the part of the tissue inoculated with an infectious agent of novocain anesthesia cause a diminished production of immune bodies and an increased susceptibility to infection (Friedberger et al).

Immune phenomena also involve endocrine glands which participate in the organism's response reactions to the action of infectious agents. For example, in thyroid insufficiency man shows a tendency toward relapsing erysipelas and certain other diseases of the mucous

membranes, while dogs exhibit a reduced sensitivity to diphtheria toxin.

In experiments exclusion of the function of the adrenal cortex has resulted in a lowered resistance of the organism to diphtheria toxin, typhoid vaccine and tuberculous infection. Administration of desoxycorticosterone favourably affects the course of tuberculosis and certain other infections, (adrenocortical hormone), whereas that of hydrocortisone reduces the formation of antibodies and lowers immunity.

The influence of the hypophysis on the course of infections and immune reactions is apparently effected by means of its erinogenic hormones.

Allergy

*Allergy is a heightened and qualitatively altered sensitivity of the organism to the action of infectious agents or other substances of antigenic nature (allergens).** Like immunity, allergy is an expression of the organism's immunobiological reactivity and underlies the pathogenesis of a number of diseases.

The phenomena of increased and qualitatively altered sensitivity of the organism include *anaphylaxis***, one of the most widespread allergic diseases.

Anaphylaxis

Anaphylactic phenomena in dogs were first observed by Richet (1902). Soon afterwards an analogous reaction was reproduced in guinea pigs (T. Smith, G. Sakharov; 1905).

Anaphylaxis is a state of increased susceptibility or hypersensitivity following a repeated parenteral injection of a foreign protein.

To produce anaphylaxis, the animal is first sensitised, i.e., it is rendered hypersensitive, for which purpose a small amount (0.1-1 ml) of serum protein, for example, horse serum, is administered parenterally. Such primary injection of serum is known as a sensitising injection.

Sensitisation may be effected by any parenteral method—subcutaneously, intramuscularly, intraperitoneally and intravenously. Enteral administration usually fails to effect a sensitisation because the gastrointestinal mucosa is impermeable to protein, while the enzymes of the digestive juices destroy the ability of the protein to produce anaphylaxis. Only in injuries to the epithelium of the mucosa, for example, on administration of an antigen simultaneously with bile does the permeability of the intestinal wall increase and the organism become sensitised.

* From the Greek: allos--other, and ergon—work.

** From the Greek: ana—negation, and phylaxis—guarding.

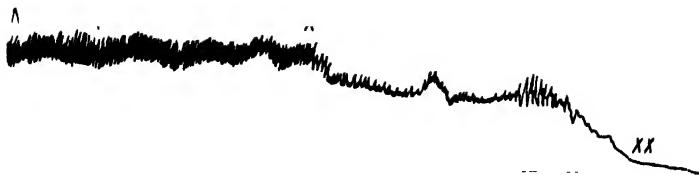


Fig. 13. Curve of the blood pressure in the carotid artery of the rabbit during anaphylactic shock.

N—normal blood pressure; *R*—resolving injection; *X*—beginning of the drop in blood pressure; *XX*—end of the drop in blood pressure and the animal's death.

In guinea pigs a state of hypersensitivity may be produced by parenteral administration of even negligible doses of foreign protein (0.01-0.001 and sometimes even 0.000001 ml of horse serum, milk or egg albumen). The state of hypersensitivity does not develop at once, but after a certain period of time, which is known as the *incubation period*.

In the guinea pig the latent (incubation) period is at least 10-12 days. The smaller the requisite sensitising dose, the shorter this period, and vice versa.

The state of hypersensitivity is retained for a long time—in guinea pigs sometimes for 2 years.

At the end of the latent period a second, so-called *resolving injection* is made, i.e., a dose of protein larger than the first dose is injected in the animal's blood. The organism's hypersensitivity manifests itself in response to the second administration of the same protein with which the animal was sensitised. This denotes the specificity of anaphylaxis.

The resolving injection is usually made intravenously because this ensures rapid delivery of the antigen and the highest intensity of the subsequent phenomena of anaphylactic shock.

Anaphylactic Shock

The first symptoms of anaphylactic shock in the guinea pig appear 2-3 minutes after the resolving injection. The animal becomes restless, rubs its muzzle with a paw and bristles up; the whole body begins to twitch convulsively. Several minutes after the beginning of the attack the guinea pig falls on a side, tonic and clonic spasms develop, involuntary urination and defecation occur, respiration becomes intermittent and gradually slows down, and the animal usually dies of asphyxia within a few minutes.

Of the other phenomena occurring in anaphylactic shock mention must be made of severe circulatory disorders characterised mainly

by a sharp drop in blood pressure (Fig. 13), dyspnea, diminished oxidative processes, lowered body temperature, acidosis, decreased erythrocyte sedimentation rate, leukopenia, disappearance of complement from the blood and increased permeability of vascular endothelium.

The picture of anaphylactic shock is particularly noticeable in dysfunction of the nervous system. This dysfunction is manifested in general excitement followed by depression and convulsions, as well as respiratory and circulatory disturbances.

Autopsy of the guinea pig killed by anaphylactic shock reveals greatly distended, air-filled lungs. The lungs do not collapse and cover the heart which for some time continues to contract. The direct cause of asphyxia is contraction of the smooth muscles of the bronchi resulting in constriction of their lumens, which leads to retention of the air and distention of the lungs.

The phenomena observed in anaphylactic shock vary in intensity with the dose of antigen and the method of its administration.

Different animals are differently susceptible to anaphylaxis; for example, rabbits and dogs are less susceptible than guinea pigs; rats and mice can hardly be sensitised. The picture of shock and the character of dysfunction of the organs in anaphylactic shock also vary. In guinea pigs, as was already mentioned, the lumens of the bronchi become considerably constricted; spasm of the muscles of pulmonary arterioles is most pronounced in rabbits, while in dogs the circulation in the system of the portal vein is sharply impaired probably because of spasm of the sphincters in the hepatic veins.

Passive Anaphylaxis

In normal animals it is possible to produce passive anaphylaxis, for which purpose they are administered the serum of actively sensitised animals of the same or another species. Anaphylactic shock may be produced in such sensitised animals if they are administered a relatively large amount (5-10-20 ml) of the antigen used in sensitising the animal from which the serum was taken.

Passive sensitisation does not take place at once but some time after injection of the serum of the sensitised animal (latent period). In cases of subcutaneous administration of the serum the latent period is 24-48 hours; this period decreases to 12 hours in cases of intraperitoneal and to 4 hours in cases of intravenous administration. It varies with the species of animal and the conditions of passive sensitisation.

Passive anaphylaxis may be produced experimentally in guinea pigs, rabbits, dogs, white mice, horses and other animals. For this purpose the rabbit is the most suitable experimental animal. In passive (unlike active) sensitisation the anaphylactic state lasts but a short time—up to 3-4 weeks.

Local Manifestations of Anaphylaxis

These include *Arthus' phenomenon* (1903) which is produced as follows: a rabbit is subcutaneously administered 3-5 ml of horse serum every 5-6 days. Already after the fourth injection an infiltrate appears at the site of administration and persists for 2 days. The fifth or sixth injection is followed by phenomena of acute inflammation with necrosis and edema of the tissue (allergic, hyperergic inflammation). At the same time structural disturbances develop in the walls of the blood vessels, the basic substance of connective tissue, the nerve endings and nerve trunks.

In a sensitised organism it is also possible to produce phenomena of allergic inflammation on the mucous membranes and in internal organs. Allergic inflammation was observed not only in rabbits which, in this respect, are classic experimental animals, but also in goats, guinea pigs, horses and, in fewer cases, in man (Fig. 14).

The *Schwartzman phenomenon* is considered by some people to belong to the same category of phenomena. The filtrate of a broth culture of microbes, for example, the colon bacilli (0.1-0.2 ml), is administered into the rabbit's skin. Twenty-four hours later a filtrate of the same microbe is administered into a vein (0.1-0.5 ml per 1 kg of the animal's weight). Depending on the dose of the filtrate used in the second injection the animal either soon dies or (when given smaller doses) develops at the site of injection a hemorrhagic infiltrate which becomes necrotic.



Fig. 14. Hyperergic reaction in man at the site of a repeated injection of antitetanic serum several weeks after the first injection of the same serum.

The same phenomenon can be produced with the filtrate of broth cultures of other microbes—pathogens of cholera, tuberculosis, brucellosis, etc. But this phenomenon, unlike Arthus' phenomenon, is not a strictly specific reaction.

"Local" anaphylaxis (Arthus' phenomenon) may develop only in preliminarily sensitised animals. This is evident from the fact that administration of an antigen into the general circulation produces anaphylactic shock. Anaphylaxis may be transmitted passively, for which purpose the rabbit is administered serum from another rabbit sensitised with horse serum. After the former is administered 1-2 ml of the same serum subcutaneously it develops a hyperergic reaction.

The intensity of allergic reactions in the tissue is also dependent on the state of the organism's metabolism. The allergic reaction is more strongly pronounced when the liver is rich in glycogen. Moreover, already in the course of sensitisation it is possible to observe a certain intensification of the oxidative processes, while the dynamics of hyperergic reaction shows disturbances in carbohydrate metabolism—decreased glycogen in the liver, incomplete oxidation of carbohydrates and accumulation of acid metabolites (D. Y. Alpern, N. N. Trankvilitati et al.).

Desensitisation

The process of terminating the state of hypersensitivity is called *desensitisation*. Desensitisation may be produced by various substances acting mainly on the nervous system (nonspecific desensitisation)—ether, chloral hydrate, alcohol, adrenalin, atropine, calcium chloride, and ultraviolet and roentgen rays. However, the desensitising effect of all these substances is unstable.

Of considerable theoretical and practical interest is desensitisation of an animal by an injection of a small dose of a specific antigen before the end of the latent period or when hypersensitivity has already developed (specific desensitisation). This method developed as a result of observations of sensitised animals which have survived anaphylactic shock. Such animals resist the effects of subsequent administration of antigen. In these animals the state of anaphylaxis is replaced by a state of antianaphylaxis or immunity.

Experimental production of a desensitised state has served as the basis for preventing phenomena of anaphylaxis in man. Thus, in diphtheria, 4 hours before administration of the main dose of anti-toxic serum, a small dose (1-2 ml) of this serum is injected prophylactically, which prevents the development in the patient of anaphylaxis during the subsequent administration of a massive dose of antidiphtheria serum for therapeutic purposes.

Specific desensitisation usually develops rapidly, the desensitised state lasting from several hours to several weeks, depending on the

species of the animal and the method of injection. Thus the desensitised state in rabbits is of shorter duration (sometimes 3-4 days) than it is in guinea pigs (2-3 weeks and longer). Injections of several increasing doses at intervals of 15-30 minutes produce the longest desensitised state.

Pathogenesis of Anaphylaxis

The mechanism of anaphylaxis was studied from the point of view of *humoral and cellular changes*.

According to one of the first humoral hypotheses, sensitisation produces antibodies which freely circulate in the blood where, after the second injection, they meet with the antigen. The reaction results in formation of *anaphylatoxin* which conditions the picture of shock. However, it has been impossible to isolate anaphylatoxin. It has developed, moreover, that the properties of the blood serum ascribed to anaphylatoxin are also obtained by treating fresh serum with agar, kaolin, starch, etc., i.e., in cases where the serum comes in contact with substances not hydrolysed under its influence.

The hypothesis according to which the antigen-antibody reaction liberates *histamine* is more popular. The amount of histamine in the blood in anaphylaxis and other allergic states increases. Antihistaminic preparations suppress the manifestations of anaphylaxis. However, administered to an animal histamine does not completely produce anaphylactic shock. Furthermore, there is no parallel between the extent of histamine accumulation and manifestations of anaphylaxis. Other vigorously acting histamine-like substances, as well as acetylcholine, adeninenucleotides, heparin and proteolytic enzymes, apparently also play some part in the pathogenesis of shock. All of these substances may form not only in the blood but also in the tissues.

According to the cellular hypothesis, the antigens meet with the antibodies mainly in the tissues. This is attested by the following facts: 1) specific reaction to an antigen on the part of survived organs taken from a sensitised animal and carefully washed from the blood, for example, a horn of the uterus of the guinea pig (Fig. 15) or vessels from the rabbit's ear; 2) anaphylactic reaction in the tissue in which the antigen is injected; 3) retention of the anaphylactic reaction to the antigen in a sensitised animal even after replacement of its blood with the blood of a normal animal; 4) necessity of a latent period for the development of passive anaphylaxis; 5) clearly marked decrease in the adsorption capacity of the reticuloendothelial cells. It is supposed that in allergy the interaction between the antigen and antibody in the cell is accompanied by formation of roughly dispersed complexes which adsorb and thereby block intracellular enzymes. However, there is no authentic proof in support of this view.

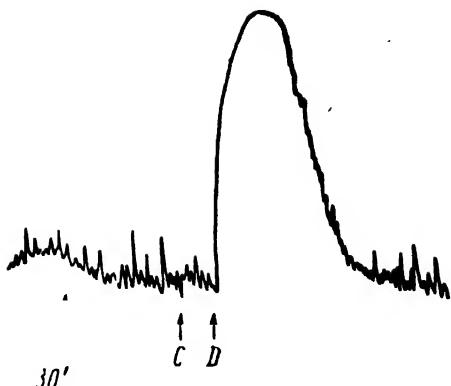


Fig. 15. Reaction of the horn of the uterus of the guinea pig sensitised with horse serum.

Additions to the perfusion liquid: A—0.5 ml of sheep serum; B—0.5 ml of cat serum; C—irrigation with Ringer's solution; D—addition of 0.01 ml of horse serum (Dale).

At the same time numerous experiments have revealed that changes in the function of the nervous system are of paramount importance in the origination of anaphylactic phenomena.

Thus nervous phenomena prevail in the general picture of anaphylactic shock. Alexander Besredka was the first to observe the significance of the nervous system in the development of anaphylactic shock. He substantiated his opinion by the possibility of experimentally preventing shock in guinea pigs by means of narcotics.

It is also well known that it is impossible to produce anaphylactic shock in hibernating animals during their long sleep.

Moreover, sensitised animals show, especially after the resolving injection, an altered functional state of the cerebral cortex, a predominance of the inhibitory process, a prolonged latent period of conditioned reflexes and development of a parabiotic state (presence of phasic phenomena). The parabiotic nature of anaphylactic shock is also attested by the possibility of its elimination by stimulating the medulla oblongata with the anode of direct current which increases the lability of the nerve centres.

Lastly, there are also numerous experimental observations concerning the effect of antigen on the receptor apparatus and the reflex nature of anaphylactic phenomena. For example, the chemoreceptors of sensitised animals show increased sensitivity to the repeated action of antigen. This may be established by the circulatory and respiratory changes produced in such animals by injection of the antigen in the carotid sinus disconnected from the blood stream (A.D. Ado).

The dependence of anaphylactic reactions on the properties of the organism as a whole and on the functional state of its nervous system has also been confirmed by studies of allergy in man.

Phenomena of Allergy in Man

The closest to experimental anaphylaxis in man is the *serum sickness*. It may be caused by a therapeutic injection of horse serum with respect to which the organism happens, at the given moment, to be sensitised. It may also set in after the first administration of the serum (within 9-20 days). In these cases the onset of the serum sickness may be explained by the fact that the injected antigen (horse serum) has caused formation of antibodies which, having accumulated before the antigen was completely eliminated from the organism, react with its remains.

The serum sickness is characterised by a rise in body temperature, a drop in blood pressure, a redness and itching at the site of injection, an eruption all over the body, inflammation of the joints, swelling of the lymph nodes, nausea, vomiting, and edema of the lips and face. Occasionally it results in death. The blood shows at first leukocytosis which is soon, as in anaphylactic shock, replaced by leukopenia and lymphocytosis. Within several days or weeks these phenomena usually disappear without leaving a trace.

However, a true anaphylactic shock, like the one observed in experiment, very rarely occurs in the serum sickness in man.

An injection of the serum in the skin of a person sensitised to it may cause an inflammation with edema and necrosis—Arthus' phenomenon. Man may manifest an increased and altered sensitivity to substances of an antigenic as well as nonantigenic character—*food and drug allergies*. These substances may be foodstuffs (milk, strawberries, lobsters, eggs) or drugs (iodine, iodoform, bromides, salicylates, sulfonamides, etc.), and their action cannot be connected with their specific pharmacological properties.

Ingestion of the foregoing foods and drugs produces characteristic allergic phenomena mainly in the skin and the vascular system; these phenomena include hyperemia of the mucous membranes, edema, urticaria (an eruption in the form of wheals on the skin attended with itching or burning), pyrexia, vomiting and sometimes a state of shock. The allergic reaction sometimes appears merely at the sight of the antigen (allergen), which indicates a possibility of its conditioned reflex origin. This circumstance, as well as the rapidity with which these phenomena develop, their character and intensity depending on the reactivity of the organism, denote the important role played by the nervous system, particularly its higher part, in allergy.

It is also possible to sensitise the skin to 2-4 dinitrochlorbenzol, nickel and chromium salts.

The pathogenesis of allergic disturbances has not yet been established. There are reasons to believe that food allergy is due to absorption of protein through the intestines. Owing to the altered permeability of the intestinal wall, food protein foreign to the organism penetrates into the latter in a nonhydrolysed state and produces phenomena resembling anaphylaxis. Drug allergy in which the ingested substance is not a protein may be likened to anaphylaxis only in so far as the substance of a nonantigenic character by combining with proteins in the organism may cause transformation of these proteins with the result that the latter become foreign and acquire antigenic properties. Such allergy could be explained as sensitisation of the organism with its own proteins modified by some exogenous substance (hapten).

Man's increased sensitivity to certain substances underlies a number of special *allergic diseases* which set in suddenly and run a paroxysmal course. These diseases are characterised either by a skin affection taking the form of edema, wheals or eczema, or by irritation of the mucous membranes of the eyes and nose, or by spasm of the blood vessels and smooth muscles. Such diseases include *bronchial asthma* manifested in attacks of dyspnea resulting from spasm of the smooth muscles and swelling of the mucosa of small bronchi. The allergens causing attacks of bronchial asthma gain entrance into the organism through the respiratory tract and may be of various origin—pollen, hair, wool and animal epidermis.

Attacks of bronchial asthma in a person formerly affected with it may also be provoked by conditioned reflexes. A patient sensitised to pollen may sometimes have an attack of the disease at the mere sight of a flower.

Hay fever is another allergic disease; it affects, predominantly in the spring or beginning of summer, persons particularly sensitive to pollen of certain plants (rye, asters, hyacinths, etc.), and is characterised mainly by inflammation of the nasal mucosa and the conjunctiva—rhinitis and conjunctivitis—which usually develop during the blooming period.

The group of allergic diseases includes certain *inflammatory changes in the skin* (dermatitides). They are sometimes observed in industry as a result of frequent contact of the skin with resinous substances, lacquer, paints and nickel. The development of such dermatitides requires previous sensitisation of the organism to these substances, which is easily avoided if the rules of industrial safety are observed.

Phenomena of allergic reactivity—*infectious allergy*—play an important part in some infectious diseases. The organism's hypersensitivity to bacteria or, more frequently, to the products of their vital activity is apparently of considerable importance in the pathogenesis of tuberculosis, glanders, acute rheumatism, syphilis and septic

diseases. These diseases are characterised by increased sensitivity of the organism to extracts from cultures of corresponding microbes. Allergic phenomena include, for example, an intensified reaction of the organism affected with tuberculosis to subcutaneous administration of tuberculin (tuberculin reaction) or development of inflammatory phenomena in response to application of tuberculin to a superficial abrasion of the skin (the Pirquet test). An analogous phenomenon is observed in glanders on intradermal administration of malein (malein test). These phenomena are of diagnostic importance.

In acute rheumatism allergic phenomena are manifested in hypersensitivity mainly of the serous membranes of the heart and joints to infectious agents or their toxins reaching them from the primary focus. The primary foci of rheumatic infection may be the oral cavity, the nasopharynx (tonsils) and dental granulomas. In rheumatism allergic manifestations are also characterised by changes in the heart and joints, as fibrinoid degeneration of connective tissue and walls of vessels, as well as formation of peculiar granulomas. Analogous structures are observed in rabbits on production of Arthus' phenomenon in their joints.

Certain symptoms manifesting themselves in tertiary syphilis, vascular and tissue changes in rheumatism, croupous pneumonia and round ulcer of the stomach are also of an allergic character. As a result of the development of allergic reactions in the organism, morphologic changes in elements of mesenchymal origin, in the vessels in particular, are discovered (A. I. Abrikosov).

Allergy is now recognised as one of the important pathogenic factors of certain collagenoses (collagen diseases) based on an affection of the intercellular substance of connective tissue in the form of a mucoid and fibrinoid swelling, hyalinosis and sclerosis. Collagenoses are characterised by progressive processes of systemic disorganisation and polymorphous changes in the connective tissue of the heart valves and vascular walls (A. I. Strukov).

In addition to the usual reactive manifestations of an allergic character, mention must be made of so-called *nonspecific allergies* in man. These allergies appear as a result of changes in the reactive properties of the organism under the influence of factors of both antigenic and nonantigenic character. They include the form of allergic reaction known as *para-allergy*. This implies an altered reaction of the organism sensitised by one allergen to the action of another, nonidentical allergen. A manifestation of the tuberculin reaction or a flare-up of encephalitis following smallpox vaccination may serve as examples.

Nonspecific allergies also include the Schwartzman phenomenon, and the altered reaction of a repeatedly protein-sensitised organism to the action of a stimulus of nonantigenic nature, for example, cooling.

The mechanism of development of nonspecific allergies is not as yet completely clear. Disturbances in the function of the nervous system play a definite part in their pathogenesis. The phenomena of para-allergy may in some measure be explained in the light of the theory of parabiosis. Indeed, the state of para-allergy is characterised by a change in the excitability of the organism and its nervous system with respect not only to an antigen, but also to other stimuli. This is one of the typical features of a parabiotic state.

Allergic reactions may also appear on sensitisation of the organism with autoantigens and autoallergens formed as a result of transformation of the organism's own proteins in pathologically altered tissues. In response to the formation of autoantigens corresponding antibodies are formed in the organism. Some diseases may apparently develop on this basis, for example, allergic thrombopenia, leukopenia and agranulocytosis, allergic phenomena in endocarditides, glomerulonephritides, etc.

The development and manifestations of allergic reactions in man are more complex than in animals. Unlike experimental anaphylaxis, in human allergy the portals of entry and the nature of the allergen or presence of primary sensitisation cannot always be established.

PATHOLOGY OF NUTRITION. STARVATION

DISTURBANCES IN BASAL METABOLISM

The basal metabolic rate is of considerable importance for the study of nutritional disorders and the energy balance.

Basal metabolism is the minimum amount of energy expenditure necessary to maintain cellular activity when the body is at complete rest in a warm atmosphere ($16\text{-}18^{\circ}\text{C}$) 12-18 hours after the intake of food.

The basal metabolism of an adult of medium height and weight is 1,600-1,700 Cal. In terms of 1 kg of weight basal metabolism is 1 Cal/hr; in terms of 1 m^2 of body surface it is 984 Cal/day.

In pathology basal metabolism may vary, i.e., either increase or decrease.

Disturbances in basal metabolism occur in endocrine disorders because basal metabolism is considerably influenced by the endocrine glands.

An increase in basal metabolism, sometimes 70 per cent and higher, is observed in *exophthalmic goitre* (Basedow's disease), which is caused by hyperfunction of the thyroid. The same state is produced by administration of thyroxin—the hormone of the thyroid. Basal metabolism is also increased in *acromegaly* as a result of hyperfunction of the anterior lobe of the hypophysis.

Basal metabolism is decreased in cases of hypofunction of the thyroid, as in *myxedema* and *cretinism*. A similar state is observed in cases of destruction or atrophy of the anterior lobe of the hypophysis (hypophyseal cachexia), and in adrenal afunction.

Determination of basal metabolism helps to elucidate the origin of *endocrine forms of obesity* which are characterised by a certain decrease in metabolism.

Basal metabolism is also affected by other pathologic processes: it increases in fever, infectious diseases, blood diseases and disturbances in cardiac activity.

Another criterion for evaluating disturbances in nutrition and energy metabolism is the *specific dynamic effect of food*, which implies the ability of foodstuffs to produce additional energy.

The greatest specific dynamic effect is produced by proteins, a lesser effect—by carbohydrates and a still lesser—by fats. After ingestion of proteins the increase in heat production reaches 20 per cent (an average of 16 per cent), after ingestion of carbohydrates—10 per cent and after an intake of fats—3-4 per cent. The individual properties of an organism and its complex reflex activity affect the specific dynamic effect of food. It has been established that the specific dynamic effect of protein is also produced by sham feeding with meat.

The specific dynamic effect of food is altered by environmental factors (temperature, character of work) and the functional state of the central nervous system which exerts its influence through lower parts of the nervous system and the endocrine glands (thyroid, hypophysis and gonads).

All pathologic states in which basal metabolism is increased are also characterised by a corresponding increase in the specific dynamic effect of food.

A decrease in the specific dynamic effect of food, especially in a high-caloric diet, may be one of the factors contributing to obesity.

STARVATION

Starvation is a state in which the organism either receives no food at all, ingests insufficient food or inadequately assimilates the food necessary for normal existence. To cover its energy expenditures a starving organism consumes its own nutrient reserves. Starvation accompanies various diseases, for example, infectious, gastrointestinal and metabolic. The treatment of certain diseases, for example, those of the digestive organs sometimes requires a limited ingestion of food. Some nurslings starve because of poor sucking, defective development of the oral cavity, or defects in the mother's organism (flat nipples, insufficient lactation, changes in the quality of the milk). Starvation also occurs in natural calamities (floods and earthquakes) and in connection with war or economic dislocation.

The following forms of starvation are distinguished: *total*, quantitative, i.e., when the organism is completely deprived of food; *incomplete*, when the food is calorically insufficient to cover the energy expenditures or its assimilation is disturbed; *partial* (qualitatively inadequate, one-sided diet), i.e., calorically normal food, but lacking some constituents—proteins, carbohydrates, fats, salts or vitamins.

The laws governing the starving organism have been established mainly by the experimental research of V. V. Pashutin and his pupils—P. M. Albitsky, P. P. Avrorov, A. V. Reprev et al, and the data furnished by Voit, Rubner and, later, Benedict.

Total Starvation

During total starvation the organism lives by consuming the substances of its own tissues.

Total starvation (without limitation of water intake) is endured much more easily than absolute starvation.

According to *clinical phenomena*, total starvation observed in experiment may be divided into four periods: 1) period of indifference, when the animal behaves relatively calmly; 2) period of excitement; 3) period of depression (the longest); 4) period of paralyses ending in the animal's death. No deviations from the habitual state are observed during the first period of total starvation. The increasing feeling of hunger is accompanied by phenomena of excitement. Subsequently the animal displays sluggishness, weakness and depression, and for the most part lies rolled up into a ball. During the last period of starvation, following a brief decrease in the excitability of the nervous system, the latter is paralysed and the animal dies.

The *duration of total starvation* (with intake of water) varies with different people and, especially, with different animals.

A human adult can starve for 50-70 days and even longer; a dog—more than 40 days. Generally, a starving animal lives until it has lost 45-50 per cent of its initial weight.

The duration of total starvation varies with the ratio of the mass of the body to its surface: the greater the surface per unit of weight, the higher the expenditure of energy. The period of possible starvation of an animal is inversely proportional to the ratio of its surface to its weight, for which reason larger starving animals live longer than small ones. Thus the horse lives longer than the dog, the dog longer than the cat, etc.

However, this so-called law of surface requires essential amendments. Other things being equal, it is necessary to take into account the specific features of the body surface, for example, the hair of mammals or feathers of birds, the degree of development of the subcutaneous layer of fat in animals and, most important of all, the dependence of metabolism on influences of the external environment and neuroendocrine activity. It is well known that wild animals spend more heat than do domestic animals of the same size.

The starvation period of animals of the same species also depends on the intensity of basal metabolism, state of nutrition, muscular activity and surrounding temperature. The period of possible starvation diminishes by intensified muscular activity, increased basal metabolism and lowered surrounding temperature. The younger the organism, the more intense its metabolism and the shorter the period of its total starvation. Other factors being equal, well-nourished animals can starve a longer time.

Basic Functions of the Organism in Total Starvation

A starving organism exhibits disturbances in heat and gas exchange, as well as in protein, fat, carbohydrate, salt and water metabolism, the animal losing weight correspondingly; at the same time changes are observed in the functions of the heart, blood vessels, the respiratory apparatus, gastrointestinal tract, liver and kidneys (Figs. 16 and 17).

The *animal's weight* diminishes gradually; in the beginning, during the first days of starvation, the curve of the daily loss of weight drops relatively steeply because of the excretion of feces and insufficient adjustment of the organism to the new conditions of existence. Subsequently, the weight is reduced slowly and evenly. During the last days of starvation the weight curve begins to drop sharply again as a result of rapid tissue decomposition.

In starvation the *different organs do not lose weight equally*. The fat depots lose the most weight, the abdominal organs (spleen, liver) lose less, the heart and the organs of the nervous system, very little (Fig. 18).

These differences in the loss of weight by the different tissues show that during starvation, processes of decomposition are accompanied by synthesis with the result that some organs retain their weight almost until death. For example, starvation hardly affects the intensity of energy metabolism in the heart, whereas in the liver it drops appreciably, the processes of utilising glucose diminishing in particular because of the decreased activity of the enzyme necessary for phosphorylation of glucose.

The *temperature of the body* changes but little all through the period of starvation and persists at the lower limits of the norm. An appreciable drop in temperature (to 30-28°C) may be observed only at the very end of starvation. The production of heat is gradually established on a minimal level, the curve of heat production dropping somewhat more sharply only towards the end of the second period of starvation.

The different periods of starvation may be characterised only on the basis of the changes occurring in the biochemical processes, and general and energy metabolism.

As regards the *changes in metabolism*, starvation may be divided into *three basic periods*. The *first period* (1-2 days) is marked by insufficient economic expenditure of energy; the respiratory quotient is equal or close to 1, which denotes oxidation mainly of carbohydrates; expenditure of proteins is decreased (6-7 g of nitrogen is excreted per day instead of the normal 10-12 g). The *second and longest period* is the period of greatest adjustment; the organism's expenditures are reduced to the minimum, the carbohydrate reserves have been exhausted and mainly fats are beginning

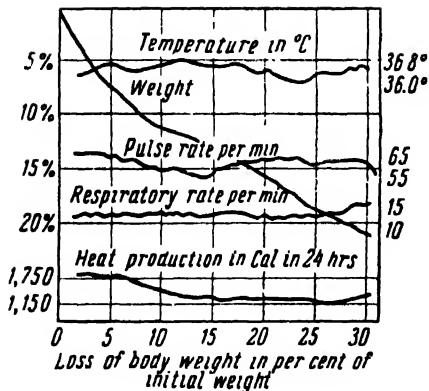


Fig. 16. Curves showing changes in the weight, pulse, respiration, temperature and heat production during total starvation of the dog (V. V. Pashutin).

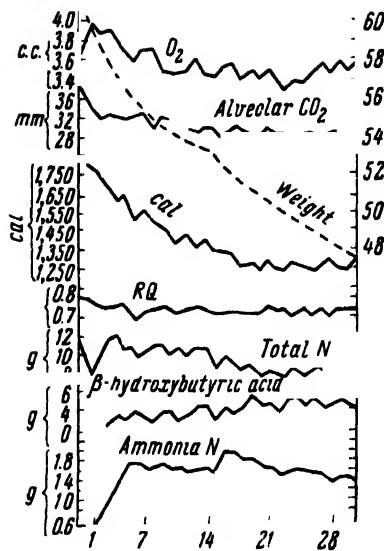


Fig. 17. Curve showing changes in the metabolism of a starving man.

Axis of the ordinates shows the indices of disturbances on the left and weight on the right; axis of the abscissas—days of starvation (from Benedict); the three lower curves show the substances contained in the daily amount of urine.

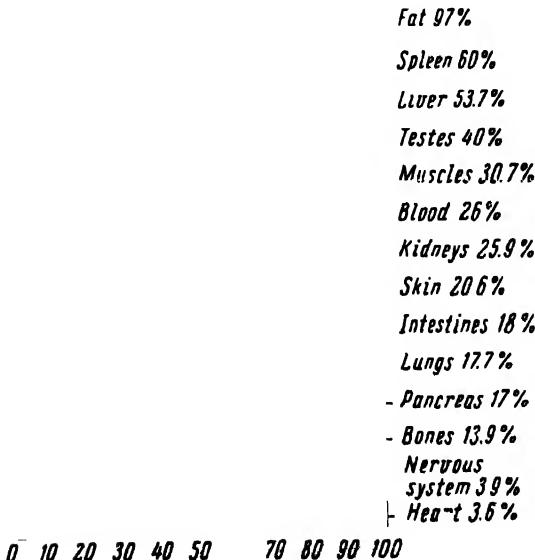


Fig. 18. Weight loss by different organs during total starvation.

to be expended; the respiratory quotient drops to 0.7 (oxidation mainly of fats) and the expenditure of proteins is reduced to the minimum, constituting 10-12 per cent of the total caloricity. The *third* and conclusive period (2-3 days) is characterised by decomposition of proteins needed by the tissues, increased excretion of nitrogen in the urine and intense intoxication with products of tissue decomposition.

In the course of the second period of starvation it is sometimes possible to observe appreciable fluctuation of the respiratory quotient. Its excessive drop (below 0.7) apparently reflects the complex reorganisation of metabolism and is possibly the result of the conversion of fats into carbohydrates (which requires an expenditure of oxygen) or of incomplete oxidation of fats. On the other hand, rises in the respiratory quotient are perhaps due to the occasional relative predominance of oxidation of carbohydrates and proteins over that of fats. Increased utilisation of incompletely oxidised fat by the liver is accompanied by intensified formation of ketone bodies, a certain accumulation of these bodies in the blood and, consequently, their passage into the urine.

Accumulation of products of incomplete oxidation of proteins and, especially, fats results in acidosis. The alkali reserves in the blood diminish, and more potassium, sodium and ammonium is excreted in the urine. Retention of chlorine and water is observed. Excretion of sulfur and phosphorus in the urine increases (sulfur forms part of a number of proteins, phosphorus—of lipid substances). The total amount of ash increases with respect to the total weight of the animal (Fig. 19).

Changes in the Functions of Various Organs and Systems. During the second and longest period of starvation reflex activity noticeably weakens, conditioned reflexes disappear and inhibition develops in the cerebral cortex. The functional activity of the cardiovascular system and respiratory apparatus is close to normal. The end of the second period of starvation is characterised by a certain acceleration of the heart and respiratory rates which subsequently slow down. The functional activity of the gastrointestinal tract is greatly weakened. The excretion of urine decreases, increasing again only towards the end of starvation when more intensive decomposition of proteins begins. No appreciable disturbances in the blood constit-

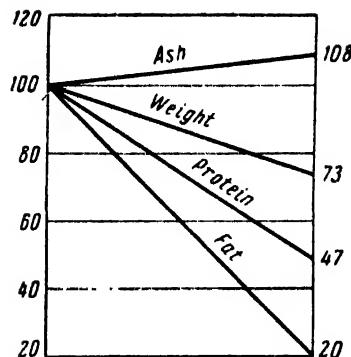


Fig. 19. Changes in weight, amount of protein, fats and ash during total starvation.

uents are observed with the exception of hydremia, i.e., a certain dilution of the blood. In the course of starvation the quality of the formed elements somewhat changes, macro- and microcytes and degenerate forms of leukocytes appearing in the blood stream. The microscopic changes in the organs are not in any way specific; only phenomena of atrophy, mainly in the parenchymatous organs, are observed.

Total starvation without consumption of water, or absolute starvation, is governed by the same basic laws, but is much more severe and does not last so long because of accumulation of noxious metabolites in the organism and the concomitant general intoxication. The organism utilises the water of its own tissues, which is conducive to still more intensive decomposition. The increase in tissue decomposition is due to increased protein disintegration. The accumulating metabolites may produce a febrile process by affecting the central nervous system.

Incomplete Starvation (Chronic Undernourishment)

Incomplete starvation is observed in certain pathologic states, for example, in partial gastrointestinal obstruction and in chronic diseases. It may also be caused by war and low living standards.

The course of incomplete starvation depends on the amount of food consumed and the degree of the organism's adjustment to the insufficient coverage of its energy expenditures.

Chronic undernourishment implies that the organism long fails to receive with the food the number of calories necessary for its energy metabolism; for example, instead of the 2,500-3,000 Cal and more (depending on the work done) it receives only 2,000-1,500 Cal, or even less. Incomplete starvation is usually also qualitative.

In incomplete starvation the *weight* decreases more slowly than in total starvation, the intensiy of the weight loss depending on the amount of food consumed.

Incomplete starvation lasts longer than total starvation.

The organism dies after a loss of about 40 per cent of its weight. This is due to qualitative disturbances in metabolism which are deeper in quality than in total starvation and more significant dystrophic changes in tissues accompanying incomplete starvation. The weight loss in incomplete starvation is not so regular as it is in total starvation. Not infrequently the weight loss due to the organism's consumption of its own tissue reserves is camouflaged by water retention.

In incomplete starvation *metabolism* is perceptibly altered. Basal metabolism and the specific dynamic effect of food are diminished. The oxidative processes are weakened and acidosis develops. Excretion of nitrogen in the urine decreases and with predominantly

carbohydrate food may drop to 3-4 g per day, long remaining on a low level.

The decrease in blood protein causes a reduction of the colloid osmotic pressure which is more strongly pronounced than in total starvation. This often causes development of *edemas* which may run different clinical courses.

The *respiratory quotient* does not drop appreciably in incomplete starvation since the organism continues to receive some carbohydrates from without. The blood becomes hydremic.

Protracted incomplete starvation is usually accompanied by development of anemia. Extinction of the sexual instinct due to atrophy of the gonads is particularly strongly pronounced. Nervous activity is disturbed. A somewhat excited state develops, the depression stage taking long to set in. The processes of internal inhibition, especially of differentiating inhibition, are weakened. Mental derangement is sometimes observed. Cardiac activity is decelerated, hypotension develops, respiration weakens and the amount of circulating blood diminishes.

Partial (Qualitative) Starvation

Carbohydrate starvation, especially in cases of surplus fats in the food, leads to development of acidosis owing to deposition of fat in the liver, its insufficient oxidation and accumulation of fat metabolites—ketone bodies.

Proteins and, to a lesser extent, fats may, as is well known, serve as material for the formation of carbohydrates, for which reason even in complete absence of carbohydrates in the food a certain amount of carbohydrates is formed in the organism from other substances. Disturbances in carbohydrate metabolism may not occur even if the food contains very little carbohydrates.

If the food is sufficiently caloric, *fat starvation* does not cause any particular changes in the organism since, according to the laws of isodynamia, fats can be replaced by carbohydrates and proteins. However, at least 5 g of fats is necessary in the daily food ration because of the indispensable fatty acids (linoleic and linolenic acids) they contain.

Protein starvation occurs in cases in which the organism receives no proteins at all or receives them in lesser amounts than is necessary to maintain the nitrogen balance. According to the Voit diet, the amount of protein in the daily food ration corresponds to 16-20 g of nitrogen (118 g of protein). However, in a person of medium weight the nitrogen balance may be long maintained by consumption of 70-80 g of protein a day, provided his food contains enough fats and carbohydrates.

The absence of protein in the food, even if the latter contains sufficient fats and carbohydrates, causes deep changes in metabo-

lism. The nitrogen minimum is established gradually and is maintained relatively long because of the protein-preserving action of carbohydrates and fats, but then the protein reserves and, finally, the structural protein of the tissues begin to be expended. The different tissues consume their own proteins unevenly. The proteins of the liver are utilised the most.

The fermentative processes change and the intermediate phases of protein metabolism are disturbed.

Protein starvation may be caused, not only by an insufficient amount of proteins in the food, but also by their inadequacy, i.e., insufficiency of essential amino acids in them. For example, protein food devoid of leucine, isoleucine, lysine, tryptophan, phenylalanine, methionine and valine is inadequate and does not cover the minimum nitrogen requirements. In such cases the functions of vitally important organs are disturbed and the growth and development in a growing organism are retarded.

Chronic undereating with a predominant deficiency of proteins in the food may lead to *dystrophy*. This is characterised by extreme emaciation, diminished basal metabolism, lowered body temperature, decelerated cardiac rhythm, drop in blood pressure and neuropsychic disturbances. Decomposition of tissue proteins increases, the plastic processes and formation of hormones are disturbed and endocrine disorders result. Stable metabolic disturbances develop and manifest themselves primarily in low concentration of protein in the blood (hypoproteinemia), diminished excretion of nitrogen in the urine, reduced sugar level in the blood and decreased carbohydrate tolerance. Hypoproteinemia and disorders of general protein metabolism often give rise to edema (nutritional edema). The reactivity of the organism is considerably disturbed and its resistance to infectious diseases is lowered.

Mineral starvation in its pure form is observed only under experimental conditions when the food is devoid of or deficient in one or more mineral salts.

A deficiency of common salt in the food leads to loss of appetite and vomiting. The protein synthesis appreciably diminishes, the secretory processes are disturbed and the amount of hydrochloric acid in the gastric juice decreases.

Absence of calcium and potassium salts causes changes in the structure of bones, retards growth and affects the functions of the muscles and nervous system.

A deficiency of iron in the food produces pathologic changes in the blood and the hematopoietic system.

Water starvation or xerophagia causes severe changes. The organism cannot long exist without consuming water because the fluids formed in the tissues are not enough to excrete the end products of metabolism. Within a day or two the animal refuses food and thereby absolute starvation sets in. During water starvation the

organism exhibits phenomena of intensified decomposition, metabolites accumulate and cause general intoxication. Animals die from water starvation much sooner than they do from total starvation. The amount of water decreases in the organs and in the blood. Morphological changes of a dystrophic character are clearly marked.

Vitamin Starvation

An absence or, more frequently, deficiency of one or more vitamins causes pathologic processes known as *avitaminoses* or *hypovitaminoses*.

The causes of hypo- and avitaminoses are: 1) inadequate (as regards vitamins) food, most frequently as a result of its improper processing or storage; 2) insufficient assimilation of vitamins due, for example, to intestinal disease or failure of bile, necessary for absorption of fat-soluble vitamins (A, D, K and E), to be delivered into the duodenum; 3) excessively high vitamin requirements as a result of increased metabolism, for example, in infectious diseases, pregnancy and lactation, hard physical work, excessive carbohydrate consumption, which increases the organism's requirements in vitamin B₁, or consumption of proteins, which increases the requirements in vitamin C; 4) disorders of the functions of various organs, especially the liver, for example, disturbed conversion of provitamin A (carotene) with the aid of carotenase into vitamin A, or impaired conversion of the vitamin B group into coenzymes; 5) increased loss of vitamins, for example, in excessive perspiration (vitamin C) and polyuria (vitamin B₁); 6) presence of antivitamins—chemical

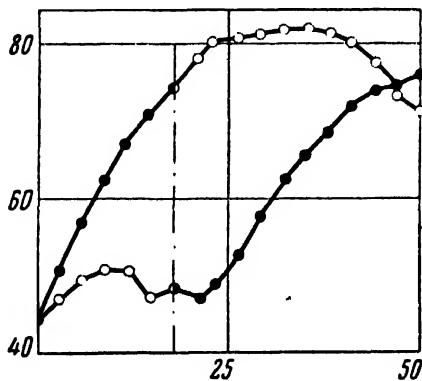


Fig. 20. Changes in weight of rats given vitamin-deficient food.

Axis of the ordinates—mean weight of the animals in grams; axis of abscissa—time in days. The lower curve shows the weight of the animals given vitamin-deficient food for 18 days. The upper curve shows the weight of the animals daily given vitamins with the milk for 18 days. After 18 days (beginning of dotted line) the diet was changed, the former rats receiving milk and the latter vitamin-deficient food.

substances capable of displacing corresponding vitamins, for example, displacement by sulfanilic acid of paraaminobenzoic acid—the coenzyme necessary for the growth of many bacteria.

Thus, in addition to exogenous factors (absence of deficiency of vitamins in the food), avitaminoses and hypovitaminoses may develop as a result of disturbances within the organism (endogenous hypo- and avitaminoses). Both exogenous and endogenous factors may be present.

The *manifestations* of various *vitamin deficiencies* have common features, namely, loss of weight, muscular weakness, fatigability, reduced resistance to infections, retarded growth and diminished regenerative ability of the tissues (Fig. 20). Many hypo- and avitaminoses are characterised by affections of the nervous system (avitaminoses B, C, A, etc.), the gastrointestinal tract (avitaminoses C and B) and the endocrine glands, for example, the adrenals in avitaminosis C or the thyroid in vitamin A deficiency.

Deficiency in Water-soluble Vitamins

The human diseases associated with the absence of three group B water-soluble vitamins— B_1 , B_2 and PP—are now well known.

The absence of *vitamin B_1* (thiamine or aneurin) causes beriberi, a disease similar to experimental polyneuritis in rats and birds (Figs. 21 and 22). It is characterised by dystrophic changes in the peripheral nervous system, contracture of muscles, cardiac insufficiency and edematous phenomena (Fig. 23).

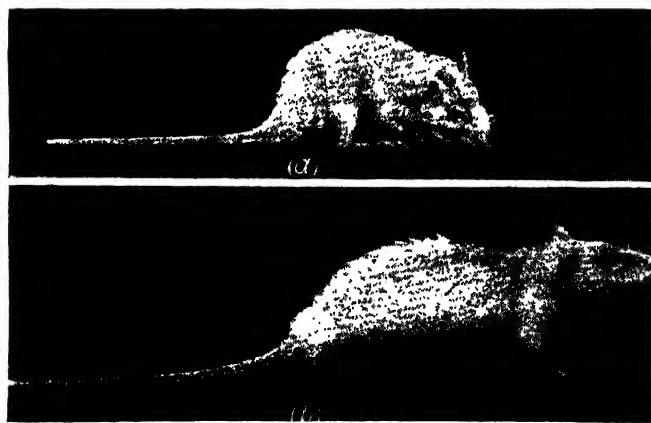


Fig. 21. Effects of vitamin B deficiency in the food.

a—rat fed vitamin B deficient food (weight—42 g); *b*—control rat given food containing vitamin B (weight—178 g).



Fig. 22. *a*—pigeon showing developed avitaminosis (pigeon polyneuritis); *b*—same pigeon 3 hours after administration of 4 mg of the yeast fraction containing the vitamin B₁ factor.



Fig. 23. Contracture of the hands in beriberi (Bicknell and Prescott).

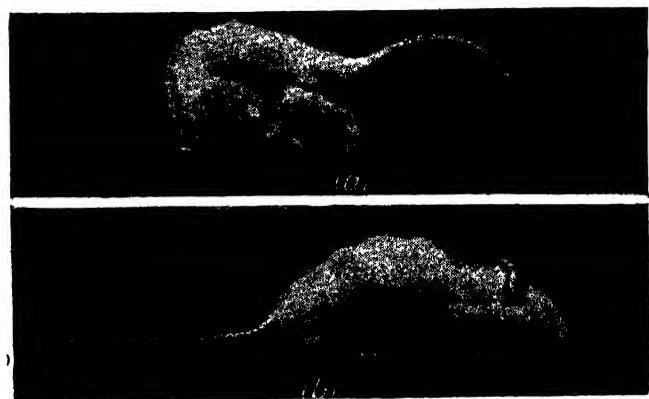


Fig. 24. Effects of vitamin B₁ deficiency in the food.
a—rat in a state of spastic paralysis resulting from vitamin B₁ deficiency in the food; *b*—same rat 24 hours after receiving food containing vitamin B₁.

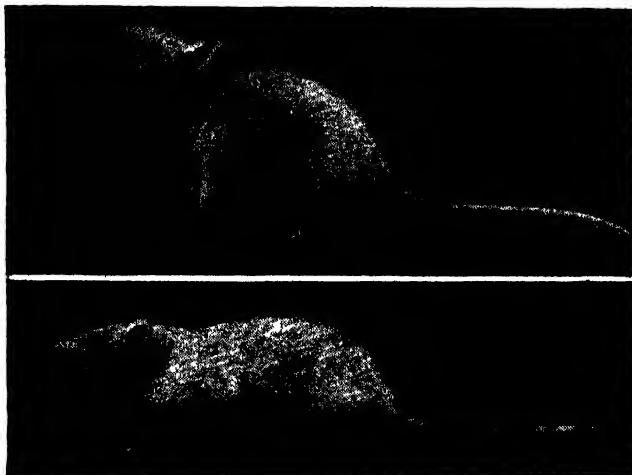


Fig. 25. Effects of vitamin B₂ deficiency in the food.

a—considerable emaciation caused in a rat by food deficient in vitamin B₂; *b*—same rat after receiving food containing vitamin B₂

Addition of rice bran or yeast to the food cures beriberi. The cure is effected even faster by injections of yeast extracts.

In the tissues vitamin B₁ is phosphorylated and as pyrophosphoric ether forms an active group of enzymes necessary for hydrolysis of pyruvic acid which is an intermediate product in glucose oxidation. A deficiency of this vitamin gives rise to disorders of carbohydrate metabolism, especially in the tissues of the central nervous system, and disturbances in oxidation, not only of pyruvic acid, but also of oxalic, succinic and ketoglutaric acids. Formation of acetylcholine decreases and the action of cholinesterase is inhibited. Nervous tissue is particularly sensitive to all these disturbances and avitaminosis B₁ is therefore characterised mainly by dysfunction of the central and peripheral nervous systems in the form of neuritides, paryses, sensory disturbances, etc. (Fig. 24).

Vitamin B₂ (riboflavin) deficiency is characterised by trophic changes in the mucosa of the lips and tongue, the conjunctiva and skin of the face. Experimental avitaminosis B₂ in rats is marked by retarded growth, loss of hair, dermatitis, increased growth of blood vessels about the cornea and their penetration into the cornea followed by keratitis (inflammation of the cornea) and a cataract (opacity of the crystalline lens). Vitamin B₂ forms part of the yellow oxidative enzyme which plays an important role in tissue respiration.

Deficiency of nicotinic acid (vitamin PP, the antipellagra factor) is the cause of pellagra.*

* *Pelles agra*—Italian for “rough skin”.

Pellagra is characterised by disturbances in the gastrointestinal tract (vomiting, diarrhea), inflammatory changes in the skin (dermatitis) and nervous disorders (psychoses).

Changes in the tongue which becomes smooth, red and edematous are characteristic of pellagra. Pellagra in man, like blacktongue (so called because of appearance of dark, necrotic sections), a pellagra-like disease induced in dogs, is caused by the absence of nicotinic acid in the food. It is supposed that a certain part in the development of pellagra is also played by the absence of other factors of the vitamin B complex (riboflavin, and thiamine).

The absence in the food of vitamin B₆ (pyridoxine), which takes part in processes of decarboxylation and reamination of amino acids, leads to development in animals of a special pathologic condition resembling pellagra. Analogous cases in man develop into a special form of dermatitis (Fig. 26).

Avitaminoses B also include diseases developing as a result of deficiency of biotin, pantothenic acid, paraaminobenzoic acid, inositol, folic acid and vitamin B₁₂ in the food.

The absence of biotin in man's food results in an avitaminosis characterised by dermatitis, loss of hair and increased secretion of the sebaceous glands (seborrhea).

The absence or deficiency of pantothenic acid leads to development of dermatitis, keratitis, depigmentation of the hair, fur or feathers, disturbances in growth, affection of the adrenals and dystrophic changes in the nervous system.



Fig. 26. Pellagra in a child. Face showing dermatitis and pigmentation (Bicknell and Prescott).

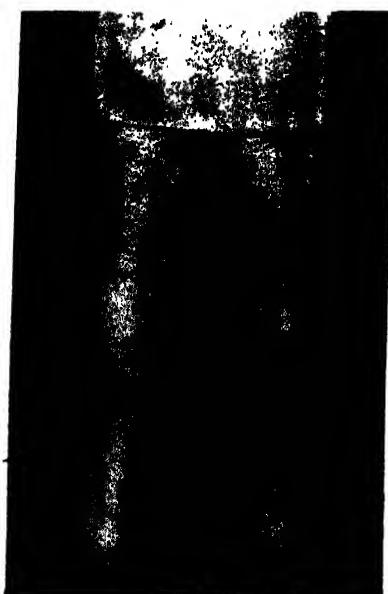


Fig. 27. Scurvy. Hemorrhages into the skin of both lower limbs and dextral edema.



Fig. 28. Scurvy. Phenomena of gingivitis with ulcerations (Bicknell and Prescott).

Depigmentation of hair in man and animals is ascribed to the absence of paraaminobenzoic acid in the food.

The absence of inositol in the food of animals causes retarded growth and loss of hair.

Folic acid and, especially, vitamin B₁₂ play an important part in the regulation of hematopoiesis. The absence of these vitamins in the food causes disturbances in hematopoiesis.

Deficiency of the water-soluble vitamin C (ascorbic acid) which abounds in vegetables, fruit and the green parts of plants causes development of scurvy.

Experimental avitaminosis C is very easily produced in guinea pigs and monkeys. Inclusion of green vegetables rich in vitamin C in the diet of scurvy patients cures them of this disease.

Scurvy is characterised mainly by changes in the blood vessels and bones. The capillary walls become more permeable and fragile, and hemorrhages occur, especially in easily traumatised places—the skin, subcutaneous tissue and muscles (Fig. 27). Capillary hemorrhages in the gums cause them to swell and become spongy (Fig. 28). Changes in the bones are observed less frequently and are marked by disturbances in their growth, rarefaction of their substance and spontaneous fractures. Owing to changes in the alveolar processes the teeth loosen and fall out.

The absence or deficiency of vitamin C in children causes *infantile scurvy* (Moeller-Barlow disease) which differs from adult scurvy in greater bone changes. Vitamin C has been observed to increase the organism's resistance to infections and to possess bactericidal and antitoxic properties.

Deficiency of Fat-soluble Vitamins

Feeding mice and rats on calorically adequate food containing, as its fat constituent, only lard which is devoid of vitamin A results in arrested growth and changes in the eyes. These phenomena disappear after addition to the food of butter or fish-liver oil, which contain vitamin A.

Vitamin A deficiency causes reduced dark adaptation—*night blindness* (*nyctalopia*). This impairment of vision results from a disturbed resynthesis of the photosensitive pigment of the retina (*visual purple*) which contains vitamin A. The condition also involves alteration of epithelial tissue, namely, epithelisation and metaplasia with subsequent cornification. These phenomena occur in the skin and the mucosa of the digestive, respiratory and urogenital tracts, but are the most strongly pronounced in the conjunctiva. The skin and mucous membranes dry and desquamation of the superficial layers of the epithelium increases. Cornification of the conjunctival epithelium arrests the functional activity of the mucous-secreting cells and develops so-called *xerophthalmia* (from the Greek words *xeros*—dry and *ophthalmos*—eye). This is subsequently followed by *keratomalacia* (softening of the cornea). Penetration of infection may cause ulceration and perforation of the cornea with subsequent inflammation of all the tissues of the eyeball—*panophthalmitis*.

Deficiency of vitamin D, another fat-soluble vitamin, causes development of *rickets*. Hence, its name—*antirachitic vitamin*. Feeding dogs and rats on food lacking vitamin D₂ results in



Fig. 29. Young dog with experimental rickets.



Fig. 30. Rachitic child.

experimental rickets mainly in the osseous system. These phenomena closely resemble, but are not entirely identical (Fig. 29) with those observed in human rickets (Fig. 30).

An important part in the development of this avitaminosis is played by lack of sunlight. The ultraviolet part of sunlight is necessary to transform the provitamin found in the skin into vitamin D.

Vitamin D designates a group of substances possessing antirachitic properties and chemically closely resembling cholesterol. The chief of these are: 1) vitamin D₁—a preparation containing, in addition to the active substance D₂, an admixture of an inactive substance—lumisterol; 2) vitamin D₂ prepared artificially by irradiating ergosterol with ultraviolet rays; in nature there is no vitamin D₂ and ergosterol may therefore be regarded as provitamin D₂; yeasts and mushrooms are particularly rich in ergosterol; 3) vitamin D₃ found in the organism of man and animals and forming in the skin from 7-dehydrocholesterol under the influence of ultraviolet rays; vitamin D₃ is a natural antirachitic vitamin; a particularly large amount of vitamin D₃ is present in fish-liver oil.

The mechanism of action of the group D vitamins on calcium and phosphorus metabolism is not quite clear. Vitamin D helps in the absorption of phosphates from the intestines and in transformation of organic phosphorus into inorganic, which by combining with calcium forms an indissoluble calcium phosphate deposited in the bones. This view of the mechanism of vitamin D action is confirmed by modern research with the aid of tracer atoms.

In avitaminosis D the phosphorus and calcium decrease in the blood and the ability of the bones to assimilate calcium phosphate diminishes. Rickets is effectively treated by administration of vitamin D preparations and by ingestion of more food with a high vitamin D content.

Deficiency of vitamin E (tocopherol, the reproduction vitamin) causes premature cessation of pregnancy in female and testicular degeneration and sterility in male animals.

It has also been demonstrated that in some animals the absence of this vitamin in the food causes dystrophic changes in the muscles and nervous system. The effect of vitamin E is realised through the hormonal function of the hypophysis.

Avitaminosis E due to consumption of food lacking vitamin E has not been observed in man. Of some interest in this connection are the observations of a number of researchers concerning the successful utilisation of vitamin E in the treatment of habitual abortion and muscular dystrophy.

Vitamin K (2-methyl-1,4-naphthoquinone) or antihemorrhagic vitamin, is a factor necessary for normal blood clotting. Diminished blood clotting in avitaminosis K is due to a deficient supply of prothrombin in the blood (hypoprothrombinemia) since vitamin K is necessary for the synthesis of prothrombin in the liver. In hemor-

rhages caused by diminished prothrombin in the blood administration of vitamin K restores the prothrombin content and arrests the hemorrhages.

Vitamin K is found in many foodstuffs (it is particularly abundant in green leaves of plants). It may also be synthesised by intestinal bacteria. That is why avitaminosis K is very rarely caused by the absence of this vitamin in food. It is observed much more often in connection with disturbed absorption of vitamin K from the intestines.

Absorption of fat-soluble vitamins requires the presence of bile salts in the intestines. Disorders of bile secretion (for example, in obstruction of bile ducts) therefore disturb absorption of vitamin K and slow down blood clotting.

The animal organism is affected not only by a deficiency, but also by an *excess of vitamins* in the food ration. Administration of large doses of vitamin A to rats is followed by sluggishness, exhaustion, hardening of the hair, softening and fragility of the bones, degeneration of the kidneys and ovaries, and myocarditis.

Excess doses of vitamin D cause rarefaction of the bone substance and deposition of calcium in the renal tubules and walls of large blood vessels.

Feeding After Starvation

After long-continued total starvation feeding must be resumed gradually because the digestive organs cannot, in view of their atrophy, immediately adjust themselves to ingestion of food. As a rule, weight is gained faster during feeding after starvation than it is lost during starvation.

However, frequently recurring starvation causes more stable changes in the organism with irreparable damage to the gastrointestinal tract and cardiovascular system. Recurring starvation also perceptibly affects the central nervous system. Incomplete but long-continued starvation produces a particularly noticeable effect on the organism. After partial starvation accompanied by considerable changes complete recovery of the organism takes place slowly. The consequences depend on the character and duration of starvation, the period of restorative alimentation, its intensity, etc.

PATHOLOGY OF METABOLISM

In discussing the disorders of metabolism it is best to deal with each form of metabolism separately. However, it is necessary to make an important reservation, namely, that the various forms of metabolism are closely interrelated.

DISTURBANCES IN CARBOHYDRATE METABOLISM

It is necessary to distinguish disturbances in absorption, intermediate metabolism and processes of regulation of carbohydrate metabolism.

Disturbances in carbohydrate absorption occur as a result of disorders of fermentative hydrolysis of polysaccharides in the intestines or of the very process of monosaccharide absorption, for which purpose monosaccharides have to be phosphorylated in the intestinal mucosa. Disturbances in phosphorylation may be caused by a diminished secretory function of the adrenal cortex (decreased secretion of glucocorticoids), inflammation of the intestinal mucosa, or poisoning with toxins which depress the processes of phosphorylation.

Disturbances in intermediate carbohydrate metabolism consist in weakened glycogen synthesis (glycogenesis) in the liver and muscles, increased formation of glucose from glycogen (glycogenolysis) or from protein or fat decomposition products (glyconeogenesis), and disturbances in glucose conversion in the tissues (Fig. 31).

Changes in glycogenesis may be the result of dysfunction of the nervous system (for example, in myasthenia gravis pseudoparalytica) and oxygen starvation in which the oxygen deficiency is responsible for the lack of energy necessary for the synthesis of glycogen. Intensified glycogenolysis is most frequently a result of increased energy metabolism, for example, in disorders of nervous and endocrine regulation (intense emotional excitement, pain, cooling, etc.).

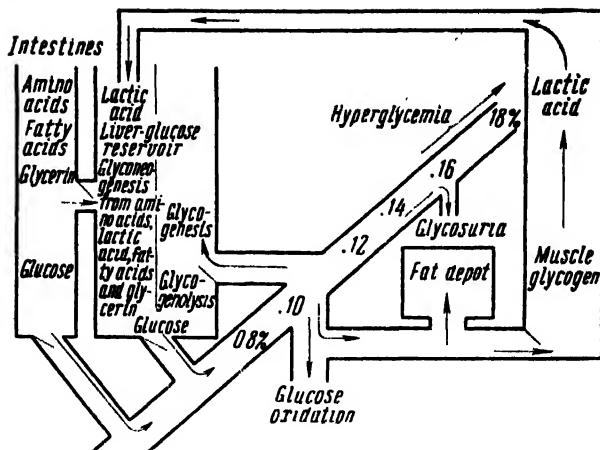


Fig. 31. Diagram showing origin of sugar in the blood and maintenance of its normal level.

Glyconeogenesis is observed mainly in diabetes.

As for intermediate glucose metabolism in the narrower sense, i.e., the intermediate phases of glucose utilisation in the tissues, what is meant here is the disturbances connected with the mechanisms of its oxidation and conversion. Such disturbances usually arise in infections and intoxications, states of hypoxia, cancer involving increased glycolysis accompanied by accumulation of lactic acid in the blood, avitaminoses, especially avitaminosis B₁ associated with difficulties of pyruvic acid oxidation.

A particularly important part in disorders of carbohydrate metabolism is played by *disturbances in the processes* of its regulation.

Disturbances in the Regulation of Carbohydrate Metabolism

Regulation of carbohydrate metabolism ensures a constant sugar concentration in the blood and helps in the selective utilisation of sugar by the tissues. The diagram presented in Fig. 32 shows the main links of the mechanism of carbohydrate metabolism regulation.

In 1885 Claude Bernard discovered the carbohydrate metabolism regulating centre in the floor of the fourth ventricle in the medulla oblongata. A puncture in this centre causes a temporary increase in the concentration of sugar in the blood and its appearance in the urine. The effect of the puncture does not appear after transection of the spinal cord on the level of the fifth thoracic segment, after transection of the splanchnic nerves or removal of both adrenals. These experiments warranted the conclusion that the paths from the higher

vegetative centres of carbohydrate metabolism regulation run through the spinal cord and splanchnic nerves to the adrenals whose hormone—adrenalin—causes conversion of glycogen in the liver and, as a result, an increased concentration of sugar in the blood. A slight sugar increase in the blood, as a result of a puncture in the medulla oblongata, can also be produced after preliminary removal of the adrenals, which denotes that there are apparently direct neural connections between the carbohydrate metabolism regulating centre in the medulla oblongata and the peripheral organs in which the processes of carbohydrate metabolism operate (mainly the liver and muscles).

Central regulation of carbohydrate metabolism is effected not only in the medulla oblongata, but also in the tuber cinereum and lenticular nucleus of the corpus striatum, which are connected with the medulla. At higher stages of phylogenesis the cerebral cortex also participates in the regulation of carbohydrate metabolism. Thus, various emotions and psychic overstrain may serve to raise the sugar level in the blood (W. B. Cannon).

Cortical regulation of carbohydrate metabolism is also attested by the possibility of influencing the level of sugar in the blood and its appearance in the urine by means of conditioned reflexes. For example, after an animal is repeatedly given sugar in milk glucose appears in the urine when the animal is fed on milk alone.

An important part in the regulation of carbohydrate metabolism is played by the endocrine glands, mainly the pancreas, hypophysis and adrenals.

The most reliable index of disturbances in carbohydrate metabolism is change in the sugar concentration in the blood, which in man normally ranges from 80 to 120 mg%.

An excess of sugar in the blood is called *hyperglycemia*, while a low sugar level in the blood is known as *hypoglycemia*.

Normal urine contains no glucose. An increased glucose concentration in the blood (up to 160-180 mg%) is accompanied by excretion of glucose in the urine (*glycosuria*).

Glucose filtration in the renal glomeruli corresponds to glucose concentration in the blood. An increased glucose content in the blood is accompanied by intensified glucose filtration. But hyperglycemia causes glycosuria only at a certain level of glucose concentration in the blood, i.e., when reabsorption of glucose in the renal tubules falls short of its filtration in the glomeruli.

Reabsorption of glucose in the renal tubules is, as is well known, connected with the fermentative processes of phosphorylation and dephosphorylation. At first, as glucose filtration increases, these processes become more active and more glucose is reabsorbed as a result. After reaching a certain level (renal threshold for glucose), however, hyperglycemia is accompanied by glycosuria because of insufficient reabsorption of glucose; the higher the hyperglycemia, the more pronounced the glycosuria.

In pathology there are disturbances in carbohydrate metabolism, which are characterised by glycosuria without hyperglycemia. In these cases changes in the functional capacity of the kidneys (lowered renal threshold for glucose) plays the principal part. Renal permeability may also be increased when the glucose concentration in the blood is normal.

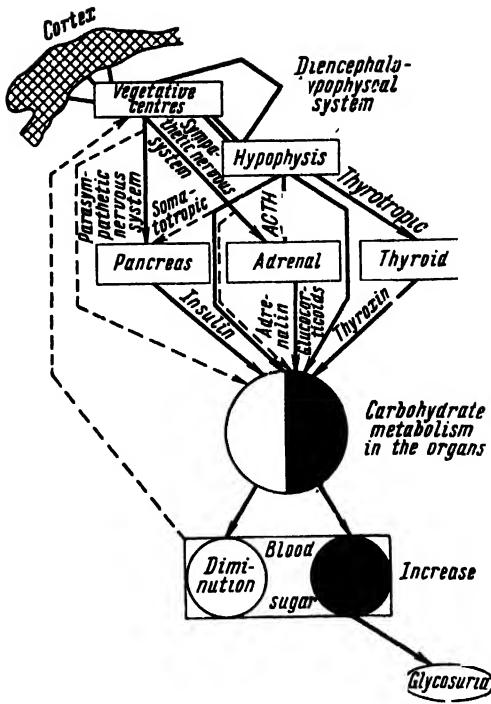


Fig. 32. Diagram showing regulation of carbohydrate metabolism.

Experimentally *renal glycosuria* is produced by administration of phlorhizin (a glycoside derived from the bark and root of apple, cherry, pear and plum trees), in which case the glucose concentration in the blood remains normal or drops below the norm. The development of phlorhizin glycosuria is based on a reversible disturbance in reabsorption of glucose in the kidneys, which leads to an increased loss of carbohydrates by the organism even when the glucose level in the blood is normal. Renal glycosuria may also occur in pregnant women.

Experimental Hyperglycemias and Glycosurias

Experimental reproduction of various hyperglycemias and glycosurias is very important for the understanding of carbohydrate metabolism disturbances.

Alimentary Hyperglycemia and Glycosuria

The amount of glucose which the organism can ingest without developing glycosuria is called the *sugar assimilation limit*. In man this is 160-180 g of glucose ingested on an empty stomach. If

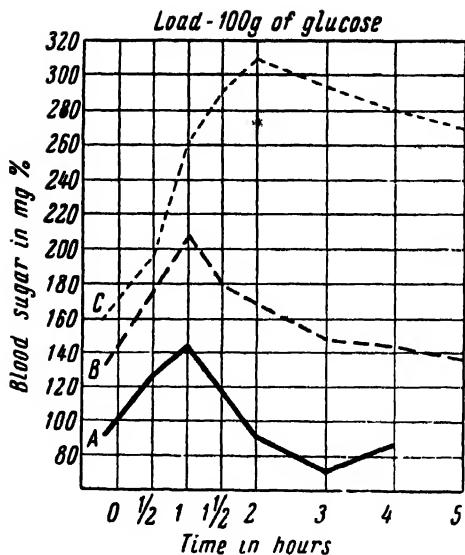


Fig. 33. Alimentary hyperglycemia A—normal, B—in mild and C—in severe diabetes mellitus.

glycosuria is observed after ingestion of a lesser amount of glucose, the condition is referred to as a reduced sugar assimilation limit and disturbed regulation of carbohydrate metabolism.

After ingestion of 100 g of glucose hyperglycemia usually does not exceed 170 mg%. By the end of the second hour following the ingestion of this amount of glucose the sugar level in the blood returns to normal. An analysis of the hyperglycemia curve with no disturbances in glucose absorption offers an idea of the extent of sugar assimilation. Thus, a strongly-pronounced and long-continued hyperglycemia with glycosuria denotes a reduced carbohydrate-assimilating capacity (for example, in diabetes and dysfunction of the thyroid and hypophysis) (Fig. 33).

Hyperglycemia and Glycosuria Caused by Influences Exerted on the Central Nervous System

Hyperglycemia and glycosuria caused by a puncture of the floor of the fourth ventricle develop within 1-2 hours and last 5-6 hours in rabbits and 1-2 days in dogs. They are produced by the mobilisation of glucose from liver glycogen and its passage into the blood and urine. The glycogen reserves in the liver become exhausted some time after the puncture.

Hyperglycemia and glycosuria of central origin are also observed in man, for example, in cerebral traumas and tumours, hemorrhages, inflammatory foci in the brain, emotional strain and severe psychic shock.

Narcotics (ether, chlorophorm* and morphine) cause hyperglycemia by inhibiting the cerebral cortex, disinhibiting the underlying centres of the hypothalamic region and intensifying secretion of adrenalin, but may also act directly on the liver and intensify glycogenolysis.

Adrenalin-induced Hyperglycemia and Glycosuria

The capacity of adrenalin to produce hyperglycemia and glycosuria consists in its intensification of glycogenolysis in the liver. The extent and rapidity of the rise in the curve of sugar concentration in the blood (Fig. 34) after injection of adrenalin in certain measure reflect the state of the carbohydrate reserves in the organism and may be used as an index of disturbances in carbohydrate metabolism. In man adrenalin-induced glycosuria develops independently very rarely, for example, in pheochromocytoma—tumours of the adrenal medulla—when a large amount of adrenalin enters the blood.

Pancreatic Hyperglycemia and Glycosuria

After complete removal of the pancreas (Mering and Minkowski, 1899) the dog develops marked disorders of carbohydrate metabolism; however, it is enough to leave but a small part of this gland to prevent the onset of these phenomena.

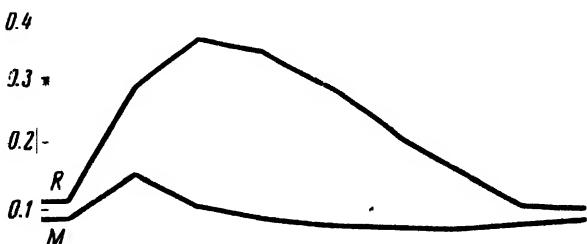


Fig. 34. Adrenalin hyperglycemia.

R—in rabbit after subcutaneous administration of 1 mg of adrenalin; M—in man after subcutaneous administration of 1 mg of adrenalin (mean of 4 experiments). Axis of ordinates—blood sugar in %; axis of abscissas—time in hours.

Experiments with ligating the pancreatic duct have shown that development of diabetes is due to cessation of the internal secretion of the pancreas; depriving the organism of the external secretion of this gland by ligation of its duct does not cause development of diabetes.

Removal of the pancreas leads to *hyperglycemia* and *glycosuria* (the sugar concentration in the blood may reach 0.5-0.6 m%), *acidosis* and *phenomena of intoxication* with underoxidised products of fat and protein conversion.

In pancreatic diabetes *lipemia* is a result of diminished glycogen in the liver, mobilisation of fat in the fat depots and its transfer to the liver.

Protein metabolism is also intensified, the amount of nitrogen in the urine increasing because of greater expenditure of proteins which are converted into carbohydrates.

Three or four weeks after removal of the pancreas the animal dies of polyuria, considerable emaciation and intoxication.

In 1900 L. V. Sobolev showed in experiments on animals that ligation of the pancreatic duct caused atrophy of the acinar elements of the pancreas without affecting the islets of Langerhans. Under these conditions diabetes did not develop. Thus the participation of the islets of Langerhans in carbohydrate metabolism and pathogenesis of diabetes was established and a method of obtaining insulin was outlined.

Insulin was discovered in 1922 by F. G. Banting, C. H. Best and J. J. R. Macleod. The discovery of insulin ushered in a new era in the studies of the role played by the pancreas in carbohydrate metabolism and the pathogenesis of diabetes; it also served as a new point of departure in the treatment of this disease.

Insulin eliminates the changes arising after removal of the pancreas. Firstly, it possesses glycogenostatic action, i.e., it inhibits glycogenolysis and intensifies the synthesis of glycogen in the liver. As experiments with administration of glucose labelled with C¹⁴ have shown, insulin stimulates the conversion of carbohydrates into fat and intensifies the synthesis of proteins with amino acids. Secondly, insulin causes increased consumption of glucose by the tissues, which is due to increased permeability of the tissues for glucose and its better utilisation by them. These properties of insulin make it clear why a function of the pancreas leads to accumulation of glucose in the blood and its passage into the urine.

It has been established that in the islets of Langerhans insulin is formed in and secreted by beta-cells, while alpha-cells produce another hormone—glucagon (Bürger and Murlin). Unlike insulin, glucagon causes hyperglycemia because it stimulates glycogenolysis in the liver. However, the question of whether hypersecretion of glucagon is of any importance in the pathogenesis of diabetes is still unsettled.

Alloxan Hyperglycemia and Glycosuria

Administration of alloxan (mesoxalyl urca) to animals causes degeneration of the insulin producing beta-cells of the pancreas, which gives rise to protracted hyperglycemia and glycosuria. Alloxan diabetes greatly resembles diabetes in man because alloxan selectively damages beta-cells and thereby inactivates their enzymatic complex which contains the S-S group. Compared with what occurs after removal of the pancreas the alloxan method of producing carbohydrate metabolism disorders has the advantage that it preserves the external secretion of the gland and the function of the alpha-cells of the islets of Langerhans which produce glucagon.

The function of the pancreatic islets can also be reduced by administration of dithizone (diphenyl-thiocarbazone) which likewise affects the beta-cells by forming a complex with zinc, a constituent of insulin.

Hypophyseal Hyperglycemia and Glycosuria

Parenteral administration of the extract from the anterior lobe of the hypophysis for 2-3 weeks causes appreciable hyperglycemia with glycosuria and ketonemia in dogs. At the same time degenerative changes are observed in the pancreatic islets. Participation of the hypophysis in carbohydrate metabolism disorders is also evident from the fact that removal of the gland causes hypoglycemia, especially in a starving animal. On the other hand, if pancreatic glycosuria is produced in the dog before removal of the hypophysis, the manifestations of glycosuria considerably diminish (Houssay).

The capacity to producing hyperglycemia and glycosuria is ascribed to the somatotropic and partly the adrenocorticotropic hormones of the anterior lobe of the hypophysis. The somatotropic hormone possesses the ability to activate production of glucagon by the alpha-cells of the pancreatic islets. Some researchers explain the hyperglycemic action of the somatotropic hormone by its stimulatory influence directly on the insulin-producing cells of the pancreas, which in the end leads to exhaustion of the beta-cells. Long-continued administration of the somatotropic hormone into the organism increases formation of carbohydrates from proteins and, possibly, fats in the liver and depresses consumption of glucose by the tissues. The adrenocorticotropic hormone increases production of glucocorticoids in the adrenal cortex. Administration of large doses of cortisone (one of the glucocorticoids) also causes hyperglycemia and glycosuria. However, under the influence of hypophyseal hormones and glucocorticoids real diabetes can develop only in cases of latent insufficiency of the beta-cells of the pancreatic islets.

Diabetes Mellitus

Diabetes mellitus* in man is a disease based on insufficiency of the pancreatic islets. It is characterised by disturbances in metabolism of carbohydrates and other food elements.

The main manifestations of diabetes mellitus are *hyperglycemia* and *glycosuria*, which differ in intensity. The increase in the concentration of glucose in the blood does not always correspond to the excretion of glucose in the urine, which is probably due to disturbed reabsorption of glucose in the kidneys.

In severe cases of diabetes hyperglycemia reaches 600 mg% and higher. In mild cases the sugar excreted in the urine amounts to 1-3 per cent and in severe cases—6-7 per cent. The source of sugar accumulating in the blood and excreted in the urine of diabetics is (in addition to the food carbohydrates) glycogenesis—formation of carbohydrates from proteins and, partly, fats.

The disease is marked by *increased excretion of nitrogen in the urine*, which is not infrequently paralleled by the increase in sugar in the urine. This is evident from the fact that in diabetes the D/N quotient (ratio of dextrose to nitrogen in the urine) is a constant value (2.8) when the diet contains no carbohydrates. Moreover, ingestion of proteins, especially in a high-caloric diet, is conducive to increased glycosuria.

The content of fats and lipoids in the blood increases (to 2-3 g% and higher instead of the 0.5-1 g%). Fats accumulate in the blood as a result of the increased transport of fat from the fat depots to the liver to replace the glycogen which disappears from the liver in diabetes. The liver often undergoes fatty degeneration.

Addition of raw pancreas to the food of depancreatized dogs prevents development of fatty degeneration of the liver, although the other phenomena characteristic of diabetes remain. This is apparently due to the action of lipoproteins derived from the pancreas (L. R. Dragstedt). Some researchers hold that fatty degeneration of the liver in diabetes develops as a result of insufficient production of this substance (S. M. Leites et al.).

The mobilisation of fat by the liver in diabetes and the increased formation of ketone bodies from it lead to accumulation of ketone bodies in the organism and their increased concentration in the blood—*hyperketonemia* (up to 20-60 mg% and higher instead of the normal 2-6 mg%) and their increased excretion in the urine. Certain amino acids (leucine, isoleucine, phenylalanine) may in some measure serve as sources of formation of ketone bodies.

In diabetes ketosis occurs when acetoacetic acid is formed faster than it is oxidised and resynthesised into higher fatty acids.

An increase in the amount of acid metabolites causes *acidosis* which in mild and moderately severe forms of diabetes is compen-

* From the Greek *diabetes*—to pass through, and the Latin *mel*—honey.

sated by alkali reserves, while in severe forms it becomes uncompensated and the blood pH decreases (to 7-6.9)..

The toxic action of intermediate metabolites, mainly ketone acids, may cause *diabetic coma*. Its manifestations are extraordinarily varied. In the main it is characterised by dysfunction of the central nervous system (unconsciousness, sometimes convulsions, circulatory and respiratory disturbances) with fatal results if no insulin is administered.

Polyuria (passage of an excessive amount of urine—up to 5-10 litres per day) and *polydipsia* (excessive thirst) are usual concomitants of diabetes. Polyuria is conditioned by a plentiful passage of glucose into the primary urine and a resultant increase in its osmotic concentration, which renders reabsorption of water in the renal tubules difficult. Polydipsia follows polyuria and is considered a compensatory phenomenon.

Mechanism of Metabolic Disorders in Diabetes Mellitus

Several factors are considered of prime importance in the mechanism of metabolic disorders in diabetes mellitus.

The insulin deficiency in diabetes leads to increased formation of glucose and the development of *hyperglycemia* and *glycosuria*. The increased formation of glucose in the liver is the result of intensified *glycogenolysis* (conversion of glycogen into glucose by hydrolysis) and *glyconeogenesis* (formation of glucose from proteins [amino acids] and fats). The accumulation of glucose in diabetes is also due to *reduced utilisation of glucose by the tissues* because the permeability of tissues for glucose diminishes and the enzymatic conversion of glucose is disturbed.

However, insufficient utilisation of glucose by the tissues in diabetes cannot fully account for the high glucose content in the blood. There are reasons to believe that in diabetes the *conversion of glucose into fat is also disturbed and the synthesis of proteins from amino acids is retarded*, while formation of carbohydrates from them is increased (in the liver and partly in the kidneys).

These assumptions are supported by the studies of animals with pancreatic and alloxan diabetes, in which only one-tenth of the glucose administered into the organism is converted into fat. One of the indices of carbohydrate formation from proteins in diabetes is the relative constancy of the D/N quotient in a carbohydrate-free diet and increased glycosuria in a high-protein diet.

Etiology and Pathogenesis of Diabetes Mellitus

Diminished function of the pancreatic islets is the main pathogenic factor of diabetes. This is attested by: 1) atrophy of the

islets in severe forms of diabetes in man; 2) results of experimental pancreatic and alloxan diabetes; 3) effects of insulin.

At the same time the entire carbohydrate metabolism regulating apparatus is disordered in diabetes; the various links of this apparatus are intimately interconnected and are controlled by the central nervous system. As was already mentioned, disturbances in the function of the central nervous system may produce hyperglycemia and glycosuria. The pancreatic islets are also affected by hyperfunction of the hypophysis. Hypophyseal hyperglycemia and glycosuria may also be produced by extracts from the anterior lobe of the hypophysis or occur in acromegaly when the function of the anterior lobe of the hypophysis is increased. Lastly, development of insulin deficiency involves the participation of the adrenal cortex (glucocorticoids) and the thyroid, since diabetes occurs more frequently in cases of their hyperfunction.

Several factors are involved in the etiology of the affection of the insulin-producing cells of the pancreas: long-continued overeating of carbohydrates which exhaust the function of the insulin-producing cells, negative emotions—psychic shock or protracted neuropsychic overstrain, infectious and toxic affections of the pancreatic islets, and their congenital insufficiency.

Hypoglycemia

Hypoglycemia (a low level of glucose in the blood) may occur as a result of disturbed carbohydrate regulation by the nervous system and various endocrine glands. It may be based on increased insulin secretion (hyperinsulinism) caused by hypertrophy of the pancreatic islets, for example, in certain tumours of the pancreas. Hypoglycemia also develops in hypofunction of the anterior lobe of the hypophysis and the adrenal cortex, for example, in hypophyseal cachexia and Addison's disease. Hypoglycemia may accompany liver disease and glycogen deficiency in the liver, for example, in toxic hepatitis connected with severe septic infection of the biliary tract.

Hypoglycemia is most frequently caused by disturbances in neuroendocrine regulation of carbohydrate metabolism.

Hypoglycemia manifests itself mainly in dysfunction of the nervous system which is particularly sensitive to decreased sugar concentration in the blood. Hypoglycemia is marked by general weakness, excessive perspiration, tremor, tachycardia, headache, nausea, impaired memory, sleepiness and periodic paralysis. Decrease of sugar in the blood to 35-30 mg% may lead to convulsions, hypoglycemic shock and sometimes even death. Experimentally these phenomena are produced by injection of large doses of insulin. Their development may be prevented or eliminated by intravenous administration of glucose solution.

DISTURBANCES IN LIPID METABOLISM

Disturbances in Fat Metabolism

Fats consumed by the organism are digested mainly by pancreatic and intestinal juices and are absorbed through the wall of the small intestine. Fat is resynthesised from fatty acids and glycerin already in this wall. A certain amount of neutral fats may, apparently, be absorbed without splitting into fatty acids and glycerin. Fat is absorbed mainly through the lymphatic system and partly (about 30 per cent) through the system of the portal vein. In the end fats enter the blood and their bulk is deposited in fat depots—the subcutaneous adipose layer, omentum and mesentery, as well as the adipose layer of various organs. The fats from the fat depots are oxidised mainly in the liver, especially in cases in which the reserves of easily mobilised carbohydrates, liver glycogen in particular, are exhausted. Regulation of the fat transport and fat metabolism is effected by the nervous system. The loss of glycogen by the liver stimulates its interreceptors which transmit the impulses to the central nervous system whence they are conducted along efferent paths through the spinal cord to adipose tissue and mobilise the fat. This is borne out by the fact that denervation of the liver or transection of the splanchnic nerves, as well as high transection of the spinal cord—above the sixth cervical segment—severs the reflex arc and blocks mobilisation of fat from the fat depots and its transport to the liver. According to some data, the central area of fat metabolism regulation is in the hypothalamus. After removal of the forebrain in pigeons deposition of fat and the weight of the body increase. There are also data attesting that intensification of impulses along sympathetic paths increases mobilisation of fat from the fat depots and inhibits its formation from carbohydrates, whereas stimulation of parasympathetic nerves acts contrariwise.

Of the endocrine glands fat metabolism is influenced mainly by the anterior lobe of the hypophysis, the pancreas, adrenal cortex and gonads.

Disturbances in Fat Absorption and Accumulation

The digestion and absorption of fat may be disturbed for the following reasons: 1) disorders of external pancreatic secretion and failure of lipase necessary for splitting fat to enter the intestine; 2) considerable diminution or complete absence of bile secretion which is necessary for emulsifying fat; 3) disorders of the motor function of the intestines (increased peristalsis) owing to which fat cannot be duly absorbed; 4) impaired ability of the epithelium of the intestinal mucosa actively to absorb fat.

Disorders of fat absorption are observed in enteritis, hypovitaminoses and inadequate resynthesis of triglycerides as a result of dysfunction of the adrenal cortex.

The presence in the feces of 20 per cent of the fat consumed with the food (instead of the normal 5-10 per cent) is considered a pathologic phenomenon.

Accumulation of fat in unusual amounts or of unusual chemical composition in the cells which do not form part of fatty tissue is called *fatty degeneration*. Fatty degeneration is based on cell injury and disturbance in cell metabolism.

The fat found in the cell in fatty degeneration may be a result of the retention of fat brought to the cell by the lymph or blood (fatty infiltration); it may also be a result of disturbed physicochemical and biochemical processes in the protoplasm. To establish the origin of fat in the injured cell is often practically impossible.

The chemical composition of fat in fatty degeneration may vary. In addition to neutral fat phosphatides or cholesterol and its compounds (anisotropic adiposis) are deposited. Fatty degeneration occurs mainly in the liver, myocardium and kidneys.

The main pathogenic factors causing accumulation of fat in the cells are: 1) disturbance in splitting of neutral fat and in oxidation of higher fatty acids under the influence of various poisons, for example, carbon tetrachloride, phosphorus, chloroform and bacterial toxins; 2) insufficient supply of oxygen to the tissues or its utilisation therein (hypoxia), for example, in pernicious anemia and certain avitaminoses; 3) disturbance in the release of fat from tissues due to disordered metabolism of phospholipids (which ensure a fine dispersion of fat) and to lack of choline, methionine and other substances which exert lipotropic action, in the food.

The mechanism of lipotropic action of choline consists in its participation in the synthesis of phospholipids whereby it activates the release of fat from the liver, while methionine takes part in the formation of choline by splitting off its own methyl group. The onset of fatty infiltration of the liver can therefore be prevented by administration of choline and methionine which are found, in the main, in casein and in the proteins of pike, codfish, etc.

Hyperlipemias

An increase in the content of neutral fat in the blood (above 200 mg%) is called hyperlipemia. The following forms of hyperlipemia are distinguished: *alimentary hyperlipemia* (resulting from consumption of large amounts of fat with the food) which begins to develop 2-3 hours after ingestion of food, reaches its maximum usually within 5-6 hours and disappears 9-10 hours after ingestion of food; *transport hyperlipemia*—in pathologic states accompanied by mobilisation of fat from the fat depots because of glycogen deficiency in the liver, for example, in starvation, severe diabetes or nephrosis; *retention hyperlipemia*—due to retarded passage of

fat from the blood into the tissues because of disturbed complexes of fats and plasma proteins, for example, in hemorrhagic anemia, obstructive jaundice, diabetes, nephrosis and certain other diseases.

Disturbances in Intermediate Fat Metabolism

One of the manifestations of disordered intermediate fat metabolism is the increase in ketone bodies (acetone, acetoacetic and beta oxybutyric acids) in the blood—*ketonemia*, and their presence in the urine—*ketonuria*.

Ketone bodies are, in the main, formed in the liver and are oxidised in other tissues to carbon dioxide and water. Exhaustion of the glycogen reserves in the liver is accompanied by accumulation of fat in this organ and ketone formation, for example, in starvation and diabetes. Insufficient resynthesis into higher fatty acids or disturbed oxidation in the tricarboxyl cycle gives rise to *ketosis*, i.e., accumulation of ketone bodies in the organism, and *ketonemia*. Diminution in liver glycogen and *ketonemia* may also occur as a result of a one-sided diet rich in fats.

In all these cases, owing to a carbohydrate deficiency, increasing amounts of fat are used to cover the energy deficit, for which reason more ketones are formed in the liver than can be utilised by the tissues. Administration of carbohydrates into the organism reduces the transport of fat to the liver and may thus prevent or eliminate development of *ketonemia*.

Obesity (Adiposis)

Obesity is a pathologic deposition of fat in fat depots with the result that the weight of the body considerably increases (especially, in general obesity) and sometimes reaches 190 kg and more.

The causes of obesity are: 1) increased consumption of food with a relatively low expenditure of energy; 2) insufficient consumption of the fat reserves and their resultant increased formation in cases of normal nutrition; 3) combination of both factors.

Of considerable importance in the first case is an *excessive appetite*, especially connected with injury to the diencephalic region which regulates the appetite, for example, after an attack of encephalitis, in tumours or trauma of the hypothalamus—hypothalamic obesity (Figs. 35 and 36).

Insufficient utilisation of fat may be the result of *disturbances* mainly in neuroendocrine and endocrine regulation. These disturbances include: 1) *adiposogenital dystrophy* which is based mainly on dysfunction of the diencephalic area, sometimes combined with hyposecretion of the somatotropic hormone by the anterior lobe of the hypophysis; this *adiposis* is often characterised by retarded



Fig. 35. Cerebral adiposis in 14-year-old boy after attack of encephalitis.



(a)

Fig. 36. Experimental hypothalamic adiposis.
a—rat with artificially induced hypothalamic adiposis, age—493 days, weight—897 g; hypothalamus injured at the age of 39 days; b—control animal, age—493 days, weight—290 g.

growth, hypofunction of the gonads, feebly marked secondary sex characters, and deposition of fat mainly in the regions of the buttocks, thighs, chest and abdomen (Fig. 37); 2) *hypophyseal adiposis* in Cushing's disease based on basophilic adenoma of the anterior lobe of the hypophysis with hypersecretion of the adrenocorticotrophic hormone, or on a primary tumoral affection of the adrenal cortex; this condition is marked by deposition of fat on the trunk, face, neck and occiput; 3) *hypothyroid adiposis*, caused by hypofunction of the thyroid, with a uniform deposition of fat on the trunk and limbs; 4) *hypogenital adiposis* (for example, in castrates) with deposition of fat in the regions of the buttocks, abdomen, chest and medial sides of the thighs (Fig. 38); 5) *insulin adiposis* caused by increased production of insulin which intensifies conversion of carbohydrates into fat and depresses the mobilisation of fat; 6) *regional adiposis* (Fig. 39) resulting from injury to the vegetative nervous system, a function of sympathetic or stimulation of parasympathetic nerves; stimulation of the sympathetic nervous system may cause a diminution in and even exhaustion of the fat

depots; some part in the pathogenesis of regional adiposis is apparently also played by the property of subcutaneous cellular tissue to accumulate fat.

Development of endocrine forms of obesity must not be regarded as a result of dysfunction of only one of the endocrine glands. In most cases obesity is caused by a combination of disturbances in the central nervous system and in the functions of several endocrine glands with predominant dysfunction of one of them.

An important part in the development of obesity is also played by other factors among which mention must be made of lack of sufficient exercise, for example, in muscular weakness, especially in paryses and pareses, in cases of already developed obesity or heart diseases.

The causes of obesity also include chronic intoxication (for example, with alcohol) as a result of which the tissue oxidative processes are diminished and liberation of energy in the organism increases owing to combustion of alcohol.

Disturbances in Fat Excretion. Fat is excreted through the intestines, and sebaceous and sweat glands. In pathology this function may be increased or diminished. Excessive excretion of fat by sebaceous glands—*seborrhea*—is observed in some inflammatory

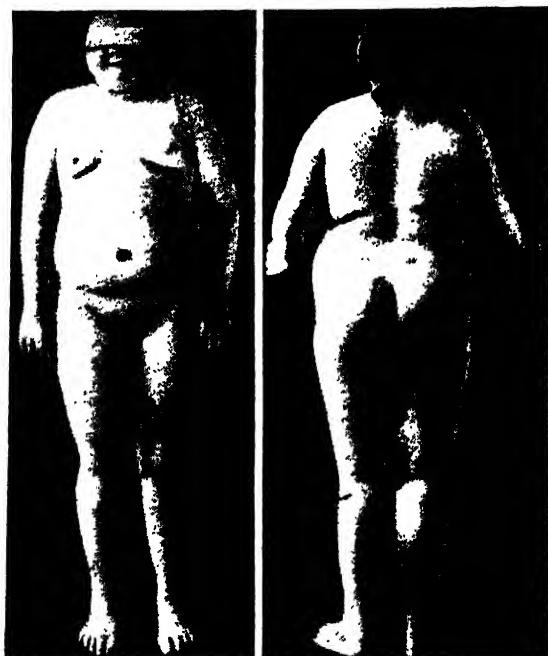


Fig. 37. Adiposogenital dystrophy in 13-year-old girl.



Fig. 38. Hypogenital adiposis in 67-year-old woman.



Fig. 39. Adiposis of the lower parts of the body. ✓

skin diseases. *Lipuria*—presence of fat in the urine—occurs after ingestion of large amounts of fat, in fractures of tubular bones, vast trauma to fatty tissue, and lipoid nephrosis. Formation of a fistula between chylous vessels and the urinary tract leads to appearance of chyle in the urine—*chyluria*.

Emaciation. Emaciation is produced by the following causes:

1) Insufficient consumption of food due to insufficiency of food, its low caloric value, compared with the expenditure of energy, or to anorexia caused by disturbances in the activity of the nervous system, infection and intoxication.

2) Disturbances in fat assimilation or increased loss of fat.

Disturbances in fat assimilation may be the result of its insufficient absorption in the intestines in cases of frequent vomiting, gastrointestinal disorders, avitaminoses and intoxications.

Disorders of the regulatory functions play an important part in the disturbances which lead to loss of fat and emaciation. Mention must be made of nervous disorders, for example, certain affections of the diencephalic region which regulates metabolism, and

overexcitation of the sympathetic nervous system caused by long-continued pain sensations, overstrain and thyrotoxicosis.

3) Disorders of endocrine functions, as in hypophyseal cachexia, diabetes mellitus, hyperthyroidism and Addison's disease

Disturbances in Lipoid Metabolism

Disturbances in Phospholipid Metabolism

Similar solubility and not infrequently common location of lipids and fats, both normally and in pathology, permit of establishing a connection between fat and lipoid metabolism, although in their chemical and physiological properties lipoids differ from fats.

Phospholipids take part in fat metabolism. In their molecule fatty acids are easily eliminated from cells. This underlies the action of lipotropic substances participating in the formation of phospholipids.

An excess of phospholipids in the blood is often observed to accompany lipemia.

The concentration of phospholipids in the blood is most frequently altered in connection with disturbances in fat metabolism, hematopoiesis and certain other functions.

In tissue dystrophies phospholipids easily split and liberate higher fatty acids which are used in building complex cholesterol esters.

There are certain pathologic states connected with deposition of cerebrosides. For example, in Gaucher's disease cerebrosides are deposited in the macrophagal cells of the spleen, in the liver, lymph nodes and bone marrow. Certain other pathologic states are associated with deposition of sphingomyelin and lecithin in the cells (for example, in splenomegaly—Niemann-Pick disease in children).

Disturbances in Cholesterol Metabolism

An excess of cholesterol in the blood (above 180-200 mg%)—*hypercholesterolemia*—may be due to: 1) excessive consumption of cholesterol with the food—egg yolks, butter, liver (alimentary hypercholesterolemia); 2) excessive mobilisation of cholesterol from the tissues, for example, in diabetes; 3) insufficient excretion of cholesterol by the liver and intestines, for example in obstructive jaundice and chronic liver disease; 4) altered cholesterol-protein complex in the blood caused by disturbances in protein fractions, for example, in lipoid nephrosis in which the amount of cholesterol in the blood may exceed 1 per cent; 5) disturbed oxidation of cholesterol observed in connection with hypofunction of the thyroid, administration of thyroxin appreciably reducing the level of cholesterol in the blood.

Disturbances in cholesterol metabolism and accumulations of cholesterol in the blood may give rise to certain pathologic processes: deposition of cholesterol mainly in reticuloendothelial elements, so-called anisotropic obesity (S. S. Khalatov), deposition of cholesterol in the histiocytes of the skin and tendons with a reactive growth of tissue (xanthomatosis) and an opaque ring at the edge of the cornea (arcus senilis or gerontoxon).

Disturbances in cholesterol metabolism give rise to *atherosclerosis* which consists in a thickening of the intima mainly of the large arteries and deposition of lipoid substances (cholesterol and its esters) in it. N. N. Anichkov ascribes this disease to accumulation in the organism, the blood in particular, of cholesterol and its infiltration of vascular walls. In his experiments feeding rabbits on cholesterol-rich food or cholesterol dissolved in oil produced atherosclerotic changes similar to atherosclerosis in man. Atherosclerosis is thus due mainly to disturbances in cholesterol metabolism. Metabolic disturbances in the vascular wall itself (for example, impairment of its innervation) are probably also of some significance. Experimental stimulation of oxidative processes in the tissues inhibits the development of atherosclerosis, for example, during long-continued administration of vitamin C or thyroidin (desiccated thyroid preparation).

Considerable importance is now also attached to the altered colloidal state of cholesterol in the plasma, which is considered due to changes in the plasma protein fractions. A certain part in the pathogenesis of atherosclerosis may apparently be played by changes in the vascular wall, developing as a result of intoxication or hemodynamic disorders.

Formation of radial cholesterol concretions in the gallbladder is connected with disorders of cholesterol metabolism. Mobilisation of cholesterol from the depots and its increased content in the blood and bile are apparently the main cause of formation of these concretions.

DISTURBANCES IN PROTEIN METABOLISM

Disturbances in *protein metabolism* may occur during all of its stages.

Disorders of the intestinal function give rise to increased putrefaction accompanied by greater deamination and decarboxylation of amino acids (formation of indole, phenol, skatole, cresol, cadaverine and putrescine), as well as formation of products of incomplete protein conversion. The resultant products of protein conversion are absorbed through the intestinal wall and may lead to intoxication. Such forms of intoxication vary in their clinical manifestation and occur mainly in intestinal diseases, especially

in children. Various pathologic conditions of the gastrointestinal tract associated with digestive disorders also involve disturbances in protein metabolism.

Disturbances in Intermediate Protein Metabolism

Various disturbances may be observed in *intermediate protein metabolism*. Conversion of proteins under the influence of proteinases causes accumulation of polypeptides which possess physiologic activity. Disturbances in intermediate protein metabolism result in phenomena of intoxication. They are observed in chronic sepsis, vast traumatic and inflammatory affections, and in so-called injury exhaustion. Disorders of intermediate protein metabolism also arise in connection with complex and varied processes of decarboxylation, deamination, reamination and synthesis of amino acids.

Increased decarboxylation leads to accumulation of proteinogenic amines which possess considerable physiologic activity, for example, histamine forming from histidine, or tyramine from tyrosine. This occurs in burns, local tissue anemia, necrobiosis and allergic states.

Disturbances in oxidative deamination occur in cases of insufficient consumption of vitamin C by the organism; this involves disturbances in oxidation of tyrosine and phenylalanine. Insufficient consumption of vitamin B₁ disturbs the fermentative systems of reamination, deamination and amination and is accompanied by disturbances in ureagenesis and increased excretion of amino acids. Avitaminosis B₆ is characterised by a weakening of the processes of decarboxylation and reamination, as well as decreased tryptophan metabolism which leads to disturbances in protein synthesis. Amino acid metabolism is also altered in deficiency of other vitamins of the B group.

There are also isolated disturbances in intermediate protein metabolism, which at the time of their onset exert no perceptible influence on general metabolism but subsequently cause changes which run a certain clinical course. These disturbances include such rare anomalies of protein metabolism as cystinuria, diaminuria and alkaptонuria.

Cystinuria is characterised by excretion of a large amount of cystine into the urine where it is found partly in a dissolved state and partly in the form of hexagonal crystals. Precipitating in the form of crystals, cystine often provides an impetus for formation of concretions containing oxalates and phosphates. Cystinuria is in all probability based on disturbances in the process of reducing cystine to cysteine or the process of reconverting cysteine into cystine which cannot be oxidised.

It is possible, however, that cystinuria is a result of disturbed deamination at the first stage of splitting of amino acids. Cystinuria

is not infrequently accompanied by *diaminuria* when the urine contains an excess of other amino acids—leucine, tyrosine, lysine, and diamines—putrescine and cadaverine; such an excess of amino acids in the urine is particularly noticeable when the latter is artificially loaded with them. However, aminoaciduria and diaminuria do not always occur simultaneously with cystinuria so that cystinuria may be regarded as a relatively isolated disturbance in protein metabolism.

Alkaptonuria is also one of the anomalies of intermediate protein metabolism. In the normal organism homogentisic acid formed from phenylalanine and tyrosine is oxidised. In alkaptonuria homogentisic acid is not oxidised and is excreted in the urine. The urine of an alkaptonuria patient turns dark in alkaline fermentation, or from addition of alkalis, and sometimes becomes almost black. This change in the colour of the urine is due to the presence of homogentisic acid which is easily oxidised in the air, forming dark-coloured products of oxidation. The reducing properties of such urine are clearly pronounced. A protracted course of alkaptonuria gives rise to pathologic changes in the joints (*arthritis alkaptonurica*) and diseases of the heart valves. Impregnation of the tissues with homogentisic acid results in a blue-black pigmentation (*ochronosis*) of the skin of the face, scleras, nails, blood vessels and cartilages.

Disorders of intermediate protein metabolism are also judged by the *increase or decrease in the content of nitrogen in the blood and urine and the altered correlations between the various fractions of nitrogenous products of protein metabolism*. Disturbances in protein metabolism are marked by disturbances in the correlations between the various fractions of protein in the blood, an increase in the amount of nonprotein nitrogen and a decreased ratio of the total nitrogen to residual nitrogen. Normally the ratio of albumin to globulins in the blood varies between 1.5 and 2.5.

Hypoproteinemia is, as a rule, characterised by a decreased concentration of albumins, for example, in renal disease or partial starvation. Hyperproteinemia is a relative excess mainly of globulins. An increase in the gamma-globulin group is connected with development of immunity.

In some forms of renal disease the concentration of nonprotein nitrogen in the blood increases (retention hyperazotemia). Severe hepatic insufficiency is also accompanied by increased nonprotein nitrogen in the blood (production hyperazotemia). In the urine nitrogen increases (hyperazoturia) mainly through an increase in ammonium salts. In this case the content of ammonia increases as a result of the failure of the liver to synthesise urea. It is also possible that the increased excretion of ammonia in cases of hepatic insufficiency is due to the neutralising action of ammonia on the accumulating acid metabolites.

General Disturbances in Protein Metabolism

General disturbances in protein metabolism arise in various pathologic states of the organism. They are characterised by disorders of the nitrogen balance and are most frequently observed in starvation, infection and intoxications.

Protein metabolism is considerably disturbed in *infectious processes*.

Disturbances in protein metabolism in infectious processes are due to intercurrent intoxications (toxigenous protein splitting) and fever. In high fever the share of protein in the total energy balance amounts to 30 per cent and more (instead of the normal 15-20 per cent). The specific dynamic effect of protein in severe forms of fever also increases. Protein metabolism is very important in infectious processes because it determines the patient's nutrition and the degree of his resistance to infection.

Various intoxications are also characterised by a negative nitrogen balance, the blood containing an excess of nonprotein nitrogen. Such intoxications are observed in poisoning with carbon monoxide, lysol and mercury bichloride.

Usually the poisons producing atrophy and other deep changes in the liver simultaneously cause disturbances in protein metabolism. Poisoning with phosphorus, arsenic and antimony leads to an excessive concentration of nonprotein nitrogen in the blood and its increased excretion in the urine.

Disturbances in protein metabolism are also observed in *malignant tumours and diseases of the kidneys, liver, blood and hematopoietic organs*. Protein hypermetabolism is observed in certain *endocrine disorders*, especially in exophthalmic goitre and parathyroid tetany.

Disturbances in Creatine and Creatinine Metabolism

Appearance of creatine in the urine where it is usually not present denotes a disturbance in creatine metabolism. Creatinuria is observed in starvation, carbohydrate deficiency in the food, especially in exhaustion of the glycogen reserve in the muscles, for example, in muscular dystrophies, tetany, adynamia due to adrenal cortical insufficiency, marked cachexias and disturbances in muscle innervation. Of considerable importance in all these cases are metabolic disturbances in the muscles where creatine plays an essential role by forming part of phosphagen.

The fact that creatinuria is observed in carbohydrate deficiency in the food indicates a connection between carbohydrate and creatine metabolism in the muscles. This is also attested by studies of the creatinine coefficient, i.e., the daily amount of creatinine nitrogen in the urine per 1 kg of weight. This coefficient is lower

in women and children apparently because of their weaker muscular development and lower carbohydrate metabolism in the muscles. It increases in vigorous muscular activity (physical training, etc.).

Appearance of creatine in the urine is also observed in certain disturbances in renal function. Excretion of creatinine decreases in most cases of creatinuria as a result of retarded conversion of creatine into creatinine.

Disturbances in Nucleoprotein Metabolism

Pathology of nucleoprotein metabolism implies a disturbance in assimilation of nucleoproteins—complex protein bodies consisting of protein and nucleic acid and forming part mainly of the nuclear substance of the tissues.

Nucleoproteins are the source of formation of uric acid. In cases of purine-free diet the amount of uric acid in the blood varies between 2 and 3 mg%. The content of uric acid in the blood may increase depending on the amount of exogenous purines. The amount of uric acid in the daily urine varies between 0.6 and 1.2 g.

Increased formation of uric acid and its accumulation in the blood is observed not only because of more exogenous nucleic substances (meat diet, consumption of liver and thymus) but also because of pathologic destruction of cells, for example, in pneumonia, leukemia, malignant neoplasia and fever.

Disturbances in the excretory ability of the kidneys may be the cause of uric acid accumulation in the blood.

Elucidation of the process of purine metabolism and of formation of uric acid in the organism assumes particular importance in connection with the changes in the purine balance which underlies gout.

Gout is characterised by attacks of inflammation of the joints. It is marked by considerable accumulation of sodium urate and its precipitation in crystals mainly in mesenchymal tissues—cartilages, joint capsules, tendons, fasciae, as well as muscles, skin and even kidneys. In these cases formation of concretions is often observed (Fig. 40).

The amount of uric acid in the blood is usually increased, especially before attacks (10-15 mg% and higher). The attacks are characterised by acute pain in the affected joint (mainly the great toe)..

Unlike other cases of uric acid accumulation in the blood its excretion in gout patients is retarded, which is particularly noticeable when it is administered artificially. Along with a high concentration of uric acid in the blood, gout is characterised by its low concentration in the urine. During attacks and immediately

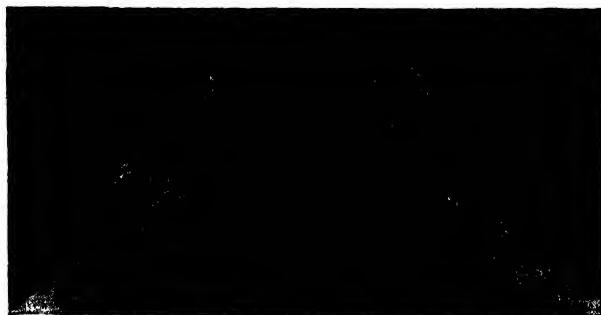


Fig. 40. Arthritis urica. Multiple gouty tophi on the hands.

following them the amount of uric acid excreted in the urine sharply increases and then decreases again.

Most researchers hold that gout is caused by functional changes in the kidneys leading to a decreased excretion of uric acid with the result that it accumulates in the blood and is deposited in the tissues. In gout excretion of uric acid indeed appreciably decreases.

The nature of this disturbance in renal function is not yet clear. It is supposed to be due mainly to a disturbance in renal innervation. It has been established experimentally that stimulation of sympathetic nerves increases and their inhibition decreases excretion of uric acid by the kidneys.

Functional disturbances leading to development of gout attacks are believed to be of the nature of an *allergy* to some as yet unknown substances consumed with food. The advocates of this view liken gout to allergic diseases. Like gout, these diseases take the form of attacks and often exhibit disturbances in purine metabolism.

The deposition of urates in cartilages, tendons and bursae is due primarily to the physicochemical peculiarities of these tissues. Cartilages and tendons are rich in sodium ions; this probably affects the solubility of sodium urate in the joints and tendons. Moreover, precipitation of sodium urate in the joints and tendons is favoured by the extremely slow circulation of tissue fluid in these organs.

Development of gout is facilitated by nuclein-rich food, alcohol and lead poisoning probably because all these substances aggravate nuclein metabolism and renal function.

DISTURBANCES IN PIGMENT METABOLISM

All pigments found in the body may be divided into three basic groups: chromoprotein, albuminogenic and lipogenic.

The chromoprotein pigments are globulin derivatives: hemin ($C_{34}H_{32}O_4N_4FeCl$), hemosiderin, porphyrins and bile pigments.

Disturbances in hemoglobin metabolism occur when the organism does not receive pyrrole compounds and iron, which are the main components of hemoglobin, or when the assimilation of these components and metabolism of hemoglobin in the organism are impaired. Formation of hemoglobinogenic pigments may be observed at sites of hemorrhages. The different types of hemoglobinogenic pigments are usually distinguished by their characteristic absorption spectra.

Toxic effects of hemolytic poisons, chronic infectious diseases, pernicious anemias and hemorrhages give rise to *hemosideroses* characterised by deposition of hemosiderin, a golden-yellow iron-containing pigment. The deposition occurs mainly in the cells of the macrophagal system. Hemosiderin is found in the spleen, liver and bone marrow. It may also be deposited in the epithelium of the uriniferous tubules, the organs assuming a rusty-brown hue.

Clearly marked hemosideroses develop in hemochromatoses. *Hemochromatoses* are characterised by deposition of hemosiderin in the liver, lymph nodes, pancreas and salivary glands, cirrhotic changes usually developing in the liver, and bronze diabetes in cases of cirrhosis of the pancreas. The bronze colouring of the skin is due to deposition of an iron-containing pigment and lipofuscin. Hemochromatosis is observed in cachexias, progressive atrophic processes, chronic intoxications with alcohol, arsenic and copper.

Some diseases are accompanied by increased elimination of *porphyrins* in the urine.

Various types of porphyrins are synthesised from intermediate protein and carbohydrate metabolites—glycocol and succinic acid. One of the first stages of such synthesis—formation of porphobilinogen—is accompanied by its excretion into the urine where it is oxidised into uroporphyrin which gives the urine a reddish colour. Decarboxylation and dehydration of porphyrins lead to their successive conversion into coproporphyrin and protoporphyrin or hematoporphyrin which as yet contains no iron and is a material for formation of hemin.

The diseases characterised by a disturbance in the synthesis of porphyrins may be congenital, in which cases, in addition to uroporphyrin III participating in the synthesis of the heme, uroporphyrin I is also formed. The amount of excreted porphyrins appreciably increases and porphyrinuria develops. The chronic form is characterised by a disturbance in the erythropoietic function of the bone marrow and porphyrins are deposited in the tissues (skin, bones, teeth). The exposed parts of the skin change because of the photosensitising properties of porphyrin and the development of high sensitivity of the skin to light. Acute prophyrinuria may arise in cases of inherited hepatic pathology and is characterised by intoxication with a predominance of nervous or abdominal symptoms, as vomiting, constipation and meteorism.

Secondary, acquired porphyrinurias arise in cases of lead poisoning, pernicious anemia, pellagra, and poisoning with arsenic, mercury and barbiturates.

Bile pigments, bilirubin in particular, are also formed from the iron-free part of hemoglobin. The fact that hematoidin produces certain reactions similar to those of bilirubin long warranted the assumption that bilirubin was formed not only in the liver, but also in other tissues. This assumption has been confirmed. In some forms of jaundice bilirubin formation is impaired.

Another large group are *pigments of albuminous origin*. These include *melanins*, dark brown pigments deposited in the organs as a result of chronic nutritional disturbances. Pathologically these pigments are found in tumours—*melanomas*. *Addison's disease* caused by dysfunction of the adrenals is characterised by very intense pigmentation (bronzing) of the skin and mucous membranes produced by deposition of melanin.

The pigments of albuminous origin are formed from products of protein splitting, in which the most important part is played by tyrosine and the product of its oxidation—dioxypyphenylalanine. Under the influence of oxidative enzymes dioxypyphenylalanine passes through a quinone stage and is transformed into a darkly stained substance which in pathology is deposited in tissues. This process takes place in melanocytes. In Addison's disease the pigment is apparently formed from tyrosine oxidised under the influence of tyrosinase or a similar enzyme into melanin. Melanin formation in the skin is activated by paraaminobenzoic acid. Deposition of this kind of pigments may also be observed after administration of phenols into the organism.

Lastly, *lipochrome* is a pigment which usually accompanies fat and is normally deposited in places of fat accumulation. Its origin is not yet clear. It is soluble in alcohol, ether and chloroform, and may thus be regarded as a substance of lipoid origin. It is particularly easily discovered in sebaceous cysts. Lipochromes also include lipofuscin (a wear-and-tear pigment) found in cells undergoing atrophy.

DISTURBANCES IN MINERAL METABOLISM

Disturbances in the Acid-Base Balance

The condition characterised by a reduction of the alkali reserve of the blood (normally 50-75 vol. %), especially, the bicarbonate reserve, or by an excess of acid-reacting substances is called *acidosis*. A condition in which the bicarbonate content of the blood is relatively high is known as *alkalosis*.

The most important role in compensating for disturbances in the acid-base balance is played by: 1) the buffer properties of the blood; 2) the function of the respiratory centre which reacts to

changes in the CO_2 and pH of the blood; by influencing the respiratory rhythm it regulates the elimination of CO_2 by the lungs and the CO_2 content of the blood; 3) the function of the excretory organs which are capable of eliminating acid and alkaline compounds, for example, the acid-reacting monobasic sodium phosphate and ammonium salts; 4) the cation exchange between the erythrocytes and the plasma; as the concentration of carbon dioxide in the blood increases, chlorine ions begin to pass from the plasma into the erythrocytes, which leads to an excess of alkali-reacting salts that bind the carbon dioxide. The compensatory mechanisms are in their turn regulated by the function of the regulatory systems which are very sensitive to all physicochemical changes in the environment.

Acidosis or alkalosis which are compensated and, as a result, are not accompanied by an appreciable shift of the blood pH are called *compensated acidosis* or *compensated alkalosis*.

Phenomena of *compensated acidosis* are observed in respiratory disturbances, administration of acids, starvation, intoxication and nephritis, and especially in diabetes as a result of accumulation of keto acids. In these cases the alkali reserve drops (for example, in diabetes to 40-45 vol.%). *Compensated alkalosis* occurs in hyperventilation, i.e., increased elimination of carbon dioxide by the lungs, in altitude sickness and in excessive treatment with alkalis. Acidosis sometimes alternates with alkalosis in accordance with hyperfunction of the systems which regulate the acid-base balance.

Gaseous and *nongaseous* (or metabolic) *acidosis* and *alkalosis* must also be distinguished. Gaseous acidosis is characterised by an accumulation of carbon dioxide in the fluids and tissues as a result of its insufficient elimination from the organism and is observed in long-continued inhalation of carbon dioxide and in respiratory disturbances; nongaseous acidosis is observed in excessive concentration or insufficient oxidation of acid-reacting substances, for example, in diabetes, starvation and administration of acids. Gaseous alkalosis develops in cases of accelerated elimination of carbon dioxide, for example, in hyperventilation and the altitude sickness; nongaseous alkalosis—in cases of administration of alkalis, loss of a large amount of gastric juice, and parathyroid tetany.

Uncompensated acidosis or *uncompensated alkalosis* may be observed only in deep pathologic disorders, often before the organism's death, for example, in experimental intravenous administration of acids or alkalis to experimental animals, in diabetic coma or severe tetany. In diabetes the pH may be 7.2-6.9 and in severe tetany—7.6.

Disturbances in Sodium Metabolism

The sodium cation is found mainly in extracellular fluid. It serves to maintain the osmotic pressure. Entering the organism in the

form of common salt and with food sodium penetrates into the cells in insignificant quantities. In pathology it penetrates into the cells when the latter are injured, as in burns. The shift of the sodium cation and its concomitant chlorine anion is connected with water metabolism, which is particularly manifest in the development of edema.

Disturbances in sodium metabolism are closely connected with disturbances in water metabolism; the more sodium is retained in the organism, the more pronounced the retention of water. During the development of edema elimination of sodium chloride in the urine decreases. The highest content of sodium chloride is found in the skin, kidneys and blood (0.45-0.5 per cent). A big loss of sodium chloride, for example, in profuse perspiration or abundant recurring vomiting leads to disturbances in osmotic pressure and increased decomposition of tissue protein—phenomena of hypochloremic hyperazotemia. This is associated with elimination of sodium from the cells into the extracellular fluid and the blood, with a consequent toxic effect of the disturbed electrolytic balance on the muscular and nervous systems.

The loss of sodium chloride by the organism in connection with excessive perspiration must be compensated by drinking salt water, otherwise the sodium deficiency will increase.

The loss of sodium by the organism causes an increase in adrenal function with its subsequent exhaustion. The adrenocortical hormones which regulate salt metabolism intensify reabsorption of sodium and retain it in the tissues. An adrenalectomy in rats causes increased excretion of sodium.

Insufficient consumption of sodium chloride results in gastric hypoacidity. Experimental animals soon completely refuse food deprived of sodium chloride and, if fed by force, develop intense vomiting.

Decreased elimination of chlorides in the urine is observed in some pathologic states, namely, *in excessive secretion of gastric juice and its hyperacidity, and in protracted vomiting.*

Elimination of chlorides is disturbed in general metabolic disorders. For example, fever is accompanied by retention of water and sodium in the tissues.

The same thing takes place in starvation, especially in connection with development of edema. Excretion of sodium from the organism increases in thyroid hyperfunction and on administration of thyroxin.

Some *renal* diseases are associated with disturbed elimination of sodium in the urine. This underlies the retention of hydrophilic sodium in the blood and tissues, which is conducive to development of edema.

Disturbances in Potassium Metabolism

Blood serum contains much less potassium (16-22 mg%) than do erythrocytes (400-420 mg%), while cells contain ten times as much potassium as does intercellular fluid. For potassium to gain entrance into the cells requires an expenditure of energy. Carbohydrates are the source of this energy, and potassium metabolism is therefore closely connected with carbohydrate metabolism. In cases of increased glycogenesis in the liver and muscles the potassium content in the serum decreases, whereas in cases of glycogenolysis it increases. Potassium is eliminated through the kidneys, its elimination being connected with that of water.

An excess of potassium in the muscles causes their intense contraction, while potassium deficiency is characterised by muscular weakness. Excessive accumulation of potassium in the blood serum is also accompanied by muscular fatigue.

Potassium metabolism is regulated mainly by the adrenals. Aldosterone (an adrenocortical hormone) mobilises potassium and causes its increased excretion in the urine by inhibiting its reabsorption in the kidneys. A function of the adrenals produces the opposite effect.

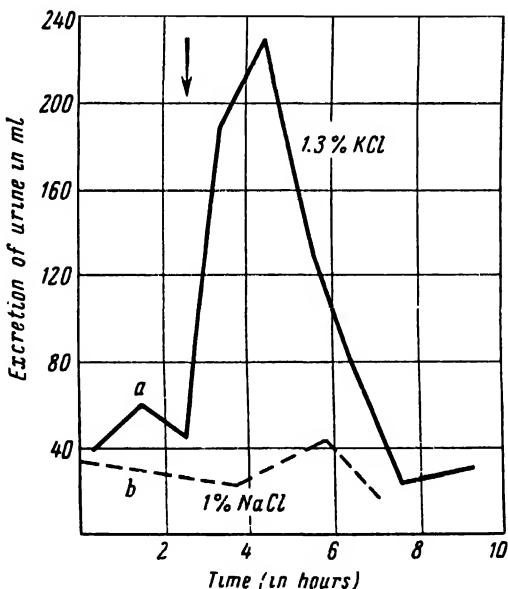


Fig. 41. Effect of isotonic potassium chloride and sodium chloride solutions on output of urine in the dog.

a—administration of 500 ml of a 1.3 per cent potassium chloride solution per os; b—administration of 1,000 ml of a 1 per cent sodium chloride solution to the same animal (Adolph)

In excessive administration of potassium salts potassium ions displace sodium ions, which are excreted in the urine, and less water is retained by the tissues as a result. This fact warrants administration of potassium salts for the purpose of increasing the excretion of urine (Fig. 41).

Disturbances in Calcium and Phosphorus Metabolism

Since the greater part of phosphorus is combined with calcium, the metabolism of phosphorus in the organism is most intimately connected with calcium metabolism.

Calcium metabolism is altered in all pathologic states which are usually also accompanied by changes in phosphorus metabolism. The daily phosphorus balance is 1.5-3.5 g in terms of P_2O_5 .

Consumption of food deficient in phosphorus causes *changes in the bones*, especially of a growing organism, since the Ca/P in the food plays a very important part in normal bone formation. Phosphorus forms part of lecithin and nuclein compounds, and participates in the processes of muscular contraction. In pathology disturbances in phosphorus metabolism may therefore be connected with disturbances in nuclein and lecithin metabolism, as well as in carbohydrate metabolism in the muscles.

Endocrine disorders (disturbances in the functions of the hypophysis and, especially the parathyroids) are accompanied by changes in the phosphorus composition of tissues, for example, the blood and skin. The negative phosphorus balance is particularly strongly pronounced in *avitaminoses* because vitamins (A and especially D) play an important role in assimilation of phosphates and organic compounds of which phosphorus forms a part.

Calcium is found in the organism in dissociated and nondissociated states and combined with colloids. The concentration of H-ions determines the degree of dissociation of calcium salts and the content of calcium cations.

A decrease in calcium in the serum (to 7-8 mg% instead of the normal 10-11 mg%) is observed in *tetany* caused by deficiency of parathyroid secretion. In this case the Ca/P drops mainly because of the decrease in ionised calcium. The concentration of hydrogen ions diminishes and that of phosphorus ions increases.

Similar phenomena develop in other forms of alkalosis, for example, in increased pulmonary ventilation and recurring vomiting. The calcium decrease is apparently one of the factors leading to increased excitability of the neuromuscular system.

Another disease based on disturbances in calcium and phosphorus metabolism is *rickets* which is characterised by an opposite change in the Ca/P during the first stage of the disease when the calcium content does not alter, while that of phosphorus decreases. In this disease it is mainly phosphorus metabolism that is affected. The

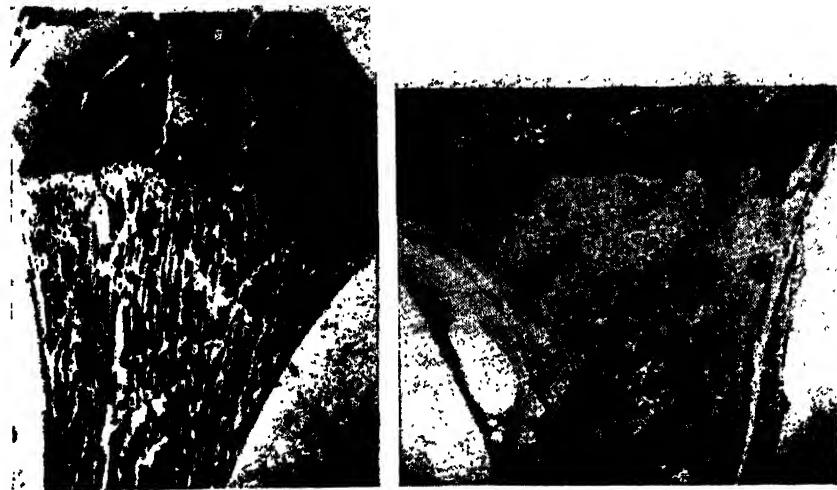


Fig. 42. Normal epiphyseal border (left); histological picture on epiphyseal border in rickets (right).

total balance of calcium and phosphorus is negative only in strongly pronounced forms of this disease. In contrast to tetany the alkali reserve of the blood is diminished and an acidotic condition develops.

In rickets calcification of the cartilage in the zones of enchondral ossification is disturbed (Fig. 42). An excess of osteoid tissue is formed from the epiphyseal cartilage, endosteum and periosteum, but the osteoid tissue is not calcified and remains soft. Moreover, the already formed osseous tissue loses calcium and is transformed into osteoid tissue. All this leads to osteomalacia resulting in various deformities.

Experimental and clinical observations show that rickets accompanied by an altered Ca/P in the tissues develops as a result of vitamin D deficiency in the organism.

Disturbances in calcium and phosphorus metabolism also underlie *osteomalacia*, a disease of adults. As in rickets the calcium-phosphorus balance in the organism is negative and the Ca/P in the blood is altered. This disease is a result of dysfunction of the gonads.

Local depositions of calcium salts (calcinosis) is observed in inflammatory foci, mainly in connective tissue elements, for example, in necrotised parts of tissue in tuberculosis, in the kidneys in mercury bichloride poisoning, at sites of hyalin degeneration, and in vascular walls in atheromatosis. The pathologic factors which may alter the physicochemical state of calcium in the blood not

infrequently lead to its deposition in the tissues. Specifically, the change in the tissue reaction involving a certain decrease in acidity is apparently one of the essential pathogenic factors of deposition of calcium salts, because in hypoacidity calcium salts become less soluble.

Disturbances in the Metabolism of Iron, Magnesium and Microelements

Iron metabolism is connected with hemoglobin since the hemoglobin of the blood and the hematopoietic tissue contains the greater part of the organism's iron (about 4,000 mg). Iron is very important also because it forms part of oxidative enzymes.

The iron required for the synthesis of hemoglobin is taken from ferritin—the iron-protein complex found in the liver, spleen and bone marrow.

These organs contain about 1,000 mg of reserve iron which, whenever necessary, is transported by the blood plasma. A deficiency of iron in the food causes development of anemia with a diminution in the amount of iron in the erythrocytes.

According to some observations, iron metabolism plays an important part in the struggle of the organism against infections and toxins. In these cases the iron is mobilised, less iron is used in hemoglobin formation, and the life span of erythrocytes diminishes. At the same time the iron content increases in the reticuloendothelial elements which, as is well known, play an important part in immune reactions. In experiments on guinea pigs it was possible to inactivate diphtheria and tetanus toxins by means of iron-containing hemosiderin. The mechanism of this phenomenon is not quite clear as yet.

Magnesium deficiency in the food causes excessive irritability of the nervous system. In such cases the functional state of the nervous system is restored by administration of magnesium salts (not calcium).

Disturbances in the Metabolism of Microelements. Microelements are mineral substances of which the organism needs negligible quantities—from thousandths to millionths of one per cent. The animal organism needs iodine, zinc, manganese, fluorine, bromine, copper, cobalt, etc. The connection of microelements with vitamins, hormones and enzymes is particularly important.

The concentration of *iodine* in the blood and its excretion increase in hyperfunction of the thyroid because iodine is a constituent of its hormones. In some regions consumption of food and water deficient in iodine gives rise to hypofunction of the thyroid and development of endemic goitre.

Zinc forms part of the molecule of insulin. Moreover, some enzymes are compounds of protein and zinc. These enzymes include, for example, carbonic anhydrase, the enzyme found mainly in

erythrocytes and playing an important part in transporting carbon dioxide to the lungs. Removal of the zinc from the carbonic anhydrase molecule destroys the enzyme. A deficiency or excess of manganese leads to pathologic changes in the bones and gonads, and depresses the action of some enzymes (for example, phosphatase).

Fluorine forms part of dental tissues. A deficiency of fluorine in the organism causes development of caries, whereas an excess of fluorine in the soil, water or air is believed to be the cause of a special condition of the enamel—mottled enamel which is characterised by formation of opaque, lustreless or cretaceous patches on the dental enamel sometimes stained yellow. This condition weakens the enamel and renders the teeth fragile. An excess of fluorine in the organism produces changes in the bones, which make them brittle; bone deformities are also observed.

Copper participates in hematopoiesis and the synthesis of hemoglobin. Some forms of hypochromic anemia are connected with a deficiency of copper salts. Copper combined with iron is a valuable therapeutic factor in treating hypochromic anemia in children, chronic anemia in women and anemia caused by hemorrhages.

Cobalt forms part of the antianemic vitamin B₁₂. A cobalt deficiency in the soil of certain areas causes diseases of cattle characterised by anemia, cessation of lactation and extreme emaciation.

Altered *bromine* metabolism has been discovered in disorders of higher nervous activity. The organism's sensitivity to bromine perceptibly increases as its content of chlorides decreases.

Deposits and Calculi

Deposits and calculi are often a result of general disturbances in mineral metabolism.

Phosphatic, oxalatic and uratic deposits may be found in the urine (Fig. 43).



Fig. 43. Section of a mixed urinary calculus. Urate in the centre, phosphate on the periphery.

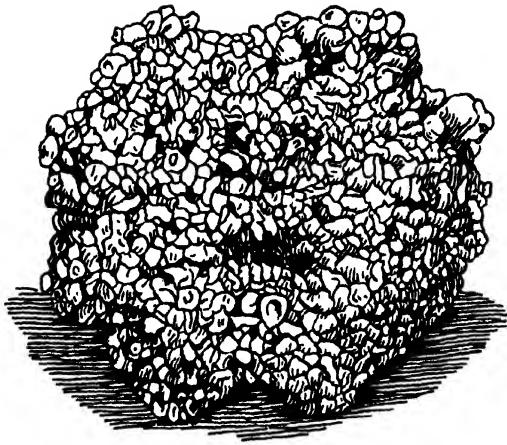


Fig. 44. Urinary oxalatic calculus.

Phosphaturia is characterised by deposition of calcium phosphates in the urine in cases of an alkaline reaction.

An acid reaction and increased excretion of oxalic acid—*oxaluria*—lead to deposition of oxalates (Fig. 44).

Deposition of phosphates and oxalates is favoured by changes in the amount and dispersion of the so-called protective colloids of the urine (a form of mucin). Elimination of large amounts of calcium in phosphaturia and oxaluria is in some measure conditioned by an increased excitability of the nervous system.

Uricaciduria is a condition characterised by the presence of excessive amounts of uric acid in the urine; *uraturia* is the presence of urates in the urine, the urine having an acid reaction in both conditions. Uric acid is precipitated in the form of crystals because of its poor solubility in acid urine. Precipitation of uric acid does not always correspond to its increased excretion. In this case, as also in deposition of urates, an important part is played by precipitation of the protective colloids of the urine, which retain the uric acid in solution.

The salt parts of the urine, which are usually in a dissolved state, may settle out of the solution and take part in formation of calculi.

Formation of calculi is not always conditioned by the same factors which lead to deposits. Calcium phosphate, oxalatic and uratic calculi may form in the urinary bladder and ureters (Figs. 43 and 44).

Several factors are involved in the pathogenesis of calculus formation.

Formation of calculi (concretions) requires some organic basis—protein, mucus, desquamating epithelium of the urinary tract and

foreign substances such as pieces of tissue, microorganisms, eggs of helminths, etc. These substances serve as crystallisation centres about which salts are deposited in concentric circles. The character of the calculi is determined by the reaction and physicochemical properties of the urine, the increased concentration of particular salts, and precipitation of the protective colloids about which the salts from the oversaturated solution are deposited. Subsequently a colloidal deposit settles on this core again and salt crystals are deposited anew.

DISTURBANCES IN WATER METABOLISM

The *water balance* is determined, on the one hand, by the consumption of water by the organism and the formation of water in the process of metabolism, and, on the other hand, by the ability of the tissues to retain water and excrete it through the kidneys (1.5 litres), skin (0.5-1 litres), lungs (250-350 ml) and intestines (50-200 ml).

A *positive water balance*, or retention of water in the organism, is a result of excretory dysfunction of the kidneys and skin, disturbances in the interchange of water between the blood and the tissues, for example, in various forms of starvation, fever and, especially edema, hypofunction of the thyroid and increased production or administration of adrenocortical hormones—mineralocorticoids, which by stimulating reabsorption of sodium and depressing reabsorption of potassium facilitate the retention of water. Insulin also causes retention of water by the tissues due to intensified synthesis of carbohydrates and proteins. A positive water balance is established when the food abounds in carbohydrates and proteins or when excessive amounts of sodium chloride are consumed; contrariwise, a predominance of potassium and calcium salts is conducive to increased excretion of water.

A *negative water balance* causes *dehydration* of the organism. It is observed in cases where insufficient water is consumed or an excess of water is excreted, for example, in profuse perspiration, copious urination, frequent diarrheas or recurring vomiting.

The loss of even 10 per cent of water uncompensated by water intake causes serious pathologic phenomena. Dehydration is marked by loss of weight, thirst, hemoconcentration, increase in the dry residue and specific gravity of the blood, relative increase in erythrocytes and hemoglobin, dystrophic changes and greater decomposition in the tissues, diminished oxidative processes, reduced blood pressure, renal dysfunction and a negative nitrogen balance; the nitrogenous products of decomposition accumulating in the tissues cause intoxication. The tissues lose their turgor, the mucous membranes become dry, and the eyes sink in. The activity of the central nervous system is considerably disturbed.

The loss of 20 per cent of the organism's water is dangerous to life.

The water metabolism is regulated by the *neuroendocrine system*.

Experimental studies of animals have long since established the dependence of water metabolism on the function of the nervous system, mainly the mesencephalon and the medulla oblongata.

The diencephalon and hypophysis form a single system which regulates water metabolism in the tissues.

By means of the antidiuretic hormone which is secreted by the posterior lobe of the hypophysis (according to some studies, in the tuber cinereum) this system establishes the level of water retention by the tissues and water reabsorption in the renal tubules.

Injury to the hypophysis or diencephalon may result in reduced secretion of the antidiuretic hormone and development of a disease known as *diabetes insipidus*. This disease is characterised by passage of extremely large quantities of urine (5-10-20 litres per day), increased osmotic pressure of the blood and a resultant stimulation of the "drinking centre". Intense thirst (polydipsia) develops; the thirst is of a compensatory significance for it prevents prolonged dehydration of the organism. Some influence on water metabolism is also exerted by the pancreas and adrenals. This is attested, for example, by increased water excretion in diabetes mellitus and excessive elimination of sodium and water by animals deprived of adrenals.

Experiments with stimulation of various parts of the cerebral cortex and the possibility of elaborating a conditioned reflex to excretion of urine denote participation of cortical regulation in water metabolism effected through the underlying parts of the brain and the endocrine glands.

Edema and Dropsy

Concept of Edema. Edema is an accumulation of fluid in the tissues, mainly in intercellular substance, due to disturbed water metabolism. Accumulation of fluid in serous cavities is known as dropsy. An accumulation of serum in the subcutaneous connective tissue is referred to as *anasarca*, accumulation of serous fluid in the peritoneal cavity—*ascites*, collection of a serous effusion in the pericardial cavity—*hydropericardium*, collection of serous fluid in the pleural space—*hydrothorax*, an increase in the volume of cerebrospinal fluid within the skull—*hydrocephalus*, accumulation of fluid in the sac of the tunica vaginalis of the testis—*hydrocele*.

The signs of edema are an increased tissue volume and a change in the form and tension of the tissue, particularly evident in edema of the skin; the skin becomes pale and cold and the surface can

be indented by pressure; such indentation is temporary and disappears soon after the pressure is released.

The *transudate* is characterised by low specific gravity and negligible protein content (usually 0.3 per cent). The amount of protein in the transudate varies with the character of the edema and its pathogenesis.

The transudate is formed by filtration of the blood plasma through the semipermeable vascular walls and its subsequent retention in the tissues because of the difference between the colloid osmotic pressure of the plasma and the tissue fluid.

The pathogenesis of edema is based on a complex of changes in the inflow and outflow of tissue fluid or lymph.

Pathogenesis of Edemas. An important part in the mechanism of edema is played by *increased transudation of fluid* from vessels into tissues and *retention of fluid by the tissues*. The impeded outflow of the fluid through the lymphatic vessels is likewise conducive to development of edema, although it plays a secondary role because there are many collateral lymph channels and the outflow of tissue fluid may also be effected through veins. Hence, edema is caused by disorders of water interchange between the blood and the tissues.

The water interchange between the blood and the tissues depends on three colloidal systems—the blood, connective tissue (interstitial substance) and cellular protoplasm (Fig. 45). The blood pressure and the rate of the blood flow, the physicochemical properties of the environment on both sides of the vascular and cellular membranes, as well as the properties of these membranes, determine the quantity and composition of the fluid that passes from the vessels into the tissues and vice versa. The direction in which a fluid moves in a capillary depends on the relation between the hydrodynamic and colloid osmotic (oncotic) pressures in the capillary.

Normally the hydrodynamic pressure in the arterial part of a capillary (35-40 mm Hg) is higher than the oncotic pressure (25-30 mm Hg) and fluid flows from the blood into the tissues. In the venous part of a capillary the oncotic pressure (25-30 mm Hg) is

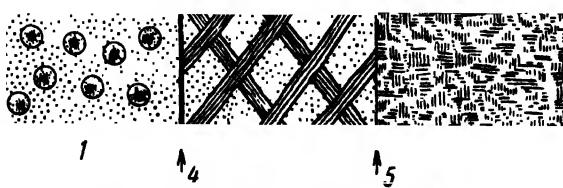
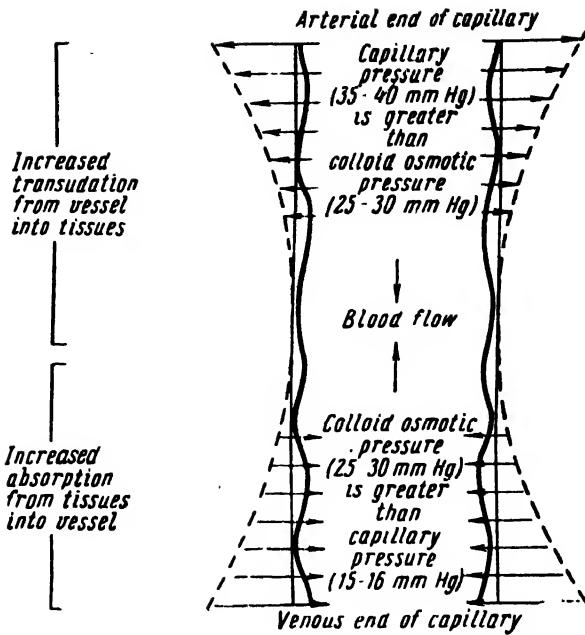


Fig. 45. Three-chamber system of tissue.

1—blood; 2—connective tissue; 3—cellular protoplasm; 4—capillary wall, dialytic membrane;
5—osmotic membrane of the cell.



. 46. Diagram showing fluid exchange between capillary and tiss

higher than the hydrodynamic pressure (15-16 mm Hg) and for this reason fluid passes from the tissues into the blood (Fig. 46).

Edema develops as a result of changes in 1) the *hydrodynamic* (or mechanical) factor—capillary pressure and rate of the blood flow, and 2) physicochemical factors, mainly *colloid osmotic* (*oncotic*) and, partly, osmotic pressure of the blood and tissues, as well as the resultant disturbance in the ability of tissue colloids to bind water (swell). In each concrete case the development of edema may be due predominantly to any one of these factors. But the aforesaid factors do not exhaust all the possibilities of formation of edema. Increased permeability of the *capillary wall* apparently also plays an important part in the pathogenesis of edema.

The *hydrodynamic* factor is determined by increased capillary pressure and decelerated blood flow in the capillaries. The pressure in the venous part of capillaries may rise to 25-40 mm Hg instead of the normal 15-16 mm. These changes lead to *increased filtration of fluid from the blood into the tissues* (Fig. 47). Increased blood pressure and decelerated blood flow in the capillaries occur in pathologic states accompanied by venous congestion, for example, in cases of impaired outflow of the blood from underlying parts

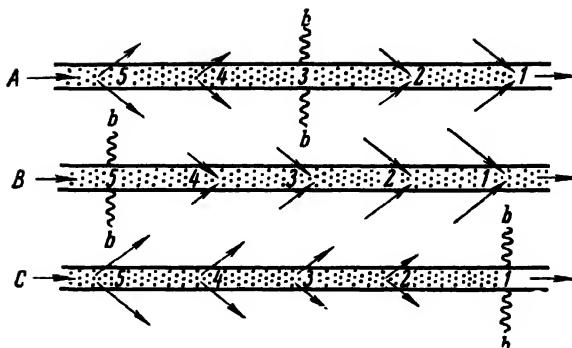


Fig. 47. Dependence of the rate of fluid flow on the degree of mechanical pressure exerted by the fluid through the vessel.

A—normal mechanical pressure; B—diminished mechanical pressure; C—increased mechanical pressure (b—border of flow reversibility).

of the body, as a result of cardiac insufficiency or obstruction of the veins of the lower limbs.

Increased formation of tissue fluid in cases of venous congestion may be demonstrated in the following experiment on the dog: a cannula is inserted in the peripheral end of one of the lymph vessels near the great saphena (*v. saphenae magnae*) and the limb is ligated with an elastic bandage with the result that lymph begins to be discharged within 15-20 minutes. The increased lymph formation, its accumulation in the tissues and formation of edema are the result of increased capillary pressure, injury to the vascular walls and tissues, and impeded outflow of lymph due to development of venous congestion.

This experiment shows that the mechanical factor plays an important part in the development of edema, but is by no means the only factor. Increased pressure in the capillaries alone, for example, in arterial hyperemia does not cause edema of the tissues despite the increased formation of tissue fluid, but combined with venous congestion arterial hyperemia may be conducive to development of edema. For example, constriction of the femoral vein in the dog does not of itself cause edema, but simultaneous transection of the sciatic nerve of the same limb leads, through arterial hyperemia, to edema.

Another very essential factor conducive to development of edema is *decreased colloid osmotic pressure* of the plasma and relatively high (compared with the colloids of the blood) ability of tissue colloids to bind water. In this respect proteins are of paramount importance. The capillary wall is impermeable to plasma proteins, for which reason even a slight decrease in the colloid

osmotic pressure of the plasma proteins results in higher hydrodynamic (or mechanical) pressure and becomes an effective factor in increasing the passage of water from the blood into the tissues (Figs 48-49).

The ability of tissue colloids to bind water (or swell) depends on the properties of the colloids themselves and the influence exerted on them by osmotic factors, for example, a change in electrolytes, a concentration of hydrogen ions in particular.

Some edema patients show a decreased colloid osmotic pressure of the plasma. This is due, not only to a decreased total amount of proteins in the plasma (hypoproteinemia), but also to an altered interrelation between the proteins of the plasma, for example, a decrease in albumins and relative preponderance of globulins, as is the case in certain diseases of the kidneys (nephroses).

A decrease in the concentration of proteins in the plasma to 5.5 g%, or of albumins to 2.5 g%, may lead to development of edema. Edema was observed to develop in rats fed protein-free food; the edema was accompanied by a decrease in the plasma albumin. As soon as proteins were added to the food the albumin content of the plasma rose and edema disappeared. In experiments on dogs repeated bloodletting and administration of washed erythrocytes into the blood stream resulted in a decrease in plasma proteins to 3 g% and development of edema of subcutaneous connective tissue.

However, decreased colloid osmotic pressure of the plasma does not of itself always lead to development of edema. Other factors are also required. Clinical observations have shown that sometimes low colloid osmotic pressure of the plasma is not accompanied by appearance of edema. To understand the pathogenesis of edema it is necessary to consider the basic factors concerned in the development of edema, not apart from each other, but in their *interaction*.

The different factors, however, are not equally important in the development of the different forms of the disease. Mechanical and

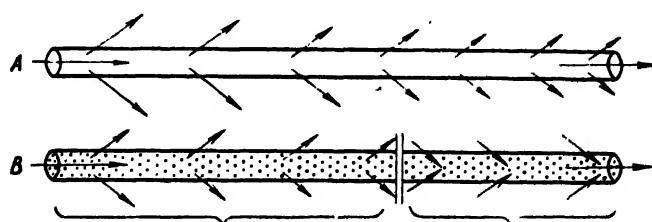


Fig. 48. Difference in the direction of flow of fluid from and into a vessel in cases of colloidless (A) and colloidal (B) fluids in a dialytic capillary.

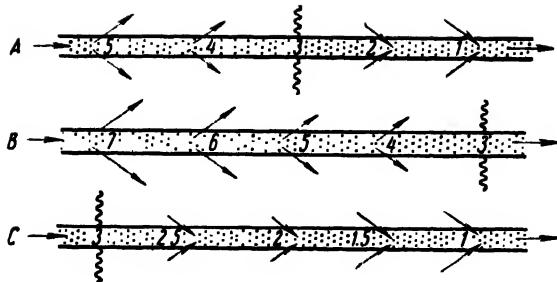


Fig. 49. Dependence of the rate of fluid flow on the degree of colloid osmotic pressure of the fluid in the vessel.

A—normal colloid osmotic pressure; B—diminished colloid osmotic pressure; C—increased colloid osmotic pressure.

colloid osmotic edemas are distinguished pathogenically, according to the predominance of a particular factor. However, it is often difficult to decide on the form of edema because of the impossibility of establishing the predominant factor.

The state of the capillary walls—their permeability, particularly to proteins—is also of considerable importance in the development of edema.

Experimentally it is possible to disturb the permeability of vessels by altering the function of the vasomotor nerves, disturbing tissue metabolism or administering poisons. For example, it is possible to produce edema of half the tongue in the frog by long-continued stimulation of the vasodilator lingual nerve with increasingly stronger electric current. The permeability of vessels is appreciably disturbed in inflammatory processes, diseases of the kidneys, avitaminosis C, and poisoning with silver nitrate, uranium and arsenic.

It is important to note that the effect of the aforementioned pathogenic factors of edema in certain measure depends on *disturbances in the functions of the nervous system* since the nervous system regulates the hemodynamics, tissue metabolism and vascular permeability. For example, it has been demonstrated experimentally that administration of large amounts of physiologic saline solution to the rabbit (several times the volume of its blood) does not of itself cause edema, but, if this influence is combined with stimulation of the interoceptors of an intestinal loop which has retained only neural connections with the organism, severe pulmonary edema very rapidly develops (within 3-8 minutes). The same result is produced by applying the additional stimulation to the proximal end of the vagus or by injuring the brain.

The *endocrine glands* which regulate water metabolism (thyroid and hypophysis) also take part in the pathogenesis of edema. A connection between certain forms of edema (cardiac and renal) and

disturbances in adrenal cortical function has lately been established. Increased secretion of mineralocorticoids causes retention of hydrophilic sodium in the organism. The most potent in this respect is aldosterone which increases reabsorption of sodium in the convoluted tubules of the kidneys and blocks all other routes of its excretion from the organism.

An excess of aldosterone is indeed found in the blood and urine of edema patients with heart and kidney affections. The reason for increased excretion of aldosterone is not clear as yet. According to some data, in incipient edema the increased secretion of aldosterone by the adrenals may be caused by a decrease in the volume of the blood and the resultant stimulation of the receptors of the carotid sinus, right atrium or directly the diencephalon.

Etiology of Edemas. In addition to being classified according to their pathogenesis, edemas are also distinguished according to their etiology as *congestive*, *renal*, *cachectic*, *toxic*, *inflammatory*, *neurotrophic*, and *endocrine*.

The *edemas of congestive origin* include those which result from obstruction of veins (thrombi and emboli) and their *constriction* by tumours; the latter are mainly *cardiac edemas* often accompanied by development of ascites or hydrothorax. Disturbances in cardiac activity lead to development of edemas through a rise in blood pressure caused by congestion in the venous capillaries and increased transudation of fluid from the blood into the tissues. At the same time the outflow of fluid from the tissues is observed to be impeded as a result of weakened aspiration by the right heart. But increased capillary pressure is not enough to cause development of cardiac edema.

In addition to the mechanical factor, the appearance of cardiac and other congestive edemas is due to increased permeability of capillaries as a result of distention and disturbed nutrition of their walls which become more permeable to proteins. The colloid osmotic pressure is also disturbed in cardiac edemas because cardiac insufficiency affects metabolism and the physicochemical state of the blood and tissues. Congestive edemas manifest themselves for the most part in places which offer relatively strong resistance to the outflow of blood, for example, in the lower limbs. A *lymphatic congestive edema*, for example, ascites is sometimes observed; it is due to obstruction of the thoracic duct.

Renal edemas observed in diseases of the kidneys may partly result from retention of sodium, which leads to increased osmotic pressure in the tissues. In these edemas the transudate contains more sodium chloride than does the blood.

The most important part in the pathogenesis of renal edemas, in nephroses in particular, is played by a decreased concentration of proteins in the blood (hypoproteinemia), rarefaction of the

plasma and the resultant decrease in its colloid osmotic pressure. In glomerulonephritis renal edema is mainly due to disturbances in the colloidal properties of the tissues and permeability of the vessels as a result of poisoning of the organism by accumulating toxic substances.

Cachectic edemas develop in organisms emaciated by chronic diseases, for example, severe anemia, malignant tumours, and qualitative starvation. The leading part in the origin of these edemas is played by an increase in the permeability of the capillary walls (as a result of malnutrition of the endothelium) and a decreased concentration of proteins in the blood (due to their insufficient consumption by the organism). As a result, the colloid osmotic pressure in the plasma diminishes, the plasma filters more easily through the capillaries, and less tissue fluid is resorbed.

Toxic edemas develop under the action of various toxic substances. The development of these edemas is due to increased colloid osmotic pressure in the tissues, disturbances in their physico-chemical state and injury to vascular walls. Toxic edemas of the skin develop at points stung by certain insects and as a result of application of mustard and croton oils; in the lungs they develop as a result of inhalation of chlorine, phosgene and, especially di-phosgene.

Inflammatory edemas are similar in pathogenesis to toxic edemas. An essential role in the origin of inflammatory edemas is played by altered oncotic and osmotic pressure in the tissues, and by changes in the permeability of vascular walls. Tissue edemas of an inflammatory character are observed in infectious diseases, as in diphtheria, scarlet fever and especially anthrax, and as the effect of certain chemical warfare agents, for example, mustard gas and lewisite.

The edemas caused by lesions in the *nervous system* include those of *vasotrophic origin*, for example, edemas of limbs in hemiplegia and syringomyelia, edema of the face in neuralgia of the trigeminal nerve, Quincke's edema in injuries to or constriction of nerves, and edemas of the skin in hysterias. Some edemas are due to dysfunction of *endocrine glands*, for example, the thyroid. In hypothyroid edemas tissue nutrition and the properties of the tissue colloids are greatly disturbed. The leading role in the origin of neurotrophic edemas is played by disturbances in innervation of vascular walls, which results in their altered permeability; metabolic disturbances in the tissues are also of some importance in these forms of edema.

The *outcome* of an edema depends on the course of the pathologic process responsible for the retention of water in the tissues. After elimination of the cause the fluid accumulated in the tissues is resorbed. Protracted edemas, however, are sometimes characterised by a loss of elasticity by the tissues with the result that the tissues

do not contract and the fluid remains in them for a long time after elimination of the cause.

The consequences of edema for the organism consist in dysfunction of organs. This is due to compression of the cells by the fluid accumulated in the tissue and a change in their vital activities. In dropsy the accumulation of fluid in a cavity often leads to compression of the surrounding organs and tissues. Dysfunction of organs as a result of accumulation of fluid in functionally important cavities plays a particularly significant part. This is the case, for example, in pulmonary edema in which fluid accumulates in the alveoli, the respiratory surface of the lungs thus considerably diminishing.

Edematous tissues easily become infected and are often subject to inflammatory processes. For example, pulmonary edema may give rise to pneumonia. Protracted edema may lead to excessive growth of connective tissue.

LOCAL CIRCULATORY DISORDERS

The present chapter deals with typical circulatory disturbances in the tissues. These disturbances are called local somewhat conditionally, since they are closely connected with general circulatory disorders. For example, elevated general blood pressure in hypertensive vascular disease often leads to circulatory disturbances in the brain and kidneys, while cardiac weakness results in congestive phenomena in the liver. On the other hand, occlusion or protracted spasm of vessels (of the brain or heart) gives rise to disturbances in general blood circulation.

The following circulatory disorders are distinguished: arterial and venous hyperemia, stasis, anemia or ischemia, hemorrhages, thrombosis and embolism.

ARTERIAL HYPEREMIA

Arterial hyperemia may be physiologic or pathologic. *Physiologic arterial hyperemia* arises normally during hyperfunction of organs and increases delivery of nutritive substances to these organs by the blood. *Pathologic arterial hyperemia* arises under the influence of pathogenic agents and is usually characterised by a lack of correspondence between the circulation and the function of organs; the blood circulation may be increased even when the organs are in a state of relative rest.

Arterial hyperemia is an *increased content of blood in a part with more blood flowing through its dilated vessels*. The blood flows through the given part rapidly and fails to give off enough oxygen to the tissues and to become saturated with carbon dioxide. Arterial hyperemia is marked by: 1) *redness* of the tissue, which is particularly noticeable on the mucous membranes and the skin; 2) *pulsation* of small vessels due to dilatation of the supplying arteries, acceleration of the blood flow and propagation of the pulse wave along the dilated blood channel; 3) *elevated blood pressure*.

in the vessels of the hyperemic part due to increased inflow and greater mass of circulating blood; 4) *swelling* of the tissues and enlargement of the hyperemic part due to increased lymph formation and greater filtration of fluid through the capillary walls (Fig. 50); 5) *elevated temperature* of the skin and mucous membranes due to increased inflow of arterial blood and greater heat loss; the latter is clearly perceived on the mucous membranes and the skin and is unnoticeable in the internal organs which are not cooled by contact with the external environment.

Arterial hyperemia may be caused by: 1) greater-than-normal effect of usual physiologic stimuli, for example, prolonged exposure of the skin to sunlight or effect of too much food on the gastrointestinal tract; 2) effects of unusual stimuli—poisons, toxins, lowered atmospheric pressure, elevated temperature, etc.; 3) increased sensitivity of the vessels to physiologic stimuli as in allergic sensitisation of the organism; 4) primary lesions in the nervous system, leading to pareses and paralyses.

The mechanism of arterial hyperemias is essentially *neurogenic*.

Arterial hyperemia may be a result of *reflex* action of stimuli on the central nervous system or on the peripheral nervous apparatus (according to the axon reflex principle) or may be due to *direct action* on the central vasoconstrictor structures. Both, the increased tone of the vasodilators and diminished tone of the vasoconstrictors based on the principle of reciprocity between the vasoconstrictor and vasodilator centres, play an important part in such cases.

The rush of blood to one arm on immersion of the other arm in warm water or the redness of the conjunctiva caused by a foreign particle (dust, grain of coal) in the eye must be referred to the group of reflex arterial hyperemias. The redness of the face in pneumonia or toothache is also of a reflex nature. Lastly, arterial

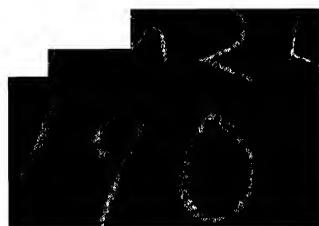


Fig. 50. Red dermographism with subsequent edema.

hyperemia may develop by the conditioned reflex mechanism in cases of blushing caused by strong emotions (rage, shame), or as a result of repeated application of a thermal stimulus combined with an indifferent stimulus (auditory or optic), following which hyperemia may be produced by application of the conditioned stimulus alone.

The role of the reflex mechanism must not be completely ignored in the development of such hyperemias whose pathogenesis directly involves dysfunction of the muscular coat of the vessels. These include hyperemia caused by an increased inflow of blood to a rarefied space, for example, intense hyperemia of the skin produced by suction of dry cups or a sudden rush of blood to the body surface in cases of rapid change from an environment with an elevated pressure to usual atmospheric conditions.

Postanemic hyperemia develops in various vascular cavities of the body (pleural, abdominal) when fluid of a congestive or inflammatory character is rapidly aspirated from them, as in pleurisies. This hyperemia is called postanemic because it is preceded by ischemia due to constriction of vessels. On aspiration of the fluid and subsequent lowering of external pressure the vessels, which have lost a good deal of their tone, immediately dilate under the pressure of the blood rushing through them. The same thing is observed on removal of an elastic tourniquet applied to a limb during an operation; the blood immediately rushes into the vessels of the exsanguinate part.

A certain role in the pathogenesis of postanemic hyperemia is apparently also played by stimulation of the receptor apparatus of the anemic part by the products of disturbed metabolism (histamine, acetylcholine, etc.).

Arterial hyperemia due to damaged vasoconstrictor nerves (neuroparalytic hyperemia) may be the result of injury to the vasoconstrictor centres, as in trauma of the cervical or thoracic divisions of the spinal cord or as in transection of vasoconstrictor nerves. Of the chemical substances which produce a paralytic effect on the vasoconstrictor centres and sometimes cause symmetric hyperemia of the skin and mucous membranes mention must be made of the toxins of certain infectious agents (*Rickettsia prowazekii*, diphtheria bacilli, pneumococci, etc.). Arterial hyperemia develops as a result of paralysis of the splanchnic nerve, as in infectious collapse or high spinal (subarachnoid) anesthesia.

Arterial hyperemia easily develops in the rabbit after transection of the peripheral sympathetic nerve (Fig. 51).

In the dog hyperemia can be produced by removal of the superior cervical ganglion or transection of the sciatic nerve.

If the transection of the sciatic nerve is immediately followed by stimulation of its peripheral end, the peripheral vessels are constricted. Four or five days after transection, when the vaso-

constrictor fibres have degenerated, the same stimulation produces arterial hyperemia in the corresponding regions because the vasodilator fibres in the trunk of the sciatic nerve are still intact.

Vasodilator and vasoconstrictor fibres are found in the cervical part of the sympathetic nerve. Stimulation of the cervical sympathetic trunk causes, in addition to anemia of the ear, tongue and soft palate, hyperemia of the mucosa of the nose, gums, lips and cheeks. Vasodilators, apparently of parasympathetic origin, are also found in the posterior roots of the spinal cord.

The effects of arterial hyperemia are due to circulatory changes in the tissues and elevated blood pressure. The increased blood supply favourably affects tissue nutrition, especially during simultaneous hyperfunction of the given organs. The nervous system participates in tissue metabolism chiefly through exerting a regulatory influence on the lumens of the vessels. In pathology arterial hyperemia sometimes leads to hemorrhage. Arterial hyperemia is the most dangerous in the central nervous system which is more sensitive than any other organ to changes in the blood supply and local elevation of blood pressure. An intense rush of blood to the brain is usually accompanied by unpleasant sensations, for example, vertigo and tinnitus cranii, and sometimes excitement.

Hemorrhages from cerebral vessels, as in cases of pathologic changes in their elasticity and permeability, are particularly dangerous.

VENOUS HYPEREMIA

Venous hyperemia is an *excess of blood and diminished blood circulation in a part due to impeded outflow of the blood*. As a result the venous network of the part becomes visible while the blood flow is slowed down. Venous hyperemia is generally caused by some obstacle to the blood flow either in- or outside the vessel.

Venous hyperemia may be caused by:

- 1) constriction of veins without injury to the arteries as a result of a ligature, pressure by a tumour, gravid uterus or constriction of the lumen of a vessel by cicatrising tissue;

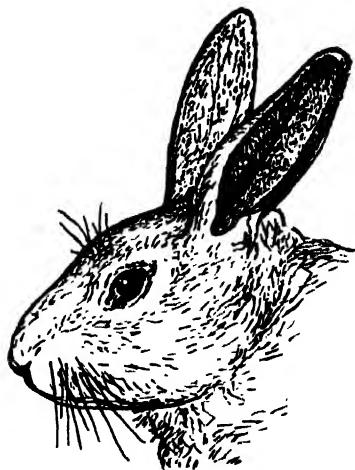


Fig. 51. Head of a rabbit with severed sympathetic nerve on the left side of the neck and extirpated upper cervical sympathetic ganglion. The left ear is highly hyperemic.

2) action exerted on tissues by physical and chemical agents which disturb nutrition and cause relaxation of vascular walls, for example, the action of adhering and irritating apparatus (cups), heat and cold; in these cases arterial hyperemia changes to venous hyperemia with all its characteristic consequences;

3) thrombosis of veins, i.e., occlusion of vessels, which hinders the outflow of blood from a corresponding part;

4) cardiac weakness in cases of heart disease, especially in right ventricular insufficiency; in these cases the blood flow towards the heart slows down and venous congestion is observed in the underlying parts, mainly in the large and medium-sized veins;

5) dysfunction of the pulmonary apparatus accompanied by diminished elasticity of pulmonary tissue with resultant changes in intrathoracic pressure, decreased aspirating action of the thorax and consequent venous hyperemia in the lower part of the body;

6) long confinement to bed, which may cause development of congestive hyperemia in the lower parts of the body. This form of hyperemia is also observed as a result of pendulous limbs, long-continued sedentary life (for example, hemostasis in hemorrhoidal veins) or long standing; in all these cases the outflow of blood through the veins is impeded.

In the pathogenesis of venous hyperemia a very important role, in addition to the obstruction to the blood flow, is played by impairment of the nervous mechanisms of its regulation. This is evidenced by the fact that venous hyperemia sometimes develops outside the part in which the obstacle to the blood flow has arisen.

The characteristic signs of venous hyperemia are: 1) *redness of the part with a bluish tint (cyanosis)** due to hemostasis and the excess of reduced hemoglobin (more than 5-6 g per 100 ml of blood) in the blood; 2) *lowered temperature of the affected part*; at first the temperature of the given part somewhat rises, but the subsequent diminished outflow of blood and continued heat loss lead to drop in its temperature; 3) *elevated blood pressure* in the veins peripherally from the obstruction as a result of the impeded blood flow towards the heart and diminished rate of the blood flow coupled with accumulation of blood in the veins below the site of obstruction (Fig. 52); 4) *enlargement*, swelling of the hyperemic part due to increased filling with blood and intensified transudation of fluid into the tissue, as well as possible development of edema (Fig. 53); this phenomenon is a result of elevated intravascular pressure, change in the permeability of the vessels due to insufficient delivery of oxygen and disturbed tissue metabolism; 5) *decelerated blood flow* due to an obstruction on the way to the heart; 6) *disturbed tissue nutrition* of the hyperemic part; this also depends on the site and duration of venous occlusion and

* From the Greek word *kyanos*—dark-blue.

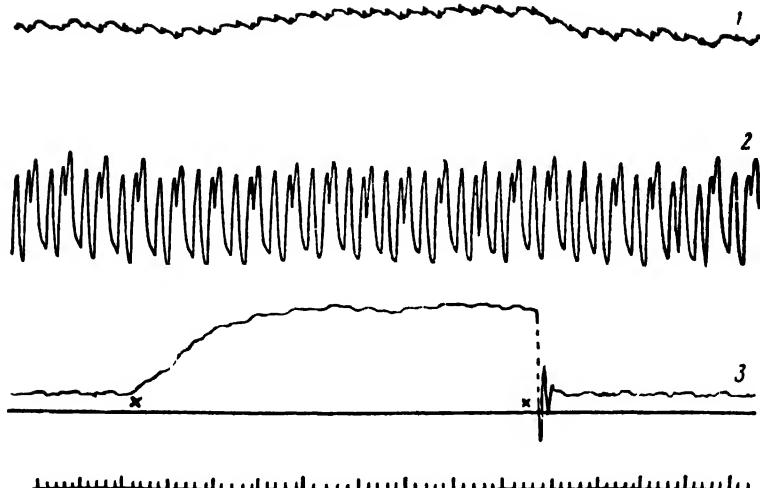


Fig. 52. Blood pressure in the vessels of the dog's leg in venous stasis (A. I. Talyantsev).

× on the left—compressed femoral vein; × on the right—the clamp is removed. The curves show: 1—girth of the leg; 2—blood pressure in the femoral artery; 3—blood pressure in the femoral vein; bottom line shows time intervals.

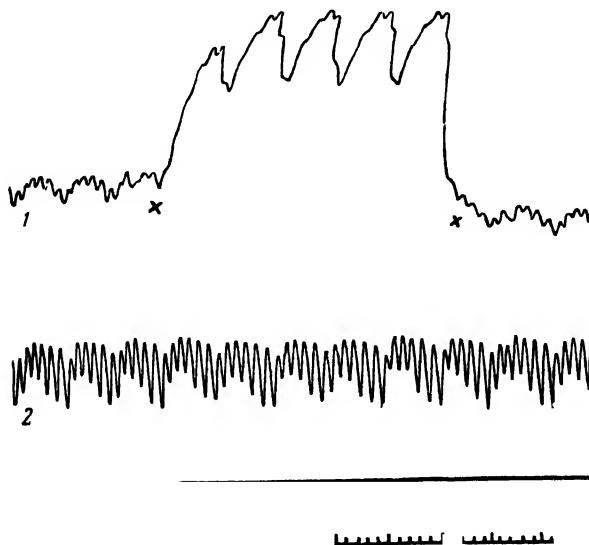


Fig. 53. Volume of kidney with renal vein clamped. × on the left—vein is clamped; × on the right—clamp is removed.

The curves show: 1—volume of kidney; 2—blood pressure in the femoral artery.

the extent of development of collateral circulation, which is of compensatory importance; nutritional disorders due to insufficient delivery of oxygen in chronic stasis increase the permeability of vessels and affect the endothelium, thereby often causing hemorrhages; 7) *induration, atrophy of specific elements* (for example, brown atrophy of the heart or nutmeg liver) and *reactive growth of connective tissue* due to protracted venous congestion, nutritional disturbances in and dysfunction of the hyperemic organs.

Phenomena of venous hyperemia with its characteristic signs are easily discovered on the frog's tongue by the following method: the tongue is smoothed out over the opening in the cork plate, the neurovascular bundle is exposed and the lingual vein is ligated, at first on one side, the microscope showing considerable dilatation of the veins and a decelerated blood flow. However, development of collateral circulation prevents the appearance of venous hyperemia. But, if the lingual vein is also ligated on the other side, the blood flow slows down sharply and the blood in the veins and capillaries begins to flow now in one and now in the opposite direction, according to the pulse wave. The reason for these fluctuations in the blood flow is that in its flow towards the heart the blood encounters an obstacle (the ligature) and turns back. Increased pressure distends the vessels and red blood cells begin to pass through their walls. Rupture of capillaries may also frequently be observed. The tongue becomes cyanotic and edematous.

General circulatory disorders due to venous hyperemia are particularly strongly pronounced when rapid occlusion of large vessels occurs. For example, in cases of occlusion of the portal vein the abdominal organs, whose vessels can accommodate a large amount of blood, become congested. This is responsible for the drop in general blood pressure, cardiac and respiratory weakness, and deficiency of blood in the other organs. Especially dangerous in such cases is protracted cerebral anemia which may lead to syncope, respiratory paralysis and death.

In some cases, however, venous hyperemia is beneficial. For example, venous congestion produced artificially by compression of veins may favourably affect the course of the infectious process in the given part, since venous congestion alters metabolism and fosters accumulation in the tissues of biologically active products which create unfavourable conditions for the development of micro-organisms in the focus of affection. Oxygen starvation and accumulation of carbon dioxide in protracted venous congestion are conducive to nutritional disturbances and growth of connective tissue. This gives rise to atrophy of the organ, for example, atrophy of the liver (in cases of venous congestion in the liver) or congestive cirrhotic dystrophy. Chronic venous congestion may hasten the healing of wounds by stimulating the growth of connective tissue.

STASIS

*Stasis** is a complete cessation of the blood flow with the vessels dilated and filled with a mass of closely adhering erythrocytes. *Venous* and *capillary*, or *true*, stasis is distinguished.

Venous stasis is a result of impeded outflow of blood through a draining vein. A certain part in its origin is played by a slowing of the blood flow and paralysis of the vasomotor nerves due to disturbed nutrition of the vascular walls and concomitant vascular dystonia.

Capillary stasis may appear irrespective of any obstacles to the outflow of blood. It occurs as a result of *various excessively strong influences*, for example, tissue desiccation (exposed peritoneum), the effects of heat or cold, acids, alkalis, and mustard or croton oil. There are also infectious and toxic forms of capillary stasis occurring in severe infectious diseases, for example, stasis in the limbs, pinnas of the ears and other peripheral parts of the body in typhus, and inflammatory stasis in acute and rapidly developing inflammatory processes, as in hyperergic inflammation.

The *development* of capillary stasis is due to vasomotor disturbances. These disturbances are characterised by a reflex constriction of arterioles and small arteries, which leads to a drop in blood pressure and diminished blood flow in the corresponding capillaries; the blood flow slows down sharply, red blood cells congest the small arteries, capillaries and veins, and, unable to move on, increasingly accumulate, filling the lumens of the capillaries and veins which are sharply dilated (prestasis). These phenomena are followed by complete cessation of the blood flow—stasis proper. But in addition to the main cause—vasomotor disturbances—the development of stasis is also due to chemical and physical disturbances in the tissues.

The action of harmful agents on the tissues liberates physiologically active products, for example, histamine, substances of the adenyl system, etc. By affecting the permeability of vessels these substances cause transudation of fluid from the vessels into tissues, which leads to hemoconcentration. Furthermore, acid metabolites alter the physicochemical properties of the blood colloids, causing the swelling and adhesion of erythrocytes and thereby obstructing their movement.

The *results of stasis* vary. In cases where no major disturbances in the vascular walls and the blood of the given part have occurred the blood flow may be restored after elimination of the cause of stasis. But in cases of damage to the vascular walls and adhesion of erythrocytes in the blood stasis is irreversible and necrosis of the corresponding part develops.

* In Greek the word *stasis* means standing.

LOCAL ANEMIA (ISCHEMIA)

Local anemia, or ischemia,* is a *local diminution in the blood supply due to diminution or cessation of inflow of arterial blood*. The blood pressure in the artery below the obstruction drops as a result of diminished filling of the artery with blood.

Such a drop in blood pressure can be demonstrated in an experiment with measuring the pressure in the femoral artery (Fig. 54). By compressing the vessel above the inserted cannula it is possible to lower the blood pressure which does not, however, go down to zero. After a while the blood pressure curve somewhat rises and even shows respiratory and pulse waves. The latter is explained by reflexly developing collateral hyperemia in the branches anastomosing with the main arterial trunk. In the femoral vein the blood pressure does not change.

Several forms of ischemia are distinguished according to the causes of their development.

1. *Compression ischemia due to compression of the supplying artery* or of the given part, may be produced by ligature of the artery, application of a tourniquet, or compression of a vessel by a growing tumour, cicatrix or foreign body.

2. Ischemia due to *obstruction of the supplying artery* (thrombus, embolus) or *obliteration*, i.e., occlusion of the vascular lumen as a result of pathologic changes in the wall (for example, inflammatory growth of the intima).

3. *Neurotic (or spastic) ischemia* due to a reflex spasm of vessels (angiospasm) caused by stimulation of the vasoconstrictor apparatus. Angiospasm may be evoked by the following stimuli: cold applied to the body surface, severe trauma, and certain poisons. for example, ergotin. A sharp constriction of the vessels and marked ischemia may be observed on the rabbit's ear during stimulation of the sympathetic cervical nerve on the corresponding side or of the proximal end of the transected sciatic nerve.

Ischemia caused by stimulation of the vasomotor centres in the brain must be regarded as a form of angiospastic ischemia; it is sometimes manifested as a symmetrical spasm of the supplying arteries in different parts of the body. Neurogenic spasm of vessels apparently underlies the affection of the limbs in spontaneous gangrene and angiospasm of the coronary vessels. Pallor of the face due to strong emotion (for example, fear) is also a result of a reflex stimulation of the vasoconstrictor apparatus of the vessels of the face.

Local anemia may develop in cases of an increased blood flow to some other part of the organism (*collateral ischemia*). Cerebral ischemia due to a sharp dilatation of the vessels in the abdominal

* From the Greek words: *ischein*—to check, and *haima*—blood.

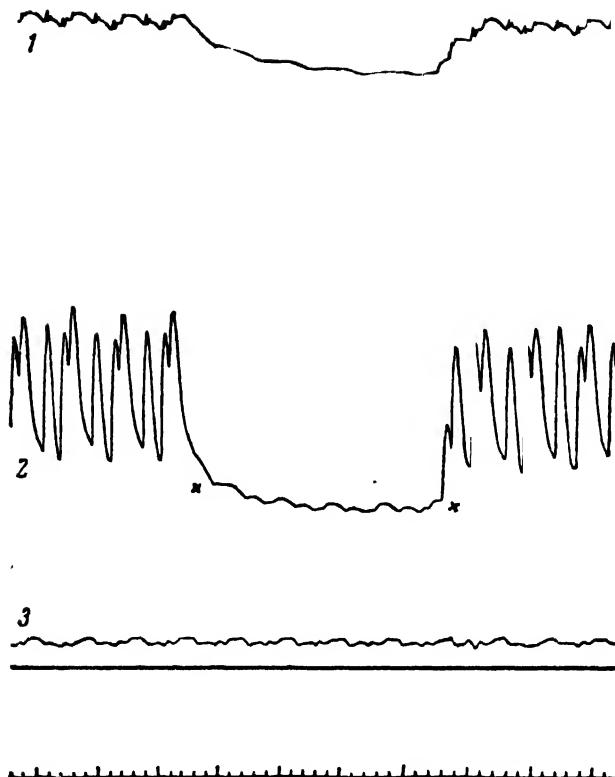


Fig. 54. Blood pressure in the vessels of the dog's leg in ischemia.

× on the left—femoral artery is clamped; × on the right—clamp is removed

(A. I. Talyantsev).

The curves show: 1—girth of the leg; 2—blood pressure in the femoral artery; 3—blood pressure in the femoral vein.

cavity and an increased flow of blood to the abdominal organs may serve as an example.

Phenomena of collateral ischemia may be observed in the following experiment. A lateral incision is made in the frog's abdomen, the sympathetic trunk is exposed and the site of confluence of the right and left aortas, the intestinal artery and three neural branches running from the sympathetic trunk to the intestinal artery are found. A redistribution of the blood is observed after transection of these branches. The vessels of the mesentery and abdominal organs become engorged with blood (as a result of transection of the vasoconstrictors), the vessels of the tongue and the web become constricted and collateral ischemia develops.

Collateral ischemia is of neurogenic origin.

Ischemia is characterised by: 1) pallor of the tissue and loss of the normal colour; 2) cooling of the tissue; 3) contraction of the

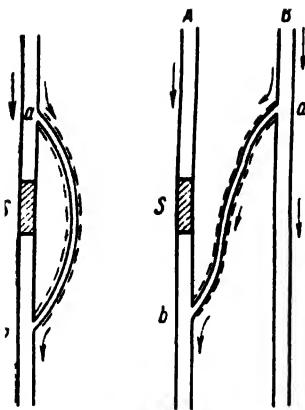


Fig. 55. Diagram showing development of collateral blood circulation (for explanation see text).

ischemic part due to diminished blood supply; 4) metabolic disturbances, which in their turn cause dystrophy to the extent of necrosis; 5) dysfunction of the organ concerned; ischemia produces particularly important changes in the central nervous system (pareses and paralyses); 6) pain, numbness, pricking, itching and creeping sensations in the skin, and a number of other phenomena, depending on the site and extent of development of ischemia.

Ischemia often terminates in restoration of the functions of the affected tissue (even if the obstruction to the arterial circulation has not been removed). Favourable results depend on the extent of development of compensatory *collateral*

circulation. The sooner collateral circulation develops, the less danger there is for the tissue. In virtue of collateral circulation a weak pulse appears in the radial artery already 3-4 days after ligation even of the brachial artery. Ischemia is particularly dangerous in cases of occlusion or spasm of vessels which do not have sufficiently well-developed collateral branches, as, for example, the coronary, renal and splenic arteries.

Collateral circulation is established because the blood pressure drops below the obstruction in the vessel and the blood rushes through capillaries from the higher parts of the vascular bed to the lower parts (Fig. 55).

The diagram in Fig. 55 shows how collateral circulation develops. Normally only a very small amount of blood flows through arterial anastomoses because the difference in pressure between *a* and *b* is negligible. But the obstruction of the vessel at *S* causes a drop in blood pressure below *b* and a rise in *a*. The difference in blood pressure between *a* and *b* appreciably increases and the blood current is directed through the anastomosis. The right part of the diagram illustrates a similar phenomenon: above obstacle *S* in vessel *A* the blood pressure rises, owing to which the adjacent vessels, *B* in particular, are overfilled with blood, and, since the blood pressure in vessel *A* below the obstacle has dropped, the blood rushes through anastomosis *ab*. The dilatation of the collateral vessels due to occlusion of the main trunk may be prolonged and strongly pronounced; in such cases the structure of the arterioles is often altered—the lumens grow wider and the walls thicker.

An important part in the mechanism of collateral circulation is

played by reflex stimulation of the collateral vessels by the products formed in the tissues during the development of ischemia.

The state of the vascular walls also plays quite an important part in the development of the collateral vessels. A sclerotic, calcified wall is less capable of dilating, for which reason collateral circulation does not so readily develop in such vessels. The condition of the heart which must pump the blood through the collateral vessels is another important factor. Cardiac weakness renders the flow of blood difficult.

The part of tissue supplied by an arterial branch usually has the form of a cone. In cases of occlusion of an artery and limited collateral circulation due to circulatory disturbances the corresponding part of tissue undergoes certain changes. A focus of tissue necrosis, called an infarct,* develops. An infarct usually has the form of a cone with its base toward the surface of the organ. In section an infarct looks like a wedge or triangle.

Infarcts may occur as a result of protracted vascular spasm; some myocardial infarcts are caused by protracted spasm of the coronary arteries.

In most cases the infarct is pale—*white infarct*. The reason for it is that the ischemia of the part reflexly produces spasm of the vessels of the given and surrounding parts and involves expulsion of the blood through the anastomoses. A white infarct is most frequently formed where developed collateral vessels are absent, as in the spleen, kidneys, heart and brain. Experimentally a white infarct can be produced in the rabbit's kidney by ligature of a branch of the renal artery.

The necrosis is often accompanied by a hemorrhage, in which case the result is a *red* (or *hemorrhagic*) *infarct* (Fig. 56). This infarct is most frequently observed in the lungs. A red infarct develops in the following way. On occlusion of an artery the small collateral vessels become engorged with blood as a result of a drop in blood pressure in the ischemic part. The pressure in these

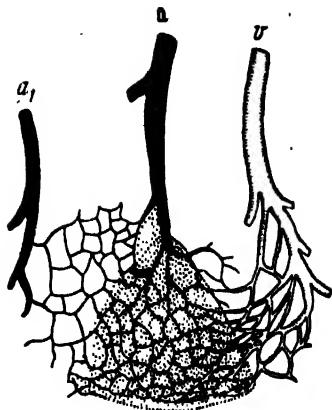


Fig. 56. Diagram of red (hemorrhagic) infarct. Artery *a*, obstructed by an embolus, has very small capillary anastomoses with adjacent artery *a*₁. The branches of the obstructed artery are filled partly through these anastomoses and partly from the vein (return flow) and a red infarct is formed.

From the Latin word *infarcire*—to stuff into.

collateral vessels is not enough, however, to restore circulation, and the result is stasis whose development is favoured by congestion in the draining veins, as in cardiac weakness. In consequence of impaired nutrition and dystrophic changes in vascular walls the latter become more permeable and erythrocytes exude through them and fill the necrotic tissue.

Both white and, especially, red infarcts are usually resorbed, the resorption being accompanied by formation of a scar. Under the influence of proteolytic enzymes, however, the necrotic tissue may soften.

Infection of the infarct (infection from without or infection of emboli) accompanied by its purulent dissolution is a dangerous complication; from the infarct the infection not infrequently spreads throughout the organism.

HEMORRHAGE

Hemorrhage is an escape of blood from the vessels into the environment. Hemorrhages may be *external* or *internal*, depending on whether the blood exudes to the exterior or inside an organ or cavity. The hemorrhages are distinguished according to the bleeding organs as *arterial*, *venous* and *capillary* or *parenchymatous*. The latter are characterised by the mixed blood that effuses from the surface of the tissue cut (for example, in injuries to the liver or spleen). According to their volume, the hemorrhages into tissues may occur in the form of petechiae—minute hemorrhages, ecchymoses, hematomas (focalised extravasation of blood) or the aforementioned red infarcts.

Hemorrhages are also distinguished according to origin: *hematemesis* (from the stomach), *pneumorrhagia* (from the lungs), *hematuria* (from the urinary tract), *menorrhagia* and *metrorrhagia* (from the uterus), etc.

A hemorrhage may be the result of a rupture of vascular walls (*per rhexis*),* their corrosion (*per diabrosis*)** or exudation of erythrocytes through the vascular wall without noticeable injury to the latter (*per diapedesis*).*** Rupture and corrosion may occur in any vessel, whereas exudation of erythrocytes through unruptured vessel walls (*per diapedesis*) is possible only from small vessels and capillaries.

Vessels may rupture for various reasons, for example, as a result of *trauma* (cuts, punctures, gunshot wounds, contusions, etc.) and *pathologic changes in the structure of the vascular wall* (in aneurysms and, most frequently, sclerosis), especially in connection with elevated blood pressure and congestive phenomena (in hemorrhoidal veins or in lungs).

* From the Greek word *rhexis*—a breaking.

** From the Greek word *diabrosis*—corrosion.

*** From the Greek words: *dia*—through, and *pedesis*—a leaping.

Corrosion of vessels occurs as a result of an *ulcerative or inflammatory process*, as well as *invasion of vessels by tumours*. for example in pulmonary tuberculosis when the tuberculous process destroys a pulmonary vessel, in gastric or typhoid ulcers, and in malignant tumours.

Diapedesis is most frequently a result of *congestive phenomena, inflammatory processes* (hemorrhagic inflammations, inflammations in cases of anthrax or plague) and *disturbances in the nutrition of vascular walls*, as in cases of their impaired innervation (angiotrophic hemorrhages). These include toxic hemorrhages (due to effects of phosphorus and arsenic), infectious hemorrhages (in typhoid fever, plague, etc.), and a number of forms belonging to hemorrhagic diathesis. The mechanism of development of diapedesis is not entirely clear as yet. Diapedesis apparently occurs as a result of disturbances in the colloidal structure of the vascular wall without involving any perceptible anatomic changes in it.

Hemorrhages are not always due only to local changes. They may appear as a result of *general disturbances in the organism*—elevated blood pressure, intoxications, hemophilia, and certain nutritional disorders, as in scurvy.

Lastly, there are *hemorrhages caused by primary dysfunction of the nervous or neuroendocrine systems*. These include hemorrhages into body cavities in hysteria, or hemorrhages from the nose and lips during menstruation, etc.

The *effects* of hemorrhages on the organism vary with the amount of extravasated blood and the site of hemorrhage. Hemorrhages due to ruptures of large vessels, especially arteries, and cerebral hemorrhages are particularly dangerous. Hemorrhages are accompanied by compensatory phenomena. In acute hemorrhages the loss of blood may reach 50-60 per cent in which case recovery is impossible and, if no blood transfusion is made, the following phenomena are observed: drop in blood pressure, lowered body temperature, pallor, acute cerebral anemia and, lastly, cardiac failure and death. The faster the hemorrhage, the more strongly pronounced these phenomena. Mild recurrent hemorrhages cause a slow development of anemia.

In many cases hemorrhages caused by ruptures of small vessels end spontaneously. The hemorrhages are arrested primarily by reflex spasm of vessels due to the stimulation issuing from the site of injury. Furthermore, the effused blood coagulates from contact with the damaged vascular wall and other adjacent tissues, the blood clot obstructing the vessel and leading to cessation of the hemorrhage.

After clotting the blood goes through various transformations. The red blood cells are destroyed and an amorphous blood pigment—hemosiderin—is formed. In the blood effused into large cavities where it is not immediately affected by the surrounding

cells a crystalline pigment—hematoidin—may form. Slight hemorrhages are completely resorbed. In more massive hemorrhages an important role in resorbing the extravasated blood is played by the connective tissue of the given part, the tissue proliferating and replacing or encapsulating the coagulated blood; this results in formation of a cavity whose content is gradually resorbed, leaving only a light-coloured fluid—a serous cyst (for example, in the brain or pancreas).

THROMBOSIS AND EMBOLISM

Thrombosis

Thrombosis is the formation of blood clots in blood vessels with the result that they impede the circulation. These blood clots are called thrombi*.

The first stages of thrombogenesis are easy to trace under the microscope in the blood of the frog's mesentery stretched on a cork plate. A small crystal of common salt is placed near the wall of a small vein and the formation of a thrombus is observed. At first individual colourless corpuscles begin to adhere to the inner side of the vascular wall that is closer to the crystal. This is followed by precipitation of a grey mass consisting mainly of fibrin and blood platelets. A similar process begins at the opposite wall of the vessel. Gradually growing by addition of leukocytes the thrombus may occlude the vessel and cause hemostasis. Injection of 1 ml of a 0.5 per cent methylene blue solution in the femoral vein stains the leukocytes and the thrombus blue.

Intravenous administration of thrombin-rich defibrinated blood into the rabbit's jugular vein sets off a rapid thrombogenic process in the pulmonary circulation with the result that the thrombi occlude the branches of the pulmonary artery and the animal soon dies with signs of asphyxia and convulsions. The thrombogenic process develops in two phases—agglutination and coagulation.

The *agglutination phase* is the partial *precipitation* from the circulating blood of plasma proteins and then blood platelets (thrombocytes) which are deposited on the internal surface of the vascular wall. The process of precipitation is accompanied by *agglutination* of the *platelets* and formation of trabeculae (white part of the thrombus). The deposit formed on the wall of the vessel and gradually increasing by addition of leukocytes presents a certain obstacle to the blood flow and thereby stimulates further precipitation of platelets and leukocytes.

The significance of thrombocytes in the formation of a thrombus is evident from the following experiment: the rabbit is bled several times in rapid succession. After each bleeding the animal is adminis-

* From the Greek word *thrombos*—lump, clot.

tered defibrinated thrombocyte-free blood. After a while the thrombocyte content of the blood considerably decreases. If the rabbit's various vessels are cauterised or subjected to mechanical trauma after that, no thrombi are formed.

The agglutination and precipitation of platelets are due to a decrease in their electric charge (the smallest compared with the other blood cells). The decrease in this charge is a result of disturbances in the proportions of the protein fractions in the blood plasma, increase in globulins and decrease in albumins. The decrease in the charge of the platelets is also favoured by accumulation of carbon dioxide in the blood, which is due to a slowing of the blood current at the given site and disturbance in the gas exchange between the blood and the tissue. Furthermore, carbon dioxide intensifies the fermentative process of glycolysis and accumulation of underoxidised products (for example, lactic acid) which hasten coagulation.

During the coagulation phase the thrombokinase liberated from the platelets and leukocytes causes coagulation of the blood flowing between the white layers of the platelets and leukocytes. The coagulated blood forms the red layers of the thrombus. The middle of the thrombus is of a mixed structure and consists of alternating red and white layers. The tail end of the thrombus consists of red coagulated blood. Such a thrombus is called a *stratified or mixed thrombus*.

In cases where agglutination of blood platelets predominates, a white (*agglutination*) thrombus is formed; when coagulation of the blood predominates, a red (*coagulation*) thrombus is formed.

Three principal factors are involved in thrombogenesis: *a break in the wall of a vessel, a slowing of the blood flow and a change in the composition of the blood*.

The effects of the foregoing factors of thrombogenesis are largely determined by the reactivity of the whole organism.

For example, an injury to sympathetic cervical ganglions or a trauma of the carotid sinus may cause formation of thrombi or transportation of emboli to pulmonary vessels. A reflex spasm of vessels is sometimes the preliminary stage of thrombogenesis. A certain part in thrombogenesis is not without reason ascribed to an allergic factor which is conducive to inflammatory injuries to the walls of vessels.

A break in the wall of a vessel may be due to trauma, the action of chemical substances, atherosclerosis, hemostasis, inflammation, infections, intoxications and various nutritional disturbances. It is easy to produce a thrombus experimentally by mechanical injury to the wall of a vessel.

Breaks in the endothelium give rise to roughness on the internal surface of a vessel, which is responsible for the adhesion of the blood platelets and the uneven parietal blood flow. Moreover, the changes in the endothelium cause certain disturbances in the physi-

cochemical properties of the circulating blood. However, alteration of the vascular wall alone does not always lead to thrombogenesis. For example, in the aorta, where atherosclerotic changes in the wall are often observed, thrombi are very rarely formed. This is accounted for by the particularly rapid blood flow through the aorta.

That *deceleration and irregularities of the blood flow* play an important role in thrombogenesis is demonstrated by the fact that thrombi are formed mainly in parts of the vascular system where the blood current most frequently slows down, namely, in the veins (especially in the lower parts of the body). The slowing of the blood flow and formation of thrombi are favoured by general circulatory disorders with cardiac and respiratory insufficiency involving an aspiratory weakness of the thorax, and by disturbances in peripheral circulation, for example, appearance of obstructions above the site of thrombogenesis, as compression of a vessel by a tumour, etc. Conducive to thrombogenesis are also disturbances in the regularity of the blood flow, for example, vortical movement of the blood arising at sites of vascular confluence, in pockets of venous valves, pathologically distended vessels and vessels with various roughnesses on the internal surface of their walls.

These disturbances in the blood flow favour precipitation and adhesion of blood platelets (blood cells with lower specific gravity) to the walls of vessels. A slowing of the blood current alone is not enough to cause formation of a thrombus. For example, the blood remains liquid in a vessel between two ligatures. Formation of a thrombus apparently requires an injury to the wall of the vessel in addition to the slowing of the blood flow.

Thrombogenesis is also favoured by *changes in the quality of the blood*, i.e., an increase in its coagulability.

A multiple thrombosis may be produced experimentally, for example, by injection of a serum wrung out of coagulated blood and rich in thrombokinase. A similar effect may be produced by intravenous injections of hypertonic solutions of sodium chloride, ether, iron sesquichloride, pepsin, peptone, gelatins, and extracts from organs, and by transfusion of foreign blood.

An increased predisposition to thrombosis is observed in various pathologic states, for example, after surgical intervention (apparently due to the increase in the number of blood platelets), in inflammation and infections (in connection with the changes in the walls of the vessels), in starvation and emaciation (as a result of nutritional failure and a slowing of the blood current) and in chlorosis and myeloid leukemia (due to changes in the composition of the blood and its increased coagulability).

Impending thrombogenesis and excessive coagulation of the blood can be in a certain measure prevented by administration of anticoagulants—hirudin, heparin, etc.—into the blood.

The *effects of thrombosis* vary with the location of the thrombi in the vascular system, the rapidity of their formation and appearance of emboli produced by their disintegration and abruption of their fragments. A thrombus forms an obstacle to the blood flow by obstructing the lumen of a vessel with circulatory disturbances developing in the given part as a result. The larger the thrombosed vessel, the more serious the effects and the more difficult the compensation for the disturbed circulation. Venous obstruction creates an obstacle to the outflow of blood and causes venous congestion which may lead to edema. The thrombi formed in veins may produce a reflex spasm of vessels; for example, thrombosis of pulmonary veins may cause a reflex spasm of the coronary vessels. The faster a thrombus has formed, the less favourable are the conditions for development of collateral circulation and the more strongly pronounced are the local circulatory disturbances. In cases where a thrombus obstructs the lumen of an artery and collateral circulation fails to develop the tissue necroses (for example, in thrombosis of cerebral arteries).

Thrombosis usually results in organisation of a thrombus with ingrowth of connective tissue into it. Cavities may form in the middle of the thrombus (due to its shrinking) and between the thrombus and the walls of the vessel, the cavities subsequently being encapsulated by endothelium and filled with blood; as a result the blood flow through the given vessel is resumed, i.e., the thrombus is canalised.

A very dangerous complication of thrombosis is abruption of a thrombus or part of it from the wall of the vessel and the subsequent formation of an embolus. Particularly dangerous is infection of a thrombus, its purulent softening and the subsequent generalisation of the infection.

Embolism

*Embolism** is *occlusion of blood and lymphatic vessels with bits of matter carried by the blood or lymph and usually foreign to the blood stream*. The bits of matter are called *emboli*. The emboli may be of endogenous or exogenous origin, endogenous emboli occurring more frequently. Several types of endogenous embolism are distinguished according to the material of which the emboli consist.

1. *Embolism originating from thrombi* formed anywhere in the organism is the most common type. It originates from newly-formed, soft, loose thrombi. Particularly easily abruped are parts of thrombi formed on heart valves where the conditions for the transfer of these parts to the systemic and pulmonary circulation are the most favourable.

* From the Greek word *embolos*—wedge.

Very dangerous is embolism of cerebral vessels resulting from abruption of parietal thrombi formed in large arteries.

2. *Tissue embolism* arises in cases where groups of cells are carried by the blood stream from one organ into another, as when branches of the pulmonary artery are obstructed by groups of liver cells in eclamptic affection of the liver, by placental syncytium and parts of heart valves in cases of their ulcerative disintegration.

3. *Fat embolism* is produced by droplets of fat liberated into the circulatory system from adipose tissues, for example, after fracture of long tubular bones or a crushing injury of adipose tissue. Fat emboli are carried into the lungs and through arteriovenous anastomoses and pulmonary capillaries into the systemic circulation. This may lead to embolism of cerebral capillaries, renal glomeruli and other vessels.

Exogenous embolisms are distinguished according to their origin.

1. *Air embolism* is occlusion of vessels with air bubbles which have gained entrance into veins from the surrounding atmosphere. An air embolism occurs particularly easily in injuries to large veins (superior vena cava, subclavian and jugular) where there is negative pressure due to the aspirating action of the thorax. The danger of an air embolism is all the greater since the walls of some veins, for example, the large cervical veins, are imbedded in dense tissue which does not collapse in injuries to the vessels. Air embolism of large veins causes multiple occlusion of pulmonary arteries. A large amount of air gaining entrance into a vein may cause occlusion of the right atrium. A moderate air embolism is tolerated relatively easily because the air is readily absorbed by the tissues. An air embolism may be produced experimentally by introduction of air into a vein.

Gas embolism which may be observed in caisson disease is a variety of air embolism.

2. *Bacterial and parasitic embolisms* occur as a result of clumps of bacteria or parasites gaining entrance into the blood stream from some focus of infection, as in purulent thrombophlebitis or inflammation of the heart valves; parasitic embolisms occur when trichinæ are carried from the intestines into the lungs through the lymphatic vessels and the thoracic duct.

3. *Foreign body embolism* is observed in injuries when foreign bodies penetrate into the blood and are carried by the blood flow into the vessels of the systemic or pulmonary circulation. Such an embolism can be produced experimentally in the dog by intravenous administration of a lycopodium suspension (Fig. 57).

The hemodynamic disturbances connected with embolism depend on the distribution of vascular branches, quality of the emboli, intensity of the blood flow and reflex influences from the site of origin of the emboli.

Emboli may be carried in three main directions.

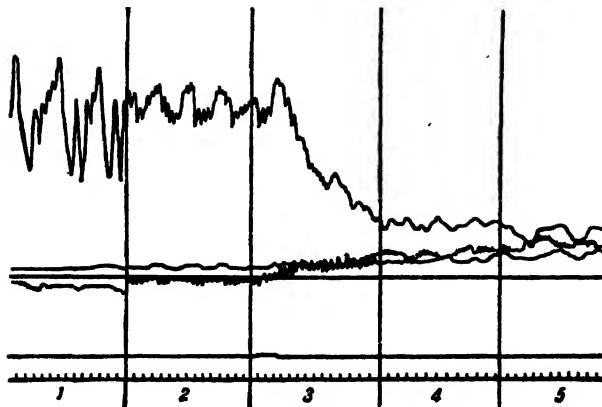


Fig. 57. Changes in blood circulation caused by a lycopodium embolus. Upper curve—arterial pressure; lower curves—venous pressure.

1—normal; 2—compensatory acceleration of pulse; elevation of pressure in the veins during the initial stage with mild embolic phenomena; 3, 4 and 5—drop in arterial and elevation of venous pressure in pulmonary circulation during increasing embolism.

1. Embolism in the pulmonary circulation, i.e., in the branches of pulmonary arteries. The emboli are brought in from the veins of the systemic circulation and the right heart. These emboli can be easily produced experimentally by an intravenous injection of some powdered substance, for example, a suspension of lycopodium, India ink, carmine or cinnabar. The larger particles lodge in the branches of the pulmonary arteries, the smaller particles—in the capillaries. Some particles may pass through capillaries into the pulmonary veins, into the left heart and thence into the systemic circulation. An embolism of a pulmonary artery is characterised by pallor of the face as a result of a reflex spasm of the vessels, reflex spasm of bronchi and sometimes sudden coronary insufficiency also of a reflex origin.

2. Embolism of the systemic circulation is the result of an embolus being carried from the left heart, the arteries of the systemic circulation and sometimes from the pulmonary veins.

The direction taken by emboli depends on many factors—the size of the emboli, character of the blood flow, ramifications of the vessels, angle of origin of the branches from the main trunk, and general reactivity of the organism. Only occasionally do emboli gain entrance into branches issuing from the main trunk at a right angle, for which reason in the systemic circulation they get into the lower limbs more frequently than they do into the upper limbs; this also explains why embolisms are more common in the left cerebral hemisphere than they are in the right hemisphere.

3. Emboli in the branches of the portal vein are brought from numerous abdominal veins. In animals an embolism of the portal

vein can be produced experimentally by administration of a lycopodium suspension into one of the mesenteric veins. Such an embolism is usually multiple. In the end it causes a drop in general arterial pressure and an elevation of pressure in the portal vein, which, owing to accumulation of blood in the abdominal cavity, leads to hepatic dysfunction. The drop in arterial pressure may sometimes be preceded by its brief elevation due to stimulation of the receptors of the portal vein system.

It is necessary to bear in mind the possibility of *retrograde embolisms*, i.e., movement of emboli not in the direction of the blood flow, but against it. In such cases bits of matter which have gained entrance into the veins are carried, not to the right heart, but against the blood current, for example, from the inferior vena cava into the hepatic or renal veins, or those of the lower limbs. A certain part in this phenomenon is played by the specific gravity of these bits of matter and the character of the blood flow. The origin of such embolisms is connected with increased intrathoracic pressure in sudden exhalations, for example, in intense coughing or constriction of the chest; elevated blood pressure in the right heart may be conducive to development of a retrograde embolism.

Paradoxical embolisms occur when emboli, after gaining entrance into the right heart from the veins of the systemic circulation, get directly into the left atrium and further into the left ventricle and the systemic circulation without passing through the pulmonary circulation. In these cases the emboli cross over to the arterial side through a patent foramen ovale.

The *results of embolisms* depend on the site of their occurrence. It is very important to take into account the particular vessel to which the embolus has been delivered, the possibility of reflex influences and the collateral communications of the given vessel with other vessels. Coronary and cerebral embolisms are especially dangerous. When collateral circulation is inadequate embolisms are usually accompanied by necrosis of tissue or formation of red infarcts. The quality of the embolus is also of some importance. Phenomena developing from a usual tissue embolus differ from those connected with emboli originating in a malignant tumour or with infected emboli, etc.

LOCAL DISORDERS OF LYMPH CIRCULATION

The passage of increased amounts of tissue fluid into lymphatic vessels may cause their engorgement. Any obstruction to the outflow of lymph also leads to engorgement of the lymphatic vessels and stagnation of the lymph. This occurs only in large lymphatic vessels because the small vessels are extensively anastomosed. Lymph stagnation may give rise to edema. An important part in the development of edema is played by disturbances in the hemodynamic

and physicochemical processes on both sides of vascular walls. Sometimes thrombi are observed to form in the lymphatic vessels in connection with inflammatory and necrotic processes in the tissue and injury to the lymphatic vessels. The lymph contains neither thrombocytes nor erythrocytes. Lymphatic thrombi consist of leukocytes and fibrin. Thrombosis of lymphatic vessels is of no particular consequence. The abrupted parts of lymphatic thrombi are usually retained in regional lymph nodes.

Lymphatic vessels very often serve to transport microorganisms and cancer cells. This leads to development of metastatic foci of inflammation or neoplasia in the regional lymph nodes. Subsequently the causative agents or cells may be conveyed to other nodes and on through the thoracic duct to the blood stream, in which case the metastasis becomes hematogenic. The obstacles to the outflow of lymph, which cause lymphostasis and dysfunction of the valves of the lymphatic vessels, create conditions for the conveyance of the causative agents and cells in a direction opposite to that of the lymph flow, i.e., for retrograde metastasis. This is observed, for example, in metastasis of cancer of the stomach from the retroperitoneal lymph nodes to the ovaries.

The pressure of lymph in the lymphatic vessels is very low, for which reason no large amounts of lymph are usually observed to pass into the surrounding tissues in cases of ruptured lymphatic vessels (lymphorrhagia). Large amounts of lymph flow out of lymphatic vessels only in cases where the lymph gains entrance into the pleural or abdominal cavities after injury to the thoracic duct or its branches. In such cases chylous ascites is formed.

INFLAMMATION

DEFINITION OF INFLAMMATION, ITS CAUSES AND MAIN SIGNS

Inflammation is a complex reaction of the organism to the action of noxious agents manifested in functional and structural changes in the vessels and tissues. It has developed in the process of evolution and is characterised by three main, closely interconnected and simultaneous phenomena: tissue dystrophy (alteration), circulatory disorders (with exudation and emigration) and proliferation of cells. These phenomena reflect the processes which disturb the vital functions of the organs and tissues, as well as the processes of adjustment, defense and restoration of the functions.

The causes of inflammation vary very widely. Inflammation is most frequently due to the effects of various exogenous factors: infectious (bacteria and toxins), mechanical (contusions or wounds), thermal (burn or frostbite) and chemical (acids or alkalis).

The endogenous causes of inflammation may be tissue necrosis, thrombosis, infarction, massive hemorrhage, and deposition of salts.

The inflammatory process begins variously.

In some cases the harmful agent (X-rays, toxic substance or mechanical trauma) affects the tissue and causes its primary alteration or injury. The injury to the tissue liberates physiologically active products of disintegration which evoke the inflammatory reaction.

In other cases inflammation develops as a response reaction to the action of the stimulus, while the alteration is a component of the inflammation. This happens in cases of infection, entrance of foreign bodies or protracted irritation with chemical substances (dermatitides caused by benzene, aniline, etc.). Biologically active substances also forming in these cases participate in the mechanism of inflammation and exert a considerable influence on it.

Thus the properties of the inflammatory agent and the complexity of its interrelations with the affected tissue and with the reaction of the whole organism account for the variety of the manifestations

of inflammation although inflammation always retains the general regularities of its course and is accompanied by development of the complex of characteristic processes.

The intensity of an inflammatory reaction depends on the reactive properties of the organism, the site of origination of the process, the anatomic and physiologic characteristics of the affected tissue, and the conditions under which the inflammation is developing. The same cause acting with the same force but under different conditions may therefore produce different inflammatory reactions.

The external signs of inflammation are: redness (*rubor*), swelling (*tumor*), heat (*calor*), pain (*dolor*) and dysfunction (*functio laesa*). The aggregate of these signs is characteristic mainly of acute inflammation of the skin and mucous membranes (for example, in abscesses and burns).

The signs of development of an inflammatory process are easily observed in the following experiment: the rabbit's ear is immersed for 2-3 minutes in water heated to 53-55°C. The ear that was immersed in water grows intensely red, then turns cyanotic, becomes swollen and hotter than the other ear. Another sign of dysfunction is that the inflamed ear lolls and for some time fails to resume its usual position.

In a number of cases of inflammation, especially of internal organs, the foregoing signs are either feebly marked or totally absent. For example, in the liver, kidneys and heart the inflammatory redness is often camouflaged by the organ's normal colour.

In chronic inflammation there may be no swelling, redness, heat or pain, as is the case in cirrhosis of the liver and kidneys.

To designate most of the inflammatory processes it is customary to add the Latin suffix "itis" to the Greek or Latin appellation of the affected organ or tissue, as nephritis (inflammation of the kidneys), arthritis (inflammation of a joint), dermatitis (inflammation of the skin), etc. However, the inflammation of some organs has been given a special designation, for example, pneumonia (inflammation of the lungs) or angina (inflammation of the fauces).

TISSUE ALTERATION IN THE FOCUS OF INFLAMMATION

Tissue alteration (lesion) is due to injury or development of dystrophy, i.e., disturbance in the nutrition and metabolism, function and structure of the tissue; it is most clearly marked at the site of contact of the harmful agent with the tissue. Primary and secondary alteration is distinguished.

Primary alteration arises in the focus of inflammation in the very beginning of the action of the harmful agent and affects a relatively small area, while secondary processes come into operation during the subsequent development of the inflammation, as a result of metabolic and circulatory disturbances in the inflamed zone.

In the beginning the injury to the tissue is manifested in increased or diminished vital functions of the cells. For example, in cases of weak irritation division of the cells and an increase in their vital functions are observed; in cases of strong irritation the metabolism diminishes in the centre of the focus of affection and increases on its periphery. Inflammation is characterised by turbid swelling, granular, mucous and fatty degeneration, necrobiosis and necrosis. Changes are also observed in intercellular substance—in the collagenous and elastic fibres which sometimes swell and dissolve.

The extent of these changes depends on the site of the process, the virulence and properties of the harmful agent, the reactivity of the organism, and the characteristics of the affected tissue. For example, the very same cause produces different alterations in the brain and on the skin.

Necrotic phenomena are most frequently the result of considerable traumas, burns, action of strong acids and alkalis, or influences causing the organism's altered reactivity, as in so-called hyperergic inflammation when the organism is hypersensitive to the inflammatory agent.

Dystrophic tissue changes are often so feebly marked as to be almost unnoticeable, while other inflammatory phenomena, for example, vascular, are clearly pronounced. Contrariwise, there are inflammations, especially in parenchymatous organs (parenchymatous inflammations), which are characterised mainly by dystrophic processes that predominate over all the other inflammatory phenomena.

A diminution in the oxidative processes is usually observed in the centre of the inflammatory focus where the injury to the tissue is most clearly pronounced; in the other parts of the inflamed zone there is an increase in the oxidative processes, an *increase in metabolism*.

In inflammation the increased metabolism involves mainly carbohydrates. In inflamed tissue carbohydrates are not only vigorously oxidised, but are also intensely glycolysed without the participation of oxygen (anaerobic glycolysis). Subsequently the glycolysis increases still more owing to accumulation of leukocytes in the focus of inflammation, the carbohydrates being split by the leukocytes mainly anaerobically.

The amount of oxygen absorbed by inflamed tissue exceeds the amount of carbon dioxide excreted by it. This shows that in inflamed tissue carbohydrates are not always completely oxidised. For this reason large amounts of underoxidised metabolites, primarily carbohydrate metabolites, such as lactic acid, accumulate in the tissue, in addition to carbon dioxide.

Disturbances in fat and protein metabolism in the focus of inflammation give rise to accumulation of fatty acids, ketone bodies and amino acids, and to formation of certain physiologically active sub-

stances which, as we shall see below, play a very important part in the subsequent defensive physiologic phenomena.

Accumulation of acid metabolites results in *acidosis*. At the outset acidosis is compensated because the alkali reserves of the blood and tissue fluid neutralise the acid-reacting substances; moreover, part of these substances is removed from the focus of inflammation by the blood and lymph flow. Subsequently, as a result of exhaustion of the alkali reserves and insufficient outflow of blood from the inflamed tissue, the concentration of free hydrogen ions in the tissue increases and uncompensated acidosis develops.

Measurements of hydrogen ion concentration in the focus of inflammation have shown that the more acute the course of the inflammatory process, the more marked the acidosis. For example, in chronic inflammation the pH=7.1-6.6, while in acute purulent inflammation the pH=6.5-5.39. The concentration of hydrogen ions in the centre of the focus may increase 50-fold.

The concentration of hydrogen ions and the osmotic pressure gradually decrease towards the periphery of the inflammatory focus, i.e., toward normal tissue.

With the development of inflammation acidosis increases.

In exudative inflammations, owing to processes of autolysis and accumulation of alkaline products of protein disintegration (ammonia) in the exudate, the reaction of the exudate may become alkaline, while the reaction of the surrounding tissues will be acid.

In addition to the increased concentration of hydrogen ions in the focus of inflammation, the content of other ions also increases because of the intensified dissociation of salts in an acid medium.

The proportions of electrolytes also change; for example, the concentration of potassium ions in the tissue and the K/Ca coefficient increase.

Furthermore, the processes of tissue disintegration and increased metabolism accompanied by splitting of large molecules into numerous small molecules and ions lead to increased molecular and ionic concentration. As a result of the accumulation of ions and products of tissue disintegration the *osmotic pressure in the inflamed tissue rises* (Fig. 58).

Whereas depression of normal tissue fluid is 0.62° in purulent inflammation it is 0.80° and even 1.4°, which corresponds to an osmotic pressure of 19 atm instead of the normal 8 atm. Like acidosis, osmotic pressure gradually decreases from the centre towards the periphery of the inflammatory focus.

Disturbance of the physicochemical properties of the inflamed tissue leads to changes in tissue colloids, mainly proteins. The dispersion of colloids increases as does their ability to attract and retain water, i.e., the *colloid osmotic or oncotic pressure of tissue colloids rises*. The oncotic pressure likewise gradually diminishes towards the periphery of the focus of inflammation.

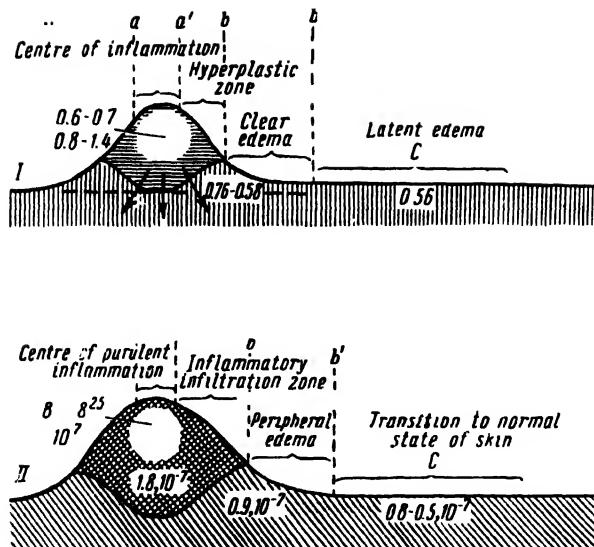


Fig. 58. Schematic representation of a section through an inflamed focus in the skin.

I—changes in osmotic pressure in different parts of the section; II—changes in the actual reaction of the tissues (Schade).

Thus, phenomena of increased metabolism and the following physicochemical disturbances connected with them are observed in the focus of inflammation: 1) accumulation of ions, especially an increase in the concentration of hydrogen ions; 2) increase in colloid osmotic pressure.

As a result of trophic tissue changes, these disturbances in their turn influence the extent of the subsequent changes developing in the cells of the inflamed tissue. In the altered physicochemical environment the colloidal structure of the cells is disturbed with phenomena ranging from turbid swelling to necrobiosis and even necrosis.

CIRCULATORY DISTURBANCES

The effect of the inflammatory agent on the receptors of the affected part gives rise to reflex circulatory disturbances.

A *brief vascular spasm* appears first. The vascular spasm and pallor of the injured part are the result of stimulation of vasoconstrictor nerves. Since this phenomenon rapidly disappears it is not always possible to observe it.

The spasm is followed by dilation of arterioles and capillaries, the volume of capillary circulation increases and *more blood is*

brought to the inflamed part (arterial hyperemia). The blood flow is temporarily accelerated and the blood pressure rises.

The vascular phenomena develop the faster, the stronger the stimulation and the more abundant the blood supply of the given part. The increased blood flow is responsible for greater hemorrhages in injuries to the vessels of the inflamed region, faster pulse wave and lesser utilisation of blood oxygen by the tissues of the inflamed part.

The increased blood flow produces two of the main signs of inflammation—redness of the inflamed part and the rise in its temperature. The rise in temperature is evident in inflammation of the skin and mucosa and is due to the affluxion of arterial blood.

The elevation of temperature in inflammation of internal organs is barely perceptible because of the negligible difference in the temperature between the organs and the surrounding environment.

The rise in the temperature of the inflamed tissue may be partly due to intensification of the processes of tissue metabolism since the temperature of the blood drained from the inflamed part is somewhat higher than that of the inflowing blood, while ligation of the supplying artery does not at once cause a drop in the temperature of the focus of inflammation.

Vessels dilate under the influence of several factors. In the very beginning they dilate as a result of a *reflex effect of the harmful agent*. The dilatation of vessels usually follows their constriction, but may occur at once owing to rapid paralysis of the vasoconstrictors and excitation of the vasodilators. Participation of the vasomotor apparatus explains the sudden dilatation of the arteries and the increased flow of blood to the periphery of the inflamed focus.

The dilatation of the vessels occurring in the beginning of inflammation is subsequently maintained by gradually developing physicochemical and chemical changes.

Very important, in particular, is the *increased concentration of hydrogen ions*. The acidity developing in the focus of inflammation is of itself capable of causing dilatation of the vessels.

A certain part in the dilatation of vessels and affluxion of blood is also played by *electrolytic changes*, the increase in potassium ions in particular.

V. V. Voronin ascribes the dilatation of capillaries and development of active hyperemia in some measure to impaired distensibility i.e., diminished elasticity of the connective tissue surrounding the capillaries.

However, the greatest vasodilator effect is produced by *metabolites and products of tissue disintegration*. In addition to histamine and histamine-like substances, an important part in the dilatation of vessels during inflammation is played by acetylcholine, and adenine nucleotides.

Already in the very beginning of the development of inflammation the amount of these substances increases in the blood flowing out of the focus of affection and in the inflamed tissue, these substances playing an important part in the development of the subsequent inflammatory phenomena.

Some time after the increase in the blood flow in the vessels of the inflamed focus the blood current gradually slows down, the dilated vessels become engorged with blood and congestive phenomena develop.

The slowing of the blood current is due to the effects of several factors: 1) paralysis of the neuromuscular apparatus of the vessels, which leads to loss of vascular tone; 2) concentration of the blood and an increase in its viscosity due to increased permeability of the vessels and greater transudation of fluid from the vessels into the tissue; 3) resistance to the blood flow offered by the roughness of the internal wall of small vessels due to adhering leukocytes (see below) and a certain swelling of blood and endothelial cells as a result of changes in their physicochemical properties; 4) mechanical obstacle to the outflow of blood caused by partial compression of small veins by developing edema; 5) formation of thrombi and occlusion of vessels, which may develop in the focus of inflammation and obstruct the blood current.

Another factor responsible for the slowing of the blood current is the discrepancy between the increase in the cross-section of the vascular bed and that in the volume of the circulating blood. The broadening of the vascular bed is due to dilatation of the capillaries and small veins which until then were collapsed.

In the course of inflammation the disturbances in the blood current and the congestion increase; in some branches of the blood vessels complete cessation of the blood flow—*stasis*—with all consequences is observed, i.e., disturbances in the physicochemical properties of the vascular walls, formation of thrombi, hemorrhages, etc. These circulatory disturbances impair the nutrition of the tissue still more. Trophic disorders develop and are likely to involve new parts of tissue; toxic products of decomposition accumulate and in their turn tend to aggravate the inflammatory phenomena. At the height of inflammation the reaction of the vessels in the affected focus to vasoconstrictor substances (for example, caffeine, adrenalin) and to stimulation of the vasoconstrictor nerves considerably weakens.

The weakened or altered vascular reaction is easily observed in the rabbit's ear in which an inflammation has been provoked by stimulation with hot water or croton oil. Subsequent irrigation of the ear with Locke-Ringer's solution shows that the doses of adrenalin which usually produce a sharp vascular spasm (in a 1:10,000 dilution) cease to produce this effect, or the effect is weaker than normal; in cases of a strong inflammatory reaction, the effect is

not observed at all and sometimes is even paradoxical, i.e., adrenalin constricts rather than dilates the vessels. In other experiments stimulation of the sympathetic nerves in the rabbit's neck, which usually sharply constricts the vessels and causes pallor of the tissue in the unaffected ear, ceases to produce this effect on the vessels of the inflamed ear. This disturbance in the vascular reaction is due mainly to the changes in the acidity and other physicochemical properties of the tissue.

Changes inside the vessels of the inflamed part develop soon after the slowing of the blood flow and appearance of congestive phenomena.

EXUDATION AND EMIGRATION

The dilatation of the vessels and the slowing of the blood current are followed by *exudation*—passage of protein-containing fluid through the walls of vessels into the tissue.

The fluid that passes from the vessels into the tissue in inflammation is called *exudate*. It differs from transudate (the fluid of edema) in that it contains more protein (5-8 per cent) and also contains blood cells, mainly leukocytes, sometimes erythrocytes and thrombocytes, as well as certain local tissue elements—cells and products of tissue disintegration.

Exudation is caused by the following three main factors: 1) disturbance in the colloid structure and, as a result, in the permeability of capillaries; 2) elevated blood pressure in the vessels of the inflamed focus; 3) heightened colloid osmotic pressure in the inflamed tissue, which increases the passage of fluid from the vessels into the tissue.

The most important of these factors is the *altered permeability of the capillary walls*.

It is apparently caused mainly by changes in the colloidal properties of the intercellular conglutinants and not of the cells of the endothelial layer, since endothelial cells offer greater resistance to the action of chemical and physicochemical factors. Moreover, the dilatation of the vessels is in itself conducive to increased permeability of vascular walls.

The permeability of the vessels may be altered by provoking inflammation in one of the rabbit's ears with subsequent administration of a vital dye, for example, trypan blue, into the blood, in which case the inflamed ear stains more rapidly and intensely than the normal ear. The more intense colouring of the tissue of the inflamed ear is retained even after disappearance of hyperemia.

The increased permeability of capillaries may be the effect of such physiologically active substances as histamine, active globulins (Miles' globulin permeability factor) and polypeptides, certain nucleotides, nucleosides and serotonin, as well as of neurotrophic dis-

turbances and tissue acidosis. Mention must also be made of the possible effect of the inflammatory agent.

The passage of protein particles through walls of vessels depends on the size of the colloidal particles of protein and the permeability of these walls. This accounts for the certain sequence in the transit of proteins. Albumins exude first, as the most dispersed blood proteins; as permeability increases, the albumins are followed by globulins (less dispersed proteins) and, lastly, by fibrinogen (the least dispersed protein).

Elevated blood pressure in the vessels of the inflamed focus is conducive to exudation of fluid from them. As the fluid exudes from the vessels, the blood pressure in them gradually drops and the blood flow slows down.

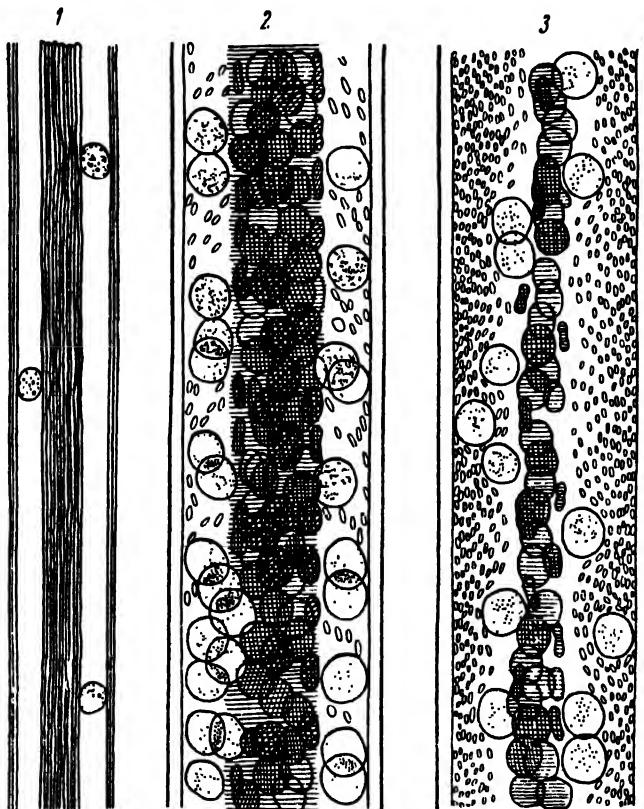


Fig. 59. Diagram of the blood flow—normal and in inflammation.

1—normal circulation; axial flow, marginal plasmatic zone with individual leukocytes; 2—decelerated circulation in the central axial zone, showing red blood cells; marginal position of leukocytes and platelets; 3—considerable hemostasis, marginal position of leukocytes and platelets; diminished marginal plasmatic zone.

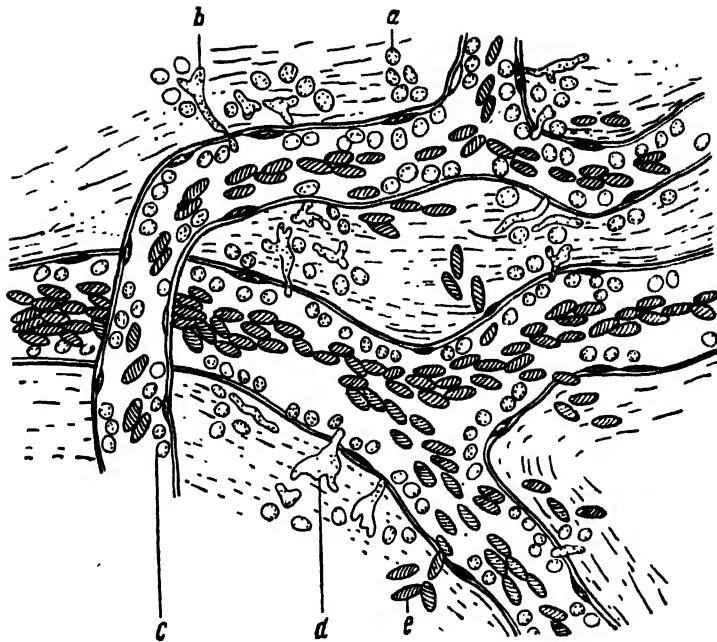


Fig. 60. Inflammation of the frog's mesentery.
emigrated leukocytes; *b* and *d*—emigration of leukocytes; *c*—marginal position of leukocytes in vessels; *e*—red blood cells in the tissue.

Lastly, an important part in exudation is played by *elevation of the colloid osmotic pressure* in the inflammatory focus, which stimulates the passage of fluid from the blood stream into the tissue.

Emigration, i.e., passage of leukocytes from the vessels into the tissues, develops in inflammation simultaneously with exudation. The leukocytes pass through the walls of capillaries and small veins.

At first, as the blood current slows down, the leukocytes gradually accumulate in the plasmatic parietal layer on the side turned to the inflammatory focus and seem to adhere to the vascular wall—marginal position of leukocytes (Fig. 59).

Some time after assuming the marginal position the leukocytes begin to extend narrow protoplasmic protrusions (pseudopodia) which pierce the wall of the vessel. A prominence appears on the external wall of the vessel; this prominence is the pseudopodium that has penetrated through the wall. The prominence gradually increases by taking in the body of the leukocyte. Then the leukocytes which have emigrated from the vessel detach themselves from the wall of the vessel and proceed with ameboid movements through

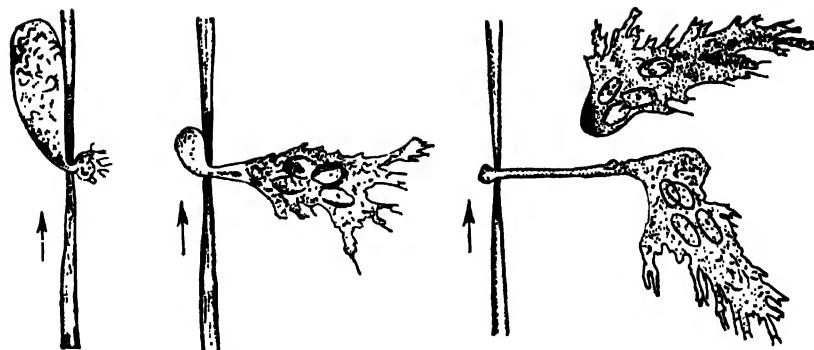


Fig. 61. Leukocytes passing through vascular wall of the frog (Thoma).

tissue spaces in the direction of the centre of the inflammatory focus where they perform the function of phagocytes with respect to bacteria, foreign bodies and particles of cell elements.

Some of the leukocytes—those closer to the centre of the inflammatory focus—are destroyed in the unusual environment; in other places phenomena of phagocytosis prevail. The destruction of leukocytes is accompanied by liberation of various enzymes which digest the products of decomposition, as well as of substances possessing bactericidal action or capable of detoxicating the poisonous bacterial waste products. The surviving leukocytes may subsequently take part in proliferative phenomena or be carried by the flow of body fluid back into the blood stream.

The vascular reaction and exudation with emigration can be observed under the microscope (Fig. 60) in a preparation of the frog's inflamed mesentery in Cohnheim's experiment (1867).

A curarised frog is fastened to a cork plate. Through a small incision on a side of the abdomen an intestinal loop is brought out to the exterior by means of a forceps and is fastened to the edge of the orifice in the cork plate, the mesentery being stretched over the orifice. Contact with the air or (even sooner) with a sodium chloride crystal gives rise to an inflammatory process in the mesentery. The following phenomena are observed under the microscope during the first moments: the vessels dilate (first the arterioles and then the capillaries) and the blood circulation is accelerated; the latter is more noticeable in the arteries, although it is also observed in the veins and capillaries. Sooner or later this acceleration is followed by a slowing of the blood current. In view of the developing obstruction to the blood current and the concentration of the blood due to exudation the blood flows with greater difficulty during cardiac systole, while during diastole it is forced back, i.e., it moves back and forth. As the blood flow slows down the small veins and capillaries reveal continuous movement of erythrocytes in the centre of the blood current, a filling of the parietal plasmatic layer with colourless corpuscles (leukocytes) and their apparent adhesion to the internal surface of the walls of the vessels. The leukocytes begin to emigrate from the marginal position within 2-4 hours, sometimes later.

With the leukocytes in the marginal position the external surface of the vascular wall soon shows protrusions which gradually grow longer and thicker and are transformed into round colourless structures. The latter form new protru-

sions and gradually detach themselves from the wall of the vessel (Fig. 61). Exudation of fluid from the vessels into the tissue is observed simultaneously with the emigration of leukocytes, the exudation being particularly noticeable if 1 ml of a 0.25 per cent methylene blue solution is preliminarily injected in the femoral or abdominal vein.

The numbers and types of emigrant leukocytes vary with the character of the inflammatory process and the stage of its development. In serous inflammations relatively few leukocytes emigrate. In purulent inflammations leukocytes accumulate in enormous numbers and most of them are destroyed, forming one of the principal constituents of pus. In the beginning of inflammation most of the emigrant leukocytes are neutrophils (microphages), especially in cases where pyogenic microorganisms are the object of phagocytosis. In allergic inflammation, when foreign proteins gain entrance into the organism the emigrant leukocytes also included eosinophils which have in their protoplasm coarse oxyphilic granules. Lymphocytes and monocytes (macrophages) emigrate the last. Macrophages take part mainly in phagocytosis of the destroyed tissue elements—cell particles.

At one time emigration of leukocytes was accounted for purely by *mechanical causes*. It was supposed that, as the blood flow slowed down, the leukocytes, as formed elements with a lower specific gravity, were repelled towards the periphery of the blood stream and were arranged in its parietal layer (A. S. Shklyarevsky, 1868).

The emigration of leukocytes from the vessels was explained by elevated blood pressure in the venous and capillary current and increased permeability of vascular walls, while the total process of emigration was conceived as a passive movement of leukocytes from the vessels into the tissue.

But emigration of erythrocytes is not always observed, and, if it occurs, it does so to a lesser extent than that of leukocytes. The weight of leukocytes may increase as they capture cinnabar administered into the blood, but emigration takes place just the same. Nor can the differences in the cellular composition of the exudate be explained by mechanical causes alone. It is not clear why only neutrophils exude in some cases, for example, in purulent inflammation, and lymphocytes in other cases, as in tuberculosis. Lastly, the hypothesis of the mechanical origin of emigration does not explain the essence of the "marginal position" of leukocytes, which precedes the phenomena of emigration. The mechanical factors apparently only help in all these processes, but do not wholly account for them.

According to Mechnikov, the whole process of emigration of leukocytes must be explained by *chemotaxis*, i.e., chemical attraction of leukocytes from the blood stream by substances causing inflammation and forming in inflamed tissue. From this point of view

leukocytes manifest a special sensitivity to certain chemical substances.

Bacteria, especially streptococci and staphylococci, their waste products and the products of disturbed metabolism of the inflamed tissue possess chemotaxis.

A special substance (leukotaxine) has been isolated from inflammatory exudates; this substance increases capillary permeability and exerts chemotactic action. It is a polypeptide forming in protein disintegration (Menkin). However, leukotaxine was isolated from exudates as a result of their complex chemical treatment, and there is no complete certainty that it really forms in the focus of inflammation under natural conditions.

Moreover, various products of nuclein metabolism and certain active globulins possess greater chemotactic action.

Experimental observations show that these substances play an important part in the emigration of leukocytes and in their phagocytic function.

There are also substances which repel leukocytes, for example, quinine, chloroform, benzene and alcohol.

The data on physicochemical changes occurring in the focus of inflammation were subsequently used to explain the emigration of leukocytes.

Among the products of disturbed metabolism and microbial waste products in the inflamed focus there are *substances capable of reducing surface tension*. These substances include altered proteins, albumoses, peptones, organic acids and histamine. Gaining entrance into the vessels and, acting on the leukocytes, these substances reduce the surface tension mainly of the side of the leukocyte which faces the focus of inflammation. This makes for uneven surface tension in different parts of the leukocyte.

At the site of reduced surface tension the protoplasm begins to project, the whole body of the leukocyte gradually moving into the projection. Thus, owing to the change in surface tension the protoplasm of the leukocyte moves from the part with a higher surface tension to that with a reduced surface tension, i.e., towards the focus of inflammation.

Electrokinetic phenomena may play a certain part in the emigration of leukocytes. The increased concentration of hydrogen ions in the tissues in inflammation causes the difference in potentials between the tissues and blood elements. The leukocytes carry a negative charge and are attracted to the positively charged hydrogen ions accumulated in the tissues. According to the principles of electrophoresis, the leukocytes move from the vessels into the tissue.

Physicochemical phenomena cannot account for the entire complexity of the processes of emigration of leukocytes.

The emigration of leukocytes is in some measure also caused by the increased exudation from the vessels into the tissues.

The ameboid movement of leukocytes is now explained by energy processes operating in the protoplasm and leading to reversible changes in various parts of cytoplasm from sols to gels; in this process the rarefaction (Fig. 61a) of the protoplasm on the side of the leukocyte facing the focus of inflammation is believed to play the most important part. The projection and formation of pseudopodia take place at the sites of rarefaction. According to this point of view, the ameboid movement of leukocytes is connected with liberation of energy in the process of metabolism in the leukocyte itself.

The effect of chemotaxic substances determines the site of the reversible change of a sol to a gel.

However, emigration of leukocytes is not altogether clear as yet and requires further investigation.

Upon reaching the focus of inflammation some leukocytes are destroyed in the altered environment. Other leukocytes begin to perform their phagocytic function. On contact with microbes, cell particles or small foreign bodies the leukocytes surround them, engulf them and often digest them. (Fig. 61b).

The exudate as a whole plays a certain part in the further development and result of the inflammatory process. It dilutes the concentration of the poisonous substances formed during inflammation and washes them out of the tissues more intensely. Since the exudate contains antibodies and leukocytes it helps to detoxicate and destroy the microbes in the tissues. Precipitation of fibrin in the exudate, the slowing of the blood current and the stasis, as well as the coagulation of lymph in the inflammatory focus, lead to formation of a mechanical barrier which prevents the microbes and toxins from being absorbed from the focus of inflammation and spreading through the organism.

Thus exudation plays a protective physiologic role which, in addition to proliferation, counteracts the injury inflicted by the inflammatory agent. But the exudate does not always perform its "protective" role. For example, in certain disturbances in hematopoiesis (connected with benzene poisoning) the number of leukocytes capable of phagocytosis sharply decreases in the blood and exudate, which appreciably affects the defence reactions in inflammation with the result that phenomena of necrosis begin to prevail. In other cases the intense reabsorption of the exudate may lead to a spread of microbes and their toxins in the organism.

In some cases the accumulating exudate is excreted into body cavities (as in pleurisy, pericarditis and peritonitis) where it may compress the adjacent organs. In other cases the exudate and its cells are distributed among the tissue elements of the inflamed part, making them tense and compact. An inflammatory *infiltrate* is formed. In addition to the leukocytes which have emigrated from the vessels, the infiltrate also contains cells of local origin. The



Fig. 61a. Inflamed venule of a rat.
A polymorph (1) has passed through the endothelium (E) and has sent out a particularly long pseudopod parallel to the endothelium. 2, 3 and 4 are polymorphs. P is a platelet ($\times 15,500$) (Marchesil).



Fig. 61b. Chemotaxis, phagocytosis and abscess formation.
Rat polymorphs which have ingested pneumococci. The pneumococci are contained in "phagocytosis vacuoles." The vacuoles are clearly bounded by a discrete membrane ($\times 13,500$).

exudate accumulated in the tissues is the cause of the *swelling* of the inflamed part.

The pressure of the exudate on the endings of the sensory nerves and their stimulation by the inflammatory agent and products of tissue disintegration are the causes of pain sensations.

PROLIFERATIVE PHENOMENA

In addition to the phenomena of alteration developing in the centre of the inflammatory focus, a slight proliferation of cells is observed on its periphery. These phenomena become particularly noticeable during the later stages of inflammation.

An essential part in the mechanism of proliferation is played by products of decomposition and disturbed metabolism and often also by the inflammatory agent in cases of its prolonged action on the tissue. In inflammation metabolic disturbances inevitably lead to physicochemical changes which on their part also in some measure affect the proliferative processes.

Low acidity in the peripheral zones of the inflammatory focus and corresponding changes in colloid osmotic pressure are apparently conducive to proliferation of cells, whereas a higher degree of the same physicochemical changes in the centre of the focus leads to dystrophic phenomena.

The most important part in the formation of new tissue elements in the focus of inflammation is played by endothelial cells of the blood and lymph capillaries, adventitious and reticular cells, which undergo various transformations, swell, become round and multiply mainly by mitosis. All of them together with the emigrant mononuclear cells become motile (so-called wandering cells) and actively participate in phagocytosis. These cells are known as macrophages which include clasmacytocytes, polyblasts, various histiocytes and leukocytoid cells. According to some scientists, they may also serve as the source of formation of granulocytes and lymphocytes. In some cases plasma cells, which participate in production of immune bodies, accumulate in the focus of inflammation.

Small thrombi, destroyed tissue and products of cell disintegration are digested as a result of phagocytosis and fermentative processes. In favourable cases the fluid part of the exudate is resorbed (through blood and lymphatic vessels). The swelling of the inflamed tissue and pain gradually disappear.

Proliferation is followed by regeneration which is not part of the complex of inflammatory phenomena proper, although it can hardly be separated from them. It consists in growth of connective tissue cells, formation of new blood vessels, and, to a lesser extent, multiplication of the specific elements of the given tissue, for example, the tegumentary and glandular epithelium. In cases where the damage to the tissue is slight the latter is almost completely re-

generated. In cases of severe injury accompanied by destruction of tissue the removal of the dead material leaves a defect in the part. The newly forming, young *granulation tissue* rich in blood vessels grows into the infiltrated parts. It gradually extends from the periphery to the centre of the inflammatory focus, fills the tissue defect produced by the inflammation, replaces the destroyed tissue and creates a barrier (demarcation) between the focus of inflammation and the healthy tissue. In the end connective tissue forms a scar.

FORMS OF INFLAMMATION

Alterative, exudative-infiltrative and proliferative (productive) inflammatory processes are distinguished depending on the character of the reaction.

An *alterative inflammation* is characterised by a predominance of phenomena of dystrophy, necrobiosis and necrosis, while exudative and proliferative phenomena are but feebly marked. Alterative inflammation most commonly occurs in parenchymatous organs in cases of infection and intoxication, mainly in the kidneys, liver, and the heart muscle, and less frequently in the brain (acute nephritis, hepatitis, myocarditis in diphtheria, etc.). There are also cases of alterative inflammation of the interstitial tissue, for example, rheumatic fibrosis. Experimentally these inflammations can be easily produced in rabbits and dogs (for example, in the kidneys) by poisoning them with various toxic substances (cantharidin, uranium, bacterial toxins).

Exudative-infiltrative inflammations are characterised by a stronger vascular reaction with a predominance of phenomena of exudation and emigration. Several forms of these inflammations are distinguished according to the properties of the exudate.

1. *Serous exudate*—a transparent fluid of low specific gravity (1015-1020) containing protein (3-6 per cent) and a small number of cells (polymorphonuclear leukocytes, histiocytes). It is most frequently observed in inflammation of serous membranes (serous pleurisy, peritonitis, pericarditis).

2. *Hemorrhagic exudate*—one containing a large number of erythrocytes which impart a pink or pinkish-red tint to the fluid. It often forms in inflammatory processes of tuberculous origin (pleurisy, peritonitis, pericarditis), anthrax and plague.

3. *Purulent exudate*—one consisting of protein-containing fluid with an enormous number of leukocytes, mainly neutrophils, mostly destroyed by the effects of toxic substances or harmful agents (bacteria, toxins). It appears mainly under the influence of staphylo- and streptococci, and also gonococci and meningococci, typhoid and pyocyanous bacilli. Abscesses may also be produced by the effect of turpentine, croton oil, war gases, etc., on the skin (Fig. 62). Pus abounds in various products of tissue decomposition—



Fig. 62. Skin on the hand affected with yperite. Exudative inflammation (Sakharov).

peptones, polypeptides and amino acids, as well as enzymes, mainly of a proteolytic character.

The cavity filled with pus and formed by mortification and liquefaction of tissue in the focus of purulent inflammation is called an *abscess*. Usually the pus subsequently makes its way from the abscess either to the exterior or into internal cavities. Accumulation of pus in a closed cavity is called *empyema* (empyema of the pleural cavity, the gallbladder, etc.). Purulent infiltration spreading through loose cellular tissue (subcutaneous, muscular, interstitial) and affecting large sections of tissue is called a *phlegmon*.

Purulent inflammation usually ends in opening of the abscess, discharge of the pus, development of regeneration at the site of the tissue defect and formation of a scar.

A general infection of the organism and formation of multiple abscesses (*pyemia*) are possible. This occurs in cases where pyogenic microbes penetrate from the purulent focus into the circulating blood. The severity of the process depends on the character of the bacterial flora in the abscess and on the organism's resistance.

4. *Putrefactive exudate*—one formed by putrefactive microorganisms gaining entrance into and developing in the focus of inflam-

mation. The result is gangrenous inflammation, for example, putrid bronchitis, pleurisy, etc.

5. *Fibrinous exudate*—one containing a large amount of fibrin freely occurring in cavities or in some measure connected with the underlying tissue.

The following forms of fibrinous inflammation are distinguished: *croupous inflammation* in which the fibrinous exudate freely covers the surface of the mucosa as a grey membrane and can easily be removed without any injury to the mucosa, as in croupous inflammation of the trachea, pericardium or pleura; *diphtheritic inflammation* in which the fibrinous exudate impregnates the mucosa which undergoes necrobiotic changes, the removal of the fibrinous membrane exposing the ulcerated surface, as in diphtheritic inflammation of the intestines in dysentery, or the fauces and tonsils in diphtheria.

In some cases the fibrinous membranes are cast off and discharged (for example, from the respiratory and intestinal tracts), while in other cases they are resorbed. Sometimes the fibrinous exudate undergoes organisation, i.e., connective tissue grows into it, and *adhesive inflammation* develops, which leads to adhesion of adjacent organs or cavity walls, for example, the visceral and parietal pleura. Such adhesions often result in displacement of organs and their dysfunction.

There are also *mixed exudates*: *serofibrinous*, *serohemorrhagic*, *seropurulent* and *pyofibrinous*. The character of the exudate depends on the harmful agent, the duration and intensity of its action, and the site of inflammation. Sometimes one form of exudate changes to another in the course of inflammation (for example, a serous exudate may change to a purulent or hemorrhagic exudate).

Proliferative or *productive inflammation* is characterised by a predominant growth of tissue elements, while all other phenomena recede into the background.

The most strongly pronounced proliferative inflammations are observed in chronic infections, for example, syphilis and tuberculosis, as well as in prolonged irritation of the skin with various chemical substances—aniline, products of petroleum distillation, etc.

In chronic inflammation it is predominantly the connective tissue of the organ that grows excessively. The connective tissue gradually grows into the inflammatory focus or organ as a whole, partly replaces the degenerating parenchymal tissue and causes consolidation, shrinkage and contraction of the organ. This process is known as *cirrhosis* (for example, cirrhosis of the liver, kidneys and other organs). Other cells, for instance, the epithelium of the skin and endothelium of the serous membranes, may also proliferate.

Sometimes the cells of the proliferating granulation tissue form small or large nodules, so-called *granulomas* which consist of cells of young connective granulation tissue. The development of granu-

lomas may be caused by tubercle bacilli, the *Treponema pallidum* and *Mycobacterium leprae*, as well as by the causative agents of rheumatism and typhus. Granulomas are often of a specific structure which is determined by the causative agent and the organism's reactivity.

Elements of formed granulomas inadequately supplied with nutritive material and poisoned by the microbial products may undergo necrobiosis and necrosis and be transformed into a cheesy mass, as is often the case with tubercles.

COURSE AND OUTCOME OF INFLAMMATION

According to its *course*, inflammation may be acute, subacute and chronic. An inflammation characterised by a brief course and very intense inflammatory phenomena is called *acute*. The predominant processes are usually vasoexudative. An inflammation that runs a protracted course and shows mild symptoms is called *chronic*. The predominant phenomena in chronic inflammation are proliferative. An inflammation running a course ranging between acute and chronic is considered *subacute*.

The sequence and reciprocity of the inflammatory phenomena depend on the reactive properties of the organism, as well as the intensity and duration of the harmful agent's action. The more intense the action of the harmful agent, the more acute, usually, the inflammation. The action of a weak stimulus most frequently causes a chronic inflammation. Both acute and chronic inflammations can be produced experimentally by application of croton oil of various concentrations, yperite and other war gases to the skin and mucosa, or by injection of toxins or microbes in the tissue.

The character of the process is largely determined by the duration of the harmful agent's action; thus a strong stimulus in most cases produces an acute inflammation, a weak, but protracted influence on a tissue commonly causes a chronic process as, for example, a chronic inflammation of the upper respiratory tract is stimulated by dust particles, while a chronic inflammation of the skin develops in response to its protracted irritation with weak concentrations of acids, alkalis or aniline dyes.

The anatomic and physiologic characteristics of the affected tissue also have some bearing on the character of the inflammation. The same inflammation runs different courses in different tissues and, all other things being equal, depends on the innervation and blood supply of the given part, the properties of its connective tissue, etc.

Outcome of inflammation: 1) return to normalcy with restoration of the anatomic and functional properties of the tissue due to restoration of its specific elements (*restitutio ad integrum*); 2) formation of scar tissue which may not affect the functional properties of the organs (for example, small scars on the skin, etc.) or may, if

extensively developed, cause displacement of organs (for example, in the thoracic cavity in cases of pleurisy and pericarditis) and functional disturbances, as in formation of scars in the central nervous system; 3) destruction of tissue and sometimes of the organism, depending on the character of the inflammation and the site of its development.

INFLAMMATION AS A REACTION OF THE WHOLE ORGANISM

The local and general phenomena of inflammation are closely interconnected.

Inflammatory processes are divided according to the character of the organism's reactivity into normergic, hyperergic and hypoergic.

A *normergic inflammation* is a usual, most common inflammatory reaction in a normal organism.

A *hyperergic inflammation* is an excessively strong reaction of a sensitised organism to the action of substances of antigenic nature on tissues. It includes Arthus' phenomenon, the Pirquet reaction, etc. The same thing is observed as regards the action of usual stimuli. For example, rubbing xylene into the skin of the rabbit's ear causes a relatively weak inflammatory reaction, but done to a rabbit, repeatedly sensitised to some protein, it will develop an inflammation with more clearly marked alterative and vascular phenomena.

A *hypoergic inflammation* is characterised by mild inflammatory phenomena. It develops in an organism possessing increased resistance to the action of the stimulus, as in intracutaneous injection of diphtheria toxin in an organism immune to diphtheria. Such altered reactivity of the tissue due to the immune state of the organism is called *positive hypo- or anergy*. But an inflammatory process may also be of a hypoergic character if it develops in an emaciated organism as a result of its lowered reactive capacity—*negative hypo- or anergy*; for example, inflammation is observed to run a sluggish course in patients with malignant tumours or in long-starving people.

The inflammatory reaction is either greatly diminished or absent in some animals during hibernation when the reactivity of the organism is altered.

The appearance and development of the inflammatory reaction also depend on the *functional state of the nervous system*.

Experimental and clinical studies have shown that reflex reactions play an important part in the appearance of inflammation. For example, resection of the afferent part of the reflex arc or administration of anesthetics capable of blocking receptor structures perceptibly weakens and sometimes stops the inflammatory process. Anesthesia of the tissue induced before the inflammation has an even stronger effect.

Moreover, there are observations indicating that inflammatory processes develop at symmetrical sites for purely reflex reasons. For example, the inflammation produced by administration of tuberculin into the skin of one limb sometimes causes a symmetrical inflammation on the other limb.

There are also data showing that various structures of the central nervous system participate in the mechanism of inflammation. It is possible to alter in experiment the functional state of the central nervous system (experimental neurosis) and produce conditioned reflex leukocytosis and phagocytosis.

Lastly, phenomena of inflammation have been observed on the human skin as a response to hypnotic suggestion that the subject's body was being touched with something hot.

That the nervous system plays an important part in the appearance of the inflammatory reaction is also attested by the studies which have demonstrated the possibility of vast inflammatory processes developing on the skin, mucous membranes and internal organs in connection with chronic injury to the tuber cinereum, and have uncovered the influence exerted by the sympathetic nervous system on the development of inflammation. Hyperfunction of the sympathetic nervous system inhibits the development of inflammation, while its hypofunction, on the contrary, tends to stimulate the process.

The more complex the organism and the more differentiated its nervous system, the more clearly and fully marked its inflammatory reaction, especially the defence physiologic phenomena, as emigration, phagocytosis and proliferation.

The participation of the endocrine glands in the development of inflammation must be regarded as closely connected with the function of the nervous system. The same harmful agent evokes different reactions in patients affected with exophthalmic goitre and myxedema; in the former inflammation runs a more intense course than it does in the latter.

A particularly strong influence on the development of inflammation is exerted by the functionally interrelated hormones of the anterior lobe of the hypophysis and the adrenal cortex. The adrenocorticotropic hormone of the adeno-hypophysis inhibits the inflammatory reaction by stimulating secretion of glucocorticoids (hydrocortisone and cortisone) in the adrenals, while the somatotropic hormone, directly or through the mineralocorticoids, desoxycorticosterone and partly aldosterone, stimulates it. The points of application of these anti-inflammatory hormones are not known with any degree of certainty, except that they affect the permeability of vessels, emigration of leukocytes and proliferation of tissue.

The inflammatory process affects the whole organism.

The general manifestations of the inflammatory reaction are revealed as alterations of the immune properties of the organism,

its metabolism and hematopoiesis, an increase in the number of leukocytes, faster erythrocyte sedimentation rate, and disturbed composition of the blood, for example, increased sugar, protein fractions and nonprotein nitrogen.

The appearance of general phenomena in inflammation may be explained by bacteria, toxins, products of disturbed metabolism and tissue disintegration, especially certain active proteins and polypeptides, substances of nucleinic nature, histamine, etc., penetrating from the focus of inflammation into the circulating blood.

Other substances of a protein nature, besides leukotaxine, have been isolated from the exudate. According to Menkin, these substances are formed in the focus of inflammation and affect the whole organism; they include the leukocytic factor which is connected with alpha-globulin and causes leukocytosis, necrosin-euglobulin capable of injuring the endothelium and producing thrombosis and degenerative phenomena in parenchymal organs, pyrexin-polypeptide which provokes fever, exudin-polypeptide which increases the permeability of capillaries during the late stages of inflammation, etc.

The influence of inflammation on the whole organism is also exerted reflexly. This may be observed in cases of development of ulcers in appendicitis or of cardiac arrhythmia in inflammations in the abdominal cavity. The reflex of Goltz, i.e., cardiac arrest following mechanical irritation of the abdomen in the frog, may serve as another example. This reflex is increased in cases of inflammatory changes in the abdominal organs.

PRINCIPAL MECHANISMS OF INFLAMMATION

In its earlier stages the theory of pathogenesis of inflammation was dominated by the views of Virchow and Cohnheim.

According to Virchow (1858), the essence of inflammation consists in increased vital activity of *cellular elements* which in response to stimulation of the tissue begin to feed intensely and multiply at the expense of the fluid part of the blood (so-called nutritive stimulation). From this point of view the other phenomena, for example, vasoexudative, are of secondary importance.

Actually, however, simultaneous alterative, vasoexudative and proliferative phenomena in the given part are considered characteristic of the inflammatory reaction. None of the aforementioned processes alone can characterise the whole of the inflammatory reaction. Moreover, the concept of inflammation as only a cellular reaction disregards the state of the organism as a whole in the pathogenesis of inflammation. The approach of cellular pathology to the problem of pathogenesis of inflammation is thus one-sided and narrowly localistic.

Cohnheim's *vascular theory* (1885) considers the vascular disorders which give rise to phenomena of exudation and emigration to

be the most important, the cellular changes to be of secondary importance and the reflex influences to have no direct bearing on the mechanism of the inflammatory process proper.

However, later observations failed to confirm the assumption that the vascular reaction is the most important in the pathogenesis of inflammation and proved the dynamics of inflammation to involve both vascular and tissue disturbances.

Mechnikov's *biological, phagocytic theory* (1892) was a step forward in the development of the theory of pathogenesis of inflammation. He attached the utmost importance to white blood cells—phagocytes—which, in his opinion, played an exceptional role in any inflammatory process. In his studies of the reaction of the organism and its tissues to the action of harmful agents, Mechanikov was the first to employ the evolutionary, comparative-pathologic method of research, which enabled him to uncover the importance of inflammation as an adaptive reaction of the whole organism.

As the general organisation of animals grows more complex, the reaction of phagocytosis enters into complex relations with the different functional systems and, at the highest stage of development, with the nervous system.

Phagocytosis and chemotaxis regarded by this theory as the most important factors are associated with the general reactivity of the organism. They raise its resistance to the action of any inflammatory, especially infectious agent.

Although the phagocytic theory does not completely explain inflammation, it nevertheless considers it a defense-adaptive reaction and relates it to immunity.

Moreover, the phagocytic theory has for the first time established the interrelation that exists between the focus of inflammation and the whole organism and has thereby shown that inflammation is, not only a local, but also a *general reaction of the organism to the action of harmful agents*.

Later Schade advanced the *physicochemical hypothesis of inflammation*. This hypothesis considers the local metabolic disturbances and the development of acidosis and other physicochemical changes connected with them and resulting in circulatory disorders and cellular phenomena to be the most important factors.

The representatives of the physicochemical trend have undoubtedly discovered a number of facts which play a part in the development of inflammation and have attempted to establish their interrelations. It is still uncertain, however, to what extent physicochemical changes precede inflammation and whether they are really its main mechanism. All the physicochemical changes characteristic of inflammation can be established only when the inflammatory process has already developed and are therefore of secondary importance. Furthermore, the physicochemical hypothesis considers inflammation to be exclusively a local process and

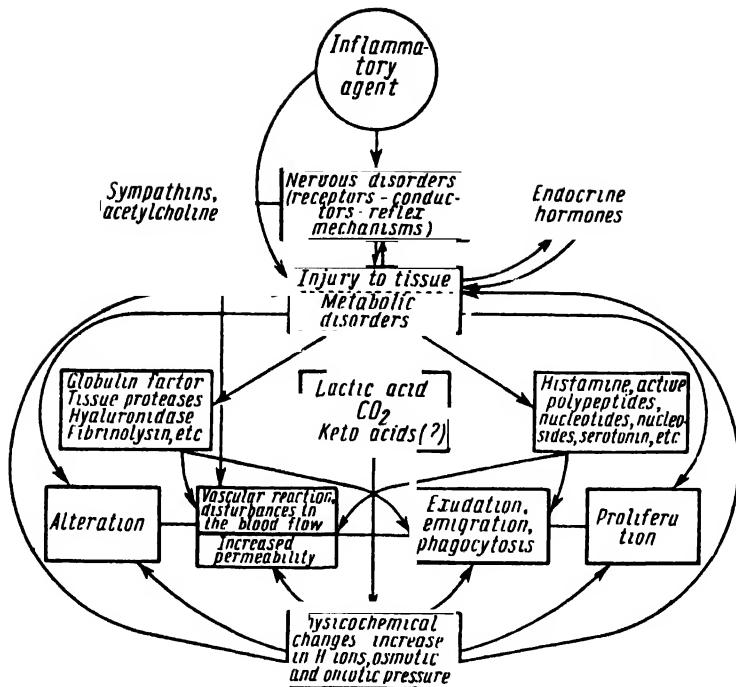


Fig. 63. Diagram showing development of inflammation.

disregards the role of the regulatory systems and the reactivity of the whole organism in its pathogenesis.

With the development of neurophysiology increasingly greater importance in the *pathogenesis of inflammation* has been attached to the *nervous system*.

According to the *vasomotor theory* (Ricker), the essence of inflammation consists in primary dysfunction of the vasomotor nerves; the strength of the vascular reaction varies with the degree of stimulation of the vasomotor nerves and determines the interrelation between the tissue and the circulating blood that leads to the appearance of inflammatory hyperemia and stasis and conditions the intensity and character of the metabolic disturbances. However, the multiformity of inflammation cannot be accounted for by the "play" of the vasomotor nerves alone. The role of the nervous system in the pathogenesis of inflammation must be given broader and deeper evaluation.

In inflammation the trophic function of the nervous system is disturbed in addition to the altered nervous regulation of the lumens of vessels. In the first place the inflammatory agent reflexly alters the permeability of the vessels and tissues. This is followed by

development of metabolic disorders characteristic of inflammation and disturbances in the physicochemical properties of the affected tissue, which does not exclude the possibility of an injurious effect produced on the tissue directly by the inflammatory agent.

The role of the nervous system in the appearance of inflammation was also uncovered in observations of the development of inflammation in cases of nervous dysfunction. In cases of hypofunction of the sympathetic nervous system the inflammatory process runs a more violent course and terminates sooner, while in hyperfunction of the sympathetic nervous system it runs a sluggish course and lasts longer, or sometimes does not develop at all. Moreover, denervation of the tissue leads to development of an unusual reaction. For example, blocking the tissue receptors by anesthesia sharply weakens the inflammatory reaction.

Two interconnected and frequently inseparable processes must be distinguished in inflammation: on the one hand, the *pathologic process proper*—damage to the tissue in the form of dystrophy, necrobiosis or necrosis, and, on the other hand, the *defensive-physiologic, restorative process* in the form of exudation, phagocytosis and tissue proliferation. It is precisely the simultaneous operation of both processes that is particularly characteristic of inflammation.

The nervous system participates in both processes: the changes in reflex activity caused by the action of the pathogenic agent are involved in the development of tissue injuries. But the nervous system plays the most important part in the formation of the mechanisms (exudation, phagocytosis and proliferation) by means of which the organism eliminates the inflammatory agent and the injury it has caused.

It may thus be concluded that the changes in the reflex activity of the nervous system definitely play a part in the appearance and development of inflammation.

The participation of the regulatory systems and the physiologically active substances in the appearance and development of inflammation is shown in the diagram presented in Fig. 63.

Chapter Nine

PATHOLOGY OF TISSUE GROWTH

HYPERTROPHY

*An increase in the size of tissues beyond normal is called hypertrophy.**

A tissue may increase in size either by enlargement of its various cells (*hypertrophy proper*) or by increase in the number of its cells (*hyperplasia***). Most frequently the increase in size is due simultaneously to the hypertrophy of the cells and the increase in their number.

True and false hypertrophies are distinguished. *True hypertrophy* consists in a uniform enlargement of all constituent parts of an organ, including its specific parenchymal elements, the functional capacity of the organ increasing at the same time. *False hypertrophy* of an organ is characterised by an enlargement of the organ, which is not due to an increase in the parenchyma, but in some other tissue (intermuscular cellular tissue or adipose tissue), while the parenchyma remains normal or is even atrophied and the function of the organ is diminished.

Hypertrophy may develop under physiologic conditions—*physiologic hypertrophy*.

Under physiologic conditions true hypertrophy of the skeletal muscles develops as a result of an increased work load, for example, physical training; other examples are true hypertrophy of the uterus during pregnancy, or hypertrophy of the breasts in nursing mothers. True hypertrophy is characterised by the similarity of the newly formed tissue with the normal tissue from which it has formed.

More frequently, however, hypertrophy and hyperplasia develop under pathologic conditions—*pathologic hypertrophy*—as an

* From the Greek words: *hyper*—beyond, above, over, i.e., excessive, and *trophia*—nourishment.

** From the Greek words: *hyper* and *plasis*—a moulding.

adaptive reaction compensating for the functional insufficiency of an organ or tissue.

Hypertrophy resulting from an *increased work load* is called *work hypertrophy* or *adaptive hypertrophy*.

Hypertrophy which adapts an organ to increased functional requirements is known as *adaptive hypertrophy*, for example hypertrophy of the heart associated with valvular deformities, particularly in cases of constriction of the mouth of the aorta, which creates an obstacle in the systemic circulation for the work of the left ventricle, or hypertrophy of the smooth muscles of the intestines and urinary bladder in cases of obstructions such as constrictions or calculi.

Hypertrophy which follows destruction or injury in the opposite paired organ or in another part of the same organ with the remaining organ or part of organ taking over the total function is referred to as *compensatory hypertrophy*, for example, hypertrophy of the left lobe of the liver in atrophy of the right lobe, or hypertrophy of one kidney after excision of the other.

The development of hypertrophies and hyperplasias is usually based on reflex activity associated with the increased requirement of an organ in energy metabolism. For example, in the mechanism of development of adaptive hypertrophy of the heart a certain part is played by the stimulation of its interoceptors by the disturbed blood circulation in the cavities with the result that the processes of blood supply and metabolism in the heart muscle are reflexly intensified.

Other forms of hypertrophies are of no compensatory significance and appear without any apparent functional requirements. They may appear as a result of prolonged *mechanical* or *chemical* irritations. Hypertrophy of the intestinal mucosa associated with its chronic irritation with coarse food, or the proliferation of the epithelium of the skin due to the effects of aniline dyes may serve as examples.

More complex in origin are hypertrophies developing as a result of *excessive proliferation and regeneration of tissue*, for example, excessive formation of callus in healing of bone fracture, or excessive granulation of tissue in tuberculosis or syphilis.

The same group includes hypertrophies in which tissue proliferation is the result of diminished mechanical pressure of adjacent tissues, for example, proliferation of interstitial tissue in atrophy of parenchymal elements in the liver or proliferation of villi in an articular cavity after removal of the fluid which was in the cavity for a long time.

Hypertrophies and hyperplasias of *endocrine origin* comprise a special category. For example, acromegaly which is based on excessive secretion of the growth hormone by the anterior lobe of the hypophysis is characterised by enlargement of the nose, lower jaw, supraorbital ridges and peripheral parts of the limbs.

Lastly, there are *congenital hypertrophies* associated with disturbances in embryonal development, as a special form of hypertrophy of the breasts, congenital ichthyosis or hypertrophy of the corneal layer of the epidermis.

REGENERATION

Regeneration is new tissue growth stimulated by injury or destruction of tissue and resulting in its complete or partial restoration.

Physiologic regeneration is restoration of tissue elements destroyed under normal conditions. It consists in replacement of outlived elements by new ones, for example, regeneration of the epidermis, glandular cells and erythrocytes.

Pathologic regeneration occurs after injury to tissue, its degeneration or necrosis produced by an inflammatory process in which part of the tissue or organ is destroyed or a defect is formed. In place of the lost or destroyed tissue new tissue begins to grow from the retained tissue elements capable of proliferation; this leads to elimination of the defect.

The capacity for regeneration has developed in the process of evolution and is one of the forms of the organism's adaptation.

Regeneration varies with different organisms and depends on the degree of the organism's differentiation. The capacity for regeneration is more strongly pronounced in the lower organisms. It is well known, for example, that in the lower organisms even whole body parts are regenerated (for example, the limbs in salamanders and the tail in lizards).

The phenomena of regeneration are the least pronounced in the higher vertebrates and man.

The more differentiated the tissue, the less capable of regeneration it is. Connective tissue and the tegumentary epithelium are the most capable of regeneration, nervous tissue—the least. The destroyed cells of the cerebral cortex do not regenerate.

Regeneration also depends on the stage of *ontogenetic development* of the organism and is the most complete in the tissues of the embryo. The tissues of a young, growing organism are more capable of regeneration than those of an adult. In elderly people the capacity for regeneration is very low.

However, the dependence of regeneration on the degree of development of the organism and its tissues is not always manifest; for example, among vertebrates regeneration is more strongly pronounced in fish and tailed amphibians, less so in tailless amphibians and reptiles, and still less in birds; but under some conditions regeneration is faster and more complete in birds than in tailless amphibians. On the other hand, highly differentiated epithelium has greater regenerative capacity than striated muscle fibres. The capacity for regeneration is apparently but one of the organism's mechanisms of restoring the functions of an affected

organ or tissue and in the process of evolution it may be compensated by development of other mechanisms. For example, an injury to one organ is compensated by a reflexly developing hyperfunction of another organ or of the intact parts of the affected organ.

In mammals the regenerating tissue is usually derived from corresponding cells of the affected tissue. But regeneration may also involve *metaplasia* which implies transformation of one form of adult tissue into another. For example, owing to adaptation to new conditions of functioning, scar connective tissue may sometimes be transformed into osseous tissue, or cuboidal epithelium of the mucous membrane of the urinary bladder becomes transformed at the site of its injury into stratified corneal tissue, or the columnar epithelium of the respiratory mucosa changes to stratified squamous epithelium.

Extraneous factors, especially *nutrition*, play a very important part in regeneration. In weak, emaciated people regeneration is very slow. Protein and vitamin deficiency in the food considerably depresses regeneration.

In addition to adequate nutrition, regeneration is favoured by *optimum temperature*, moderate or small doses of *radiant energy* and a number of other factors of the external environment.

One of the most important factors of the internal environment is the *nervous system*. Thus, denervation of tissue and various injuries to the central nervous system appreciably depress or completely suppress the process of regeneration. Regeneration is also impeded in cases of dysfunction of the diencephalon.

Regeneration is greatly influenced by the *endocrine glands*. The somatotropic hormone of the hypophysis intensifies regeneration. Small doses of insulin stimulate the healing of wounds. In thyroidectomised animals bones regenerate and wounds heal very slowly.

Lastly, regeneration is stimulated by *products of tissue disintegration*. The most important of these are substances of albuminous nature and certain physiologically active substances which have long figured under various appellations--wound hormones, trephones, etc. Thus, to understand the mechanism of regeneration, the properties of the whole organism as manifested in its reactions to tissue defect must be taken into account.

BLASTOMATOUS (NEOPLASTIC) GROWTH

Concept of Blastomatous Growth

All the aforementioned forms of tissue growth are characterised by the following: 1) they appear as a reaction to tissue injury and changes in its function and structure; 2) the growth of the tissue is arrested as soon as the causative stimulus ceases to act on the organism; 3) the new cells differentiate and assume the properties of

the cells of the tissue from which they are derived; 4) the newly formed tissue maintains its connections with the surrounding tissues and submits to the regulatory influence of the organism.

Blastomatous growth beginning with transformation of normal tissue into neoplastic tissue is characterised by atypical structure and function, as well as progressive and unregulated development.

Tumours may be derived from epithelial, connective, nervous and muscle tissue ; there are also mixed tumours. The names of the different tumours are usually formed from those of the tissue from which the tumours are derived and the suffix "oma", as fibroma, epithelioma, neuroma, myoma. There are special names for malignant tumours—*carcinoma* or *cancer* for tumours derived from epithelial tissue and *sarcoma* for those derived from connective tissue.

Occurrence of Tumours

Tumours are quite widespread among animals. They occur in poikilothermal animals—fishes, amphibians and sometimes in reptiles.

Tumours of epithelial and connective tissue origin are observed in birds, especially in chickens. Spontaneous tumours, i.e., those arising under natural conditions, are found in almost all species of mammals, each species being noted for a particular form of tumour. Mice and rats are particularly susceptible to tumours. The tumour most frequently occurring in mice is cancer of the mamma, in rats—sarcoma. According to certain data, 6-8 per cent of the mice die of cancer.

Tumours are a relatively rare occurrence in guinea pigs and rabbits, while in dogs they occur more frequently and usually as sarcomas and cancer.

Observations of tumours in different species of animals have facilitated experimental production of tumours by transplantation, which has greatly helped in the development of oncology.*

Human beings are relatively frequently affected with tumours. In some countries mortality from malignant tumours is 10 per cent of the total mortality.

British statistics show an increase in the incidence of malignant tumours. According to a number of investigators, however, this is due not so much to the actual increase in the disease incidence as to the improved methods of diagnosing cancer. The increase is accounted for mainly by the cases of formerly unidentified cancer of the internal organs (for example, of the lungs), whereas the incidence of cancer of the external parts of the body has not particularly grown.

Another factor is the considerable increase in human life expectation because of which the relative mortality from cancer (a disease mainly of elderly people) has also noticeably increased.

* From the Greek words: *onkos*—bulk, mass, and *logos*—word.

Tissue Atypicalness, or Anaplasia

One of the specific features of true tumours is their atypicalness, i.e., the peculiarity of their morphological and functional properties compared with the tissue from which they are derived. The atypicalness is based on anaplasia—decreased differentiation of the tissue.

Morphological Anaplasia

In morphological anaplasia the parenchyma of the tumours is characterised by a variety of sizes and forms of the cell elements. phenomena of hyperchromatosis, lack of correspondence between the mass of protoplasm and the mass of the enlarged and chromatin-rich nucleus, a large nucleus, an altered structure and reduced number of mitochondria, and atypical mitosis. In tumours the mutual arrangement of the cell elements is disturbed and the cells do not form normal tissue complexes. For example, in glandular tumours the lobes of glands are sometimes absent and, if they do form, they do not have their usual structure and not infrequently have no excretory ducts. The function of the glands is altered by the disturbed interrelation between their various tissue elements.

In structure tumours are organoid, i.e., like normal organs they consist at least of two tissues—parenchyma and stroma. The basic properties of a tumour are associated with those of its parenchyma. The stroma of a tumour is a fibrous connective tissue containing the vessels and nerves.

While losing a good deal of their differentiation, tumour cells sometimes retain some of their functions, for example, the secretory function—cholepoiesis in primary adenomas of the liver or secretion of mucus in tumours derived from mucous membranes. Sometimes phagocytosis (for example, in cells of sarcomas), as well as production of pigments and accumulation of glycogen and fat, is observed in tumours. The tissue of tumours derived from endocrine glands may retain its capacity to produce hormones, as is the case in some tumours of the hypophysis, the thyroid and the adrenals.

Chemical Anaplasia

This form of anaplasia consists in a certain alteration of the chemical composition of tumour cells. The more intensive the growth of the tissue, the more deficient it is in ash constituents and the more water it contains.

Tumours contain a somewhat increased amount of potassium and sodium which cause the swelling of colloids. Tumours are relatively deficient in calcium and magnesium. The faster the blastomatous growth, the more disturbed the K/Ca coefficient and the lower the content of iron. Fat infiltration and an increase in unsaturated fatty

acids may often be observed in tumours. The amount of lipids, especially cholesterol, is increased.

The amount of glycogen increases in tumours which must be associated with a disturbance in their carbohydrate metabolism. This also accounts for the accumulation of lactic acid in tumours.

In connection with the increased mass of cell nuclei the amount of nucleoproteids and nucleic acids also increases. The content of desoxyribonucleic acid is particularly high. Their increased disintegration also gives rise to accumulation of pentose.

Neoplastic tissue is characterised by disturbances in protein metabolism. The protein structure of malignant tumours somewhat differs from that of normal tissue. Some changes in the amino acid composition have been discovered; the content of cystine, methionine and tyrosine is diminished. Processes of protein synthesis predominate over those of proteolysis. The isotope method has helped to discover that tumour cells receive more amino acids, for example, alanine, glycine, asparagine and glutamine, as well as purine and pyrimidine bases.

In tumours the activity of some enzymes—proteinases, aminopeptidases, transaminases, deaminases, phosphatases, etc.—is depressed. The content of oxidative enzymes is observed to be altered; for example, the activity of cozymases, riboflavin, cytochromes and dehydrogenases is diminished. An increase in the content of reducing systems is noted. Certain disturbances in protein, fat and carbohydrate metabolism have been discovered. Disturbances in oxidation of carbohydrates and in synthesis of proteins and nucleic acids, as well as changes in the activity of certain enzymes are the most strongly pronounced.

Physicochemical Anaplasia

In tumour cells the colloidal properties of the protoplasm are altered. The dispersion of colloids is increased and their surface tension is below normal. The change in surface tension is due to the action of certain metabolites on the colloids, the content of these metabolites (for example, lactic acid) in blastomatous tissue being increased.

The acid-base balance is shifted toward acidity, which may lead to an increased concentration of hydrogen ions. An increased osmotic concentration of the tissue environment is observed as a result of the disturbed metabolism and accumulation of underoxidised metabolites.

In tumours the electric charge is higher than it is in corresponding normal tissue; this can be explained by accumulation of electropositive ions in the tissue. The electric conductivity is also disturbed. The more malignant the growth, the lower the resistance of the tissue to electric current.

All the foregoing physicochemical changes are in their turn due to the altered proportions of electrolytes in the blastomatous tissue, for example, the increase in the K/Ca. These changes together with the increased electroconductivity are responsible for heightened permeability of cellular membranes. Experiments with injection of various crystalloid and colloidal substances show a certain alteration of the permeability of blastomatous tissue cells.

Energy Anaplasia

This form of anaplasia is associated with disturbances in energy metabolism.

Particularly pronounced is the disturbance in the carbohydrate metabolism which is the main source of energy for the growth of blastomatous tissue. Depression of oxidative respiration and increased glycolysis are observed. Whereas the ratio of the energy of glycolysis to the energy of respiration in embryonal tissues averages 1-2, in cancer cells it may increase to 4-5. In other words, the cancer cell splits 4-5 times as much glucose as it can oxidise.

In 12 hours a cancer cell can produce from glucose an amount of lactic acid equal to its own weight. Cancerous tissue produces 100 times as much lactic acid as does the blood, 200 times as much as a muscle in a state of rest and 8 times as much as a muscle under the greatest work load. Blastomatous tissue can live under anaerobic conditions. While oxygen deficiency soon destroys normal tissue, blastomatous tissue can exist by anaerobic glycolysis which supplies it with the energy required for the synthesis of proteins and other high molecular compounds.

In neoplastic tissue, unlike most normal and other growing tissues, aerobic glycolysis also increases, i.e., heightened formation of lactic acid continues even in the presence of oxygen, and the Pasteur effect alters.

Thus blastomatous tissue differs from any other tissue by its increased anaerobic and aerobic glycolysis, disturbed correlation between glycolysis and respiration, and formation of more lactic acid.

The increased production of lactic acid leads to higher acidity of the environment. This results in greater swelling of connective tissue fibres, greater dispersion of colloids, altered surface tension, increased nutrition, growth and proliferation of tumour cells.

None of the foregoing forms of anaplasia can be considered typical only of neoplastic tissue because similar phenomena are also observed in other growing tissues. But in aggregate they (especially aerobic glycolysis and changes in nucleic acids) characterise the atypicalness that distinguishes blastomatous tissue from other tissues. The atypicalness is the more marked, the faster the growth of the tumour.

Disturbances in the Organism During Neoplastic Growth

Tumours, especially malignant tumours, are accompanied by changes throughout the organism. Underoxidised metabolites, especially lactic acid, accumulate in the blood, the amount of albumin decreases, the content of nonprotein nitrogen increases and that of glucose somewhat diminishes. At the same time the enzymes participating in carbohydrate metabolism become more active in the blood, and depolymerase which acts on desoxyribonucleic acid is in evidence. The activity of arginase, oxidase and riboflavin in the liver diminishes. The concentration of products of disturbed metabolism—polypeptides and certain amino acids (tyrosine, phenylalanine, tryptophane)—and the amount of lactic acid and sometimes of ketone bodies in the urine increases.

The accumulation of products of carbohydrate fermentation and the certain decrease in the amount of sugar in the blood are due to the considerably increased sugar requirements of the neoplastic tissue and its anaerobic type of metabolism.

The fact that normal serum is capable of dissolving cancer cells and the serum of cancer patients is not, has prompted the conclusion that the serum of these patients contains substances which protect the cancer cell from dissolution. A test for cancer identification based on this peculiarity has been repeatedly proposed, but it has proved nonspecific.

Despite the excess of underoxidised metabolites the acid-base balance and the pH of the blood in cancer are more often than not shifted towards alkalosis. This can be explained by compensatory phenomena, particularly accumulation of alkali-reacting elements (for example, potassium), and increased elimination of carbon dioxide through the lungs.

Cancer patients also show a diminished surface tension of the serum.

The metabolic disturbances in neoplastic tissue and all through the organism, as well as the poisoning with underoxidised products of metabolism and disintegration (of the tumour) lead to development of *cancerous cachexia* which is characterised by general emaciation, phenomena of intoxication and, not infrequently, development of severe anemia.

Characteristics of Neoplastic Growth

A tumour grows by an increase in the mass of tumour cells. Such growth of a tumour "from itself" is possible only after formation of a primary neoplastic rest which appears as a result of transformation of normal tissue into a neoplasm. In tissues closely related in origin neighbouring normal cells may be involved in neoplasia. But

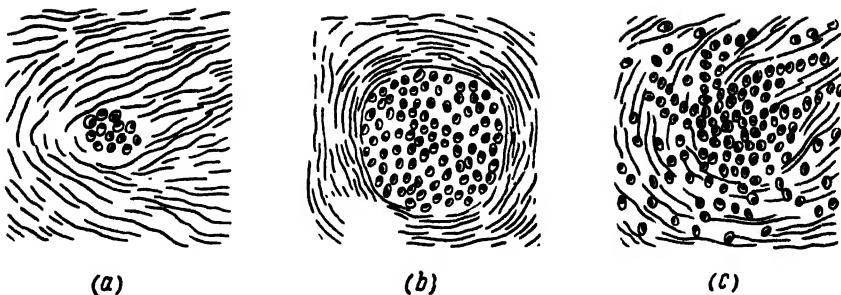


Fig. 64. Two types of neoplastic growth.

—loose connective tissue with a small group of tumour cells (tumour bud); *b*—expansive growth; *c*—infiltrative growth.

in these cases such growth (appositional) is observed during the initial formation of the tumour and is not typical of an already well-developed tumour.

A *tumour grows the faster, the less differentiated its cell elements* which have more or less lost their normal morphological and functional properties.

Blastomatous growth is influenced by the organism as a whole, its regulatory systems, metabolism, and the chemical and physicochemical properties of the part affected by the neoplastic growth. Tumours differ from other forms of tissue by unregulated growth, disturbances in the usual structure and function of the affected tissue, as well as in the regulatory influences exerted on it by the whole organism.

Tumours are characterised by relatively *unlimited growth* or tendency to continuous progressive development. This property implies a potential ability of tumours to grow without any apparent limit. In the absence of treatment (surgical or radiation therapy) a tumour continues to grow as long as the organism in which it has developed is alive. In cases of malignant tumours the organisms die before the tumours have grown very large. In other cases some tumours, for example, fibromyoma of the uterus, may reach a weight of 20-25 kg. Oophoritic cysts weighing 50 kg and more have been observed.

Since they feed on the nutritive substances taken from the surrounding tissues tumours are parasitic structures growing at the expense of the organism.

There are two kinds of neoplastic growth (Fig. 64).

Some tumours grow in relative isolation, separated by a capsule from the surrounding tissue from which only nerves and supplying blood vessels penetrate into the tumours. This kind of growth—*expansive growth*—characterises *benign* tumours, less atypical in struc-

ture, with weaker anaplasia of cell elements and lesser capacity for growth and proliferation.

Tumours with expansive growth do not invade the surrounding tissues, but merely move them aside, which may cause dysfunction by compression. These tumours grow slowly, sometimes with long intervals, without transfer (metastases) of tumour cells from the primary focus to other organs. The tissue of these tumours often retains the specific properties of the tissue elements from which it has originated.

Benign tumours may be of epithelial or mesenchymal origin. The former include adenomas and papillomas, the latter—fibromas, lipomas and chondromas.

The other type of neoplastic growth is an *infiltrative, malignant growth*. It is characterised by invasion of the surrounding tissue with obliteration of the borderline between the tumour and normal tissue. As a rule, malignant tumours produce *metastases*, i.e., after invading the blood or lymph vessels the cells of blastomatous tissue are transferred to distant sites where they form foci of new neoplastic growths. Cancer—epithelial malignant tumour—metastasises mainly through lymph channels (for example, metastases to axillary and supraclavicular lymph nodes in cancer of the breast); sarcoma—malignant tumour of connective tissue origin—usually metastasises through blood vessels.

The metastasis of a tumour often depends on the direction of the vessels. For example, malignant tumours in the stomach produce metastases (through the blood current) in the liver. However, the spread and localisation of metastases are also determined by the properties of the organs into which the metastases gain entrance.

Owing to the infiltrative growth complete enucleation of malignant tumours or their excision is very difficult, since parts of tumours may remain in the tissues and after a while may give rise to new growths—tumour *relapses*.

Malignant tumours also differ from benign tumours in that they cause considerable metabolic disturbances and emaciation of the organism (cachexia), are not infrequently accompanied by hemorrhage (owing to invasion of blood vessels) and intercurrent septic infection, and in a number of cases affect vitally important organs. Malignant tumours invariably lead the organism to destruction.

However, it is not always possible clearly to distinguish the two types of neoplastic growth by their clinical course. Sometimes benign tumours (for example, in the brain) lead to death, whereas an infiltrative growth does not always determine a malignant course of the tumour, as in angiomas, epulides, etc. There are cases in which a malignant tumour grows for years.

There are also cases in which so-called benign tumours (for example, certain forms of adenomas) develop into malignant tumours, acquiring all the typical properties of malignant growths.

Influence of Various Factors of the External and Internal Environment on the Growth of Tumours

Of the *various factors of the external environment*, which may in some measure influence the development of tumours, mention may be made of nutrition, occupation and conditions of life.

Nutrition affects the development of tumours. Low-caloric food retards the development of tumours. The growth of transplanted tumours is inhibited when the animals are fed inadequately, for example, on vegetable proteins containing no lysine, arginine and histidine, or on gelatin which has no cyclic amino acids; contrariwise, increased blastomatous growth is observed when the food abounds in carbohydrates, cholesterol and potassium.

Under certain conditions the *occupation* (considering the chemical or mechanical irritations connected with it) may contribute to cancer incidence. It is well known that workers of arsenic mines and aniline factories, as well as people working with paraffin or coal tar, by failing to observe the industrial safety rules, may be exposed to chronic irritation and, hence, be in danger of contracting cancer (so-called occupational cancer). Cancer of the skin, as an occupational disease, is also observed on the hands of roentgenologists who have worked with roentgen rays for many years and have failed to observe the necessary safety rules.

There are cases of cancer due to the effects of *various irritants of everyday occurrence*, for example, cancer of the lip in habitual pipe smokers, or cancer of the oral mucosa in Indians chewing betel.

Neoplastic growth is also dependent on *peculiarities of the organism*. In their development tumours reflect the *age and sexual characteristics of the organism*. Most frequently they arise in elderly people; cancer of the stomach and lungs—in men, cancer of the genitalia—in women.

Disturbances in the regulatory functions have been found to play a certain role in the appearance and development of tumours.

The growth of tumours has long been observed to increase under the influence of psychic trauma. Morphological data confirm disturbed innervation in tumours. Malignant growth is usually accompanied by phenomena of atrophy of the neural elements in the tissue affected with tumour. The *importance of the nervous system in neoplastic growth* has in some measure also been confirmed experimentally (see below).

Neoplastic growth is also influenced by the *endocrine glands*. For example, the somatotropic hormone of the hypophysis stimulates neoplastic growth. Estrone, a hormone found in the ovaries, accelerates the growth of tumours of the mammae and genitalia, whereas testosterone and progesterone (hormone of the corpus luteum) inhibit the development of these tumours. Development of cancer of the prostate is inhibited by administration of substances closely

related in structure to the female sex hormone. Although *heredity* is of some importance in neoplastic growth, its participation in the pathogenesis of the disease is not quite clear as yet. The importance of heredity in neoplastic growth is often overestimated.

Strains of mice characterised by frequency of spontaneous tumours are now being cultivated in laboratories. It has also been possible to produce a strain of mice with higher susceptibility to artificially produced tumours. It has developed, however, that there is no parallelism between the frequency of spontaneously appearing tumours and the susceptibility to artificially produced tumours.

There are also other facts which indicate that the importance of heredity in neoplastic growth must not be overestimated. For example, a peculiar regularity has been discovered in the appearance of mouse mammary carcinoma. If newborn mice from the strain with a high cancer incidence are nursed by females from the strain with a low cancer incidence, the incidence of mammary carcinoma in the newborn thus nursed sharply decreases. Contrariwise, if newborn mice of a resistant strain are fed on the milk of females from the high-cancerous strain, the cancer incidence in the newborn thus fed increases.

Thus the appearance of mammary carcinoma in mice may be considered dependent, not on the hereditary properties of the diseased organism, but on the composition of the maternal milk (*the milk factor*). Further investigations have shown the milk factor to be a high molecular protein with a ribonucleic component and viral properties.

Experimental Studies of Tumours

Experimentation is one of the valuable methods of studying the problem of neoplastic growth.

Transplantation of Tumours. The first systematic experiments with transplantation of tumours were conducted by M. A. Novinsky in 1875. He succeeded in transplanting sarcoma from dogs to pups and cancer from horses to horses. *Rats* and *mice* are particularly favourable objects for experimental studies of neoplastic growth (mainly malignant).

Spontaneous tumours in rats and mice can be transplanted from one animal to another. Special well-tested strains of tumours, for example, Ehrlich's mouse cancer, Jensen's rat sarcoma, Brown-Pearce rabbit cancer, Rous chicken sarcoma, etc., are used for transplantation.

By their properties transplanted tumours cannot be considered entirely identical with the tumours occurring in man, for which reason the results of experimental research cannot be unconditionally applied to man. However, when the results of clinical observations are added to the experimental data they help to understand the genesis of tumours.

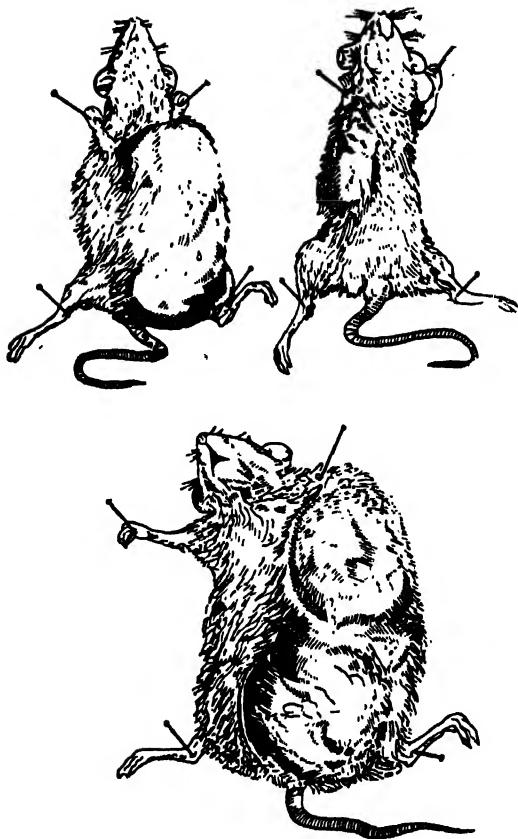


Fig. 65. Cancer in mice.

For successful transplantation *it is necessary to transfer the living tissue of the tumour from one animal to another* (Fig. 65).

Transplantation of a tumour is actually an experimental metastasis in the organism of a new animal. Most of the cell elements of the transplanted tissue are destroyed, but the surviving ones multiply and cause the appearance of a tumour which possesses (especially in the first transplantations) the properties of the transplanted tumour. In some cases the transplant does not require living cells to produce a corresponding tumour in the recipient. This is the case, for example, in transplantation of Rous sarcoma, which can also be effected by means of a noncellular filtrate.

The factor of malignancy can sometimes apparently be separated from the tumour cells and may lead to malignant degeneration, i.e., acquisition of malignant properties by normal cells.

The data furnished by the experiments with transplantation of

tumours have made it possible to draw certain general inferences on the regularities of the genesis and development of neoplastic growth.

Importance of Specificity. Transplantation is successful only in cases where the tumour is transplanted *from one animal to another of the same species*—from rats to rats, from mice to mice (specificity of tumours). Transplantation from an animal of one species to an animal of another species was successful only in a few cases, for example, transplantation of chicken sarcoma to ducks, mouse carcinoma to rats deprived of the spleen, or transplantation of a tumour of one species to the embryos of another species.

However, to give final confirmation to the identity of the transplanted tumour with the newly growing one and to determine in the recipient's organism all the peculiarities of the growth characteristic of the transplant, all these data contradicting the formerly established facts of tumour specificity require further and deeper study.

Transplantation of tumours is affected by factors of both the internal and external environment.

Importance of Factors of the Internal Environment. Scientists have repeatedly called attention to the importance of psychic trauma in the genesis of tumours.

Experimental observations of dogs have shown that long continued traumatisation of the nervous system by production of chronic experimental neurosis is conducive to neoplastic growth (papilloma, fibroma and sarcoma). Traumatisation of the nervous system by means of electric current intensifies the growth of tumours and hastens their appearance in animals subjected to the influence of cancerogenic substances, for example, dibenzanthracene (M. K. Petrova).

Various influences exerted on the subcortical region and the peripheral nervous system also have some bearing on the development of transplanted tumours and localisation of metastases (A. D. Speransky).

A state of deep inhibition in the higher parts of the central nervous system accelerates the development of tumours, whereas excitation impedes their development (R. Y. Kavetsky).

Experimental studies confirm the clinical observations of the *influence of endocrine glands* on the genesis, development and results of neoplastic growth.

The most reliable information concerning the influence of endocrine glands on neoplastic growth is that concerning the gonads and the hypophysis. Early castration of female mice of a high-cancerous strain prevents development of mammary carcinoma. Injection of large doses of estrone (hormone present in the ovaries) intensifies the growth and even causes development of such tumours in males, whereas administration of androgen (hormone of the testes) inhibits the development of the tumour.

The influence of disturbed endocrine function of the gonads on neoplastic growth not infrequently depends on changes in the gonadotropic function of the anterior lobe of the hypophysis. It happens that in mice of a low-cancerous strain the gonadotropic function of the hypophysis is relatively weak, whereas high-cancerous animals are characterised by a higher gonadotropic activity of the hypophysis. After removal of the hypophysis the development of the tumour is noticeably inhibited. Administration of the somatotropic hormone of the hypophysis stimulates neoplastic growth.

Factors of the external environment play a very important part in the pathogenesis and growth of experimental tumours.

Significance of Nutrition. Experiments with different diets have shown that the *character of nutrition* plays a certain part in the development of tumours. As has been mentioned, the growth of transplanted tumours in rats is inhibited if the rats are fed vegetable proteins devoid of lysine, arginine and histidine, or gelatin which contains no cyclic amino acids. Food rich in carbohydrates, cholesterol and potassium intensifies neoplastic growth. Long-continued feeding of animals on food containing no choline may cause cancer of the liver.

Chemical Cancerogenic Substances. Tumours may be produced experimentally by means of certain chemical irritants.

By long-continued (for a period of 6 months) application of tar to the ears of rabbits it was possible to produce cancer of the skin (Yamagiwa and Ichikawa, 1915). Cancer was later produced by coal tar also in mice. These experiments were soon reproduced and confirmed by many investigators. Some types of tar possess, it has turned out, high activity and in the course of 3 months (after 50 applications to the skin of mice) cause cancer in almost all the animals.

Pure cancerogenic chemical substances—polycyclic hydrocarbons—have been produced by distillation of coal tar at a high temperature (400-600°C): these hydrocarbons were later also produced synthetically. They are known to provoke malignant tumours in animals. Phenanthrene derivatives—benzopyrene, benzanthracene and cholanthrene—are particularly noted for their cancerogenic properties.

In addition to polycyclic hydrocarbons, cancerogenic properties are also present in nitrogen compounds (for example, orthoaminoazotoluene and dimethylaminoazotoluene), naphtylamine and substances of simpler structure (for example, carbon tetrachloride and chloroform). Inorganic cancerogenic substances include salts of arsenic, zinc, chromium, beryllium, etc. Close to 500 chemical cancerogenic substances have now been produced.

Application of cancerogenic substances to the skin of animals for a few months usually causes malignant tumours (Fig. 66). Resorption of cancerogenic substances administered subcutaneously,



Fig. 66. Cancer in rabbit produced by cancerogenic substance (9 : 10-dimethyl, 1 : 2-benzanthracene). The ear was painted with this substance twice a week for 29 weeks.

macrophages of the spleen of the chick embryo cultivated in plasma containing cancerogenic substances changed into sarcomatous cells and, administered to chickens subcutaneously, caused neoplastic growth. Other investigators, however, established that transformation of normal cells into blastomatous cells by cultivation in a nutrient medium containing cancerogenic hydrocarbon is possible only in the presence of the milk factor. For example, the normal cells of the subcutaneous tissue of mice change to blastomatous cells only if the tissue is taken from mice of a cancer strain, i.e., when it is impossible to exclude the milk factor.

In their chemical structure most cancerogenic substances—phenanthrene derivatives—somewhat resemble estrogenic hormones, the follicle-stimulating hormone in particular (common phenanthrene nucleus). Like folliculin they exert estrogenic action (cause estrus in animals). Under special conditions the follicle-stimulating hormone may also contribute to neoplastic growth, whereas administered in large doses (in chronic experiments) it even possesses cancerogenic properties.

A chemical community has also been established between cancerogenic hydrocarbons, on the one hand, and sterols, adrenocortical hormones, bile acids and vitamin D, on the other hand. The cancerogenic hydrocarbon methylcholanthrene has been synthesised from bile acids. Desoxycholic acid present in normal bile possesses, under experimental conditions, weak cancerogenic properties.

Experiments in which an extract from the liver and lungs of people who died of cancer, as well as from the liver and lungs of

intramuscularly, intraperitoneally or perorally produces cancer or sarcoma, depending on the tissue subjected to their influence. The larger the dose of the substance, the faster the manifestation of its cancerogenic effect. Some of these substances possess high cancerogenic activity. In rare cases even a single application of a 0.6 per cent solution of methylcholanthrene in benzene caused cancer in mice.

However, there is no final proof as yet that the cancerogenicity of these substances is strictly specific.

A malignant growth may be obtained by transplantation not only of tumours, but also of normal tissue cultivated in a medium containing cancerogenic substances.

According to some sources, the

corpses unaffected with cancer, was administered to mice showed that in a certain number of cases the mice developed malignant tumours, the tumours arising more frequently after administration of extracts from the organs of people affected with cancer (L. M. Shabad).

All these observations indicate a dependence of the pathogenesis of malignant tumours on the formation of cancerogenic substances within the organism in connection with metabolic disorders, especially disturbances in the metabolism of sterols (endogenous cancerogenic substances). However, the role of these substances in the genesis of tumours cannot as yet be considered definitely established.

Physical Cancerogenic Irritants. Long-continued action of mechanical irritants on the tissue may give rise to tumours. Thus, suturing of pebbles in the gallbladder of guinea pigs gives rise to cancer.

Cancer in rats and mice may be produced by small doses of *ionising radiation*, for example, X-rays. These rays, depending on their dose, cause the appearance of neoplasms, accelerate or inhibit their growth.

A special study has been made of the tumour incidence connected with the penetration of various radioactive substances into the organism, their accumulation in the tissues and their protracted action on the organism. The cancerogenic effect of radioactive substances depends on the character of the radiation, for example, the degree of hardness of gamma-rays, the chemical nature of the isotopes, their half-life and the rate of their elimination from the organism.

There are some observations indicating development of tumours as a result of protracted exposure to *ultraviolet rays* and, under certain conditions, even of massive and long continued *solar irradiation* of the skin of rats not covered with hair (N. N. Petrov). An assumption has been voiced that the sites exposed to radiation become enriched with ergosterol which is transformed into a cancerogenic substance. This assumption, however, has not as yet found its confirmation.

Biological Factors. A connection has been established between the appearance of tumour and chronic irritation caused by the action of certain biological agents on the organism.

For example, experimental cancer of the stomach was produced in rats by feeding them with cockroaches whose muscles contained helminths (*Spiroptera neoplastica*). However, these parasites were not found in the metastases of the tumour.

Sarcoma of the liver was produced in rats by helminths (*Taenia crassicolis*)—parasites in the intestines of the cat.

All these experiments attest that, in addition to other irritants, macroparasites may also cause the appearance of tumours. However, their role boils down merely to nonspecific physical or



Fig. 66a. Viral particles in cellular cytoplasm of Rous sarcoma.
(*N*—nucleus; *NM*—nuclear membrane; *CM*—cell membrane).
Electron microscopy $\times 45,000$ (Bernhardt).

chemical irritation of the tissue, which in the end leads to development of neoplastic growth.

In chickens it has been possible to produce tumours by injection of a noncellular filtrate of Rous sarcoma, i.e., by means of some agent separable from the cells of the tumour. According to some sources, this agent has characteristics typical of *filtrable viruses* (Fig. 66a), for example, it is capable of increasing quantitatively with the growth of the tumour, passing into the filial cells and even spreading in the animal's organism, i.e., it seems to possess a capacity for reproduction. A chemical analysis has shown the virus to be a ribonucleoprotein with a lipoid and carbohydrate components.

The neoplastic viruses also include the aforementioned milk factor (Bittner). The viral nature of the milk factor is indicated by its ability to multiply in tissue cultures, its physical and chemical properties, its reaction to various extraneous agents (for example, thermal influence, desiccation), its ultrastructure and cycle of development in the affected cell, which are similar to those that are characteristic of the already well-known viruses. However, it cannot as yet be considered definitely established whether this factor is really a virus, or a peculiar waste product of tumour cells closely related to viruses and possessing autocatalytic action, i.e., an ability

to cause in the new organism formation of substances similar to itself.

A tumour—papilloma—was recently discovered in some wild strains of rabbits; this tumour is transplantable to domestic rabbits also by means of its noncellular filtrate (Shope's papilloma). But here, too, there is room for doubt, since it is not quite clear whether it is a true tumour or a reactive tissue growth. In rabbits such growths can actually change to cancer. But in such cases the non-cellular extract of the malignant tumour thus formed does not produce neoplastic growth.

It must be generally noted that the number of viruses definitely known to produce tumours is as yet negligible. In addition to the foregoing, leukemia of mice, the tumour of the parotid gland in mice caused by the virus of polyoma, etc., are considered to be viral tumours. The results of the studies of the polyoma virus properties have shaken the existing concept of specificity of tumour viruses since it has developed that the polyoma virus is capable of producing tumours not only in mice, but also in certain other animals (hamsters, rats) and in different organs at that.

Chronic Regeneration and Chronic Inflammatory Proliferation. Caused by the action of various irritants on the tissue, *chronic regeneration may give rise to neoplastic growth*. This regeneration preceding neoplastic growth is regarded by many investigators as a favourable condition for the appearance of tumours.

Chronic poisoning of mice and rats with tar may increase the susceptibility of these animals to tumours developing at some point of additional irritation, for example, with subthreshold doses of cancerogenic substances combined with an inflammatory agent.

The susceptibility of cells to neoplastic transformation is also manifested in experiments with monocytes and macrophages present in the spleen of the chick embryo and growing outside the organism; these cells, more often than other cells, become sarcomatous under the influence of chemically pure cancerogenic substances combined with noncellular filtrates of some tumours.

Apparently, not only the *external factors of irritation*, but also the reactive properties of tissues, the proliferative young tissue elements in particular, play some part in the appearance of experimental tumours.

Immunity to Tumours. Experimental attempts are being made to prove the existence of immunity to tumours on the basis of naturally acquired resistance to them after spontaneous resorption of spontaneous tumours. Artificially acquired resistance is observed after resorption of a transplant. Immunity to tumours is explained variously. Some investigators attach (without sufficient reason) the decisive importance in the production of immunity to the local reaction of the tissue surrounding the transplanted particle of the tumour (so-called tissue resistance). Other researchers reject this assertion

and attach (with more reason) the greatest importance in immunity to tumours to the immunobiological properties of the organism, especially as regards certain nucleoproteins isolated from tumours.

However, strict specificity of such immunity cannot as yet be considered established. So far it has been impossible to discover specific antibodies in the blood in cases of tumour transplantation or to produce passive immunity to tumours by injections of the blood serum of animals that have survived the disease.

Etiology of Tumours

Different theories concerning the etiology of neoplastic growth have been proposed at different times as the knowledge of this question extended.

Theory of Irritation. According to this theory, tumours are caused by long-continued action of various irritants on a tissue. This theory came into existence on the basis of the observations according to which tumours may arise as a result of different traumas, injuries to tissues, chronic inflammations and other irritations of the tissues.

The proponents of this theory cited cases of cancer appearing at the sites of old scars, ulcers and erosions, cancer developing in the gallbladder in the presence of calculi therein, cancer of the lower lip in habitual smokers, long known cancer of the skin in chimney-sweepers, occupational cancer in workers of aniline and paraffin factories due to failure to observe industrial safety rules, cancer of the skin in radiologists, etc.

In certain tumours a chronic infectious process caused by the action of biological agents, bacteria and animal parasites apparently plays the role of the irritant.

The irritation theory, as it had been suggested in its time by Virchow, although subsequently receiving some confirmation, cannot be considered entirely satisfactory since it made no attempt to uncover the mechanisms of neoplastic transformation of cells and the importance of the properties of the organism therein. It merely established the fact that there is a connection between a long-acting irritant and the development of a tumour. Moreover, in many cases it is still impossible clearly to determine whether or not the tumour was caused by long-continued action of the irritant on the tissue.

Chemical Theory. A positive role in explaining the origin of tumours was played by the discovery of new facts concerning the chemical agents capable of causing neoplastic growth, especially the cancerogenic substances with known chemical composition. The modern *chemical (cancerogenic)* theory of tumours has arisen on this basis. According to this theory, the transformation of normal cells into blastomatous cells is caused by cancerogenic substances which have either gained entrance into the organism from without or have possibly formed in the organism as a result of deep changes

in metabolism. The number of known cancerogenic substances capable of causing neoplastic growth by action from without has now considerably increased. According to experimental data, they include various groups of organic compounds.

Cancerogenic substances act slowly, at first producing no particularly noticeable changes in the tissues. Phenomena of neoplastic growth appear only after a long latent period and sometimes not at the site of administration of the aforementioned substances. For example, application of 1 : 2 : 5 : 6 dibenzanthracene to the skin may cause the appearance of a tumour in a lung or a mamma. This also attests the general action of the cancerogenic substance of its metabolites, as well as the significance of the biological peculiarities of the tissues in the pathogenesis of tumours. The action of cancerogenic substances is apparently associated with disturbances in protein synthesis in the organism, which causes changes in the structural elements of the cell. These changes are transmitted to the filial cells.

From the point of view of the chemical theory any influence on the organism capable of producing a tumour must first lead to formation of a cancerogenic substance in the organism. However, the available facts do not convincingly demonstrate the role of cancerogenic substances in the development of all malignant tumours and the chemical theory therefore fails to explain the pathogenesis of all tumours. It explains the origin of only a limited group of tumours (for example, of so-called occupational cancer).

Viral Theory. Tumours were believed by many to be due to invasion of the organism by living causative agents, i.e., special microbes or parasites. Cases of development of tumours in one family or group of people living together (so-called familial cancer) have long been referred to as proof. But these observations can be explained by a combination of similar influences exerted on the tissue and the organism's general properties formed as a result of living for a long time under the same conditions. On the other hand, cases of tumours arising as a result of invasion of the organism by causative agents, parasites in particular, have found their explanation in nonspecific irritation of the tissues by these agents, development of regeneration and, on this basis, of a tumour which subsequently grows in the absence of the parasites.

On the basis of their observations of viruses and virus-like agents which cause tumours in animals some investigators are inclined to accept the *viral etiology of tumours*.

This view is based on the following data: 1) discovery of special globular, virus-like structures in the filtrates of some tumours by means of an electron microscope; 2) development of tumours in animals administered corresponding viruses; 3) antigenic properties of the nucleoproteins of cancer cell; 4) possibility of cultivating neoplastic viruses (the milk factor) in a developing chick embryo

and malignant degeneration of fibroblasts grown outside the organism under the combined influence of a cancerogenic substance and noncellular filtrate of certain tumours or the milk factor, whereas chemical cancerogenic substances alone fail to produce malignant degeneration of the tissue.

From the point of view of the viral theory cancerogenic substances are regarded merely as a factor creating in the organism foci of cellular proliferation and tissue metaplasia. These foci are a necessary condition for the activation of the viruses which have gained entrance into the organism and for the manifestation of their pathogenicity.

It is nevertheless very difficult to accept the viral theory for all tumours. Very few attempts to discover and isolate the virus, as also to demonstrate noncellular transplantation of tumours in mammals, have succeeded. The advocates of the viral theory are therefore forced to assume that the virus may very intimately combine with some constituents of the neoplastic cell or at times lose its pathogenicity ("disguise itself").

Even in cases where the viral nature of tumours has been uncontestedly established the question of the essence of the virus and its differentiation from the constituents of the cells, for example, the protein molecule, is still unsettled. At the present stage of our knowledge there is therefore as yet no sufficient reason to recognise filtrable viruses as the general cause of tumours.

As regards man, there is as yet no contestable proof of the viral etiology of even a single form of tumour.

The main experimental and clinical data on the origin of tumours suggest that tumours may apparently be caused by various harmful influences. In the organism these influences give rise to changes which become irreversible and are transmitted to the successive cellular generations. Moreover, not only the properties of the irritant and its effect on the tissue are important. An important role is also played by the reactivity of the tissue and the state of the whole organism, as well as the disturbance in the complex regulatory processes, which leads to permanent disorders of the growth and differentiation of cells.

Pathogenesis of Tumours

The theory of the pathogenesis of tumours aims at disclosing the essence of neoplastic growth or the mechanisms of the influences exerted by the factors which are capable of transforming normal tissue into neoplastic tissue.

As is well known, neoplastic tissue, especially in malignant growth, is barely differentiated and somewhat resembles young embryonal or regenerating tissue.

This gave rise to the *theory of embryonic rests* (Cohnheim), according to which tumours originate from embryonic cells remaining in the organism since the early stages of ontogenesis; in cases where the resistance of the surrounding tissues (especially, connective tissue) weakens these cells begin to display an increased growth potential. Branchiogenic cancer, hypernephroma, pigment-spotted melanoma and certain other tumours arise on an embryonal basis. It has turned out, however, that in the overwhelming majority of cases the origin of tumours has no relation to faulty embryonal development. Transplantation of embryonal tissue causes no neoplastic growth. The latter appears only in cases of transplantation of embryonal tissue combined with the action of cancerogenic substances. It has now been established that a *neoplastic growth may be set off not only by embryonal tissue, but also by any tissue capable of regeneration.*

According to other views, neoplastic growth arises as a result of proliferation or regeneration of tissue, for example, in erosions of the cervix uteri, calloused ulcers of the stomach, polypoid growth in the intestines or urinary bladder, and in hypertrophy of the prostate. *Chronic proliferative or regenerative processes* are, not without reason, regarded as possible foci for appearance of neoplastic growth (precancerous state). Their timely discovery is therefore of great practical importance since it is not infrequently possible, by means of prophylactic and therapeutic measures, to prevent neoplastic growth.

However, to uncover the pathogenesis of tumours, it is necessary to establish the cause not only of the abnormal growth, but mainly the essence of the transformation of growing tissue into neoplastic tissue. Biochemical studies of neoplastic tissue definitely indicate that *metabolic disorders* are of some importance in this transformation. Under the action of irritants normal cells become less differentiated and acquire new biological properties. The intracellular metabolism, mainly of carbohydrates and proteins, is affected, the structure and function of nucleic acids are disturbed and other physicochemical disturbances are subsequently observed (altered permeability of membranes, surface tension, etc.). Through a series of cellular generations the changes in metabolism in the end lead to transformation of normal cells into a neoplastic focus. Under corresponding conditions in the organism and the surrounding tissues the transformed cells give rise to neoplastic growth.

The new biological properties of the neoplastic cells are quite stable and are transmitted to the filial cells. But this stability of the inherited properties is relative. Under certain conditions, under the influence of altered factors of the environment, the neoplastic cells may again acquire the capacity for differentiation, as is sometimes observed in metastases of tumours, in rare cases of resorption of tumours, or in tissue cultures.

For example, among artificially grown pieces of spindle-cell sarcoma A. D. Timofeyevsky observed formation of striated muscle fibres characteristic of the structure of normal cells.

However, the question of the pathogenic essence of neoplastic growth is still unsettled. Further comprehensive physiological and biochemical research is required. But even now the *transformation of normal tissue into neoplastic tissue may already be considered dependent*, not only on the etiologic factor, but also on a certain disturbance in the reactive property of the tissue subjected to the harmful influence. Long-continued action of irritants produces a *peculiar and stable change in intracellular metabolism*. At the same time the appearance of tumours is determined not only by changes in the cells subjected to the influence of the irritant. The new biological properties of the cells, their formation and development are also subject to the influence of the functional state of the whole organism and the disturbances in the complex regulatory functions therein.

Chapter Ten

PATHOLOGY OF THERMOREGULATION

Animals are divided into two large groups--poikilothermal and homoiothermal--according to their ability to regulate their body temperature.

The body temperature of poikilothermal, i.e., cold-blooded, animals (invertebrates, fishes, amphibians and reptiles) is not constant. In a state of rest it depends on the surrounding temperature and changes in accordance with it, since poikilothermal animals have no capacity for the thermoregulation.

Unlike poikilothermal animals, homoiothermal, i.e., warm-blooded, animals (birds and mammals) are characterised by a constancy of their body temperature, which is more or less independent of the surrounding temperature. This constancy of the temperature of the internal environment was not established all at once. There are transitions from poikilothermal to homoiothermal animals. In homoiothermal animals thermoregulation has formed in the process of evolution with the development of the nervous system which plays the leading role in the complex adaptive reaction of these organisms to the changes in the surrounding temperature.

The mechanisms by which the heat balance and the temperature of the organism's internal environment are maintained are *physical and chemical thermoregulation*.

Disorders of the heat balance are manifested as overcooling--*hypothermia*, overheating--*hyperthermia* and *fever*. All these disorders are a result of disturbances in thermoregulation and are characterised by changes in body temperature.

DISTURBANCES IN PHYSICAL AND CHEMICAL THERMOREGULATION

The ability of warm-blooded animals to maintain within relatively narrow limits the constancy of their body temperature independent of the temperature of the external environment is due to the interaction of physical and chemical thermoregulation.

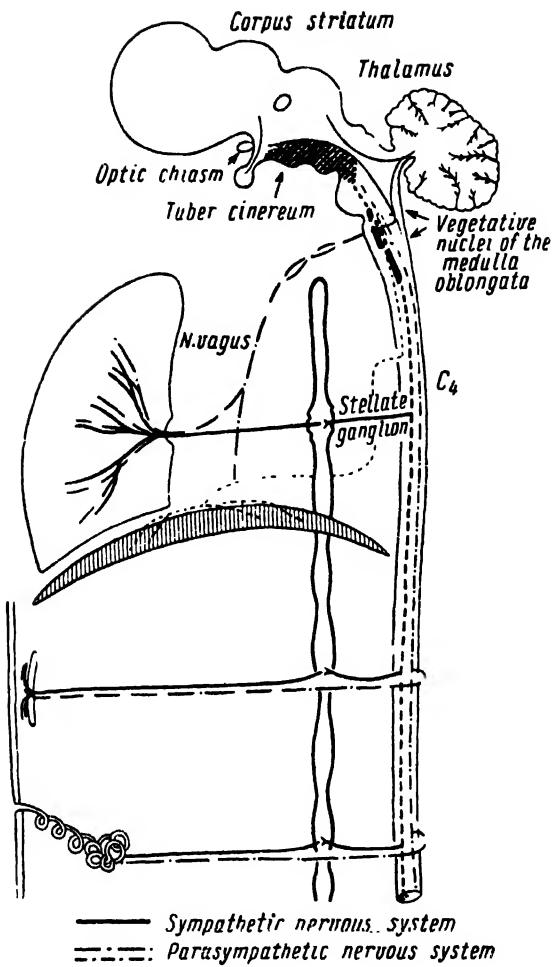


Fig. 67. Physical regulation of heat.

Physical thermoregulation is the ability, within certain limits, to regulate heat loss. Heat is lost through: a) radiation and convection; b) evaporation from the body surface and the lungs; c) heating the food and inhaled air (Fig. 67).

Of the total daily heat loss (an average of 2,400 Cal) about 70 per cent is lost through radiation and convection, some 25 per cent is lost through evaporation from the body surface and the lungs, and close to 3 per cent—through heating the food and inhaled air.

The foregoing figures do not account for the very slight, practically negligible amount of heat lost through heating the urine and

feces (30 Cal). In man the heat lost through convection, radiation and evaporation varies very widely with the clothing, properties of the skin and thickness of the subcutaneous adipose layer.

Dilatation of the peripheral vascular bed increases the amount of heat lost by the skin. Contrariwise, *constriction of the vessels* is accompanied by diminished heat loss. The vascular mechanism of heat loss is usually operated by the *reflex activity* of the nervous system. From cold the walls of the vessels contract, the skin pales and less heat is lost. From heat the vessels, on the contrary, dilate, the skin flushes and more heat is lost—the organism rids itself of the superfluous heat produced in it.

The principal part in the reaction of the peripheral blood vessels is played by the central nervous system. Its affection in the form of paralyses of the vasoconstrictors is accompanied by dilatation of the vessels, heat loss and lowering of body temperature (sometimes to 30°C); stimulation of the vasoconstrictors is attended with constriction of the vessels and retention of heat. Emotional experiences have the same effect on the vessels of the skin of the face, which either flushes or turns pale.

Physical regulation of heat is also effected by *perspiration* and evaporation of water from the body surface. This mechanism of heat loss is particularly well developed in man.

Perspiration is regulated by nerve centres located in the diencephalon and spinal cord: these centres are excited or inhibited reflexly by the action of heat or cold on the body surface or directly by heated or cooled blood. The activity of these centres is regulated by the cerebral cortex. For example, emotional experiences noticeably affect perspiration. Impulses from the central nervous system travel through internuncial neurons and along sympathetic nerves which innervate the sweat glands. For example, stimulation of the peripheral end of the transected sciatic nerve which has sympathetic fibres, causes the appearance of droplets of sweat on the pads of the cat's paws.

Lastly, physical regulation of heat is effected by *respiration*. The rate and depth of respiration determine the amount of liberated heat. This mechanism of heat loss is also regulated by the nervous system. A brief deceleration of respiration and decrease in heat loss by the lungs can be produced in the dog by a unilateral transection of the vagus nerve in the neck.

The physical regulation of heat by means of respiration also involves the function of the cerebral cortex. For example, humidity, light and sound signals, and surrounding objects may, when repeatedly combined with thermal influences, become conditioned signals of physical heat regulation by means of respiration. The main mechanisms of physical heat regulation interact. This is evident from the fact that in pathology they are capable of substituting for each other.

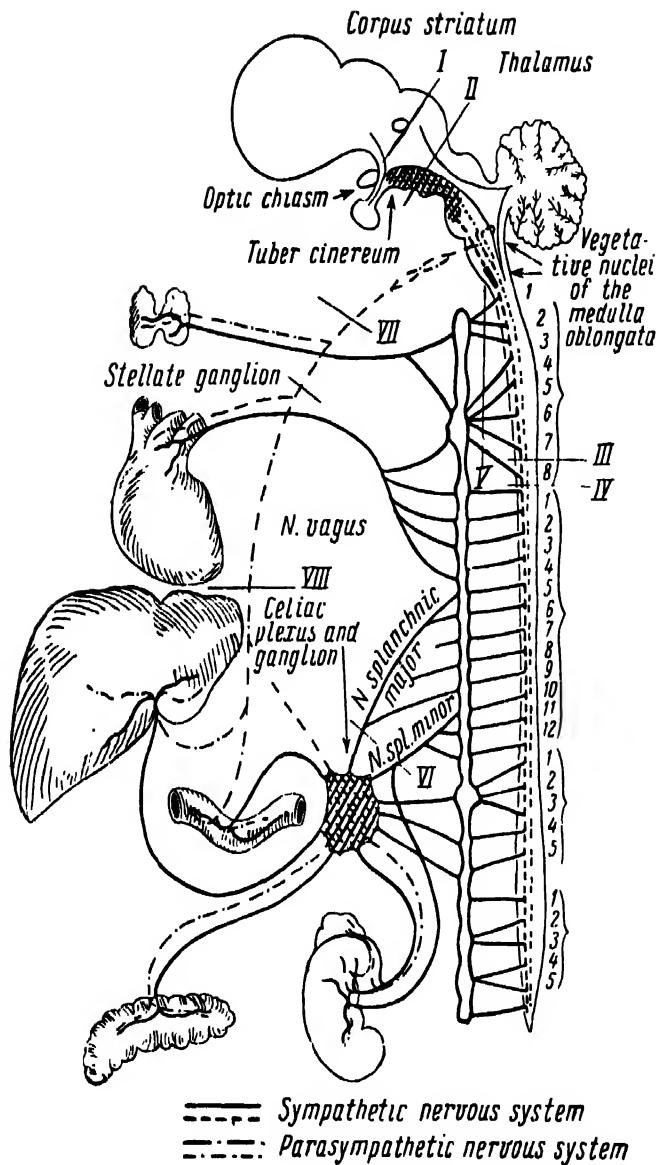


Fig. 68. Chemical regulation of heat.

Section **I**—heat regulation preserved; section **II**—heat regulation lost; section **III**—heat regulation lost; section **IV**—heat regulation limited (physical heat regulation is, for the most part, lost, chemical heat regulation is preserved, and the animal may be feverish); section **V**—heat regulation preserved; section **VI**—heat regulation preserved; section **VII**—heat regulation is preserved, but the animal is more easily overheated; section **VIII**—heat regulation preserved; sections **VI** and **VIII**—heat regulation preserved; sections **IV** and **VIII**—heat regulation lost.

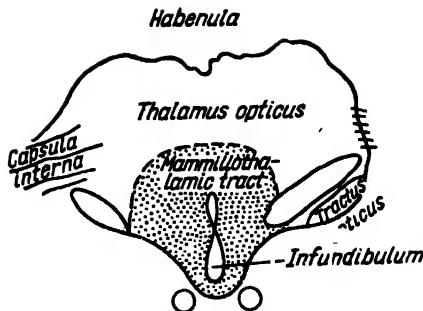


Fig. 69. Schematic section through diencephalon of the rabbit on the level of the tuber cinereum. Heat regulation zone is shaded.

Thus, the apparatus that regulates heat loss is the central nervous system: disturbances in its function lead to disorders of the heat balance.

Chemical thermoregulation plays an important role in the heat balance (Fig. 68). Chemical thermoregulation implies regulation of metabolism as a result of which heat is produced. In response to a drop in the surrounding temperature the processes of heat production in the organism intensify and, contrariwise, in response to a rise in the surrounding temperature these processes weaken.

Disorders of heat production are a result of disturbances in the function of nervous regulation. This regulation is effected by the following structures: 1) receptors and afferent paths, 2) centres of thermoregulation in the brain, 3) conductors of chemical regulation of heat in the spinal cord, and 4) conductors of chemical regulation of heat on the periphery.

Through the extero- and interoceptors stimuli, especially temperature factors, reflexly affect the central apparatus of chemical thermoregulation by means of which a relatively constant temperature is maintained in the organism's internal environment.

It has been found by experimental studies that the heat-regulating centre is located in the diencephalon—in the posterior third of the tuber cinereum (Fig. 69).

It is possible to elevate the body temperature by stimulating this zone with chemical and physical agents, for example, by injecting protein, applying electric current, cooling or making a puncture.

The rise in temperature produced by a puncture (Fig. 70) develops quite rapidly (for example, in the guinea pig sometimes within 20–30 minutes) and within a few hours disappears without leaving a trace. It is most probably the result of stimulation of the cells of the heat-regulating centre. The character of function of the heat-regulating centre is not quite clear as yet; nor is it as yet definite whether it is sympathetic, parasympathetic or mixed. Judging by

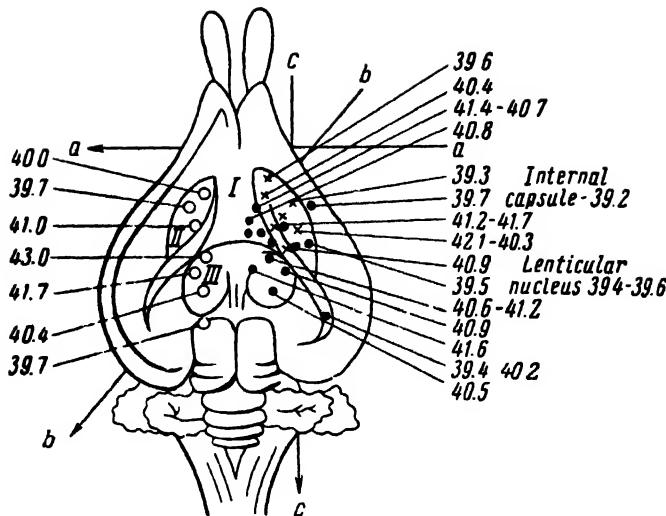


Fig. 70. Methods of puncturing the heat regulation zone.

the paths running to the periphery and by the substances capable of influencing it this centre is most probably sympathetic. It is connected with the periphery by sympathetic nerves. After removal of the sympathetic ganglions in the neck and abdominal sympathetic trunks, and after transection of the splanchnic nerves and denervation of the adrenals the thermal puncture proves ineffective.

Some investigators assume the existence of two centres in the region of the tuber cinereum, namely, heat-regulating—sympathetic, and cold-regulating—parasympathetic. From this point of view any increase in heat production is a result of excitation of one centre and depression of the other, and vice versa. This concept is based mainly on the rise in temperature from the effect of sympathetic poisons and its drop from the effect of parasympathetic poisons. However, the assumption of the existence of two centres cannot be considered substantiated experimentally.

Destruction of the heat-regulating centre deprives the organism of its ability to respond to a fall of the surrounding temperature by increased metabolism and to a rise in the temperature of the environment by decreased metabolism, i.e., the organism loses its capacity for chemical heat regulation. In such cases warm-blooded animals cannot have fever.

From the central region of chemical heat regulation *conductor nerves run to the spinal cord and switching over to new neurons* leave the cord approximately on the level of the last cervical and first thoracic segment. A dog with the spinal cord transected in its thoracic part is not completely deprived of chemical heat regulation,

whereas transection of the cord in its cervical part causes a progressive drop in temperature and leads to the animal's death. Deprived of chemical heat regulation by a high transection of the spinal cord a warm-blooded animal can survive only in a warm room where the temperature is at least 26-30°C, i.e., close to the usual temperature of the animal's body. As regards thermoregulation such an animal resembles cold-blooded animals, its body temperature noticeably varying with the fluctuations of the temperature of the external environment.

The division of thermoregulation into physical and chemical does not exclude the unity of the whole system of heat regulation, which manifests itself normally, as well as in pathology, in a constant coordination of heat production and heat loss.

The paths connecting the chemical heat regulation with the physical (vasomotor, sudoriferous, respiratory) have not as yet been found, but it is clear that they exist because any disturbance in the heat balance always affects the interrelation between heat production and heat loss.

The physical and chemical forms of thermoregulation are also united by the function of the higher parts of the brain. Experiments have shown that agents of the external environment (for example, a certain situation and time) may be conditioned stimuli of concerted action of the mechanisms of thermoregulation after their repeated combination with a thermal stimulus.

For example, the dog develops a conditioned reflex to increased metabolism as a result of being daily placed in a cold room at a definite time and under definite circumstances. If the dog is then placed at the same time and under the same circumstances in a warm room, the reaction of metabolism corresponds, not to the temperature of the warm room, but to that of the cold room.

In the process of phylo- and ontogenesis the role of chemical heat regulation diminishes, while that of physical thermoregulation becomes increasingly more important. Compared with other warm-blooded animals, physical heat regulation in man is particularly strongly developed; this must be taken into account in the pathogenesis of heat metabolism disorders.

The *peripheral organs* participating in the processes of chemical heat regulation comprise all the tissues of our organism, in which general and energy metabolism takes place. However, the main organs of heat exchange are the *muscles* and *liver* in which the greatest amount of heat is liberated. They play a greater part than the other organs in the disturbances in heat metabolism.

Experimental observations have shown that in fever the processes of protein disintegration in the liver are stepped up, metabolism is intensified and the temperature of the liver is higher than that of the blood and the other organs. When the liver is deprived of its basic innervation a certain disturbance in the heat balance occurs

as a result of interruption of the nerve tracts which connect this organ with the central zone of chemical heat regulation.

The muscles are another region of considerable heat production. The effect of cold on the organism reflexly evokes a tremor (fine clonic spasm) which results in production of a considerable amount of heat. When man and animals are cold they perform more vigorous movements, owing to which heat production increases and the body more easily maintains a constant temperature.

But the muscles take part in the chemical regulation of heat even in the absence of visible muscular contractions.

It should be noted that not only the liver and muscles, but, to a lesser extent, also all other organs and tissues participate in the processes of heat metabolism.

The endocrine glands take part in thermoregulation together with the nervous system.

Fluctuations of the surrounding temperature alter the function of the thyroid. For example, in hedgehogs, badgers, gophers and bats the thyroid shows signs of atrophy during hibernation, but these signs disappear by the time these animals have to wake up. Injection of a thyroid extract hastens their awakening. Hyperfunction of the thyroid in fever is demonstrated by the increased excretion of iodine—constituent of the thyroid hormone—in the urine. This can be observed in infectious processes involving pyrexia. Lastly, fever in persons with hyperfunction of the thyroid is associated with higher temperature than it is in cases of hypofunction of the thyroid.

Of the other endocrine glands a considerable part in chemical heat regulation is played by the *adrenals* and the *hypophysis*. For example, administration of adrenalin causes a rise in temperature. A disturbance in the heat balance and a drop in temperature are observed after removal of the hypophysis. The adrenocorticotropic hormone of the hypophysis is intensely excreted during cooling, thereby raising the resistance of rats to cold.

If we designate heat production with an A and heat loss with a B and assume that for the given species of warm-blooded animal $A : B = 1$, in cases where $A > B$ the coefficient will be more than 1 and the body temperature will have risen. The temperature will also begin to rise when B is below normal and A remains within normal limits. Lastly, both A and B may be above normal, but due to the relatively higher elevation of A the coefficient will still be more than 1. Although these ratios are schematic, they nevertheless reflect different disorders of the heat balance.

Overcooling (Hypothermia)

Overcooling is a disturbance in the heat balance accompanied by a drop in body temperature below normal. It may be the result of: 1) increased heat loss due to the effect of cold on the body; 2) con-

siderably decreased heat production; 3) combination of both the above factors.

Overcooling occurs even in an environment which is but 10-15° below body temperature. For example, staying for several hours in water at a temperature of 22°C on a hot summer day is enough somewhat to overcool the body.

At the same temperature of the external environment overcooling occurs the sooner, the more humid the air and the faster its movement. Humid air is a better heat conductor and, consequently, cools the body more. The movement of air intensifies the cooling because of the contact of continuously new layers of cooling air with the body.

Overcooling depends not only on the drop in external temperature and the humidity of the air, but also on the state of the organism, the development of its physiologic defence mechanisms and its thermoregulation.

Age plays an important part in the organism's resistance to cooling. Old people yield to cooling more readily. Infants in the first months of life are particularly easily overcooled since their thermoregulation is still very imperfectly developed.

Emaciated, malnourished, poorly clothed and inactive people, all other things being equal, are less tolerant of overcooling and suffer from cold more than do those who have a well developed adipose layer, are warmly dressed, are well developed physically, are active and eat properly. A rush of blood to the body surface is conducive to cooling because it increases heat loss. For example, alcohol and certain narcotics cause increased heat loss since they dilate the superficial blood vessels.

In the very beginning of cooling the compensatory mechanisms of thermoregulation begin to function more actively: the peripheral vessels become noticeably constricted and less heat is lost, heat production is increased, especially in connection with the development of muscular tremor and more vigorous voluntary movements, the heart rate becomes faster and the blood pressure somewhat rises. The rectal temperature is still within normal limits. These phenomena are based on reflex processes which stimulate mainly the sympathetic division of the vegetative nervous system and activate the endocrine glands (hypophysis and adrenals).

Owing to increased heat loss and greater oxygen requirement the further effect of cold produces *phenomena of oxygen deficiency* involving inhibition of central nervous activity, dilatation of the peripheral vessels and a still greater heat loss. A drop in rectal temperature to 35°C is no longer accompanied by increased metabolism. Chills usually cease at 30-33°C. The body temperature and blood pressure drop, the cardiac and respiratory rhythm slows down. Extreme fatigue and sleepiness appear, atrial fibrillation develops, and the increasing cardiac failure leads to respiratory paralysis and

death. Man dies when the body temperature drops to 25-24°C. Autopsy reveals dystrophic phenomena in the parenchymal organs.

In cases of gradual prolonged cooling the body temperature may for many hours be maintained at a low level, but it drops slowly and to a lesser extent than it does in acute hypothermia.

In man, besides cases of freezing, hypothermia is observed in traumas involving shock, during crises in infectious diseases and after considerable hemorrhages.

Hypothermia is now produced artificially (artificial hibernation) for therapeutic purposes, for example, in surgical practice, especially in operations on the heart and major vessels. In these cases the body temperature is maintained on a low level by means of appropriate drugs and cooling. Cooling combined with agents which inhibit the function of the heat-regulating centre is employed to inhibit the central nervous system, reduce metabolism and cut down the requirements of the tissues in oxygen. All these phenomena lower the organism's sensitivity to the action of pathogenic stimuli and are conducive to a slowing of the blood circulation, which makes it possible for a certain period to disconnect the heart from the blood circulation and to perform the necessary operations on it.

Overheating (Hyperthermia)

Overheating, or hyperthermia, is a result of retention of heat in the organism due to disturbed thermoregulation and impeded heat elimination into the external environment. It occurs in an environment with a temperature not below that of the body. It will not occur if the temperature of the environment is 5-10° below that of the body. Overheating is favoured by humidity of the air which limits heat loss, diminished movement of the air, moisture-proof clothing, factors conducive to decreased perspiration, and such conditions of the organism as impaired thermoregulation, well-developed subcutaneous tissue, fatigue, emaciation, effects of past diseases, overwork, etc.

In man overheating is characterised by hemoconcentration due to loss of water, acceleration of the heart's action caused by the effect of heat on the centres of the accelerator nerves, faster respiration produced by stimulation of the respiratory centre by the overheated blood, and increased metabolism as a result of intensified oxidative processes.

Overheating is observed in industry—in hot shops, at blast-furnaces, in boiler rooms and other places with a high temperature. In such cases ventilation, light clothing, an appropriate work regimen and diet, etc., help to prevent overheating.

The first period of overheating is characterised by development of adaptive reactions on the part of physical thermoregulation. Since

not enough heat is lost through the skin other channels come into play—dilated peripheral vessels, accelerated blood flow, increased perspiration and faster respiration. Continued overheating renders the regulation inadequate and the second period sets in. This period is marked by elevation of the body temperature and *excitement*—restlessness, accelerated and shallow respiration, accelerated pulse (130-140 beats per minute), excessive metabolism, particularly, increased excretion of nitrogen in the urine, intensified reflex activity, and sometimes convulsive twitchings. During the third period the excitement is replaced by diminished vegetative functions (shallow respiration and low blood pressure), disappearance of reflexes and a comatose, i.e., unconscious state resembling sleep, which may be accompanied by clonic spasm. Death occurs in respiratory arrest during exhalation and cessation of the heart's action in the systole. Prolonged and repeated overheating gives rise to protein and fatty degeneration.

Heat Stroke. This is a special state of acute hyperthermia; it may arise as a result of extreme overheating, for example, on a hot day with humid air and absence of wind, during strenuous work in a hot room, or summer long marches in warm clothing. In all these cases the increase in heat production is not accompanied by a corresponding increase in heat loss.

A heat stroke is characterised by extreme disturbances in the functions of the central nervous system—sensation of high fever, accelerated pulse, intense dyspnea, sometimes vomiting, convulsions and loss of consciousness. The temperature of the body sometimes rises to 42-43°C. Death may ensue within a few hours. After a heat stroke aberrant nervous phenomena (for example, disorders of higher nervous activity) continue for a long time.

Sunstroke. A sunstroke occurs as a result of exposure of the head directly to the broiling sun. It is characterised primarily by phenomena of extreme stimulation of the central nervous system manifested in general excitement, often mental and nervous disturbances, and sometimes convulsions. Milder cases are marked only by intense headaches, irritability, restlessness and cardiac weakness. Autopsy of sunstroke victims reveals hyperemia and petechial hemorrhages in the meninges and cerebral tissue.

FEVER (FEBRIS)

Concept of Fever

Fever is a general reaction of warm-blooded animals and man to the action of a harmful and most frequently infectious agent; this reaction has developed in the process of evolution and is a disturbance in heat regulation with elevation of body temperature regardless of the temperature of the external environment.

Unlike hyperthermia which occurs only under the influence of elevated temperature of the external environment, fever may appear under usual temperature conditions. The normal interrelation between heat production and heat loss is altered as a result of a disturbance in central thermoregulation, which in the end leads to accumulation of heat and elevation of the body temperature. A febrile process already developed in the organism is always characterised by disturbances in the entire system of heat regulation.

In fever the interrelation between physical and chemical heat regulation is altered; severe fever is characterised by diminished resistance of the organism to changes in the environmental temperature and narrower limits of heat regulation—the feverish organism is more readily overcooled and overheated.

All species of warm-blooded animals have both physical and chemical thermoregulation. In fever the disturbance in thermoregulation may be manifested variously. The disturbance in physical heat regulation plays a less important part in the development of fever in animals with their hair-covered bodies and poorly-developed sweat glands than it does in man. The higher the organisation of the particular species of warm-blooded animal, the more affected the physical heat regulation in fever. Studies by Traube, Avrorov and Likhachov established in various forms of fever the absence of a direct and permanent interdependence between the extent of the rise in temperature and intensity of heat production (for example, in malaria and pneumonia). But any elevation of body temperature is characterised by a temporary predominance of heat production over heat loss.

The state of the nervous system determines the extent of disturbance in the heat balance. For example, fever in persons with an excitable nervous system is characterised by a greater increase in metabolism than in persons with a balanced nervous system. Age is also of some importance in the manifestations of the febrile process. In infants the ability of the organism to regulate the heat balance is relatively weak. Compared with adults children running a fever are more readily overcooled and overheated, and their chemical heat regulation is more disturbed. This peculiarity is apparently due to the inadequate development (compared with adults) of the nervous mechanisms which regulate the heat balance. In very old age fever may occur almost without elevation of body temperature.

Etiology of Fever

There are *infectious* and *noninfectious* fevers.

Infectious fevers are the most common; they occur as a result of the action of bacteria, their toxins and waste products, as well as of pyrogenic substances obtained from microbial bodies or present in

products of bacterial origin and tissue disintegration, for example, in pus, extracts from foci of inflammation, putrescent tissues (nucleoproteins, lipopolysaccharides, etc.).

Noninfectious fevers include protein fever, salt fever, drug fever and neurogenic fever.

Protein fever is produced by parenteral administration of a foreign protein or various high molecular endogenous disintegration products formed in *hemorrhages, tissue necrosis, bone fractures and hemolysis*; it also results from the action of toxic products of albuminous nature absorbed through the altered intestinal mucosa, or from hypofunction of the excretory organs which normally eliminate these products.

Salt fever is produced by injection of hypertonic sodium chloride solutions; it is apparently the result of osmotic disturbances, destructive changes and consequent passage of pyrogenic substances into the blood.

Drug fever results from injections of adrenalin, thyroxin, cocaine, B-tetrahydronaphthylamine, dinitrophenol, nicotine and caffeine. These substances have different mechanisms of action. Some of them are sympatheticotropic and excite the heat-regulating centre; others, for example, dinitrophenol, directly influence tissue metabolism and cause excessive heat production.

Neurogenic fevers are due to injuries and contusions of the brain, heat puncture, psychic trauma, tumours of the diencephalon, hemorrhages into the third ventricle and reflex stimulation of the heat-regulating centre (for example, in renal or hepatic colic).

The foregoing classification of the etiologic factors of fever is, obviously, somewhat artificial because under natural conditions the aforesaid factors are often combined. For example, any infectious fever is in its pathogenesis also a protein fever. In classifying neurogenic fever as an entity (by its etiology) it is also necessary to emphasise the importance of dysfunction of the nervous system in the mechanism of any fever.

The development of fever is ascribed by some authors to special pyrogenic substances present in microbes (exogenous pyrogenic substances) or formed in the organism under the influence of various etiologic, mainly infectious agents (endogenous pyrogenic substances). Endogenous pyrogenic substances, as recent studies have shown, are secreted by leucocytes, mainly granulocytes. Fever may be produced by extracts from polymorphonuclear leukocytes, whereas extracts from macrophages do not produce such an effect. Nor are pyrogenic properties present in extracts from various tissues, except bone marrow which performs the function of leukopoiesis. And yet the possibility that endogenous pyrogenic substances are also formed by the action of etiologic factors of fever on other cells of the organism cannot be excluded.

Pathogenesis of Fever

The decisive factor in the pathogenesis of fever is a *disturbance in the function of the central nervous system* which regulates the heat balance, i.e., the interrelation between heat production and heat loss.

There are reasons to believe that the mechanism of development of fever is conditioned by the action of pyrogenic substances on the *central nervous system*. Experimental observations show that fever results from direct stimulation of the hypothalamus, i.e., the posterior third of the tuber cinereum—the location of the heat-regulating centre.

The temperature may also be raised by stimulating various points of the brain connected through conduction paths with the heat-regulating centre in the hypothalamus. An animal with the hypothalamus destroyed or severed from the peripheral organs by means of a high transection of the spinal cord usually loses the ability to run a fever. Lastly, fever is produced by administration into the hypothalamic region of even such minimal doses of pyrogenic substances which, injected subcutaneously or intravenously, never provoke fever.

Recent experiments involving extirpation of the sympathetic trunk and spinal cord with simultaneous transection of the vagi in the neck have revealed that the animal does not completely lose its ability to run a fever through severance of the heat-regulating centre from the periphery and in some measure continues to maintain a constant temperature. Some investigators hold that in these cases the heat metabolism is regulated by compensatory processes through the peripheral ganglionic apparatus of the vegetative nervous system, which is older phylogenetically, and endocrine glands which have retained connections with this apparatus.

Already Claude Bernard and S. P. Botkin showed that pyrogenic substances also act *reflexly*. A certain dependence of the severity of fever on the site of administration of the irritant, i.e., the sensitivity of the peripheral receptor apparatus, has been demonstrated experimentally. When pyrogenic substances are administered into a tissue deprived of afferent nerves fever develops somewhat more slowly. Fever produced by administration of pyrogenic substances into various organs or the blood reveals changes in the action currents of afferent nerves (P. N. Vesyolkin).

The significance of the reflex process in the mechanism of fever comes particularly to the fore in catheterisation or in renal and hepatic colic. But in the pathogenesis of fever the reflex mechanism does not detract from the basic importance of the humoral influence exerted by pyrogenic substances directly on the central nervous system.

An important part in the pathogenesis of fever is also played by

the cerebral cortex. It is well known that fever may be produced by suggestion. It is also possible to affect the temperature of a feverish animal reflexly, for example, to elevate the body temperature by repeatedly combining pyrogenic substances with an indifferent stimulus. Fever may be weakened by administration of bromides since the latter cause inhibition in the cerebral cortex and the inhibition irradiates into the subcortex.

The *endocrine glands* also participate in the pathogenesis of fever.

In fever the functions of the thyroid and, especially of the hypophysis, which is connected with the activity of the adrenal cortex, are found to be increased. The blood and urine contain more corticosteroids. In animals deprived of the hypophysis or the thyroid the ability to run a fever is noticeably diminished. The influence of the nervous system on the heat balance in fever is closely connected with the activity of the endocrine glands. But the changes in the functions of the endocrine glands play a minor part in the mechanism of the febrile reaction.

Types of temperature curves

A number of infectious processes have typical *temperature curves* characterising the manifestations of fever.

The following forms of fever are distinguished, according to the elevation of the temperature: a) subfebrile (not above 38°C), b) moderate (up to 39°C), c) high (39-41°C), and d) excessively high—hyperpyretic (41°C and higher). The body temperature very rarely rises above 41°C.

The following main forms of fever are distinguished, according to the character of the temperature curves:

1. *Continuous fever* (*febris continua*, Fig. 71) in which the elevated temperature for some time persists on a high level, the difference between the morning and evening temperature not exceeding 1°C. The fever may end abruptly (crisis) or gradually (lysis). This form includes typhoid fever early in the course of the disease, the fever in croupous pneumonia, typhus and certain other infectious diseases.

2. *Recurrent fever* (*febris remittens*, Fig. 72) in which the difference between the morning and evening temperature exceeds 1°C. It includes the temperature curves observed during the late course of typhoid fever, sepsis and catarrhal pneumonia.

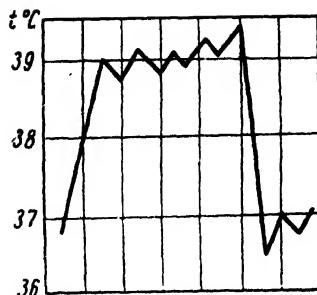


Fig. 71. Continuous fever (croupous pneumonia).

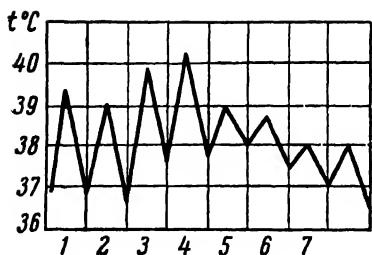


Fig. 72. Remittent fever (sepsis).

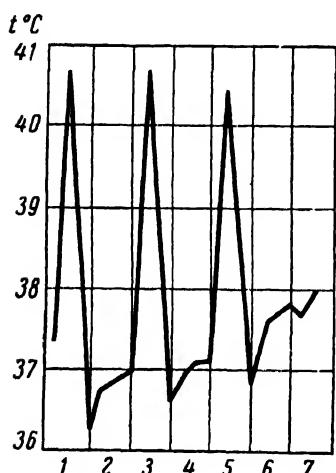


Fig. 73. Intermittent fever (tertian malaria).

(ephemeral) with an indefinite or irregular course (considerable diurnal variations in body temperature) and fevers with a perverted course, for example, an elevation of temperature in the morning and a drop in the evening (in some forms of sepsis and tuberculosis). The aforementioned types of temperature curves do not exhaust their variety.

The type of temperature curve is determined not only by the character of the infection, but also by the reactivity of the organism, the extent of its sensitisation to foreign proteins, in particular.

3. *Intermittent fever (febris intermittens, Fig. 73)* which is characterised by regular alternation of brief attacks of fever (paroxysms) with feverless periods (apexia). High temperature persists for several hours, drops to normal and then rises again. The length of the feverless periods may vary. This form of temperature curve is characteristic of malaria. Attacks of fever may occur every third day (*febris quartana*), every second day (*febris tertiana*) or every day (*febris quotidiana*).

4. *Recurrent fever (febris recurrens, Fig. 74)* which is characterised by longer periods of pyrexia than in intermittent fever (5-8 days). The duration of these periods corresponds to that of the periods of normal temperature. Such a curve is characteristic of relapsing fever.

There are fevers which at first run the course of *febris continua* and then change to *febris remittens* (for example, in typhoid fever, Fig. 75). There are also fevers of short duration

Stages of Fever

Three periods or stages may be distinguished in most fevers. These are: 1) *the stage of elevation of the body temperature (stadium incrementi)*, 2) *the stage in which the temperature is at its acme (stadium fastigii)* and 3) *the stage of decreasing temperature*

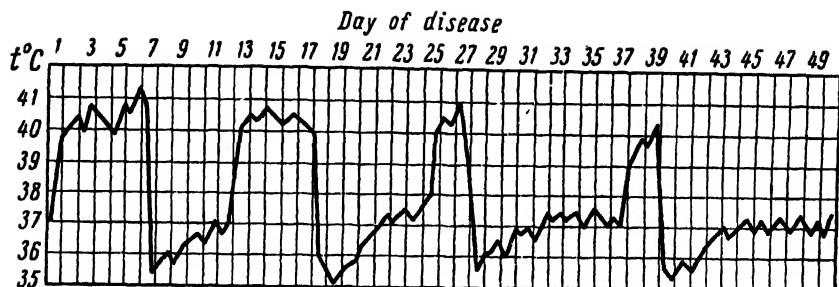


Fig. 74. Recurrent fever.

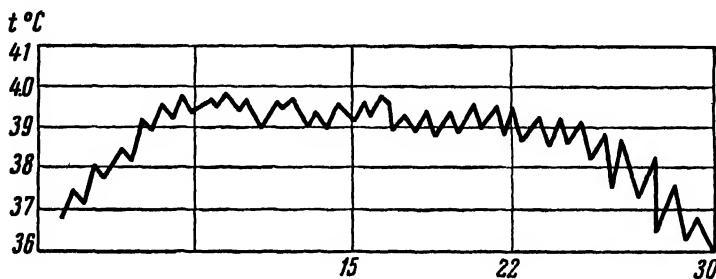


Fig. 75. Temperature curve in typhoid fever. Continuous fever during the first stage of the disease, remittent fever during the second stage.

(*stadium decrementi*). These three stages are characterised by a certain disturbance in the interrelation between heat production and heat loss, and disorders of the different forms of metabolism, excretion of urine, etc.

The first, usually short stage is characterised by a rapid or gradual elevation of body temperature. The temperature rises because in the beginning of fever, as a result of spasm of the vessels in the skin, *less heat is lost*, while heat production begins to increase. The ratio of heat production to heat loss increases, the disparity between heat production and heat loss in cases of rapidly rising temperature being accompanied by *chills*—a sensation of cold and shivering, pallor of the skin and appearance of “goose flesh”. At the same time the increase in muscle tone and the contraction of various groups of muscles lead to still greater heat production.

The chills are due to stimulation of the nerve endings in the skin as a result of the drop in its temperature caused by spasm of the superficial vessels. The cooling of the superficial layer of the skin reflexly causes shivering. Heat production increases also in the liver.

The faster fever develops, the greater the disparity between physical and chemical thermoregulation, and the more strongly pro-

nounced the chills. In these cases heat production always exceeds heat loss.

The second stage is characterised by establishment of the ratio of heat production to heat loss on a definite level. The heat loss increases mainly by dilation of the vessels in the skin and accelerated respiration. Compared with the first stage heat production may decrease, sometimes even to normal, but the balance between heat production and heat loss is established on a higher level than in healthy people.

The organism retains its ability to regulate the newly established temperature. Heat is lost through the same channels as usual and only perspiration plays a less important role.

The therapeutic measures employed during this period (cupping, wrapping, rub-downs) are aimed at facilitating physical thermoregulation.

The third stage—the stage of falling temperature is characterised by increased heat loss and its predominance over heat production which may relatively even increase. Heat loss increases as a result of excessive perspiration (sometimes very profuse) and considerable dilatation of the peripheral vessels. The ratio of heat production to heat loss is the reverse of that observed during the first stage of fever. Then heat production, heat loss and body temperature return to normal. At this stage the temperature is often unstable.

The temperature drops either rapidly (*crisis*) or slowly, gradually (*lysis*). A critical drop in temperature, especially in cases of cardiovascular insufficiency, is dangerous because it requires a rapid adjustment of the organism to the new conditions of the internal environment. This may result in a shock reaction (collapse).

In all the aforescribed stages physical and chemical thermoregulation functions concertedly. In man the disturbance in physical thermoregulation is of the utmost importance. The different stages of the febrile reaction may be characterised by noticeable fluctuations in the heat balance due to compensation for the disturbed functions, which is in its turn connected with the physiologic defence role of the central nervous system.

Thus the course of the different stages of the febrile process is determined, not only by the etiologic factor, but also by the general state of the organism, its reactivity, metabolism and intensity of the oxidative processes.

Metabolism in Fever

Metabolic disturbances in fever are caused by various factors. These factors are: 1) etiological peculiarities, most frequently of the *infectious agent*; 2) *elevation of body temperature*; 3) *starvation* which in some measure accompanies fever since, owing to loss of appetite and digestive disturbances, the organism consumes and assimilates less food than usual.

Metabolic disturbances vary with the various fevers, but are nevertheless subject to certain regularities characteristic of most fevers. In most cases metabolism is increased, this increase underlying the greater heat production. In moderately severe fevers metabolism may increase 5-10 per cent and may even remain within normal limits (Du Bois). The oxidative processes are somewhat intensified partly because of increased respiration and cardiac action. For example, in the guinea pig a 1° rise in temperature is accompanied by a 3.3 per cent increase in oxygen consumption. However, there may be a discrepancy between the amount of oxygen consumed by the organism and heat production, with accumulation of underoxidised metabolites and, in connection with it, a decrease in the respiratory quotient.

In fever *carbohydrate metabolism* is increased; this can be seen from the decrease in glycogen in the liver and the possible development of hyperglycemia.

The *fat metabolism* is appreciably increased mainly in lingering fevers of infectious origin. The increased expenditure of fats is due not only to the fever, but also to the concurrent starvation and, in a certain measure, perhaps to intoxication. Ketonemia and ketonuria are sometimes observed as a result of carbohydrate deficiency and decreased oxidation of fats.

Protein metabolism may be disturbed. In fever involving a high temperature the expenditure of protein is increased out of proportion to that of fats and carbohydrates; elimination of nitrogen in the urine is increased. In cases of moderate fever the share of protein in the total energy balance is often normal (10-15 per cent), as is, for example, the case in influenza and certain forms of tonsillitis. In fevers with a high temperature the share of protein may reach 30 per cent, in which cases the amount of urea in the urine increases. Disintegration of protein is particularly great in infectious fevers (toxigenic protein disintegration).

The loss of valuable proteins by the feverish organism may be in some measure compensated by consumption of carbohydrates, fats and proteins.

In severe fevers some investigators have observed an increased specific dynamic effect of protein, which also explains the increased loss of nitrogen with the urine in high fever.

The problem of metabolism in fever is very important for the choice of diet for feverish patients. It is difficult completely to eliminate the losses of tissue proteins in fever, especially infectious fever involving high temperature. In severe infections it is necessary to strive for a possible limitation of protein expenditure by a plentiful administration of carbohydrates. For this purpose patients are intravenously administered glucose which is more easily oxidised and is in a certain measure capable of making up for the caloric deficiency and the excessive expenditure of protein, the latter

imperilling the feverish organism which is fighting the active, in most cases infectious, agent.

In fever the *water and salt metabolism* is more or less altered. As a result of increased metabolism and accumulation of underoxidised products the tissues retain water. The dysfunction of the renal filter due to intoxication and the rise in temperature is also of some importance. The second stage of fever is accompanied by decreased excretion of urine. The retention of water is noticeable already at the height of pyrexia. But during the third stage increased excretion of water by the kidneys is observed in addition to the sharp increase in heat loss and excessive perspiration.

It is not yet entirely clear precisely what tissues retain water in fever. As in inflammation, a very important part is apparently played by connective tissue.

As for the salt metabolism, the disturbed water metabolism involves retention of chlorides; during the third period, when the excretion of urine begins to increase, more chlorides are eliminated. More phosphates and potassium salts are excreted as a result of tissue disintegration.

Changes in the Functions of the Internal Organs in Fever

Disturbances underlying the disorders of thermoregulation arise in the *nervous system*. Moreover, phenomena due to changes in body temperature and intoxication are observed. Hyperthermia may of itself (in so-called aseptic fevers), depending on its intensity, stimulate and subsequently inhibit the central nervous system. Infectious fevers are not infrequently accompanied by a sensation of heaviness in the head, general indisposition, clouded consciousness, delirium, hallucinations, etc. Children react to pyrexia by greater excitement than do adults. In emaciated patients fever is usually attended with phenomena of depression of the nervous system.

As regards the vegetative nervous system, the functions of its sympathetic division predominate.

In fever the *cardiac rhythm* is accelerated as a result of excitation of the sympathetic nervous system. The etiologic factors causing fever—mainly infectious agents and toxins, as well as toxic metabolites—stimulate cardiac activity. Usually a 1° rise in temperature is accompanied by an increase of 8-10 beats in the heart rate.

The extent of the functional changes in the heart muscle and conduction system depends on the character of the infection and intoxication. Elevation of the body temperature in fever is usually accompanied by an acceleration of the pulse, but there are also reverse phenomena which are apparently connected with stimulation of the centre of the vagus nerve in the medulla oblongata. For example, in inflammation of the meninges, tuberculous meningitis

in particular, the pulse rate clearly lags behind the rise in temperature. The character of the pulse wave (hard, full, thready, dicrotic, etc.) is, in addition to the pulse rate, also very important for evaluating the state of cardiovascular activity. The changes in the state of the vessels are connected with disturbances in physical heat regulation; for example, chills are accompanied by spasm of the peripheral vessels and a rush of blood to the internal organs; during the second and, especially, the third stages of fever the vessels are dilated.

In the beginning of fever the *blood pressure* is somewhat elevated because of the increased action of the heart and excitation of the vasomotor centres; during the last stage, however, the blood pressure drops as a result of weakened heart action and dilatation of the vessels. The drop in blood pressure may sometimes lead to shock or collapse.

In fever the *respiration* is accelerated simultaneously, with the quickening of the pulse and elevation of the body temperature. Fever also involves a rise in the temperature of the blood and acidosis developed as a result of accumulation of acid metabolites. Respiration participates in the physical regulation of heat along with the vascular system and the sweat glands. A change in respiration is thus one of the mechanisms of physical thermoregulation in fever.

The function of the *digestive apparatus* is altered: the secretion of digestive juices and bile is decreased, the mucous membranes of the mouth and tongue are dry, and intestinal peristalsis is disturbed. Some cases are accompanied by constipation with increased putrefaction, accumulation of gases and development of meteorism. Digestive insufficiency and diminished absorption lead to a lack of appetite, decreased assimilation of nutritive substances and phenomena of intoxication.

The function of the *kidneys* is also altered. Renal filtration is particularly affected by toxins in infectious fevers (for example, scarlet fever, septic diseases). At the height of fever the amount of urine perceptibly diminishes. The water is retained by the tissues. The content of nitrogenous substances in the urine is increased. The amount of urine appreciably increases during the third stage of fever when the body temperature begins to fall.

Protein, peptones and albumoses sometimes appear in the urine. The amount of excreted protein in large measure depends on the character and severity of renal affection. Here an important part is played not so much by hyperthermia, as by the infection and intoxication which have initiated the febrile process.

As for *pathoanatomical changes*, dystrophic phenomena are sometimes observed mainly in the parenchymal organs in fevers with a high temperature. The changes are of the nature of a turbid swelling, sometimes waxy degeneration, and adipose infiltration. Important in these cases is the fever itself and, to an even greater extent, the

infection and intoxication which have produced the fever. Phenomena of dystrophy in the internal organs cause disturbances in their functions, which in their turn affect the course of the febrile process.

Effects of Fever on the Course of Infectious Processes

The question of the effects of fever as a general reaction of the organism mainly to the action of infectious agents is of fundamental importance. It is important to settle this question in order to uncover the *adaptive role* of fever in the organism's fight against infection and for its therapy.

The investigators maintaining that fever harmfully affects the course of infection in the organism point out the concurrent dysfunction of the cardiovascular system, deep metabolic disturbances and dystrophic changes in the organs; however, some infectious diseases run a graver course in the absence of fever or in cases of weak manifestations of fever (for example, croupous pneumonia, influenza, typhus, etc.).

A more favourable course of pneumonia and chicken cholera is observed in hyperthermia produced in animals by injury to the corpus striatum. Carefully conducted artificial overheating favours the survival or prolongs the life of animals infected with anthrax, the *Streptococcus pyogenes* and the *Staphylococcus*.

There are also some indications that certain adaptive reactions become more intense at a high temperature; these include phagocytosis and production of immune bodies, and such physiologic functions as hematopoiesis, activity of the enzymes, and the barrier and antitoxic functions of the liver.

To produce fever for therapeutic purposes, especially in certain chronic infections, pyrogenic therapy is applied in the form of inoculation of malaria (in neurosyphilis), administration of purified pyrogenic substances (pyrexial, pyrogenal, etc.) or inductopyrexia, i.e., production of fever by electromagnetic induction.

Body temperature is a valuable index of the state of the organism in its struggle against infection since it reflects the reactive ability of the diseased organism. This does not mean that fever must always be considered a positive phenomenon in the development of the infectious process. *Both an excessive rise in temperature or its sudden drop may prove harmful to the organism.* It follows that the course of the fever and its significance to the organism must be given special consideration in each concrete case. As one of the mechanisms formed in the process of evolutionary development fever may, in cases of moderate elevation of body temperature, be useful in the organism's struggle against the infectious agent which has caused it.

Chapter Eleven

PATHOLOGY OF THE BLOOD AND HEMATOPOIESIS

The changes in the blood occurring in disease in some measure reflect the dysfunctions of various organs and tissues. The changes originally arising in the blood itself and, especially, in the organs of hematopoiesis are of particular interest. These diseases have long been classified in a special group designated as diseases of the blood and hematopoiesis.

Changes in the total volume or mass of the blood, its formed elements, and its biochemical and physicochemical composition are distinguished according to the character of the phenomena observed.

CHANGES IN THE TOTAL VOLUME OF THE BLOOD

Various forms of increased and decreased total volume of the blood are observed in pathology (Fig. 76).

An excess of the total volume of blood in the body is called polyemia, hypervolemia or plethora.*

Depending on the ratio of plasma to erythrocytes, three forms of hypervolemia are distinguished: 1) hypervolemia with a normal plasma-erythrocyte ratio; 2) hypervolemia with an excess of erythrocytes; 3) hypervolemia with an excess of plasma.

The first form—*simple hypervolemia with a normal plasma-erythrocyte ratio*—occurs very rarely. It may arise for a short time following transfusion of large amounts of blood, ejection of blood from the blood depots in the beginning of strenuous work, or under high external temperature.

Repeated experiments have been made to produce hypervolemia in animals by transfusion of homogeneous blood. However, these attempts were for the most part accompanied only by a brief increase in the blood volume and a slight, and also brief, rise in blood pressure. Processes of compensation follow immediately. The blood

From the Latin words: *hyper*—excess and *volumen*—volume.

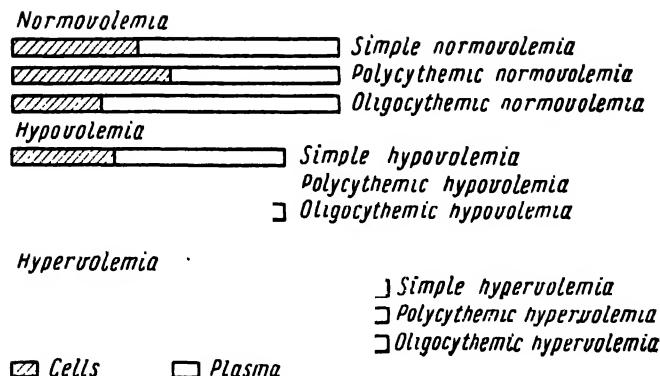


Fig. 76. Diagram of changes in the total volume of blood (Brown and Rountree).

plasma very soon passes into the tissues, while the transfused erythrocytes are gradually destroyed, which is attested by excessive formation of bile pigments from the hemoglobin.

Plethora with a 150 per cent or higher increase in the mass of blood artificially produced in animals imperils their life. It disturbs the regulation of the volume of circulating blood, reduces vascular tone, excessively dilates the vessels and causes circulatory disorders; these disturbances are soon followed by hemoconcentration (as a result of increased transudation of plasma into the tissues and serous cavities), considerable disintegration of erythrocytes and cardiac failure.

The second form is *polycythemic hypervolemia*, i.e., with an increased number of erythrocytes, the increase in the amount of hemoglobin lagging behind the increase in the number of erythrocytes. The erythrocytes may number from 10 million to 13 million per 1 mm³ of blood. This disease is also known as *true plethora or true polyemia* and is characterised by increased hematopoiesis whose signs are usually easily observed in the bone marrow, spleen and other hematopoietic organs. It is supposed that the increased hematopoietic function of the bone marrow is stimulated by some substance formed in the process of disturbed metabolism.

In addition to the increased number of erythrocytes, true plethora is, as a result of the increase in the volume of blood, often characterised by tegumentary hyperemia, elevated blood pressure, hypertrophy of the left ventricle which with each systole drives more blood into the aorta.

The third form is *oligocytemic hypervolemia or hydremic plethora with an excess of plasma*. It may be due to retention of water in the blood stream as a result of certain diseases of the

kidneys or the hematopoietic system, or disturbances in water metabolism.

Attempts have been made to produce oligocytemic hypervolemia experimentally by intravenous injections of physiologic saline solution in the dog or rabbit. As a rule, these attempts have failed because the excess of fluid rapidly passed from the blood into the tissues and was gradually eliminated mainly through the kidneys.

The changes occurring in connection with intravenous administration of physiologic saline solution are observed in the following experiment: a 0.7 per cent sodium chloride solution is slowly introduced through a cannula into the frog's abdominal vein. While this is done the circulatory changes are observed in the stretched web. The circulation of the blood in the vessels is noticeably accelerated, the blood is diluted, the volume of the fluid part increases and the mass of corpuscles relatively diminishes. Vascular permeability appreciably increases. These phenomena are soon followed by increased excretion of fluid into the lymph sac, urinary bladder and abdominal cavity. All these phenomena must be considered compensatory since they serve to restore the normal volume of blood.

Rapid administration of large amounts of fluid leads to the animal's death due to extensive disturbances in blood circulation, congestion in pulmonary circulation, hemorrhages and affections of the myocardium.

Hydremic plethora should be distinguished from *hydremia* whose characteristic feature is a decrease in the dense residue without a general increase in the total volume of blood (oligocytemic normovolemia). Such phenomena often occur in cachexias, anemias and avitaminoses.

A *decrease in the total volume of blood—oligemia or hypovolemia*—may be very brief in its pure form. Hypovolemia is most frequently accompanied by a decrease in the number and change in the quality of erythrocytes.

Analogously with hypervolemia three forms of hypovolemia may also be distinguished according to the ratio of the plasma to the erythrocytes: 1) hypovolemia with a normal plasma-erythrocyte ratio; 2) hypovolemia with a decreased amount of plasma, or hemococentration; 3) hypovolemia with a decreased number of erythrocytes.

The first form—*simple hypovolemia with a normal plasma-erythrocyte ratio*—is observed directly after *acute hemorrhages* which may be due to injuries of large vessels, ulcers, active forms of pulmonary tuberculosis or rupture of the fallopian tubes.

The *results of acute hemorrhages* vary greatly. They depend on the rate of the blood flow, the mass of blood lost and the general condition of the organism. For a healthy organism a single loss of 50-60 per cent of the total amount of blood is fatal. After such a hemorrhage restoration of the mass of blood by natural means

becomes impossible and insufficiency of oxygen in the blood (hypoxemia), oxygen deficiency (hypoxia), disorders of hemodynamics and respiration, shock and phenomena of asphyxia result. The condition is also accompanied by a drop in arterial pressure; acute cerebral anemia, extreme pallor, increasing depression of the functions of the respiratory and vasomotor centres, and cardiac failure; the pulse becomes thready. The diminution in the mass of the circulating blood and the oxygen deficiency give rise to excitation of the motor zone of the cerebral cortex and convulsions. These phenomena are the more strongly pronounced the more rapid the hemorrhage. The organism may die exhibiting a considerable drop in blood pressure, a fall of the body temperature and paralysis of the respiratory centre.

Repeated minor hemorrhages cause a slow development of hypovolemia.

Simultaneously with the disorders of a number of vitally important functions hemorrhages lead to mobilisation of the *adaptive* physiological defence mechanisms by means of which it is possible to restore the blood pressure, as well as the volume and function of the blood.

The lowered blood pressure is compensated by the following processes: 1) reflex stimulation of the vasomotor centre with a resultant increase in vascular tone and spasm of the peripheral vessels; 2) increase in the mass of the circulating blood through an inflow of blood from the blood depots and tissue fluid; 3) increased blood clotting which leads to arrest of the hemorrhage, and 4) subsequent hyperfunction of the hematopoietic apparatus stimulated by the hemorrhage and insufficiency of available oxygen (hypoxia).

Restoration of the blood pressure after a hemorrhage is noticeably accelerated by protective inhibition in the cerebral cortex. It is therefore facilitated by means of artificial sleep, which closely resembles natural sleep, but is retarded by deep narcotic sleep. This denotes participation of the higher parts of the nervous system in the restoration of the blood (Fig. 77).

The results of hemorrhage consist not only in the changed volume of the blood, but also in its altered composition. The first result is an increase in the number of blood platelets (sometimes to 1 million per 1 mm³) and in intensified blood clotting. Within a few days the number of leukocytes increases as a result of their discharge from the intensely functioning bone marrow. The number of erythrocytes at first decreases owing to dilution of the blood by tissue lymph and then gradually increases as a result of increased hematopoiesis in the bone marrow. Young forms of red blood cells—normoblasts, reticulocytes and polychromatophilic erythrocytes appear in the blood. The extent of restoration of the blood elements varies and depends on the amount of blood lost, the rate of bleeding, the regenerative capacity of the organism and its hematopoietic system.

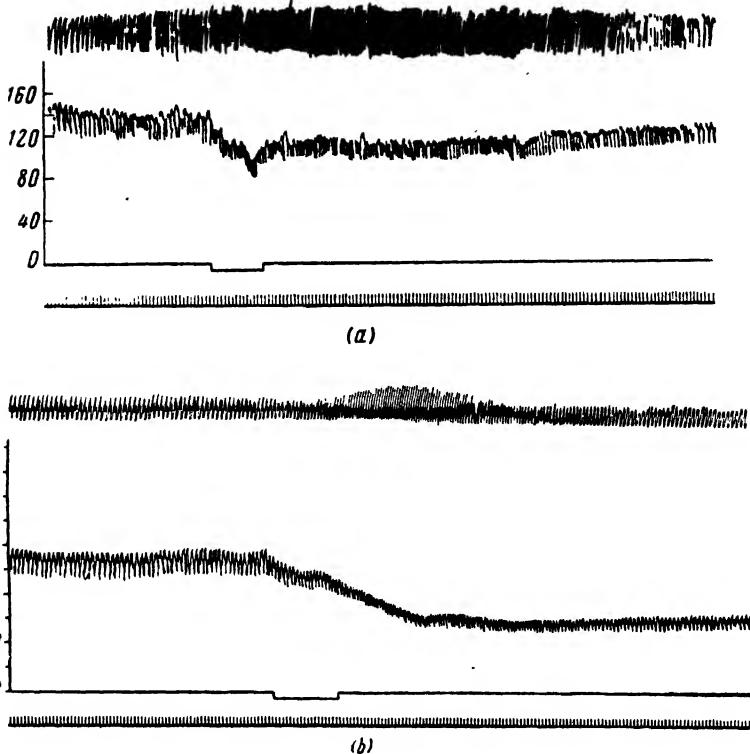


Fig. 77. Blood pressure curve in the dog.
 a—after loss of one third of the blood; b—after similar loss of blood during narcotic sleep induced by urethane. Restoration of the blood pressure is retarded. Mark on the zero line shows the moment of venipuncture. Time intervals—2 seconds.

Since the principal cause of death after a massive acute hemorrhage is a drop in blood pressure, *transfusion of blood* or blood substitutes, which is usually resorted to in operations or in cases of injuries to vessels, is the most effective measure.

The pathogenic role of the diminution in the mass of blood and of the drop in blood pressure during hemorrhage is evidenced by the favourable effect produced by blood- and plasma-substituting solutions which diffuse in the tissues slowly and are longer retained in the blood stream. In addition to blood, specially treated foreign proteins have been proposed and are successfully used (N. A. Fyodorov). Plasma or serum containing hypnotics and anodynes are used for the same purposes (I. R. Petrov).

The following rules of blood transfusion must be observed:

- 1) blood for transfusion must be taken from an organism of the same species (for man—human blood) because administration of

heterogeneous blood causes agglutination and subsequent dissolution of erythrocytes;

2) the erythrocytes of the person giving the blood (donor) must not be agglutinated by the blood serum of the person receiving it (recipient), for which reason the hemagglutination properties of the donor's and recipient's blood are established before transfusion.

Failure to observe the requisite rules and transfusion of blood of a different group may have grave consequences. A so-called *blood transfusion shock* develops. It is characterised by clearly marked respiratory and circulatory disturbances, a considerable drop in blood pressure, phenomena of erythrocyte hemolysis and altered renal permeability. Death not infrequently occurs as a result of paralysis of vitally important nerve centres. Transfusion even of homogeneous blood may sometimes be accompanied by a post-transfusion reaction in the form of a certain rise in temperature, chills and general indisposition.

However, the complex reaction of the organism to the transfused blood is not limited to colloidoclasia. The latter is but one of the manifestations of the organism's reaction to the transfused blood. The phenomena observed in transfusions of incompatible blood are also explained by disturbances in neuroreflex activity and metabolism.

This assumption is confirmed by experimental observations which have shown the dependence of the organism's reaction to the transfused blood on the site of its administration into particular vessels or the region of receptor zones excluded from the general blood stream by ligation of requisite vessels (I. I. Fyodorov). The effect of heterogeneous blood on interoceptors of the intestines and spleen also causes a drop in blood pressure (S. M. Pavlenko et al.). In all these experiments the pathologic reflexes to circulation and respiration are apparently elicited from the angioceptors which come in contact with foreign blood.

In hemorrhages, anemia, shock, etc., blood transfusion produces a very favourable effect. Firstly, the blood is for some time restored quantitatively. Secondly, by stimulating the interoceptors of the vessels the transfused blood and the physiologically active products of partial disintegration of erythrocytes reflexly stimulate the function of the hematopoietic apparatus, improve the process of blood clotting and raise the general immunobiological stability of the organism.

The second form of hypovolemia, i.e., *with a decreased amount of plasma—polycythemic hypovolemia or anhydremia*—is characterised by appreciable concentration and increased viscosity of the blood.

Anhydremia is observed in connection with considerable loss of water by the organism, as in cholera, dysentery, infantile diarrhea, intractable vomiting, and extensive burns involving loss of a great deal of fluid with the exudate and evaporation from burned surfaces.

Experimentally anhydremia is produced as follows:

A sugar syrup is injected in the frog's dorsal lymph sac and the frog's circulation is simultaneously observed in the stretched tongue through the microscope. Owing to the difference in osmotic pressure the flow of fluid from the blood into the lymph increases. The blood noticeably concentrates, becomes viscous and flows through the vessels with difficulty. The mass of red blood cells relatively increases. Subsequent intravenous infusion of physiologic saline solution restores the properties and composition of the blood.

The third form of oligemia is *oligocythemic hypovolemia*—a diminished volume of blood mainly because of a decreased number of erythrocytes. It is observed after hemorrhages in cases of increased passage of fluid from tissues into the vascular system and in certain forms of anemia, for example, pernicious anemia.

CHANGES IN THE FORMED ELEMENTS OF THE BLOOD

Disturbances in the formed elements of the blood may be *qualitative* and *quantitative*. The disturbances involve the red and white blood cells and the blood platelets. Quantitative changes in the blood rarely occur without concurrent qualitative changes.

Changes in Erythrocytes

Polycythemia

Polycythemia is a condition of the blood characterised by an increased number of erythrocytes. It may be relative or absolute.

Relative polycytemia is observed in connection with diminished plasma or hemoconcentration as a result of loss of water (in anhydremia), for example, in profuse perspiration, diarrhea, cholera, diabetes insipidus, poisoning and rapid mobilisation of depot blood, as in draining the spleen blood depot.

Absolute polycytemia (Vaquez's disease) is characterised by an increase in the total number of erythrocytes. It may be *primary* in which case it is accompanied by an increased volume of blood—plethora. Such is the so-called true polycytemia or erythremia. This disease occurs mainly in elderly people, most frequently in men. The number of erythrocytes reaches 10,000,000 and more per 1 mm³. The amount of hemoglobin in the blood is also increased (120-130 per cent), but relatively less than the number of erythrocytes, for which reason the colour index is somewhat lowered. The number of leukocytes is increased mainly by granulocytes. Thrombocytosis is observed. The characteristic signs of polycytemia are engorgement of the capillaries, tendency to hemorrhages and thrombosis, and enlargement of the spleen. The cause of polycytemia is not clear as yet. It is associated with intensified hematopoietic activity of the bone marrow and increased production of erythrocytes.

In most cases absolute polycythemia arises as a *secondary* disease and is a symptom (polyglobulia, erythrocytosis) often in no way connected with the total increase in the volume of the blood. It develops in mountain sickness as a result of hypoxia which stimulates migration of erythrocytes from blood depots and the erythropoietic function of bone marrow. It may also occur in other forms of oxygen deficiency, for example, in certain cardiovascular diseases (mitral stenosis, congenital heart disease), sometimes in pulmonary diseases (emphysema, stenosis of the respiratory tract) and in cases of poisoning (by copper, lead, phosphorus, mercury, manganese) accompanied by increased regeneration of erythrocytes.

Anemia

Concept of Anemia. Anemia is a reduction in the hemoglobin concentration and in the number of erythrocytes per unit of blood, often involving a change in the quality of erythrocytes.

In cases of marked anemia the volume of blood is diminished only rarely in view of the compensatory replenishment of the blood deficiency by the fluid which passes from the tissues into the blood stream. However a diminished blood volume is observed in hemorrhagic diathesis and pernicious anemia as a result of chronic hemorrhages. The general phenomena accompanying the development of anemia are due mainly to a decreased *hemoglobin* concentration. The respiratory function of the blood diminishes and oxygen deficiency in the tissues results. The amount of oxygen in the blood may drop from 20 to 10 vol.% and even lower. This gives rise to pallor, dizziness, fatigue, easy tiring and dyspnea. Phenomena of compensation in the form of accelerated blood circulation and better utilisation of oxygen by the tissues develop gradually.

Pathologic Forms of Erythrocytes. Anemia is characterised not only by a diminished concentration of hemoglobin, but also by a decreased number of erythrocytes in the blood. Severe cases are marked by the appearance of pathologic forms of erythrocytes unusual for normal blood. These qualitative changes in erythrocytes are varied and involve their sizes and structure, as well as the concentration of hemoglobin in them.

The pathologic forms include hemoglobin-deficient *hypochromic erythrocytes* which appear ring-like because of the decreased hemoglobin content in their central, thinnest part.

A stained blood preparation may contain red blood cells of unequal size (micro- and macrocytes). Microcytes have a diameter of less than 6μ (normally $7\text{--}8\mu$), macrocytes—more than $8\text{--}9\mu$. The presence of differently sized cells is known as *anisocytosis*.

The property of being stainable not only with acid (eosin), as is normally the case with erythrocytes, but also with basic dyes (hematoxylin, methylene blue) is called *polychromatophilia*.

An increased number of *reticulocytes* in the blood is also observed (normally 5-15%). Reticulocytes are young erythrocytes with inclusions of grains or filaments (*substantia granulo-filamentosa*) discovered by staining *in vivo* without preliminary fixation of the preparation. The increased number of reticulocytes in the blood is an indication of increased hematopoiesis.

Phenomena of *poikilocytosis*—abnormal shape of erythrocytes—may be observed in pathology. The erythrocytes may be elongated, piriform, acanthoid, morular. They arise in the blood from less stable erythrocytes.

In cases of intensified hematopoiesis *normoblasts* may appear in the blood stream; these are immature erythrocytes, i.e., nucleated cells the size of erythrocytes or slightly larger.

In their development in bone marrow erythrocytes normally go through several cellular forms. Erythroblasts which have a nucleus and basophilic colouring of the protoplasm are the earliest form. By accumulating hemoglobin they are gradually transformed into normoblasts which lose the nucleus and passing through the stage of young polychromatophilic erythrocytes become mature red blood cells.

In some severe forms of anemia (so-called megalocytic anemias) abnormally large erythrocytes, *megalocytes* and, from time to time, *megaloblasts*, which have a large pale nucleus, appear in the blood. The chromatin in the nucleus is arranged in a thin network. The appearance of such cells in the blood denotes a return to the embryonal type of hematopoiesis. These cells are found in the blood of patients affected with pernicious anemia, severe sepsis and tuberculosis.

Erythrocytes may contain inclusions in the form of detritus from nuclei located on the periphery of erythrocytes—*Jolly bodies*. The remnants of the nuclear membrane or the layer of lipoprotein detached from the membrane are the so-called *Cabot's ring bodies*.

The extent of all these changes varies with the form of anemia, reaction of the bone marrow and character of disturbance in erythropoiesis. Polychromatophilia, especially reticulocytosis and normoblastosis, develop as a result of increased physiological regeneration in the bone marrow. Jolly bodies, Cabot's ring bodies and megaloblasts are an expression of pathologic erythropoiesis. Anisocytosis and poikilocytosis are considered signs of formation of degenerative forms of erythrocytes.

Regenerative and Aregenerative Anemias. Most anemias are *regenerative*. They are accompanied by restorative, regenerative processes in the hemopoietic apparatus. One of the most important factors causing regeneration of erythrocytes after their destruction is *oxygen deficiency* which develops as a result of hypoxemia and stimulates hematopoiesis. This assumption is confirmed by the increased number of erythrocytes in dogs kept in a pressure chamber at low

barometric pressure and in guinea pigs in an atmosphere containing carbon monoxide provided they have 25 per cent carboxyhemoglobin in their blood. *Disintegration products* formed in intermediate metabolism may also stimulate the bone marrow in anemia. It was shown experimentally that administration of the serum of an animal affected with anemia causes an increase in the number of erythrocytes in a normal animal.

Lastly, an important part in stimulating erythropoiesis is played by the central nervous system and its reflex activity. This is attested by Botkin's old clinical observations concerning the role of nervous disorders in the development of anemias, as well as by modern experimental data on the participation of the nervous system in hematopoiesis.

For example, the number of erythrocytes in the blood increases as a result of lesions in the diencephalon, for example, in epidemic encephalitis.

Increased erythropoiesis—greater concentration of hemoglobin and increased number of reticulocytes—may be produced experimentally by stimulating the superior cervical sympathetic ganglion, certain parts of the diencephalon, the mechanoreceptors of Pavlov's pouch and other neural structures.

Aregenerative anemias occur much more rarely; in these anemias the bone marrow, owing to considerable depression of its activity, has lost its ability to produce and eject young erythrocytes into the blood stream. Reticulocytes disappear from the blood. Red bone marrow changes to yellow. Such aregenerative forms of anemia almost always lead to death. They develop in avitaminoses, intoxications with potent toxins entering the blood from a focus of infection in the organism, and in cases of poisoning with certain chemical substances (for example, benzene, arsenobenzene). Aregenerative anemias include aplastic anemia.

Changes in hematopoiesis are diagnosed not only on the basis of the blood picture, but also and mainly by the morphologic changes in the bone marrow. Bone marrow changes in patients suffering from anemia and other blood diseases are ascertained by a sternal puncture (M. I. Arinkin).

Etiology and Pathogenesis of Anemias. The simplest classification of anemias is based on the causes of their origin, namely, posthemorrhagic anemias caused mainly by blood loss, hemolytic anemias produced by the effect of poisonous substances which destroy erythrocytes in the blood and in the hematopoietic apparatus, and anemias due to nutritional and metabolic disturbances responsible for diminished production of erythrocytes.

In the mechanisms of anemias it is necessary to distinguish: 1) diminished or increased destruction of erythrocytes without their corresponding production in the hematopoietic system (for example, in acute blood losses or as a result of the action of certain

hemolytic poisons); 2) decreased erythropoiesis due to dysfunction of the bone marrow (for example, in osteosclerosis*, and as a result of the action of toxins, bacteria and poisons); 3) combination of both factors, i.e., increased destruction of erythrocytes and simultaneous disturbance in erythropoiesis in the bone marrow. Sometimes this combination is characterised by an almost complete absence of regenerative phenomena.

Posthemorrhagic anemias arise as a result of blood losses caused by most diverse factors—wounds, pulmonary, gastrointestinal or renal hemorrhages, severe post-partum hemorrhages, etc. Acute posthemorrhagic anemias arise after a single severe hemorrhage, chronic—after repeated even slight blood losses.

The character and course of developing anemia depend on the frequency and extent of blood losses and on the regenerative ability of the hematopoietic apparatus. Soon after hemorrhage hypochromic and polychromatophilic erythrocytes, as well as reticulocytes (up to 100% and even more) and sometimes normoblasts appear in the peripheral blood. The colour index somewhat diminishes. Leukocytosis is often observed. Chronic blood losses may, as a result of protracted stimulation, cause the appearance of extramedullary foci of hematopoiesis in the spleen, liver and lymph nodes, and considerable dysfunction of the bone marrow. In cases of repeated hemorrhages anemia may become aregenerative.

Hemolytic anemias arise mainly in cases of poisoning with substances causing increased destruction of erythrocytes in the blood stream or at sites of their physiologic destruction. These substances include certain toxic products of microbial origin such as hemolytic toxin produced by streptococci or the malarial plasmodium; erythrocytes are also destroyed by malignant tumours and various poisons, for example, lead, mercury, hydrogen arsenide, tolylenediamine, nitrobenzene and aniline.

Hemolytic anemia may also arise in blood transfusions.

Experimentally hemolytic anemias are produced in rabbits by poisoning them with phenylhydrazine, tolylenediamine, lead, sulfonmethane, saponin, toxic products of streptococcal origin and bile acids.

Owing to the lowered resistance of the erythrocytes hemolytic anemias are characterised by accumulation of bilirubin—product of hemoglobin conversion—in the blood and by increased excretion of urobilin (formed in large quantities in the intestine from the bilirubin of the bile) in the urine. The liver and spleen in which increased destruction of erythrocytes takes place are often observed to be enlarged. In some cases, for example, in anemia associated with

* A bone affection consisting in excessive density of bony tissue and constriction of the marrow spaces, involving disturbances in the function of the bone marrow.

hemolytic jaundice, signs of increased hematopoiesis—reticulocytosis and normoblastosis—are noted in the peripheral blood; sometimes poikilocytosis and anisocytosis also appear. Other cases, for example, those of food poisoning are marked by feeble regeneration.

Anemia due to decreased production of erythrocytes in the bone marrow arises as a result of *nutritional* and *metabolic* disturbances, especially a deficiency of iron and proteins (necessary for the production of erythrocytes) in the food or disturbances in their assimilation, or a deficiency of vitamins and hormones which regulate erythropoiesis.

Iron-deficiency anemias arise as a result of disturbed iron metabolism; they include *hypochromic anemias*, *chlorosis* in particular.

This form of anemias is sometimes observed in girls at the time of sexual maturation.

In adults hypochromic anemias may arise as a result of considerable diminution in hydrochloric acid in the gastric juice, infections and intoxications (for example, chronic tuberculosis, rheumatism), renal insufficiency, etc.

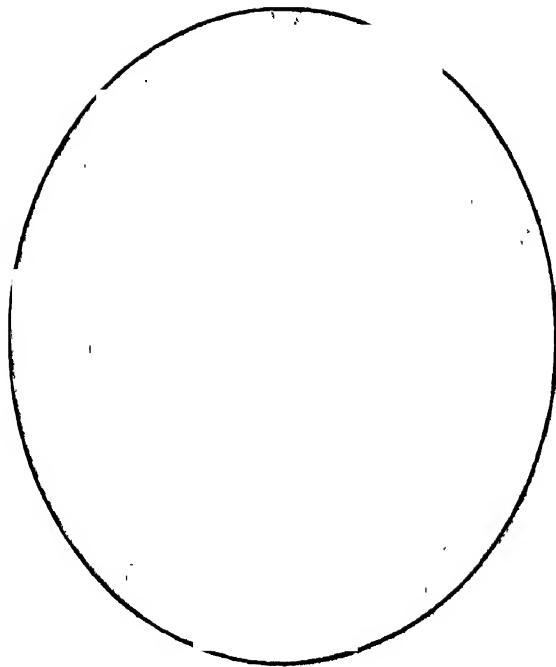
Characteristic of the blood in these cases is not so much the decrease in the number of erythrocytes as the diminished hemoglobin; the colour index drops very much below unity—to 0.6-0.5 and even lower. Blood preparations are relatively weakly stainable and the red blood cells are hypochromic. Microcytosis and polychromatophilia, more rarely poikilocytosis and anisocytosis, and very rarely normoblastosis are also observed. There is an excess of polychromatophils and reticulocytes (Fig. 78). The leukocyte count somewhat increases and the lymphocyte count decreases.

The development of hypochromic anemias is caused by disorders of iron metabolism. They may be due to insufficient consumption of iron with the food, disturbances in its assimilation, disturbed formation of ferritin (iron-protein complex required for normal erythropoiesis), as well as to disturbances in intermediate metabolism and the process of iron utilisation in the synthesis of hemoglobin.

Chlorosis may also result from an increased iron loss by the organism, for example, in connection with the beginning of the menses.

The dependence of the development of chlorosis on disturbances in nutrition and iron metabolism is demonstrated by a number of experiments. For example, phenomena similar to chlorosis were observed in an experiment on rats fed on cow's milk during the period of growth, the development of anemia with a low colour index being the result of iron deficiency in the milk. Such anemia is easily cured by iron preparations containing 0.05 mg of copper (per day).

Protein-deficiency anemias are also hypochromic. They are due to insufficient consumption of protein with the food or failure of the organism to assimilate the protein, and to disturbance in the synthesis of globin—a protein component of hemoglobin. Production



*Fig. 78. Chlorosis. Hypochromic erythrocytes. Poikilocytosis. Thrombocytes.
Lymphocyte on the right.*

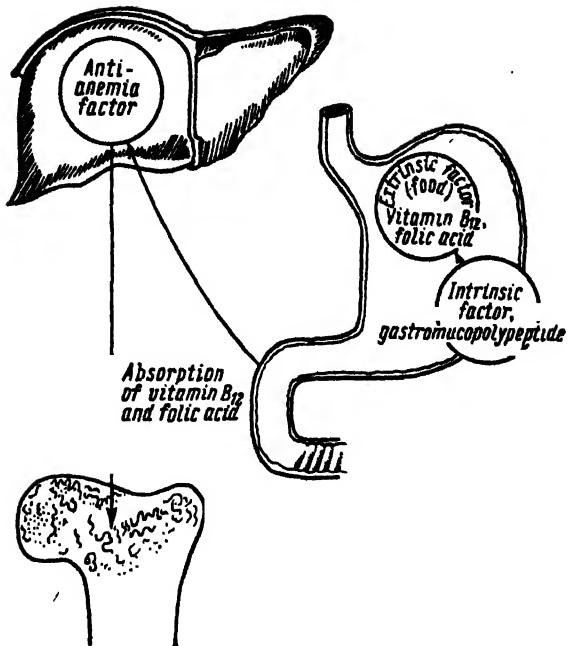


Fig. 79. Diagram illustrating action of the hematopoietic factor.

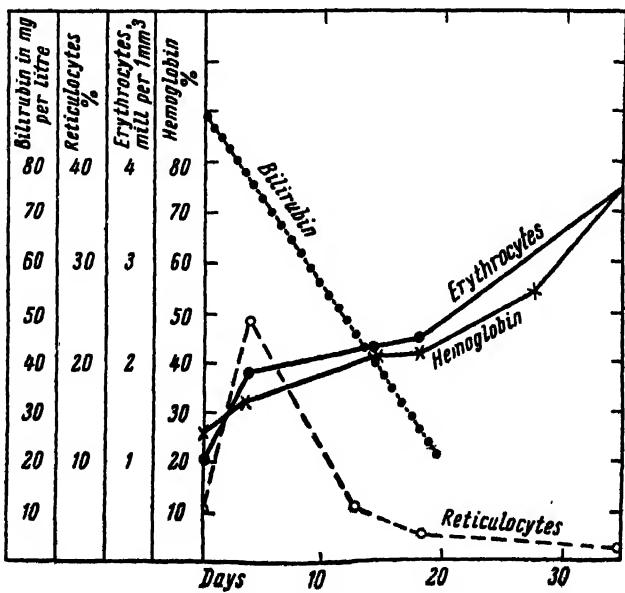


Fig. 80. Effect of liver extract therapy on reticulocytes, erythrocytes, hemoglobin and bilirubin in pernicious anemia.

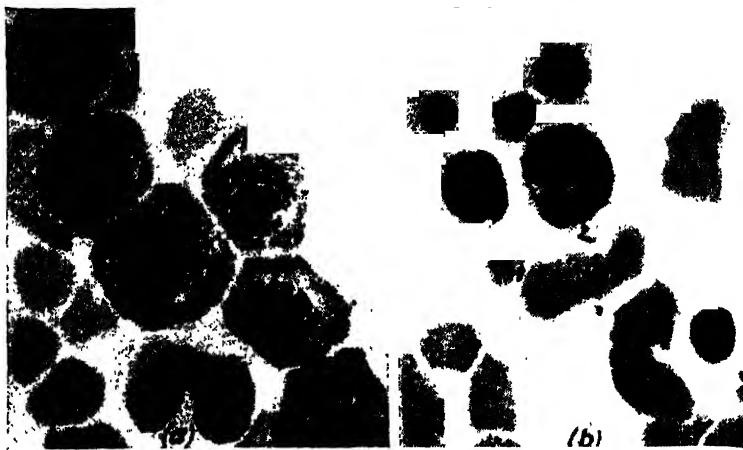


Fig. 81. a—megaloblastic erythropoiesis in the bone marrow in pernicious anemia; b—normoblastic erythropoiesis in the same bone marrow 7 days after injection of 90 gammas of vitamin B₁₂.

of 1 g of hemoglobin requires 7-8 g of food protein. The globin deficiency may be eliminated by consumption of protein with the food or by blood transfusion.

Another group of anemias is connected with nutritional and metabolic disturbances. These are *hyperchromic anemias with megalocytic and megaloblastic hematopoiesis*, for example, *pernicious (Addison's, Biermer's) anemia*; they arise as a result of a *deficiency or absence of special external and internal antianemia factors* (Castle). The external factor is vitamin B₁₂ and, to a lesser extent, folic acid. The internal factor, as has now been established, is a *gastromucopolypeptide* present in normal gastric juice of the mucosa of the fundus ventriculi and absent in patients affected with pernicious anemia. Changes in, and often atrophy of, the gastric mucosa lead to a diminution in, or cessation of, the secretion of this *gastromucopolypeptide*. Vitamin B₁₂ is found in animal substance, especially in the liver, and folic acid—mainly in plants (the green leaves of spinach), as well as in yeast and liver; it is partly formed in the intestines and has also been produced synthetically. Absorption of vitamin B₁₂ in the intestines requires the presence of the internal factor. The interaction of the external and internal factors produces the antianemia factor which is deposited in the liver (Fig. 79), for which reason in pernicious anemia liver therapy stimulates restoration of the blood (Fig. 80); a favourable effect is also produced by parenteral administration of even very small doses (40 gammas) of vitamin B₁₂, whereas administered perorally the vitamin is effective only if combined with the gastric juice of

healthy people because the latter contains the intrinsic factor (Fig. 81).

Vitamin B₁₂ and folic acid participate in the metabolism of cellular nuclei and are necessary for the synthesis of thymonucleic acid. Their absence leads to disturbances in normoblastic hematopoiesis, which gives rise to pernicious anemia.

In addition to Addison's or Biermer's pernicious anemia whose etiology is not quite clear as yet, there are also secondary pernicious anemias, as in cases of infestation with tapeworms (for example, the *Diphyllobothrium latum*), and certain severe affections of the stomach (syphilis, cancer, extreme constriction of the pylorus or duodenum, pellagra). In all these cases a pathogenetic role is also played by the antianemia factor deficiency due to its diminished absorption or utilisation in the organism.

In pernicious anemia patients the number of erythrocytes is sharply decreased and the colour index is more than unity (sometimes as high as 1.7) since the erythrocytes contain more hemoglobin than normal. Basophilic granularity in the erythrocytes is a frequent occurrence. Anisocytosis, poikilocytosis and a decreased number of reticulocytes in the blood are observed; the presence of megaloblasts, which denotes the embryonal character of hematopoiesis is characteristic of the condition. The number of leukocytes is also diminished, while segmentation of the nuclei in the neutrophils is increased. The number of blood platelets is decreased (Fig. 81).

Pernicious anemia is also characterised by a diminished resistance of erythrocytes and their increased destruction. The latter is attested by the abundant deposition of iron in the elements of the reticuloendothelial system and in the kidneys. Bile secretion is also increased; bilirubinemia develops (2-3 mg%) as a result of the diminished resistance of the erythrocytes, their partial destruction and liberation of hemoglobin; production of urobilin is also increased owing to the passage of large quantities of bilirubin with the bile into the intestines. One of the pathogenic factors in the development of this disease is probably auto intoxication associated with disturbances in the secretory activity of the stomach and intestines.

Pernicious anemia is characterised by disturbances in the function of the nervous system, which denote its participation in the mechanism of this disease.

Development of pathology of the red blood cells regardless of its cause is associated with *disturbances in the function of the hematopoietic organs*.

Dysfunction of the spleen involves considerable disturbances in the red blood cells due to the following reasons: 1) the spleen performs the function of a blood depot in which red blood cells may be retained and hemolysed; 2) it is an organ abounding in reticuloendothelial elements and participating in metabolic and hema-

topoietic processes; 3) it produces a hormone which inhibits hematopoiesis in the bone marrow.

Some forms of anemia are characterised by an *increased hemolytic function of the spleen*, in which case removal of the spleen favourably affects the course of the disease. It is also necessary to bear in mind the participation of the spleen in the destruction of low-resistance erythrocytes whose structural and physiologic properties are altered as a result of certain other primary influences. Owing to the increased hemolysis the spleen accumulates a large quantity of hemosiderin (an iron-protein complex).

After removal of the spleen its erythrocyte-destroying function is compensatorily taken over by other organs abounding in elements of the reticuloendothelial system, for example, the liver and the lymph nodes.

The *role of the bone marrow in hematopoiesis* consists mainly in production of formed elements of the blood, red blood cells in particular. Erythropoiesis increases as a result of stimulation of the bone marrow in oxygen deficiency, hemolysis, loss of blood and accumulation of products of decomposition.

In marked cases of increased erythropoiesis the bone marrow, which is yellow and consists mainly of fat cells, turns crimson because of increased blood circulation and multiplication of erythroblastic derivatives. In these cases immature forms of erythrocytes are often secreted into the blood. In pathology extramedullary foci of erythropoiesis may arise in the liver, spleen and the lymph nodes. Pathogenic factors may depress the function of bone marrow and weaken its regenerative ability as is, for example, the case in hypoplastic and aplastic anemias.

Changes in Leukocytes

Pathologic changes in leukocytes may be, as in erythrocytes, *quantitative and qualitative*.

Quantitative Changes in Leukocytes. These include leukocytosis and leukopenia. *Leukocytosis* is an increase in the leukocyte count above the upper limit of normal, i.e., above 5,000-8,000 per 1 mm³ of blood. *Leukopenia* is a decrease in the number of leukocytes in the blood below normal. Leukocytosis may change to leukopenia and vice versa, depending on the intensity of the same cause, as well as the reactivity of the organism and its hematopoietic apparatus. For example, small doses of benzene (0.3-0.5 g per 1 kg of weight) injected in the rabbit subcutaneously cause leukocytosis which is followed by leukopenia if the dose of the substance is increased 2- or 3-fold, or more injections are made. Quantitative and qualitative changes in leukocytes are often combined, when immature forms of leukocytes and leukocytes with an altered structure appear in the blood.

The number of leukocytes is altered:

1. As a result of *changes in the distribution of the circulating blood*. For example, an inflow of blood to the internal organs is accompanied by an increased number of leukocytes in the blood of the vessels supplying these organs. At the same time the number of leukocytes in the peripheral blood usually decreases. *Distributive leukocytosis and leukopenia* are associated with disturbances in the reflex activity of the nervous system, as in anaphylactic shock. In such cases the changes in the leukocyte count in the blood are most frequently very unstable.

2. As a result of *increased or diminished leukopoietic function of the hematopoietic organs* with a subsequent increase or decrease in the leukocyte count in the blood. The usual stimulators of leukopoiesis are bacteria, toxins, foreign proteins and certain products of decomposition, mainly nucleotides and their derivatives. But the mechanism of their effect on leukopoiesis is not clear as yet.

There are certain indications that the nervous system exerts influences on leukopoiesis. For example, leukocytosis produced experimentally by an injection of a suspension of microbes slows down in its development after transection of the spinal cord in its cervical part. Changes in the leukocyte count and the leukocytic formula, as well as appearance of immature forms, may be observed after stimulation of various parts of the subcortex and after removal of one or both cerebral hemispheres. Cortical influence is discovered in experiments with production of conditioned reflex leukocytosis. The central nervous system may also affect the leukocyte count in the blood through the endocrine glands, as is the case in thyroid and hypophyseal dysfunction.

In evaluation of the character of leukocytosis, not only the increase in the number of leukocytes is taken into consideration, but also the *leukocytic formula*, i.e., the percentage of their various forms. An increase in the number of some one form of leukocytes is known as neutrophilia, eosinophilia or basophilia, or lympho- and moncytosis.

Sometimes, even in cases of a normal leukocyte count, the percentage relationship of different forms of leukocytes is observed to be disturbed: for example, there may be an increase in lymphocytes and a decrease in neutrophils (relative lymphocytosis). The proportions of the different white blood cells are also important in leukopenia.

Leukocytoses may be either physiologic or pathologic.

Physiologic leukocytoses occur under normal conditions of the organism's vital activities; they include digestive leukocytosis, leukocytosis in pregnant women, leukocytosis in strenuous muscular work, etc.

The leukocytic formula may also vary with a number of physiologic conditions, for example, the character of consumed food,

duration of work done, etc. For instance, carbohydrates increase the number of lymphocytes in the blood. Muscular work at first produces a relative increase in the number of lymphocytes, which subsequently decreases, an increase in the number of neutrophils and a decrease in the eosinophil count.

Pathologic leukocytoses most frequently arise under the influence of substances of bacterial origin (toxins), products of tissue disintegration and certain chemical substances. Pneumonia, sepsis, scarlet fever, diphtheria and a number of other infectious diseases are accompanied by leukocytoses. The variations in the number of leukocytes and the changes in the leukocytic formula in the course of the selfsame infectious disease often indicate the character of the disease, the state of the organism and its reaction to the effect of the harmful agent.

Inflammation usually causes leukocytosis. In this case the increased leukocyte count in the blood is due to the influence exerted by the focus of inflammation and the products of tissue disintegration on the function of blood distribution and hematopoiesis. Chemical substances capable of causing pathologic leukocytosis include various proteins, especially foreign, nucleic acid and toxic doses of arsenic.

Leukocytosis is also observed in primary lesions in the nervous system, as in trauma of the diencephalon.

Changes in the leukocytic composition of the blood may also be observed in dysfunction of the endocrine glands, for example, the thyroid and the hypophysis.

The following forms of leukocytosis are distinguished:

Neutrophilia which most commonly occurs in infections, for example, strepto- and staphylococcus infections, in certain forms of poisoning and in malignant neoplasms. No small part in the origin of neutrophilia is apparently played by factors which intensify proteolytic processes and phenomena of phagocytosis. In evaluating neutrophilia it is also necessary to take into account the data concerning the so-called nuclear shift in the leukocytic formula.

Eosinophilia which is observed in certain infectious diseases, especially in those characterised by phenomena of an allergic character, as in scarlet fever, chronic sepsis, rheumatism, etc. Allergic diseases, for example, bronchial asthma, urticaria, serum sickness, hay fever, etc., are accompanied by eosinophilia. Eosinophilia is especially characteristic of diseases caused by infestation with helminths and other parasites; for example, in infestation with echinococci, tape-worms, trichinae, etc., the eosinophil content in the blood may in rare cases reach 50-60 per cent. Some authors regard eosinophilia as an indication of the organism's resistance to the harmful agent.

Basophilia which occurs rather rarely. It is characteristic particularly of myeloid leukemia, hemophilia and certain other blood diseases (for example, true polycythemia).

Lymphocytosis which is characterised by an absolute or relative increase in the number of lymphocytes. It occurs in chronic infections, as tuberculosis and syphilis, as well as in thyroidism, acromegaly, nutritional disturbances, neurasthenia and certain other diseases of the central nervous system. Protozoan diseases involving enlargement of the spleen are not infrequently accompanied by lymphocytosis.

Monocytosis most frequently occurs in connection with general changes in the leukocytic formula but is also observed independent of them. In certain infections (typhus, German measles, smallpox, measles, etc.) monocytosis usually denotes the termination of the disease. Parasitic diseases, and certain blood diseases, for example, Banti's syndrome* are also often accompanied by monocytosis. Monocytosis is generally thought to be associated with hyperfunction of the reticuloendothelium from whose cells monocytes originate. In chronic infections monocytosis is not infrequently combined with hyperplasia of the reticuloendothelium and appearance in the blood of histiocytic elements related to monocytes—macrophages containing inclusions of particles of destroyed tissue elements.

Leukopenia which is most frequently observed in toxic forms of certain infections, for example, typhoid fever, influenza and dysentery. It also arises as a result of poisoning with benzene, arsenic and sulfonamides, and the action of ionising radiation which depresses the function of the hematopoietic apparatus.

The leukocyte count may decrease to 2,000-1,000 and even more per 1 mm³ of blood, the leukocytic formula altering at the same time (lymphopenia, neutropenia, eosinopenia). In addition to depressed function of the bone marrow, leukopenia may be based on a disturbance in distribution of leukocytes in various vascular regions. But such distributive leukopenia is transient and is usually replaced by leukocytosis.

Sometimes leukopenia is manifested in the form of *agranulocytosis* which is characterised by a decrease or even absence of granular leukocytes in the blood. Agranulocytosis may be caused by toxic substances, large doses of aminopyrine and barbiturates, and may arise in radiation sickness, certain avitaminoses (especially avitaminosis B₁) and other nutritional disturbances.

Qualitative Changes in Leukocytes. In evaluating the various forms of leukocytosis and leukopenia certain importance is attached not only to the percentage of the different forms of white blood cells, but also to *their quality, the character and degree of lobulation of the neutrophil nuclei* in particular.

It has been demonstrated that the degree of lobulation is an index of the leukocyte's maturity. In some cases (for example, in certain

* Banti's syndrome is a complex of phenomena characterised by a considerable chronic enlargement of the spleen accompanied by slowly developing anaemia. Its later stage includes cirrhosis of the liver and ascites.

infections) the number of nonfilamented neutrophils increases (shift to the left, according to Arneth's classification), which indicates an increase in the relative content of neutrophils with fewer lobes to their nuclei, denoting stimulation of the bone marrow and delivery of younger neutrophils into the circulating blood.

Schilling's classification of neutrophils is more convenient. According to this classification, neutrophils are divided into four groups tabulated from left to right: 1) myelocytes, 2) juveniles, 3) band forms and 4) segmented mature neutrophils.

Segmented forms constitute the main mass of neutrophils. In pathologic leukocytoses accompanied by an increased number of neutrophils, the number of band and juvenile forms of neutrophils often increases and myelocytes appear, i.e., there is a *shift of neutrophils to the left*. Not only the form and structure of the nucleus, but also the structure of the protoplasm are important.

The following table shows possible shifts of the leukocytic formula in some infectious diseases.

Leukocyte Count—Normal and in Pathology

State of the organism	Number of leukocytes			Neutrophils				Young neutro- philes
		Basophils	Eosinophils	Myelo- cytes	Juven- ile forms	Band forms		
Normal	6,000	1	2	0	0	4	61	26
Possible variations within normal	5,000-8,000	0-1	2-4	0	0-1	3-5	55-67	23-35
Shift to the left (regenerative) in sepsis	15,000	0	1	0	15	25	40	14
Shift to the left (band-form) in typhoid fever	4,500	0	0	0	0	30	25	40
							55	

Determination of the content of each form of leukocyte per unit of blood volume in absolute figures is superior to the percentage leukocytic formula for judging the functional state of leukopoiesis. This method makes it possible to establish leukocytic type profiles for various diseases.

The presence of young, immature forms of leukocytes, never found in the blood of a normal organism, is important for evaluating the functional state of the bone marrow. The presence of young

forms usually denotes intensified regenerative processes. The appearance of *myelo-* and *lymphoblasts*, *myelocytes* and *juvenile cells* in the blood stream is particularly significant.

Myelocytes differ from mature granulocytes by the structure of their nucleus (unsegmented, loose, round or fabiform), larger size, larger granularity and basophilic protoplasm. Myelocytes originate from less mature cells—promyelocytes which derive from myeloblasts or hemocytoblasts. Myeloblasts are larger than myelocytes and have a larger, round, unsegmented nucleus with nucleoli and a delicate retiform structure; their protoplasm is basophilic and nongranular, or may have feebly marked azurophilic granularity.

Consequently, the appearance of younger forms of granulocytes in the blood stream must be considered a sign of qualitative changes developing in the leukocytes. These granulocytes are characterised by their larger size, unsegmented nucleus, basophilic protoplasm and low granularity.

Lymphoblasts must be regarded as immature forms of agranulocytes, particularly lymphocytes. They are large cells with a round or indented nucleus and basophilic protoplasm forming a narrow border round the large nucleus. Externally lymphoblasts, having no granularity, resemble myeloblasts, but are somewhat different in the structure of their protoplasm and the nucleus.

Several theories attempt to explain the development of qualitative deviations in the morphological composition of the blood and in the activity of the hematopoietic organs on the basis of the data concerning the genesis of the different types of blood cells. The problem can probably be solved by establishing the ways of differentiation of the blood elements and of the possible transformation of one element into another (Fig. 83).

According to the *unitarian theory* (Maximov et al), the reticular cell of the hematopoietic organs is the parental hemocytoblasts from which myeloblasts, lymphoblasts and erythroblasts derive in the process of hematopoiesis.

Myeloblasts are parental cells of promyelocytes which are successively, by differentiation, transformed into myelocytes and mature granulocytes. Lymphoblasts are successively transformed into agranulocytes. Erythroblasts, which are identical with myeloblasts, are transformed into erythrocytes through a series of cells. Thus, the principal parental cells are interrelated by the common parental cell (hemocytoblast) and are similarly capable of transformation. The more modern *moderate unitarian theory* (Pappenheim, A. N. Kryukov) recognises the origin of blood cells from hemocytoblasts and the possibility of mutual transformations of lymphoblasts, myeloblasts and erythroblasts only in pathology, but denies such possibility in the mature normal organism.

According to the *dualist theory of hematopoiesis* (Naegeli), there are not one, but two stem cells—the lymphoblast which gives rise to agranulocytes, and the myeloblast from which granulocytes originate. Mutual transformation of cells of the lymphoid and myeloid series is impossible. The paternal erythrocyte is the erythroblast which is identical with the myeloblast. All these cells are formed during the embryonal period from mesenchymal cells. During the postembryonal period the available cells only mature and differentiate in a definite direction.

Lastly, according to the *trialist theory* (Aschoff), there is also a third stem cell—histiocyte—which is the parent of promonocytes and monocytes.

The moderately unitarian theory has won the greatest acceptance since it is supported by experimental data on hematopoiesis in the bone marrow and tissue cultures.

Large cells with abundant protoplasm, weak basophilia and sometimes with azurophilic granularity may occur in the circulating blood in cases of pathologic hematopoiesis; these are *histiocytes*—reticuloendothelial cells. They often show signs of phagocytosis (inclusions of products of disintegration of cells, erythrocytes, pigment, etc.). It is supposed that they give rise to monocytes with which they have a good deal in common. Histiocytes appear in the blood current in septic infections and in all cases of stimulation and proliferation of reticuloendothelial elements.

The pathologic forms of leukocytes also include plasmocytes. These are cells with strongly pronounced basophilia of the protoplasm not infrequently containing vacuoles. Their origin has not been completely established as yet.

In some cases the white blood cells are characterised by various anomalies, signs of degeneration in the structure of the nucleus and protoplasm. The signs of degeneration include appearance of vacuoles in the protoplasm, changes in the structure of the nuclei with phenomena of chromatolysis, and changes in the granularity of the neutrophils (so-called toxic granularity). The degenerative changes in the leukocytes denote degenerative phenomena in the hematopoietic organs, although degenerative forms of leukocytes may also arise as a result of the action of harmful agents on leukocytes in the blood itself.

The various changes in the leukocytes are usually accounted for by the changes occurring in the hematopoietic apparatus, for example, the phenomena of regeneration and degeneration, hyperplasia, depression and intensification of the function of the bone marrow accompanied in some cases by leukocytosis and in others by leukopenia. Hyperplasia of the bone marrow is usually of an adaptive character, as is the case, for example, in anemias and leukocytoses. Hypoplasia of the bone marrow may arise on the basis of general nutritional disturbances, following poisoning (for example, with benzene), or exposure to ionising radiation. In addition to the bone marrow, the lymphatic system and spleen also contribute to the quantitative and qualitative changes in the leukocytes. The distribution of the blood and the destruction of the leukocytes in the blood itself are likewise of some importance.

Leukemias

Leukemias constitute a special group of leukocytic disturbances. These disturbances imply stable diseases of the organism characterised by systemic affections of the hematopoietic organs.

Unlike the usual pathologic leukocytoses, leukemias are characterised by systemic changes in the hematopoietic organs with a considerable, progressive and stable increase in the number of leukocytes, reaching several hundred thousand per 1 mm³, and appearance of immature forms of leukocytes (as myelocytes, myeloblasts, lymphoblasts, etc.) in the blood.

There are forms of leukemia in which the number of leukocytes in the blood is normal or even low—*aleukemic leukemia*. These forms are also characterised by disturbed processes of leukocyte formation in the bone marrow and other hematopoietic organs.

Three forms of leukemias are distinguished: myeloses, lymphadenoses and reticuloendothelioses (Fig. 84).

Myeloses (myeloid leukemias) are characterised by abundant development of myeloid tissue. In severe cases of myeloses the number of leukocytes reaches 1,000,000 and more per 1 mm³ of blood. In myeloses the blood contains many myelocytes and sometimes myeloblasts. Not infrequently immature forms of eosinophils and basophils, as well as erythroblasts, are observed.

In myeloses extramedullary foci of myeloid hematopoiesis usually develop in the liver, kidneys and spleen. The latter becomes greatly enlarged.

Sometimes the blood does not show any marked changes in the leukocyte count (*aleukemic myelosis*).

Aleukemic myelosis is characterised by a clinical picture typical of leukemias; myeloid cells are not infrequently observed with the leukocyte count normal or even subnormal.

Lymphadenoses (lymphocytic leukemias) are accompanied by an increased concentration in the blood of small lymphocytes, sometimes with young atypical forms. Usually the number of white cells does not exceed 100,000 per 1 mm³. There are rare forms of lymphadenoses characterised by invasion of the blood by large lymphoblast-type lymphocytes. These forms run a malignant course. The large number of foci of lymphocyte formation in various organs in this disease suggests that lymphocytes develop from indifferent mesenchymal cells in which all tissues abound. In these cases the spleen and lymph nodes (cervical, inguinal, axillary, mesenteric) are enlarged, and hyperplasia of the lymphoid elements of the bone marrow, liver and skin is observed.

Aleukemic forms of lymphadenoses run the same course as leukemic lymphadenoses, but no increase in the number of leukocytes in the blood is observed. The leukocytic formula is altered in the direction of lymphocytosis with lymphoblasts sometimes occurring among the lymphocytes. The aleukemic form may change to the leukemic form, especially towards the end of the disease if the latter runs an unfavourable course.

Reticuloses occur more rarely. Proliferation of reticular cells takes place in the bone marrow, the spleen, lymph nodes and liver. The

leukemic form of reticuloses may be characterised by a greatly increased number of monocytes in the blood. In most cases, however, reticuloses are aleukemic.

Acute forms of leukemias, especially acute myelosis, occur suddenly and last several weeks. *Chronic forms* may drag on for years. Anemia usually develops and sometimes takes a malignant course. Hemorrhages, fever and increasing debility are not infrequent. The metabolism in leukemia patients is disturbed. Purine metabolism is sharply increased, especially in the myeloid form, due to increased disintegration of leukocytes and their nuclei.

The *etiology of leukemias* is not quite clear as yet. The character of the clinical course and the multiplicity of foci of proliferation of leukocytes suggest that leukemias involve *malignant blastomatous growth*. This is confirmed by the rapid proliferation of the cells, their atypical structure, infiltrative growth, diminished oxidative processes and increased anaerobic glycolysis, cachexia and almost inevitable destruction of the organism.

It is also well known that continued administration of small doses of cancerogenic substances—methylcholanthrene or benzpyrene—produces leukemia in chickens and mice. Leukemias have also been successfully transplanted to mice, rats and guinea pigs.

The possibility of producing leukemia in chickens by transplanting the noncellular infiltrate of the emulsion taken from the organs of fowls affected with leukemia has been demonstrated. For this reason some investigators consider the active principle in the origin of experimental leukemia in chickens to be a filtrable virus. It is debatable, however, whether a complete analogy between leukemia in fowls and leukemia in man can be drawn.

Lastly, certain data indicate that leukemia, like malignant tumours, may arise as a result of prolonged exposure of the organism to ionising radiation.

There is also another and less substantiated view which considers leukemias (especially acute leukemias) to be systemic inflammatory hyperplastic processes developing in the hematopoietic apparatus on the basis of infections.

In addition to the aforedescribed forms of leukemias there are affections of the hematopoietic apparatus caused by development of neoplastic growth (lymphosarcomatosis, lymphogranulomatosis) in it. These forms involve particular parts of the hematopoietic apparatus but do not show the specific changes in the organs of hematopoiesis and the blood characteristic of leukemias.

Changes in Thrombocytes

The changes in the content of thrombocytes (blood platelets) in the blood are most frequently associated with dysfunction of the hematopoietic apparatus.

A decrease in the number of thrombocytes (*thrombopenia*) is observed in anemias and leukemias, especially in severe forms of these diseases (for example, pernicious and aplastic anemias). The number of megakaryocytes, the progenitors of blood platelets, is observed to be reduced accordingly. A decrease in the number of blood platelets is also observed in certain severe infectious diseases, as in scarlet fever, smallpox, dysentery, sepsis and, especially, hemorrhages. Thrombopenia also results from the action of physical and chemical agents, for example, ionising radiation and poisoning with benzene, thorium and quinine.

A considerable decrease in blood platelets is observed in thrombopenia. Thrombopenia and hemorrhagic phenomena are noted in certain affections of the diencephalon and the hypophysis.

Since the blood platelets play a very important part in the process of blood clotting, thrombopenia is usually accompanied by hemorrhages from the gastrointestinal mucosa and extravasations into the skin and mucous membranes (especially of the gastrointestinal tract). An increase in the number of thrombocytes in the blood (*thrombocytosis*) is observed in various infectious diseases, especially in cholera, and after removal of the spleen where they are, like the erythrocytes, normally destroyed. In infectious diseases, especially during convalescence, the number of thrombocytes in the blood increases; a certain increase in the immune bodies is noted at the same time.

Sometimes the quantitative changes in blood platelets are accompanied by their *qualitative changes*, as in thrombasthenia. In this disease the number of platelets is either barely affected or is somewhat increased, but the properties of the platelets are altered, i.e., they lose their agglutinating ability. Some cases show pycnosis of the platelets, anisocytosis of the platelets (inequality in their sizes) and basophilia. In these cases the blood clotting time is normal but the bleeding time is longer, probably because the impaired quality of the thrombocytes leads to weakened retraction of the blood clot.

Changes in the Biochemical Composition of the Blood

For biochemical studies mainly serum or plasma are used because of their more constant composition.

Changes in Proteins. A decreased concentration of proteins in the blood plasma (*hypoproteinemia*) is observed in connection with profound metabolic disorders, as in prolonged starvation, cachexia, certain affections of the liver and kidneys, following hemorrhages, and formation of extensive transudates and exudates. One of the manifestations of these disorders is hydremia (diluted blood) and decreased colloid osmotic pressure of the plasma (this pressure is normally maintained mainly by albumin).

Experimentally hypoproteinemia can be produced in animals by protein starvation or bleeding with subsequent administration of an erythrocyte suspension in Ringer's solution.

Enrichment of the blood plasma with protein is relative and occurs as a result of hemoconcentration (anhydremia), for example, in severe diarrheas, burns, pernicious vomiting and other states accompanied by a loss of water.

It is very important to determine the altered proportions of the different proteins. Of the total amount of protein (7.75 per cent), 0.25 per cent is fibrinogen, 2.5 per cent is globulin and 5 per cent (more than the others) is albumin. Variations in the protein composition of the blood are possible not only in different people, but also in the same person at different times of the day.

Albumins, the most dispersive proteins, bind water more than do the other proteins (1 g of albumin is capable of binding 18 ml of water). Albumins are carriers of salts, bilirubin and urobilin. Gamma-globulins are carriers of immune bodies, beta-globulins contain the lipids and alpha-globulins—the hormones and vitamins. Alpha- and beta-globulins increase in the blood mainly in infectious diseases, alpha- and gamma-globulins—in nephroses.

The *fibrinogen of the blood plasma increases* (sometimes to 1.5 per cent) in various infections (for example, in tuberculosis, pneumonia), especially frequently in nephroses. It *decreases* less frequently, after severe changes in the liver which is the main site of fibrinogen formation. This is also observed in experiments after extirpation of the liver or its poisoning with phosphorus or chloroform.

It is essentially important to *determine the correlation* of albumins and globulins in the serum, which is normally 1.5-2.3. In pathology the changes in the serum proteins for the most part affect the globulins which are even normally subject to certain variations. The changes in the albumin-globulin coefficient are particularly pronounced in chronic infections accompanied by accumulation of antibodies which in their chemical structure belong to globulins. This coefficient is also disturbed in affections of the liver, dysfunction of the cardiovascular system and cachexias, as well as in dysfunction of the central nervous system which regulates metabolism.

Of the protein metabolites mention must primarily be made of the substances which constitute the group of *nonprotein nitrogen*.

The amount of nonprotein nitrogen in the blood varies between 20 and 40 mg%, depending on the individual properties of the organism. As a result of functional insufficiency of the kidneys and certain disorders of the hepatic function a diminution in the blood proteins and phenomena of hydremia combined with an increase in nonprotein nitrogen in the blood (*hyperazotemia*) are often observed. The nonprotein nitrogen in the blood also increases as a result of cachexia of various origin, for example, in blastomatous growth, pernicious anemias, etc.

A deeper insight into the disturbances in the nitrogenous composition of the blood is furnished by studies of the different fractions belonging to the group of substances forming the nonprotein nitrogen of the blood. For example, the amount of *urea*, which normally constitutes 35-50 per cent of the total nonprotein nitrogen, is not infrequently increased. Abundant consumption of nitrogenous food may lead to increased urea in the blood. Starvation and pregnancy lead to a diminution in urea owing to decreased disintegration of nitrogenous substances. An appreciably decreased concentration of urea in the blood is usually observed in diseases of the liver (when the synthesis of urea is weakened) and in tissue acidosis when the ammonia is used in neutralising acids before it is transformed into urea.

Uric acid accumulates in the blood (*hyperuricemia*) in disorders of purine metabolism, for example, in gout. Normally the concentration of uric acid in the blood varies between 3 and 4 mg%. An increase in the concentration of uric acid in the blood is noted before an attack of gout (6-8 mg% and higher).

Increased uric acid in the blood is also observed in leukemia, which is accompanied by intense disintegration of cell elements, and in certain metabolic disorders, for example, in renal diseases and hepatic insufficiency.

Discovery of increased *ammonia* may be indicative of the pathogenesis of diseases of certain organs, for example, the liver and kidneys which participate in deamination of amino acids.

Amino acids, as intermediate protein metabolites, increase in the blood in certain affections of the liver, especially in acute yellow atrophy when the amount of nitrogen of the amino acids may reach 25 mg% and more instead of the normal 5-8 mg%.

Changes in Pigments. Increased bilirubin in the serum—*hyperbilirubinemia*—is observed in liver diseases, most frequently in jaundice. In some forms of jaundice the amount of bilirubin reaches 30-40 mg% (instead of the normal 0.5-1 mg%). In these cases the blood plasma or serum at first turns yellow and subsequently brown-black.

The colour of the serum may also be due to hemolysis of the red blood cells, i.e., be the result of dissolution of hemoglobin out of the red blood cells and its passage into the plasma—*hemoglobinemia*. Hemoglobin derivatives formed as a result of accumulation of toxic substances and active metabolites in the blood and the hematopoietic organs may also accumulate in the serum.

Methemoglobinemia arises as a result of the action of nitrites, ferricyanide, potassium permanganate and potassium chlorate on the blood. Methemoglobin (Mt-Hb) contains oxygen in a nondissociating form. During formation of methemoglobin the ferrous iron of hemoglobin is oxidised to the ferric state, the bivalent iron atom becoming trivalent. Methemoglobin appears in the blood in anaerobic sepsis,

Toxemias of pregnancy and certain forms of autointoxication, for example, as a result of inflammatory diseases of the intestines accompanied by absorption of nitrites from the intestine. Toxic phenomena may develop when 20-40 per cent of hemoglobin is transformed into methemoglobin. Saturation of the blood with methemoglobin above 60 per cent leads to phenomena of increasing hypoxia since release of oxygen to the tissues becomes impossible.

Carboxyhemoglobinemia arises as a result of carbon monoxide poisoning. Carboxyhemoglobin (CO-Hb) dissociates with much greater difficulty than does oxyhemoglobin; moreover, it depresses the dissociation of oxyhemoglobin. Carbon monoxide blocks the respiratory ferment which contains the hemin complex. The ability of hemoglobin to combine with carbon monoxide is 300 times as great as it is to combine with oxygen. An increase in the amount of CO-Hb to 50 per cent produces an oxygen deficiency in the blood and, as a result of it, a disturbance in the function of the nervous system due to affection of the basal ganglia manifested in motor disturbances and clouded consciousness. Of the hemoglobin derivatives mention must also be made of the appearance of porphyrins in the blood and their increased excretion in the urine—*porphyrinuria*. The latter is observed, for example, in cases of intoxication with veronal, trional, etc.

Changes in the content of glucose, fats and lipids, as well as *enzymes*, *hormones* and *vitamins*, specific *antitoxins*, *hemolysins*, *cytotoxins*, etc., are also observed in the blood and plasma. These are discussed in the chapters on the pathology of metabolism and immunity.

Mineral Constituents. The content of mineral constituents in the blood is more constant than that of organic constituents. They are present in the blood in an ionised state, as well as in the form of nondissociated molecules and in combination with colloids, mainly proteins.

Of the different mineral constituents of serum mention must be made of *calcium* and *potassium*. Serum contains 9-11 mg% calcium and 13-23 mg% potassium; whole blood contains 5-7 mg% calcium and 180-220 mg% potassium.

Determination of calcium in the serum is sometimes of considerable diagnostic significance. An increased concentration of calcium in the serum (hypercalcemia) occurs in cases of excessive secretion of the parathyroid hormone and excessive consumption of vitamin D.

A decrease in the content of general and ionised calcium is usually connected with hypofunction of the parathyroid glands; in this case the content of potassium is increased. Changes in the K/Ca quotient are not infrequently due to disturbances in the activity of the vegetative nervous system, calcium having some bearing on the function of the sympathetic and potassium—on the parasympathetic nervous system.

Whole blood contains 170-250 mg% and plasma—315-350 mg% sodium. The concentration of sodium in the blood decreases in fever, anemias and certain other blood diseases, in myxedema and mainly in diseases of the adrenals. Addison's disease in particular. Some increase in sodium is observed in pregnancy. The sodium concentration in the blood fluctuates considerably in edemas.

Whole blood contains 270-320 mg% and plasma—350-380 mg% chlorine. The chlorine content of the blood may increase in hydremia and in infectious diseases. Its concentration sharply diminishes in ileus, in certain renal diseases as a result of retention of chlorine in the tissues, and in vomiting when the organism loses a good deal of hydrochloric acid with the vomit.

Inorganic phosphorus is present in the plasma in a more or less constant quantity (2.8 mg%). A slight decrease in the content of phosphates in the plasma is observed in pregnancy and is apparently associated with bone development in the fetus. The amount of phosphates in the blood is reduced in rickets, for which reason the Ca/P in this disease persists on a high level. The phosphates of the blood increase in muscular work, under the influence of vitamin D, in uremia and certain other pathologic processes.

Iron forms part of hemoglobin. Its content in the blood usually varies with the changes in hemoglobin. Anemia is characterised by a diminution in the content of iron in the blood.

Increasing importance has been attached of late to the presence of microelements—iodine, bromine, fluorine, copper, zinc, manganese, etc.—in the blood. Some researchers ascribe the changes in the content of iodine in the blood to dysfunction of the thyroid gland, of bromine—to dysfunction of the hypophysis and diencephalon, and of fluorine—to dysfunction of the thymus and thyroid.

Changes in the Physicochemical Properties of the Blood

In pathology the blood not infrequently shows changes in its basic physicochemical properties—acid-base balance, specific gravity, osmotic concentration, electroconductivity, surface tension and viscosity.

The changes in the acid-base balance are dealt with in the discussions of alkalosis and acidosis and in the chapter on the pathology of respiration.

The *specific gravity* of the blood (normally 1.050-1.060) depends mainly on the number of erythrocytes, amount of proteins and content of sodium chloride. Disturbances in protein metabolism particularly visibly affect the specific gravity of the blood. The specific gravity of the blood increases as a result of hemoconcentration, for example, in cholera, and decreases in cases of blood dilution—hydremia—in various forms of qualitative starvation.

The *surface tension* of the blood and serum undergoes very slight changes. Such substances as bile acids, soaps and certain metabolites are capable of reducing the surface tension of the blood. The surface tension also decreases in eclampsia, uremia and asphyxia when the amount of such capillary-stimulating substances noticeably increases. Contrariwise, protein deficiency in the blood and phenomena of hydremia increase the surface tension.

The *osmotic pressure* is very constant (7.7-8.1 atm). In the venous blood it is somewhat higher than it is in the arterial blood because the former contains more metabolites. Increased carbon dioxide in the blood, as in cases of respiratory, circulatory and metabolic disturbances, increases the osmotic concentration of the blood owing to the increased dissociation of salts. The *oncotic pressure of the blood* depends mainly on the presence of albumin in it. The osmotic and oncotic properties of the blood and tissues are particularly important in the genesis of edemas.

The *viscosity* of the blood depends on the amount and sizes of formed elements, the proportions of leukocytes and erythrocytes, carbon dioxide saturation, concentration of proteins and proportions of their various fractions in the blood, and partly the mineral composition. If we assume the viscosity of water at 37°C to be unity, the viscosity of the blood in relation to water will normally be 4.5-5. In pathology it may vary between 2 and 20. Anything that contributes to hemococentration increases the viscosity of the blood. The viscosity increases in polycythemia and leukemias, and decreases in anemias and hydremia. Accumulation of carbon dioxide in the blood increases its viscosity because carbon dioxide increases the viscosity of proteins. In exophthalmic goitre (hypofunction of the thyroid) the blood usually grows more viscous owing to slight hemoconcentration; in myxedema, when the function of the thyroid is diminished, the viscosity of the blood decreases.

The viscosity of the blood is particularly affected by blood proteins. An increase in globulins stimulates an increase in the viscosity of the blood, as is the case, for example, in inflammation and certain infectious diseases.

The effect of muscular work and various forms of nutrition on the viscosity of the blood is due mainly to the changes in the proportions of the serum proteins. The viscosity of the serum (normally 1.4-1.9) is affected by all factors which increase ionisation of the proteins; acids and bases, as well as bromides and chlorides increase the viscosity of the blood, whereas neutral, iodine, sodium and potassium salts decrease it.

The *osmotic resistance of erythrocytes* or their stability in hypotonic solutions depends on the properties of the surface layer and hydrophilia of their protein stroma. It varies between a certain minimum and maximum. The normal minimum implies the hypotonicity of a solution in which the least resistant cells are hemolysed

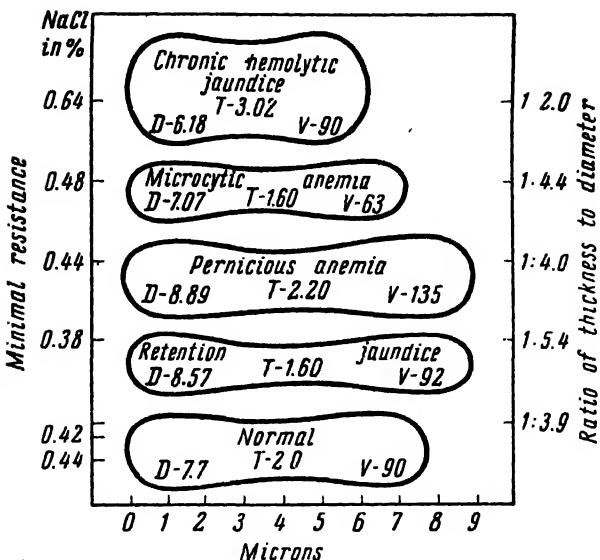


Fig. 85. Diameter (D), thickness (T) and volume (V in μ^3) of erythrocytes in different pathologic states compared with normal (Best and Taylor).

(0.44-0.46 per cent sodium chloride solution), and the normal maximum—the concentration of a solution in which the most resistant cells undergo hemolysis (0.23-0.32 per cent sodium chloride solution). The degree of resistance changes under various pathologic conditions (Fig. 85). For example, obstructive jaundice and pernicious anemia are characterised by increased resistance, whereas hemolytic jaundice and microcytic anemia are characterised by decreased resistance. Wide variations in the resistance of erythrocytes may be observed in diseases of the kidneys due to accumulation in the blood of sodium chloride and products of disintegration which affect the permeability of the cells.

A gradual decrease in the osmotic pressure of the environment causes hemolysis without affecting the stroma of the erythrocytes. Washed and transferred to a hemoglobin solution such erythrocytes are capable of absorbing hemoglobin again, which is *reversible hemolysis*.

The *erythrocyte sedimentation test* (normal—4-10 mm/hr) is based on the physicochemical properties of the blood. Today it is widely used for diagnostic purposes. The *erythrocyte sedimentation rate is quickened by an increase in the globulin and fibrinogen content in the plasma*. The increase in plasma globulin and fibrinogen reduces the erythrocyte charge and thereby contributes to agglutination of the cells, which is conducive to their sedimentation (Fig. 86).

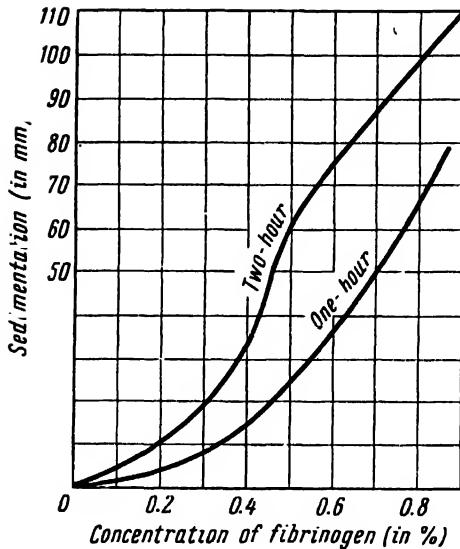


Fig. 86. Erythrocyte sedimentation rate (in mm) with different fibrinogen concentrations in the blood (one- and two-hour observation) (Oakley).

An increase in the number of erythrocytes and a heightened viscosity of the blood causes a slowing of the reaction, for example, in polycythemia; contrariwise, a decrease in the number of erythrocytes and a lowered viscosity of the blood accelerates the sedimentation reaction, as is the case in severe anemias. The erythrocyte sedimentation rate is particularly fast in inflammatory infectious processes (sepsis, tuberculosis, relapsing fever) which are accompanied by a relative or absolute increase in the globulin fraction over albumin in the blood.

Changes in the Process of Blood Clotting. Four basic phases are distinguished in the blood-clotting process: 1) formation of active thromboplastin; 2) conversion of prothrombin into thrombin; 3) formation of a homogeneous clot—conversion of fibrinogen into fibrin; 4) retraction of the blood clot, i.e., contraction of the fibrin threads and discharge of serum; the retraction occurs with the participation of retractozyme, an enzyme present in the blood platelets.

The process of blood clotting consists in transformation of soluble fibrinogen (factor I) into insoluble fibrin under the influence of thrombin. Thrombin is the product of transformation of prothrombin (factor II) under the action of the activator—thromboplastin or thrombokinase (factor III) in the presence of Ca (factor IV); tissue thromboplastin and thromboplastic elements of the blood are necessary for the formation of active plasma thromboplastin. The formation of prothrombin requires vitamin K.

Other factors of albuminous nature also participate in the process of blood clotting *by activating the conversion of prothrombin into thrombin*. They include: accelerator-globulin-labile factor V (proaccelerin or AC globulin), factor VI (accelerin), and factor VII (pro-) convertin. The appearance of a minimum of thrombin suffices for its further automatic formation since thrombin activates the transformation of factor V into active factor VI, which in its turn accelerates thrombogenesis (autocatalytic process).

The following factors participate in the formation of active thromboplastin: factor VII or antihemophilic globulin, factor IX (plasma thromboplastic component or Christmas factor), factor X and plasma thromboplastin antecedent (PTA). Several other factors present in the blood platelets also take part in blood clotting; these are: factor 1—AC globulin adsorbed on the platelets, factor 2 which helps in the reaction between fibrinogen and thrombin in forming fibrin, factor 3 which participates in the formation of thromboplastin, factor 4—antiheparin, etc.

Certain other, as yet insufficiently studied factors, for example, the Stewart factor and the Hageman factor, also apparently have some bearing on blood clotting.

Furthermore, the process of blood clotting depends in its operation on the function of the anticoagulation system (heparin and antithrombin), in virtue of which the blood maintains its liquid state.

The process of blood clotting is schematically shown in Fig. 87.

The various factors participating in the blood-clotting process are connected with the functions of the different organs and tissues; for example, prothrombin and heparin (blood-clotting inhibitor) are formed in the liver, while the bone marrow produces the blood platelets which are particularly important for blood clotting.

Since the organs and tissues participating in the production of a number of blood-clotting factors are regulated by the activity of the nervous system, its disorders may affect the process of blood clotting.

An insufficiency or absence of any of the components participating in the blood-clotting process may lead to changes in blood clotting; increased clotting leads to thrombosis, and decreased clotting—to hemorrhagic disorders.

A *diminution in or slowing of blood clotting* leads to phenomena of hemorrhagic diathesis in whose pathogenesis a certain part is also played by impairment of the vascular walls. Diminished blood clotting may also be due to:

1. Insufficient production or reduced activity of thromboplastin, which may be the result of decrease in or absence of antihemophilic globulin—factor VIII—in the plasma (hemophilia A), insufficiency or absence of the plasma thromboplastic component—factor IX (hemophilia B), and a number of other factors which activate thromboplastin.

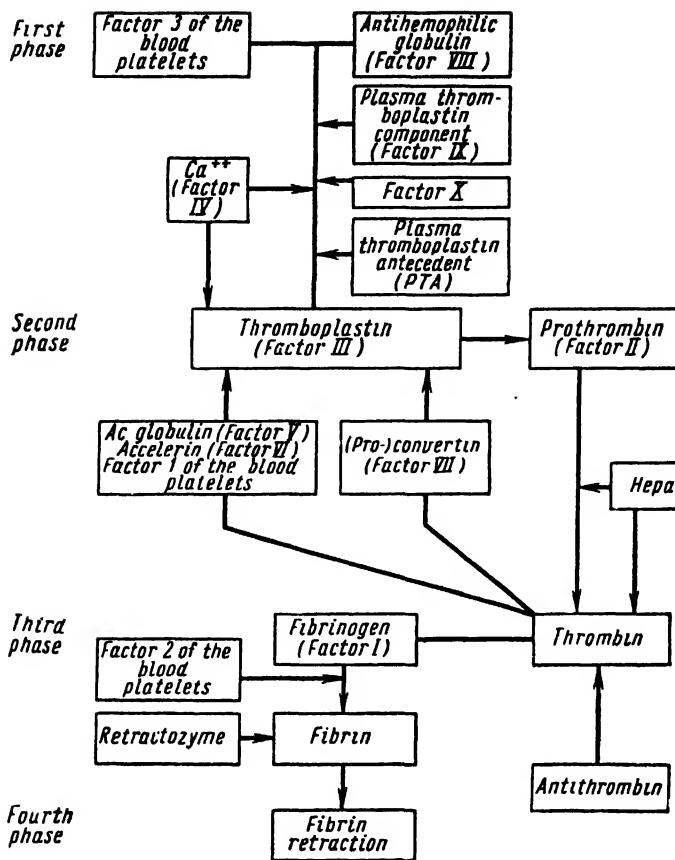


Fig. 87. Diagram of blood clotting.

2. Insufficient formation of thrombin due to a decrease in prothrombin, AC globulin and convertin. Prothrombin (glucoprotein) is synthesised mainly in the liver. Production of prothrombin is stimulated by vitamin K. Insufficient vitamin K absorption and the resultant diminution in prothrombin formation may occur in mechanical jaundice in which failure of bile and the bile acids it contains to be delivered to the intestines hinders absorption of vitamin K. Insufficient formation of vitamin K, which causes a tendency toward hemorrhages may take place in the newborn in connection with an inadequate intestinal flora required for the formation of vitamin K. A tendency toward hemorrhages may also be due to a weak hepatic function, since in the latter case administration of vitamin K fails to activate the production of prothrombin by the liver.

Diminished blood clotting can be observed in experiment involving injuries to and extirpation of the liver, acute hepatic intoxication, such as phosphorus poisoning and chloroform anesthesia, and anaphylactic shock.

AC globulin deficiency gives rise to parahemophilia. Blood clotting rarely diminishes as a result of convertin deficiency.

3. *Fibrinogenopenia* and *afibrinogenemia*—respectively a decrease in and complete absence of fibrinogen in the blood; these conditions may be due to the presence of fibrinolysins in the blood. Both conditions may be hereditary. In these conditions the blood does not clot outside the organism for as long as 24 hours. Acquired fibrinogenopenia and the hemorrhagic diathesis associated with it may result from liver affections in cirrhoses, subacute dystrophy, sometimes in pulmonary diseases of tuberculous origin, and in affections of the bone marrow. In such cases the decreased fibrinogen in the blood is due to its diminished formation. However, in diffuse affections of the liver hemorrhagic diathesis, which was formerly explained by fibrinogenopenia, is now considered to be the result of disturbances in the production of prothrombin, proconvertin and AC globulin. Fibrinogenopenia may also arise as a result of surgical intervention in the lungs, and pancreas, in cases of acute radiation sickness and, especially separation of the placenta and intrauterine death of the fetus. In affections of the aforementioned organs the blood apparently acquires enzymes which transform the inactive profibrinolysin into active fibrinolysin and the latter dissolves the fibrinogen.

4. *Thrombopenia* is a decrease in the number of thrombocytes. The most strongly pronounced form of this disease is Werlhof's disease or idiopathic thrombocytopenic purpura characterised by extravasation into the skin and mucosa. In this disease the maturation of megakaryocytes is disturbed. The number of thrombocytes in the peripheral blood decreases from the normal 100,000-300,000 per 1 mm³ to 30,000 and less. The general blood-clotting mechanism is but slightly disturbed, and only the retraction of the clot is slowed down, the bleeding time is noticeably prolonged and the spleen is enlarged. Thrombopenia is also observed in acute and chronic leukemias, sometimes in infections and intoxications, and under the influence of radioactive radiations.

A tendency to hemorrhages may also arise as a result of increased production by the organism of substances which inhibit blood clotting (heparin- or antithrombinlike substances) or artificial administration of anticoagulants—heparin, hirudin or dicumarol. A deficiency of ionised calcium in the blood may also play a certain part; for example, administration of oxalates or phosphates into the blood leads to a decrease in calcium; in mechanical jaundice the bile acids may also bind the calcium ions and thereby reduce blood coagulability. Lastly, the tendency to hemorrhages may be the result

of disturbances in the properties of the capillary endothelium. For example, in severe forms of jaundice the tendency to hemorrhages is due to the toxic effect of bile acids on the capillary endothelium; capillary bleeding is observed in avitaminosis C and in certain other diseases.

Increased or accelerated blood clotting takes place in pathologic processes accompanied by an increase in or greater activity of the factors which intensify the blood-clotting process. These factors include:

1) injury to the vessels and slowing of the blood current; in these cases thromboplastin is liberated, not only from the thrombocytes, but also from the walls of the vessels;

2) intensification of formation or activation of thromboplastin, for example, in connection with destruction of cells in cases of inflammation, especially of an infectious character, in blood transfusions and in administration of serums or extracts containing thromboplastin and thrombin;

3) excessive administration of vitamin K, which produces hyperthrombinemia and accelerates blood clotting, especially in cases of previous vitamin K deficiency, as in catarrhal jaundice or in the newborn (in cases of insufficient formation of vitamin K in the intestines);

4) increased fibrinogen and globulin in the blood leading to increased agglutination of blood platelets.

PATHOLOGY OF BLOOD CIRCULATION

Normal blood circulation ensures the supply of blood to the tissues and organs, delivery of oxygen and nutritive substances, and elimination of metabolites. Circulatory disorders are due to impairment of the circulatory apparatus, mainly disturbances in the activity of the cardiovascular system, and in the functions of the blood depots—spleen, liver, skin and lungs.

However, in the pathogenesis of circulatory disorders it is also necessary to consider the closest connections between the blood circulation, the blood system and respiration. The coordinated activity of the circulatory, respiratory and blood systems satisfies the oxygen requirements of the organism. The oxygen requirements are determined by metabolism, for which reason metabolism plays a very important part in the blood circulation.

All the aforementioned complex processes are coordinated and regulated by the nervous system. For example, a rise in blood pressure in the aorta and the common carotid artery reflexly causes (from the carotid sinus and the arch of the aorta) a slowing and weakening of cardiac contractions, a dilation of the peripheral vascular bed and a drop in general blood pressure, whereas a drop in aortic blood pressure reflexly causes an acceleration and intensification of the cardiac rhythm, an increase in vascular tone, a contraction of the peripheral vessels and an elevation of the general blood pressure.

The vasomotor reflexes from the aortic and carotid reflexogenic zones spread over the greater part of the vascular system. In cases of a considerable drop in blood pressure the reflex influences extend from these zones also to the blood depots which participate in maintaining the mass of circulating blood on a certain level. The aortic and sinocarotid zones also react to changes in the mass of the blood, as well as to oxygen deficiency and excess of carbon dioxide in the blood. This accounts for the community of many reflexes to the blood circulation and respiration. The existence of such reflexogenic

zones has now been demonstrated also in the vessels of the heart and spleen, in the pulmonary artery, at the bifurcation of the abdominal aorta and in certain parts of the venous system.

CARDIAC ADAPTABILITY AND ITS DISTURBANCES

The mass of blood ejected during each systole into the aorta is normally 50-60 ml and is called the *stroke* or *systolic volume*. The value of the systolic volume is determined by: 1) the differences in pressure in the ventricles and the large arteries of the systemic or pulmonary circulation, 2) duration of the phase of blood ejection from the ventricles, and 3) resistance at the mouth of the aorta and pulmonary artery, depending on their lumens and viscosity of the blood. The systolic volume is affected the most by the first two factors. The amount of blood which is ejected by the heart in one minute and equals the stroke volume multiplied by the number of cardiac contractions is called the *minute volume* (3.5-4.5 litres). The minute volume and the resistance in the aorta determine the value of the work of the heart. With a pulse rate of 72 per minute the mean value of heart work is 0.2 kg/m per second.

Owing to the ability of the heart to *alter the stroke volume and number of systolic contractions* a relative constancy of blood pressure is maintained in all cases involving possibilities of its disturbance. Unfavourable conditions for heart action arising in the heart itself, in large vessels or in the peripheral circulation lead to changes in blood pressure and rate of the blood flow. In such cases new relations between the heart and the peripheral vascular bed are established.

Increased heart action due to obstruction in pulmonary circulation may be stimulated in the dog by constriction of the pulmonary artery with a ligature. Constriction of the pulmonary artery does not immediately alter the blood pressure in the systemic circulation. The amplitude of right intraventricular pressure gradually increases, denoting intensification of the heart's action, increase in its stroke volume and adaptation to the obstruction. Greater constriction of the pulmonary artery is marked first by an increased and then decreased stroke volume and appreciable drop in arterial pressure. If the ligature is removed and the constriction is thereby discontinued, the stroke volume of the heart and the blood pressure return to normal.

The ability of the heart to alter its output within certain limits determines the extent of its *adaptability*.

This ability of the heart to adapt its output to altered conditions depends on the properties of the *neuromuscular system of the heart* and on the influences exerted on the heart by extracardiac *neural* and *neurohumoral* mechanisms, including neurohormonal mechanisms.

The hemodynamic disorders caused by disturbances in heart

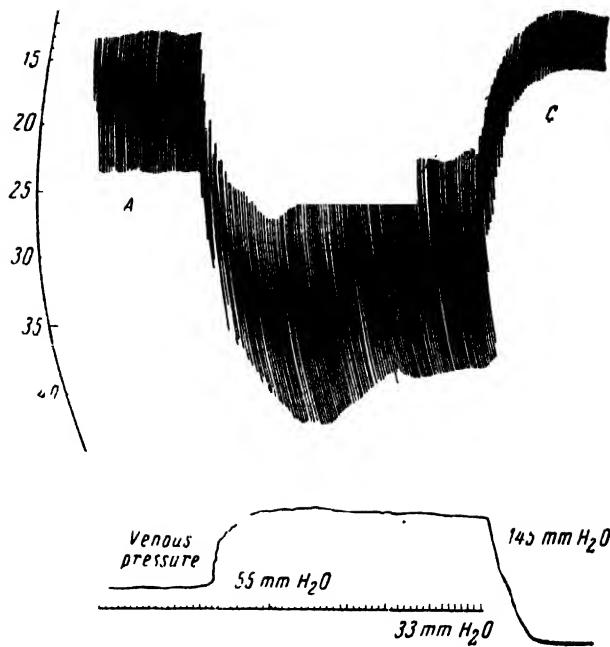


Fig. 88. Effect of dilatation of the heart on its stroke volume (Starling). Experiment on cardiopulmonary preparation.

The curved line on the side shows the recording of ventricular volume in cc by the cardiometer.

Upper curve—strength of cardiac contractions under different pressures (A, B, C) in the vena cava; the lower points of the curve correspond to the volume of the heart at the end of diastole, the upper points—end of systole. The distance between the upper and lower points of the curve of cardiac contractions, i.e., the amplitude of oscillations, corresponds to the systolic volume.

Lower curve—venous pressure in mm H₂O.

action (for example, as a result of impairment of the valvular apparatus) primarily affect the character of myocardial contractions. Any increased filling of the heart cavities with blood—*increase in diastolic filling*, if it is not excessive—*leads to an increase in the stroke volume* and, contrariwise, any decrease in the filling of the heart leads to a decrease in the stroke volume (Fig. 88). Elevation of arterial blood pressure causes increased heart action within limits required to overcome the obstruction in the arterial system. On the other hand, a drop in pressure at first causes an increase and then a decrease in the minute volume. The minute volume is also altered correspondingly as a result of changes in the stroke volume, in the number of cardiac contractions, or both.

The increased stroke volume and the associated intensification of cardiac contractions were formerly explained only by increased diastolic filling of the heart and the extent of initial tension of the fibres of the heart muscle (Starling's law of the heart). In reality, however,

it also depends on the influences exerted on the heart by the extra-cardiac nervous system which, in addition to the heart rate, regulates the metabolism and blood supply of the heart muscle. By disturbing the neural regulation of the heart, Pavlov for the first time observed on a preliminarily weakened heart that stimulation of certain efferent nerve fibres raised the muscle tone of the ventricles and simultaneously reduced their volume.

In pathologic circulatory disturbances adaptive phenomena develop as a result of reflex processes, due to stimulation of the receptors in the mouths of the venae cavae in cases of disturbances in the function of the right ventricle and of the receptors of the vessels of the pulmonary circulation in cases of left ventricular insufficiency.

Adaptive cardiac phenomena may also arise when altered blood pressure acts on the receptor apparatus in other vascular zones and in the heart itself. In addition to the changes in heart action caused by disturbances in blood pressure, the reflex changes in the tone of the peripheral vessels and the mobilisation of the depot blood are also of adaptive significance. For example, when the blood pressure drops, the adaptation of the organism may manifest itself in accelerated heart action, constriction of the peripheral vessels and mobilisation of the depot blood. A sudden elevation of blood pressure may be accompanied by a slowing of the heart's action and dilation of the peripheral vessels.

Hypertrophy of the Heart Muscle

In cases where increased functional requirements are made of the heart for a long time the result is *hypertrophy of the heart*, especially of its parts functioning under an increased load. In such cases every fibre of the heart muscle increases in size. In hypertrophy the human heart may weigh 400-500 g and more instead of the normal 250-300 g.

In addition to increased and prolonged work, development of hypertrophy of the heart also requires an increased blood supply and nutrition for the heart muscle. Owing to nervous regulation the three factors often coincide.

Hypertrophy of the heart is usually combined with *dilatation* of the heart cavities. This dilatation largely accounts for the increase in the stroke volume. In cases of increased heart action the ventricles are filled with more blood which is ejected by them in each systole into the large vessels. The dilatation of the heart cavities due to increased filling causes greater tension of the muscle fibres, but the latter do not change in size (*tonogenic dilatation*).

The extent of cardiac dilatation is determined by the state of the heart muscle and of the conduction system of the heart. The easier the reflex stimulation of the muscle fibres and the stronger the heart

muscle, the greater its ability to develop additional energy and the lesser the dilatation required to produce contraction.

Hypertrophy of the heart involving its dilatation is called *eccentric*, and hypertrophy without dilatation—*concentric*.

Hypertrophy of the heart may be physiologic and pathologic.

Physiologic hypertrophy may arise as a result of increased muscular work and even moderate physical exercise. Such hypertrophy is characterised by an increase in the weight of the muscles of all parts of the heart and maintenance of a certain correspondence between the weight of the heart and the rest of the muscular mass of the body.

Pathologic hypertrophy develops as a result of an *increased minute volume of the heart* due to its increased filling, greater obstacles to blood ejection, and sometimes as a result of an accelerated heart rhythm. In such cases the heart's action, the blood supply to the heart muscle and the metabolism in the heart increase. In intense pathologic hypertrophy of the heart muscle the latter suffers from oxygen deficiency and part of the energy necessary for contraction is covered by anaerobic consumption of carbohydrates. As a result the content of lactic acid in the heart muscle and in the outflowing blood increases, acidosis develops and the contractility of the heart muscle gradually weakens.

The mass of the hypertrophied heart muscle increases irrespective of the increase in the mass of skeletal muscles. However, it is not always possible to draw a clear line between physiologic and pathologic hypertrophy of the heart muscle.

Experimentally hypertrophy of the ventricles can be produced in rabbits by constriction of the aorta, artificial injury to the heart valves or prolonged administration of adrenalin which constricts the peripheral vessels and elevates the blood pressure. Hypertrophy of the heart also develops in pups as a result of artificial constriction of the aorta or pulmonary artery. It takes long and strenuous work of the heart to develop hypertrophy. The part of the heart that must work the harder and overcome the resistance to the blood flow is the one which is mainly hypertrophied.

Hypertrophy of the ventricles in *valvular diseases of the heart*, which most frequently develops in the left ventricle as a result of its greater filling, hypertrophy of the left ventricle in *hypertensive vascular disease* due to prolonged elevation of arterial pressure and hypertrophy of the right ventricle in pulmonary emphysema caused by obstruction to the blood flow in the pulmonary artery created as a result of distention of pulmonary alveoli and deterioration of their elastic properties may all serve as examples of development of hypertrophy of the heart muscle.

Circulatory compensation is an adaptation of the whole organism and primarily of its cardiovascular system to the altered conditions of blood circulation.

As a result of hypertrophy of the heart caused by its increased work load the existing obstacle is surmounted and normal circulation is often ensured for a long time.

An important part in the mechanism of circulatory compensation is played by reflex processes through which the central nervous system exerts its influence on the cardiovascular function. Circulatory compensation conditions a qualitatively new type of heart action, the heart responding to a greater load with a greater muscular effort.

A hypertrophied heart is capable of doing 5-6 times as much work as the normal heart. And still the relative deficiency in the blood supply and nutrition of the hypertrophied heart muscle (this may be also due to the lack of correspondence between the mass of the muscle and its innervation) in cases of an increasing obstruction in the blood stream may sooner than in a normal heart cause a weakening of the heart muscle, which is particularly easily revealed in increased muscular effort. Moreover, during the period of compensation there may already be certain deviations in the carbohydrate metabolism of the heart muscle and to some extent throughout the organism. Hence, the relativity of the very concept of "compensation".

Circulatory and cardiac decompensation develops when the heart's action fails to satisfy the circulatory requirements. Excessive obstacles in the systemic circulation and greater filling of the heart cavities with blood involve an overstretching of the heart muscle (beyond the limits of its adaptability), the *heart's action begins to weaken with cardiac insufficiency* as the final result.

Cardiac Insufficiency

Cardiac insufficiency develops as a result of: 1) weakened contractility of the heart muscle (for example, in uncompensated valvular diseases of the heart or when the heart muscle is exposed to toxic and infectious influences); 2) reduced amount of blood flowing to the heart during diastole (for example, in pericarditis or hemorrhages into the pericardium); 3) disturbances in the blood supply to the heart muscle (for example, in disturbed coronary circulation); 4) considerable disorders of the cardiac rhythm; 5) insufficiency of the peripheral vascular system.

A functional insufficiency of the heart and of all circulation develops the sooner, the greater the work load on the impaired heart. Subsequently even slight muscular effort (slight acceleration of movements of climbing stairs) causes considerable acceleration of the heart rate.

Cardiac insufficiency may give rise to excessive *dilatation* of the heart so that its borders are noticeably extended to the right or left, depending on the part of the heart that is dilated the most.

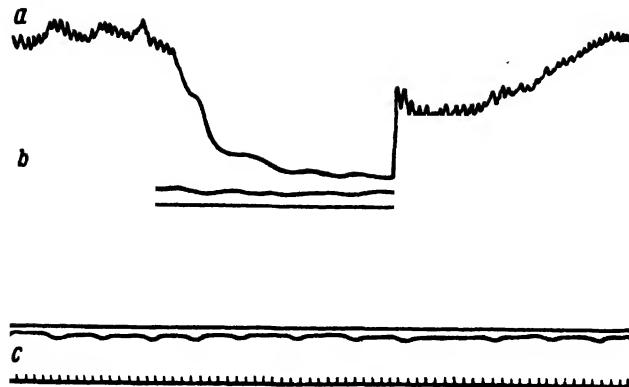


Fig. 89. Changes in the blood circulation in artificial constriction of the aorta in the dog.

Sharp drop in blood pressure in the femoral artery (a), very slight drop in pressure in the femoral vein (b), and no changes in pressure in the innominate vein (c).

If the aorta is considerably constricted in an experimental animal and a sudden obstruction to the work of the left ventricle is thereby created, the result is an excessive dilatation of the left ventricle with clear signs of circulatory disorders; the blood pressure below the site of constriction sharply drops (Fig. 89). The extent of the obstruction and the rapidity of its development determine the extent and character of the changes taking place in the heart.

Dilatation of the heart cavities, developing as a result of cardiac insufficiency, is accompanied by a *decrease in the stroke volume*. This dilatation must be characterised as congestive or *myogenic*, developing secondarily, as a result of overdistention of the cardiac walls by the increasing amount of residual blood. Congestive dilatation of the heart cavities may be temporary. Transitions from the state of decompensation to the state of compensation are also observed.

Development of cardiac insufficiency involves a number of hemodynamic disturbances.

The minute volume of the heart and the filling of the arteries decrease. But despite the insufficient filling of the arterial system the blood pressure is barely affected. This is due to an increase in the tone of the peripheral vessels, i.e., development of adaptation on the part of the vascular system. This adaptive increase in vascular tone with a drop in blood pressure is ensured by reflexes which regulate the arterial pressure; the main receptor zone of these reflexes is the arch of the aorta and the carotid sinus.

Subsequently the heart rate is quickened as a result of reflex excitation of the sympathetic nerves and inhibition of the function of the vagus nerve due to a dilatation of the mouths of the venae

cavae and stimulation of the receptors in the pulmonary vessels and the atria by the accumulated blood (Bainbridge reflex). Acceleration of the heart's action is at first favourable for it prevents, to a certain extent, a diminution in the minute volume. Subsequently, however, it leads to still greater fatigue of the heart muscle and increased phenomena of insufficiency, which may result in a fall of the blood pressure.

In cardiac insufficiency the *venous pressure rises*. Blood accumulates in veins, especially in distal parts. In cardiac failure venous pressure rises according to the extent of cardiac insufficiency. Cardiac failure may result in *venous stasis*.

The manifestations of venous stasis depend on the extent and character of cardiac failure. In cases of left ventricular failure congestive phenomena usually arise in the lungs and result in diminished pulmonary gaseous interchange, development of dyspnea and, in severe cases, even pulmonary edema. Right ventricular failure leads to congestive phenomena mainly in the liver, kidneys, large veins, lower limbs and, subsequently, to general dropsy and ascites.

In addition to the congestive phenomena, cardiac insufficiency is usually marked by *cyanosis* (as a result of accumulation of reduced hemoglobin in the blood). The difference between the arterial and venous oxygen content noticeably increases. Cardiac failure, diminished minute volume and deceleration of the blood flow give rise to oxygen starvation of the tissues.

In cardiac insufficiency the *blood flow is decelerated* as a result of failure of the heart muscle. The slowing of the blood current finds particular expression in congestive phenomena, for example, stasis in pulmonary circulation, in the veins of the systemic circulation and in the system of the portal vein. In these cases the blood supply to the tissues diminishes and oxygen starvation develops.

In cardiac insufficiency *dyspnea* at first arises only in cases of increased physical effort, while in severer cases it also occurs at rest. It is a result of congestive phenomena in the lungs and metabolic disturbances observed in cardiac dysfunction. In a number of cases pulmonary congestion, disturbed gaseous interchange in the lungs, accumulation of carbon dioxide in the blood and the resultant stimulation of the respiratory function may give rise to cardiac dyspnea which is sometimes manifested in attacks of suffocation, i.e. *cardiac asthma*. This occurs, for example, in patients affected with severe forms of hypertensive vascular disease and atherosclerosis of the heart vessels in a state of circulatory decompensation. The result is still greater cardiac failure. A reflex from the affected heart through the central nervous system to the muscles of the bronchi and pulmonary arteries is also possible, in which case, in addition to pulmonary congestion due to left ven-

ricular failure, still greater congestion and dyspnea may be produced by constriction of the pulmonary arteries.

Venous congestion due to cardiac failure may lead to development of *edema* in whose pathogenesis the hemodynamic factor plays the most important part. Another essential factor is the increased permeability of the capillary walls resulting from metabolic disturbances and increased oncotic pressure in the tissues. Mechanical factors influence the sequence in the development of edematous phenomena; first of all edema develops in the lungs in cases of left ventricular failure, and in the underlying body parts, especially in the lower limbs in cases of right ventricular failure.

An important part in cardiac insufficiency is played by *metabolic disturbances*. In cardiacs the resynthesis of glycogen from lactic acid during muscular work (and in cases of considerable circulatory disturbances even at rest) is noticeably diminished; this involves a deficiency in oxygen necessary for oxidising the lactic acid, and oxygen starvation develops.

In cardiacs metabolic disturbances are, in the main, not the cause, but the effect of the circulatory disturbances. While improving the heart's action, cardiac agents simultaneously improve the resynthesis of carbohydrates.

CIRCULATORY DISTURBANCES DUE TO LESIONS IN THE HEART VALVES

Lesions in the valves of the heart, aorta and pulmonary artery lead mainly to valvular insufficiency or to stenosis. Sometimes valvular insufficiency is combined with stenosis. This gives rise to disturbances in the blood flow and corresponding changes in the muscular system of the heart (Fig. 90).

Causes of Lesions in the Heart Valves. Diseases of the valvular apparatus most frequently occur on the basis of infectious processes and subsequent *inflammation of the endocardium (endocarditis)*. Infective agents gaining entrance into the organism through the tonsils, skin or other portals of entry may affect the heart valves. Not infrequently bacterial waste products, by first sensitising the organism, make the endocardium susceptible to a secondary invasion of the organism by the same toxins or microbes (in most cases, streptococci). Endocarditis most commonly occurs in rheumatism in whose pathogenesis allergic phenomena play an important part.

As a result of inflammatory phenomena and formation of blood clots the valves become less mobile and a connective tissue reaction develops; this reaction leads to organisation of an inflammatory focus, shrinking and subsequent insufficiency of the valves or to adhesion of their edges and constriction of the orifices

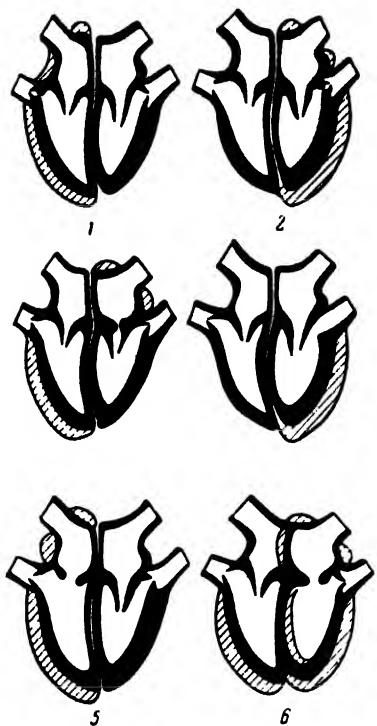


Fig. 90. Forms of compensatory hypertrophy of the heart in different valvular heart diseases (Vogl).

1—constriction of the pulmonary artery; 2—constriction of the aorta; 3—constriction of the left atrioventricular orifice; 4—aortic insufficiency; 5—insufficiency of the tricuspid valve; 6—insufficiency of the bicuspid valve.

insufficiency part of the blood flows against the blood stream back into a corresponding cavity (atrium of left ventricle) during each systole.

As a result, the cavities preceding the lesion are overfilled with blood and dilated; this leads to increased systolic contraction and hypertrophy of the muscle, especially of the ventricles. Circulatory compensation not infrequently develops. On the other hand, accumulation of blood in the atria, for example, in cases of constriction of the left atrioventricular orifice produces congestive phenomena in and dilatation of the overlying pulmonary veins since the latter are not separated from the atrium by a valvular apparatus. If the atrium is filled with a large amount of blood, the muscle of the atrium stretches, but is incapable of exerting an effort

(stenosis). Combined valvular defects with simultaneous insufficiency and stenosis are also possible.

Lesions in the valves are sometimes of a *dystrophic* character, for example, when connected with an atherosclerotic process or a syphilitic lesion in the aorta.

A considerable dilatation of the heart (especially of the right heart) may lead to a dilatation of the valvular orifices with the resultant development of *relative valvular insufficiency*.

Generally it is the valves of the left heart that are most commonly affected; the valves of the right heart are affected much less frequently. Valvular defects of the right heart occur predominantly during the embryonal period. The reason for it probably is that in intrauterine life the greater part of work is done by the right heart and after birth by the left heart.

Mechanisms of Circulatory Disorders in Valvular Diseases of the Heart. In valvular diseases of the heart the heart cavities which precede the lesion in the course of the blood flow are filled with blood the most. In cases of stenosis part of the blood fails to pass through the constriction, while in valvular insufficiency

like that exerted by the ventricles. The atria are usually but very slightly hypertrophied.

The changes in the functions of the valves assume two forms: either the valves fail to close adequately (*valvular insufficiency*) or the cusps of the valves adhering to each other and noticeably thickening constrict the orifice (*stenosis*). Not infrequently stenosis combines with insufficiency. The origin of this disease may be conceived as follows: in addition to valvular insufficiency, phenomena of stenosis begin to develop as a result of progressive sclerotic changes; the stenosis increases and gradually begins to predominate over the insufficiency.

Each valvular heart disease has its own peculiarities.

Aortic insufficiency (insufficiencia valvularum aortae). Owing to incomplete closure of the semilunar valves the left ventricle receives blood during each diastole not only from the left atrium, but also from the aorta. The diastolic filling and the stroke volume of the heart increase and hypertrophy of the left ventricle develops as a result.

In aortic insufficiency the rise in blood pressure during systole is rapidly followed by a drop in pressure during diastole because part of the aortic contents rushes back into the ventricle. Such augmented difference between the maximum and minimum blood pressure characterises even mild aortic insufficiency. In aortic insufficiency the so-called water-hammer pulse with a rapid rise and fall and large amplitude is observed.

Experimental aortic insufficiency may be produced in the dog by introduction of a probe through the carotid artery and damage to the semilunar valves. As a result, the left ventricle responds to the increased filling by its dilatation and increased cardiac contractions. The increased filling of the ventricle shortens the tension phase and prolongs the ejection phase. The duration of the systole as a whole does not change. Damage to the aortic valve is accompanied by a high and rapid rise of the pulse wave and its rapid drop. The blood pressure may remain on the normal level, as a result of a compensatory increase in heart action. In a prolonged chronic experiment the blood pressure may drop.

Aortic stenosis (stenosis ostii aortae) occurs relatively rarely; it is usually combined with aortic insufficiency. Pure forms of aortic stenosis present difficulties for discharge of the blood from the left ventricle. The blood pressure in the ventricle and the muscular tension of the ventricular walls rise, the systole is prolonged and the heart's action increases. Hypertrophy of the left ventricle develops as a result. Experimental animals show a rise in blood pressure in the pulmonary circulation in virtue of a certain increase in diastolic filling of the left ventricle. This is not always possible to observe in the clinic.

Aortic stenosis is characterised by moderate concentric hyper-

trophy of the left ventricle without perceptible dilatation or congestive phenomena in the pulmonary circulation.

Aortic stenosis may be produced in the dog by constriction of the arch of the aorta. In such cases the blood pressure rises above the site of constriction and drops below this site; the strength of cardiac contractions increases.

Mitral insufficiency (insufficientia valvulae mitralis) occurs the most frequently. During ventricular systole part of the blood from the left ventricle is returned to the left atrium. The blood pressure in the left atrium noticeably rises, the following atrial systole increases and the atrium dilates and becomes somewhat hypertrophied. During each diastole of the left ventricle the ventricle receives a larger volume of blood (the normal amount and the excess driven back into the left atrium during the systole of the left ventricle). Greater dilatation of the left ventricle, increased muscular tension and development of eccentric hypertrophy take place. In a state of compensation the emptying of the left ventricle will correspond to that of the right ventricle. If the defect in the mitral valve is more strongly pronounced, congestion and elevated pressure will develop in the pulmonary circulation. The right ventricle will encounter greater hindrance in its work and hypertrophy of the right ventricle will develop as a result.

Compression of both branches of the pulmonary artery caused by the considerable dilatation of the left atrium which accompanies mitral insufficiency is another factor in the development of right ventricular hypertrophy. This compression creates an increased obstruction to the work of the right ventricle, as a result of which it becomes hypertrophied. The insufficiency of the mitral (bicuspid) valve may be compensated only by participation of three divisions of the heart—the left and right ventricles and the left atrium.

Mitral stenosis (stenosis ostii mitralis) or constriction of the left atrioventricular orifice occurs most frequently in combination with mitral insufficiency. It involves a rise in blood pressure in the left atrium. Subsequently the atrium has difficulty in driving the blood into the left ventricle. As a result congestion develops in the pulmonary circulation and the right ventricle becomes hypertrophied. The developing circulatory disturbances in mitral stenosis lead to extreme dilatation of the left atrium which sometimes turns into a flabby thin-walled chamber. The filling of the left ventricle diminishes and the action of its muscular apparatus weakens. Sometimes phenomena of muscular atrophy develop.

Valvular defects of the right heart are in the overwhelming majority of cases congenital. In the adult organism valvular defects of the right heart usually develop as results of lesions in the left heart. For example, a severe lesion in the mitral valve due to circulatory disturbances in the pulmonary circulation may give

rise to relative tricuspid insufficiency (of muscular origin). As a result of valvular diseases of the right heart, disturbances in filling and pressure are observed in the right atrium and large veins.

The right heart is affected most by obstructions created in the pulmonary circulation, for example, as a result of congestive phenomena in the lungs, valvular defects of the left heart or multiple sclerosis of the pulmonary arteries. The increased work of the right ventricle caused by these obstructions leads to eventual development of muscular hypertrophy.

In animals an obstruction to the work of the right ventricle is produced experimentally by constriction of the pulmonary artery; in such cases the heart enlarges and contracts more slowly. Tricuspid insufficiency is produced by introduction of a probe through the right jugular vein and injury to the valve. In this case the stroke volume of the right heart is altered and the pressure in the right atrium and the large veins rises. Hypertrophy of the right heart may develop within a few weeks of the development of tricuspid insufficiency.

The *effects of valvular heart diseases vary*. When the heart fails to cope with the obstruction in the systemic or pulmonary circulation as a result of some valvular defect, the minute volume begins to diminish, the circulation of the blood is impaired and phenomena of circulatory insufficiency develop. The disturbances give rise to *congestive phenomena*. The intensity of these phenomena depends not only on the processes operating in the heart. The cardiovascular system is richly supplied with interoceptors and an important part in the pathogenesis of circulatory disorders caused by valvular defects is therefore played by disturbances in reflex processes by means of which the central nervous system regulates (physiologically) the work of the heart in conformity with the state and functions of all the organs of the body.

The pathology of the valvular apparatus of the left heart in cases of decompensation at first provokes congestive phenomena in the pulmonary circulation. Congestive phenomena in the lungs more commonly accompany mitral defects and less frequently aortic defects. In cases of valvular defects in the right heart congestive phenomena are primarily discovered in the systemic circulation.

Cardiac insufficiency gives rise to cyanosis, dyspnea and edemas and impairs the functions of the internal organs—liver, kidneys, intestines and spleen.

CIRCULATORY DISORDERS IN MYOCARDIAL DISEASES

Inflammatory and dystrophic processes may arise in the heart muscle. The main causes of inflammatory phenomena—acute and chronic forms of myocarditis—are infections, for example, acute

rheumatism, scarlet fever, sepsis, diphtheria, typhus and influenza. Miocarditis develops as a result of the action of toxins and bacterial waste products on the heart muscle. No small part in this is played by preceding allergic sensitisation of the organism.

Mainly parenchymatous forms of myocarditis characterised by dystrophic changes in the muscle fibres, and interstitial forms with a predominance of exudative or productive phenomena are distinguished.

Dystrophic processes in the heart muscle may be caused, besides infection and intoxication, by circulatory insufficiency, altered composition of the blood, exogenous and endogenous intoxication factors, for example, certain disturbances in nutrition and metabolism, dysfunction of the liver and kidneys, thyroidism, and poisoning with phosphorus and carbon monoxide.

According to Selye, the adrenocortical hormones combined with sodium salts stimulate the onset of necrotising myocarditis which develops in experimental animals under the influence of corresponding harmful agents.

Lesions in the myocardium and a diminution in the number of contractile elements result in cardiac weakness and may subsequently give rise to phenomena of venous congestion and dyspnea which are the more strongly pronounced, the more muscular tissue of the heart is involved in the process. The effects of myocarditis are most commonly associated with damage to the muscle of the left ventricle, probably because the latter has to do the greatest part of the work.

The anatomic changes in the many different forms of myocarditis do not always correspond to the extent and character of the functional insufficiency of the heart because of the differences in the pathogenesis of the various forms of myocarditis, the character of the infection which has provoked each particular form, the state of the vascular bed and the extent of injury to the conduction system of the heart.

CIRCULATORY DISORDERS DUE TO DIMINISHED FILLING OF THE HEART CAVITIES

A diminished inflow of blood to the heart during diastole may be the result of injury to the pericardium.

The affections of the pericardium are most commonly of an *inflammatory character* (pericarditis). Inflammation of the pericardium, as also of the endo- and myocardium, may be caused by rheumatism, tuberculosis, pneumonia and severe septic diseases. The inflammatory process may extend to the pericardium from the adjacent parts of the mediastinum or pleura. Experimental production of pericarditis in animals by injection of turpentine or a staphylococcus culture in the pericardium established the possibility of the inflammation also extending to the myocardium.

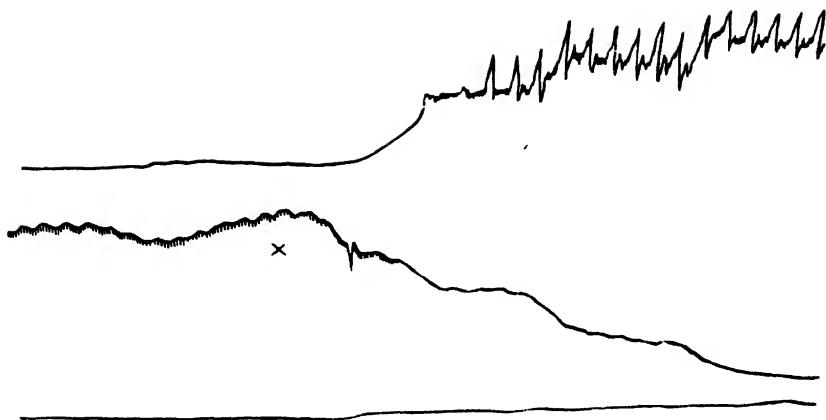


Fig. 91. Changes in the arterial pressure of the dog caused by administration of a large amount of fluid into the pericardial cavity (N. N. Anichkov).
 Upper curve—pressure in the pericardial cavity; middle curve—blood pressure in the femoral artery; lower curve—blood pressure in the femoral vein. Bottom—zero line.
 X—moment of administration of fluid into the pericardial cavity

Circulatory disturbances are also observed in cases of *hydropericardium and hemorrhages into the pericardial cavity*.

Owing to accumulation of fluid and elevation of pressure in the pericardial cavity the diastolic filling of the atria and ventricles diminishes, and functional myocardial insufficiency develops as a result. The inflow of blood to the heart decreases. Slight accumulation of fluid may stimulate a faster heart rate and give rise to dyspnea. These phenomena are based on a reflex from the distended pericardium and mouths of the venae cavae which experience the effect of increased pressure.

The aforementioned phenomena may be produced experimentally. To do this, a glass tube with a forked end is inserted in the pericardial cavity of the dog. A liquid (physiologic saline solution or vaseline oil) is introduced or air is blown into one of the branches of this cannula; the other branch serves for recording the pressure in the pericardial cavity by means of a kymograph. The blood pressure in an artery and a vein is also recorded. A slight elevation of pressure in the pericardial cavity (injection of 40-70 ml of oil) does not as yet disturb the blood pressure or heart action because in this case only the parietal layer of the pericardium is stretched owing to its elasticity. When the pericardium becomes more distended (for example, after administration of 160-200 ml of vaseline oil), the pressure in the pericardial cavity begins to affect the heart's action (Fig. 91).

Simultaneously with the elevation of pressure in the pericardial cavity (at 30-35 mm H₂O) the diastole of the atria and ventricles

diminishes, the stroke volume of the heart decreases and the arterial pressure drops. Compression of large veins gives rise to venous congestion, elevated venous pressure and even venous diastolic pulsation. The latter results from the flow of blood back into the veins during contractions of the right atrium. When venous pressure and pericardial pressure become equal, the circulation of the blood ceases.

The *results of fluid accumulation in the pericardial cavity* vary with the amount and properties of the fluid, the mechanism of its formation and a number of other factors. All other things being equal, an exudate causes greater changes than does a transudate, probably because of its higher viscosity and the greater obstruction it produces for the cardiac function. In exudative pericarditis a toxic effect on the heart muscle and sometimes its involvement in the inflammatory process are observed. The settling-out of fibrin may lead to development of adhesions which form mechanical obstructions for the heart's action. A thick capsule is formed about the heart (armoured heart), the diastole (especially of the right atrium) is weakened, the mouths of the *venae cavae* become constricted and congestive phenomena develop.

In cases of relatively low elasticity of the pericardium the accumulated fluid exerts greater pressure on the muscular wall, a *cardiac tamponade* develops and leads to cardiac arrest as a result of extreme difficulties created for the diastolic phase. A cardiac tamponade is observed not only in cases of inflammatory exudates in the pericardium. Penetration of air into the pericardial cavity in injuries to the pericardium or in hemorrhages may also produce a cardiac tamponade with all the ensuing consequences.

DISORDERS OF THE CARDIAC RHYTHM

The heart's properties of *automatism*, *excitability*, *conductivity* and *contractility* are of principal importance for its normal, rhythmic action. Rhythmic heart action is ensured not only by its muscular, but also by its conduction system (Fig. 92).

Pathologic changes in the above-mentioned properties of the heart lead to disturbances in cardiac rhythm—*arrhythmias*.

Nomotopic and *ectopic* disturbances in cardiac rhythm are distinguished.

Nomotopic rhythm is the cardiac rhythm caused by an impulse arising in the heart in the specialised tissues (the sinoatrial node); in this rhythm only the number and sequence of the impulses which arise in the node change.

Ectopic rhythm is the cardiac rhythm caused by an impulse arising in the heart outside the specialised tissues; here the number of impulses also changes and the rhythm becomes irregular.

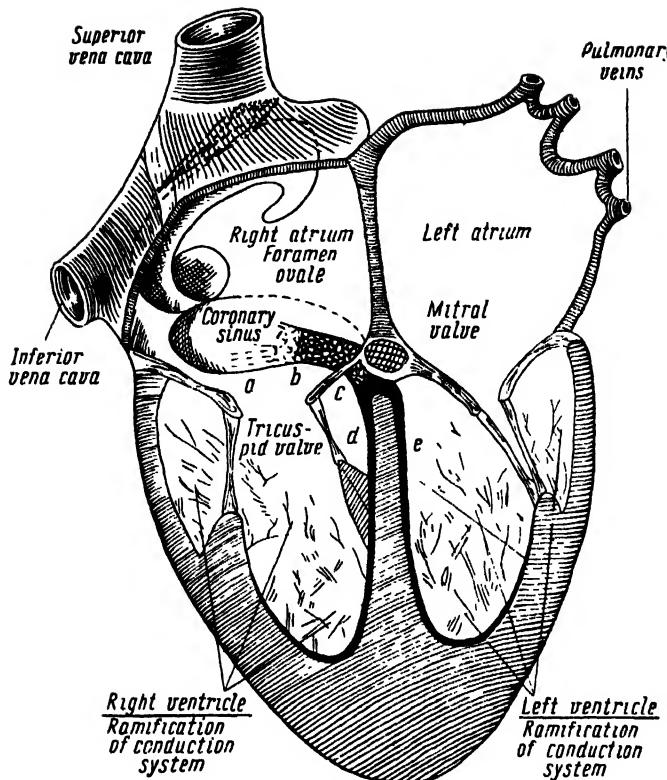


Fig. 92. Schematic representation of the conduction paths of the heart.

a—atrial part of atrioventricular (Aschoff-Tawara) node; *b*—ventricular part of atrioventricular (Aschoff-Tawara) node; *c*—bundle of His; *d*—right branch of the bundle of His; *e*—left branch of the bundle of His.

Disorders of the cardiac rhythm may arise as a result of disturbances in the coronary system, infections and intoxications accompanied by injury to the muscle and the conduction system of the heart.

Disturbances in the cardiac rhythm may also be produced by reflex influences arising in various interoceptor fields, for example, as a result of diseases of the liver, gastrointestinal tract and uterus, embolism and thrombosis of pulmonary vessels, and hemodynamic disorders, as in hypertensive vascular disease. Lastly, cardiac arrhythmias not infrequently arise as a result of dysfunction of the central nervous system.

Disturbances in cardiac rhythm are detected mainly by means of an electrocardiogram (Fig. 93).

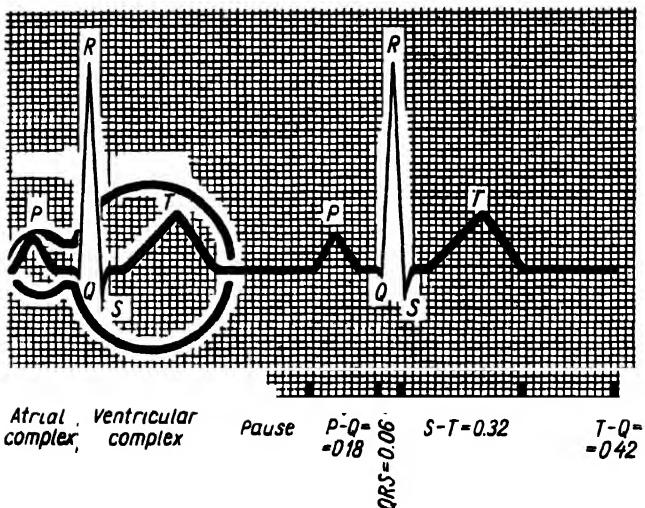


Fig. 93. Normal electrocardiogram of two cardiac cycles. The electrocardiogram of the first cardiac cycle is represented inside a schematic longitudinal atrioventricular section. The duration of the most important intervals is shown under the electrocardiogram of the second cardiac cycle. The vertical lines in the grid show the time: thin lines—0.02 sec, heavy lines—0.2 sec. Horizontal lines show height of the waves; thin lines—0.22 mm, heavy lines—2 mm. The waves of the cardiogram are designated by letters *P*, *Q*, *R*, *S* and *T*.
P—excitation of the atria; *Q*, *R* and *S*—excitation of the ventricles; *T*—repolarisation of the ventricles.

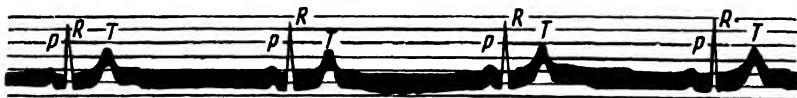


Fig. 94. Electrocardiogram in sinus bradycardia.

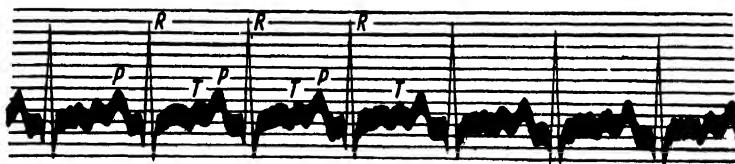


Fig. 95. Electrocardiogram in sinus tachycardia.

Disturbances in the Automatism of Cardiac Contractions

Disturbances in the sinus automatism are manifested as a slowing (sinus bradycardia) or acceleration (sinus tachycardia) of the heart rate and as phasic sinus arrhythmia.

Sinus bradycardia (Fig. 94) is characterised by a diminution in the number of impulses arising in the sinoatrial node and by a slowing of the heart rate. Sometimes the heart rate drops to 40 per minute. This condition may occur normally as a constitutional phenomenon due to increased tone of the vagi nerves and in well-trained athletes with a somewhat hypertrophied heart.

Bradycardia may be produced reflexly by pressure exerted on the carotid arteries (region of the carotid sinus) and on the eyeballs (oculocardiac reflex). In pathology it occurs as a result of increased intracranial pressure, for example, in meningitis and cerebral tumours which press on the brain and stimulate the centre of the vagus nerve, and in dysfunction of the vagal centre due to a disturbed blood supply to this centre. Sometimes bradycardia arises as a reflex from the mesentery or the urogenital apparatus. Bradycardia usually accompanies jaundice in which the salts of cholic acids accumulated in the blood stimulate the vagal centre and in some measure affect the excitability of the neuromuscular elements of the heart.

Usually sinus bradycardia does not appreciably affect the blood circulation. A sharp decrease in the minute volume may occur only in very strongly pronounced cases of sinus bradycardia. At the same time the blood supply to the organs, the central nervous system in the first place, is affected.

Sinus tachycardia (Fig. 95) is characterised by an increased number of impulses arising in the sinoatrial node and by acceleration of the heart rate up to 120 and more beats per minute. It is due to excitation of the sympathetic nervous system, in fever and especially often in exophthalmic goitre, as a result of excessive secretion of the thyroid hormone which accelerates the heart's action.

Lastly tachycardia may be observed in various heart diseases (endocarditis, myocarditis and pericarditis) as a reflex adaptive phenomenon which makes up for the diminution in the systolic volume.

Experimentally tachycardia may be produced by administration of atropine which blocks the ending of the vagus nerve, nicotine which depresses the centre of the vagus nerve and stimulates the sympathetic ganglia, and caffeine which stimulates the sinoatrial node through the central nervous system.

Tachycardia begins to affect the blood circulation only when the muscle is tired or is affected by some pathologic process.

Phasic sinus arrhythmia is characterised by irregular alternation of sinoatrial impulses. In most cases it is associated with the act of breathing (respiratory arrhythmia).

During a deep inhalation the pulse is quickened, as a result of excessive stimulation of the afferent fibres of the vagus nerve in the lung and the subsequent diminished excitation of the centre of this nerve; contrariwise, during exhalation the pulse slows again because of the increased excitation of the vagal centre. Respiratory arrhythmia is particularly clearly marked during changes in the activity of the central nervous system manifested in increased excitation of the vagus nerve and serves as one of the methods of diagnosing the latter. In addition to respiratory arrhythmia, there are cases of phasic sinus arrhythmia which are independent of respiration; these are due to rheumatic myocarditis or other disturbances in the function of the sinoatrial node, mainly of an infectious origin.

In the overwhelming majority of cases phasic sinus arrhythmia is not accompanied by any disturbances in the coordinated work of the various parts of the heart. Phenomena of irregular or uneven pulse seldom occur. The ventricles contract as usual after the contraction of the atria and the transmission of excitation in the heart develops as it does under physiologic conditions. Untimely excitation successively involves all parts of the heart.

Disturbances in Cardiac Excitability

Disturbances in cardiac excitability are most commonly manifested as extrasystoles (Fig. 96).

Extrasystole is a premature contraction of the heart or any of its parts due to an extra stimulus.

For extrasystoles to appear there must be a focus of pathologic excitation at some point of the conduction system. Such a focus may arise as a result of functional disturbances in the neuromuscular system of the heart caused by inflammatory phenomena, toxic influences or hemorrhages. Extrasystoles are observed in valvular heart diseases and, less frequently, in acute endocarditis, sclerosis of the aorta, angina pectoris and other organic affections of the heart. Extrasystoles are produced by digitalis, caffeine and nicotine. An important role in the origin of extrasystoles is played by disturbances in the functions of the vegetative nervous system, subcortical ganglia and cerebral cortex.

Extrasystoles often arise reflexly, because of a high diaphragm, meteorism, and diseases of the stomach, liver and the urogenital system.

All nodes and structures of the conduction system of the heart may be the points of origin of extrasystoles. Extrasystoles arise in the atria, the atrioventricular node, the bundle of His and the ramifications of this bundle."

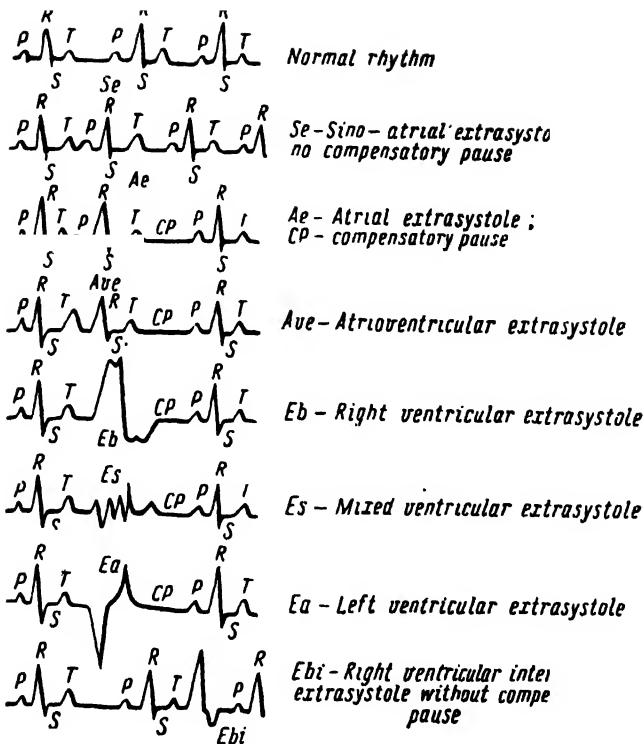


Fig. 96. Diagram of extrasystoles.

Extrasystoles are distinguished according to the origin of the stimuli as *ventricular*, *atrioventricular*, *atrial* and *sinoatrial*. There are also separate extrasystoles of the right and left ventricles, when the extra stimuli arise along either of the two branches of the bundle of His.

In these arrhythmias the character of the electrocardiographic curve depends on the excitability of the conduction system in the lower parts of the heart and the possibility of the excitation being transmitted to the upper parts of the heart (Fig. 97).



Fig. 97. Electrocardiogram.
1—atrial extrasystoles; 2—compensatory pause.

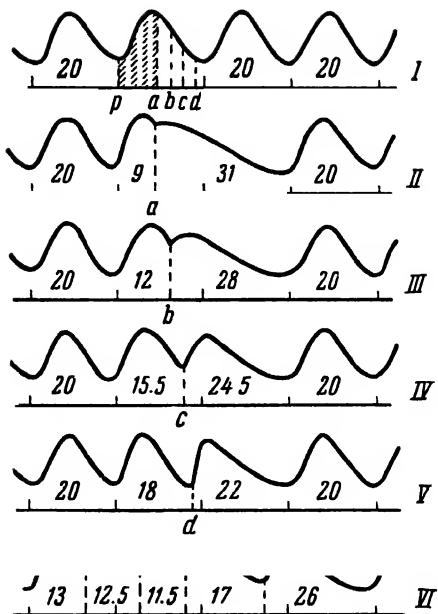


Fig. 98. Extrasystoles. Dependence of the strength of the extrasystole and length of the compensatory pause on the time of the appearance of the extrasystole after the refractory period.

I—curve of normal ventricular contractions; shaded part from *p* to *a*—refractory period; II—extrasystole following soon after the refractory period; III—extrasystole occurring in the beginning of a diastole; IV—extrasystole occurring in the middle of a diastole; V—extrasystole occurring at the end of a diastole; VI—four successive extrasystoles; *a*, *b*, *c*—time of appearance of the extrasystoles graphically shown in rows II, III, IV and V.

Ventricular extrasystoles are the most common. In ventricular extrasystole the stimulus may arise at any point of the conduction system of the ventricles from the bundle of His to its peripheral terminations.

In ventricular extrasystole an extra contraction of the ventricles breaks, as it were, into the normal cardiac rhythm. The nearest normal stimulus finds the ventricles in a refractory phase due to the influence of the extrasystole. Owing to this the ventricle does not respond to the stimulus. The next stimulus, arising in the atrioventricular node, reaches the ventricle when the latter is no longer in the refractory state and is already capable of responding to the stimulus. The characteristic feature of this extrasystole is that it is followed by a pronounced and longer-than-normal *compensatory pause* (Fig. 98). It arises because after the extrasystole the contraction of the heart does not take place in view of the refractory state. The compensatory pause together with the brief

pause before the extrasystole is equal to two normal pauses. A ventricular extrasystole is also characterised by the absence of the *P* wave because the atria do not participate in extrasystolic contraction and deformation of the ventricular complex which most frequently occurs because the ventricles do not contract simultaneously.

Atrioventricular extrasystoles appear as a result of stimuli arising in the superior, middle or inferior part of the atrioventricular node. The excitation almost always spreads downward and upward (to the atria). The extrasystole is followed by a prolonged pause which is shorter, however, than the actual compensatory pause in ventricular extrasystole. It is the longer, the longer the path along which the stimulus returns to the atrioventricular node where it evokes a premature discharge and a disturbance in the basic sinus rhythm. In atrioventricular extrasystole, especially if the stimulus arises in the upper part of the atrioventricular node, the *P* wave in the electrocardiogram will be turned downward (opposite to normal) owing to the retrograde spread of the excitation. Depending on where the stimulus arises—the upper, middle or lower part of the atrioventricular node—the *P* wave precedes the ventricular complex, merges with it or follows it.

In *atrial extrasystoles* the extra stimulus, upon reaching the atrioventricular node, evokes a premature discharge in it. As a result the next systolic contraction occurs after a normal pause. The compensatory pause is either absent or is very feebly marked. The *P* wave arises prematurely.

The *sinoatrial extrasystole* is marked by extra impulses arising in the sinoatrial node. This form of arrhythmia is accompanied by tachycardia, most frequently with a shortened diastole.

Experimentally extrasystoles may be produced in animals by various methods: stimulation of the cardiac nodes by chemical substances or toxins, cooling, alteration of the blood flow in the heart muscle, compression of the aorta or pulmonary artery, and stimulation of extracardiac nerves. However, these experiments have not as yet thrown sufficient light on the mechanism of arrhythmias in man.

Extrasystoles disturb the cardiac rhythm, but may alternate regularly and thus create a peculiar rhythm—rhythmic arrhythmia or allorhythmia. A form of this condition is arrhythmia designated in the clinic by the term *bigeminy* (or *pulsus bigeminus*)—an arrhythmia in which each normal beat is coupled with a premature beat. These may also be *tri-* and *quadrigeminy* (*pulsus tri-* or *quadrigeminus*) when an extrasystole follows each three or four normal pulse beats.

Extrasystolic arrhythmias of functional origin barely affect the blood circulation or do not affect it at all. But in cases of cardiac insufficiency they may lead to still greater *cardiac weakness* due

to the fatigue of the heart working under excessive strain and the uneven filling of the vascular bed.

Closely related to disturbances in cardiac excitability is *paroxysmal tachycardia*, i.e., tachycardia occurring periodically, in paroxysms. In a relatively normal heart the rhythm accelerates all at once and reaches 150-200 and more contractions per minute. The attacks may last from a few minutes to several weeks. A prolonged and sharp acceleration of the rhythm is accompanied by respiratory disturbances and circulatory insufficiency involving dilatation of the heart, diminished minute volume, disorders of coronary circulation and hypoxia of cerebral tissue.

Experimentally paroxysmal tachycardia may be produced in an animal by constriction of the aorta or ligation of the coronary arteries, as well as by administration of barium, calcium or digitalis. In man paroxysmal tachycardia is sometimes observed as a result of spasm of the coronary arteries or other affections of the cardiovascular system.

Atrial fibrillation is a peculiar form of arrhythmia. It may be produced experimentally by stimulating the atria with strong faradic current, mechanical stimuli and chemical substances—chloroform, barium, digitalis, etc.—with the result that rapidly alternating irregular impulses and correspondingly uncoordinated contractions of various muscle bundles of the atria occur (*arrhythmia perpetua*). The atria as a whole do not contract for they are dilated. The rate of these fibrillary contractions may reach 400-600 per minute. At this rate of the discharge of impulses arising in the atria the ventricles cannot contract in response to each impulse and therefore react with one contraction to every 3-4 impulses, these contractions becoming irregular in rhythm and strength.

The electrocardiogram (Fig. 99) shows that one ventricular systole corresponds to numerous small waves instead of the one atrial *P* wave. Sometimes a continuous oscillation of the galvanometer string is observed.

III



Fig. 99. Electrocardiogram of atrial fibrillation. The *P* wave is replaced by fibrillary waves.

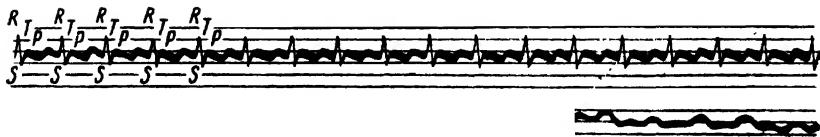


Fig. 100. Electrocardiogram of atrial flutter with 2 : 1 block. Regular ventricular complexes follow rhythmically.

This form of arrhythmia affects the blood circulation particularly unfavourably. The failure of the atria to function actively and the irregular work of the ventricles lead to a considerable diminution in the minute volume of the heart and to a drop in blood pressure. Since the diastolic filling of the ventricles is affected the latter not infrequently contract to no purpose. Moreover, accelerated and disorderly contractions exhaust the muscular system of the heart and cause disturbances in its nutrition.

Atrial fibrillation closely resembles *atrial flutter* (Fig. 100) which consists of regular but abnormal atrial contractions whose number reaches 250-350 per minute. Flutter may be produced experimentally by stimulating an atrium with weak faradic current.

Atrial fibrillation and flutter are observed in mitral stenosis, constriction of the artery supplying the atrioventricular node, cardiosclerosis, severe hyperthyroidism and digitalis poisoning.

Analogous conditions are sometimes observed in the ventricles, for example, in thrombosis of large branches of the coronary artery, which often results in sudden death.

Most investigators agree that *atrial fibrillation and flutter* are functional disturbances. Today these phenomena are ascribed to *metabolic disturbances in the atrial muscle* which increase the excitability of some of its parts and diminish the conduction. The frequently arising impulses, upon encountering the muscular tissue in a refractory state, produce only twitchings of the various atrial muscle bundles (fibrillation).

Some investigators explain these arrhythmias by ectopic foci of excitation with a varying rate of impulses arising in the heart. The impulses may meet and destroy each other after travelling but a short distance. This is responsible for the occurrence of uncoordinated contractions of the different parts of the atria.

Disturbances in Cardiac Conduction

The conduction may be disturbed in various parts of the conduction system of the heart along the course of the excitation spreading from the atrioventricular node. Disturbances in conduction may arise between the atrioventricular node and the atrial muscle or between the atria and ventricles, but are most frequently

observed in the bundle of His and its ramifications. The results vary with the site and character of break in conduction.

A *sinoatrial block* occurs as a result of an obstruction to the impulse arising in the sinoatrial node during its spread from the node to the atria. In the frog it may be produced experimentally by applying Stannius' ligature (between the sinus venosus and the atrium). The resultant disturbance in the rhythm is manifested in complete failure of the atrium and ventricle to contract. The rhythm of atrial and ventricular contractions slows down.

An *atrioventricular block* (incomplete and complete) arises as a result of impaired conduction in the atrioventricular node.

The first stage of prolonged conduction may not affect the rhythm of ventricular contractions but the electrocardiogram shows a longer interval between the *P* wave and the *QRST* ventricular complex. Instead of the normal 0.12-0.18 sec this interval may increase to 0.4 sec.

The second stage of prolonged conduction is characterised by an appreciable change in the interrelation between the atrial and ventricular contractions. From time to time, after every 7-10 beats, and in cases of greater disturbances after every 2-3 beats, one ventricular contraction is lost. This condition is called an *incomplete atrioventricular heart block* (Fig. 101).

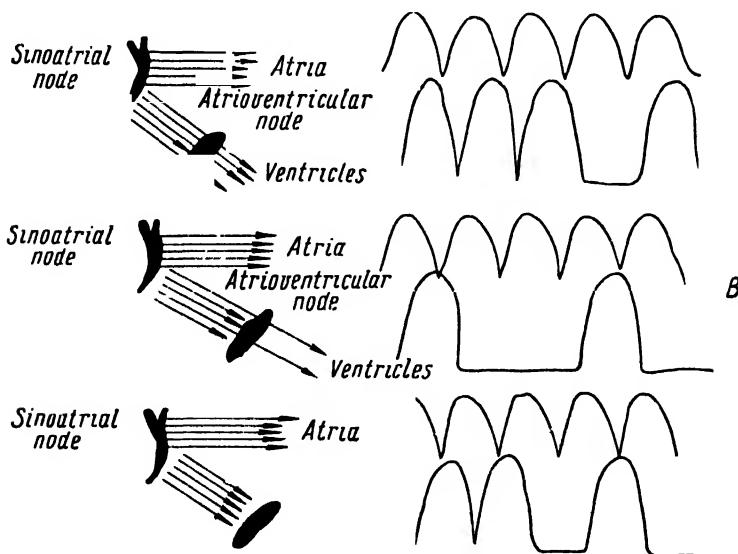


Fig. 101. Diagram showing mechanism of incomplete atrioventricular block (Wiggers).

A—three ventricular contractions to four atrial contractions; B—one ventricular contraction to three atrial contractions; C—complete block.



Fig. 102. 2 : 1 incomplete heart block. One ventricular contraction to two atrial contractions.

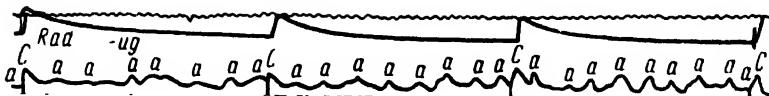


Fig. 103. Complete heart block.

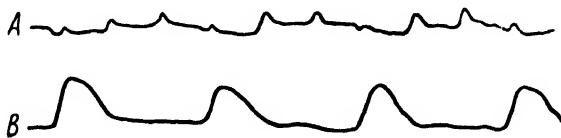


Fig. 104. Dissociation of atrial and ventricular contractions after transection of the bundle of His in the dog.

A—curve of atrial contractions, B—curve of ventricular contractions.

An incomplete block may give rise to such a rhythm when one ventricular contraction corresponds to two or three atrial contractions, which is easily seen in the electrocardiogram (Fig. 102). Lastly, completely interrupted conduction between the atria and ventricles results in complete *atrioventricular heart block* or *complete atrioventricular dissociation* (Fig. 103). In this case the atria contract in response to the impulses arising in the sinoatrial node. These impulses are not transmitted to the ventricles and the latter contract independently of the atria in response to impulses automatically arising in the atrioventricular node or in the bundle of His. The atria contract in one rhythm (60-80 beats per minute) and the ventricles in another rhythm (50-20 beats per minute). The slower rhythm of the ventricles is due to the fact that the atrioventricular node is characterised by lower automatism than is the sinoatrial node. Experimentally an atrioventricular block is more easily produced by severance of the paths which connect the atria with the ventricles (Fig. 104).

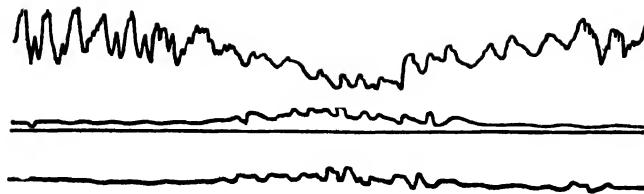


Fig. 105. Circulatory disturbance in obturation of the right atrium. Drop in arterial and elevation of venous pressure.

A blocking produced in one of the branches of the bundle of His is known as a *bundle-branch heart block*. In this block the impulse from an atrium is transmitted only to one ventricle, while the other ventricle, in virtue of a lesion (most frequently syphilitic) in the conduction system, receives no impulse at all or receives a diminished impulse and only through the septum from the normally contracting ventricle. Thus the two ventricles do not begin contracting simultaneously and the contractions are somewhat weakened (*hyposystole*).

In the end the *disturbances in cardiac conductivity result* in weakened heart action. Circulatory disorders are particularly strongly pronounced in cases of complete heart block. In these cases the ventricles contract independently of the atria, which leads to diminished ventricular filling. Sometimes even obturation of the atria may develop (Fig. 105). This happens when the atrial systole coincides with the ventricular systole. In cases of impaired conductivity the ventricular rhythm is decelerated (with the exception of the rhythm in bundle-branch heart block, when the pulse rate is accelerated). This phenomenon together with the changes in filling leads to an insufficient blood supply of various organs and sometimes to considerable disturbances in the nutrition of the central nervous system.

Other forms of disturbed conductivity are sometimes also accompanied by noticeable disorders of the blood supply. Both functional and organic factors play a certain part in the origin of arrhythmias due to disturbed conductivity. In persons with increased excitability of the parasympathetic division of the nervous system, the vagi nerves in particular, symptoms of arrhythmias sometimes manifest themselves as transiently lost systoles. Of the organic lesions which alter or interrupt cardiac conduction mention must be made of inflammatory, dystrophic and sclerotic processes which may produce pathologic changes in the muscle and in various parts of the conduction system of the heart. Lastly, conduction disorders occur as a result of disturbed nutrition of the heart caused by impairment of its blood supply, as well as of the blood supply to the conduction paths.

Disturbances in Cardiac Contractility

The most significant disturbance in cardiac contractility is characterised by an alternating pulse (*pulsus alternans*), i.e., rhythmic alternations of large and small pulsations with an invariable diastolic cycle (Fig. 106). As a result, the contractions of the various parts of the myocardium weaken and so-called hyposystole arises. Hyposystole may be produced experimentally on a long-working isolated heart by disturbing the coronary circulation, overcooling or administering digitalis, veratrine or barium chloride. A similar effect is produced by stimulation of the accelerator nerves of the heart through artificial increase of the peripheral obstruction to the blood flow. An alternating pulse is the result of considerable dystrophic changes and circulatory disturbances in the myocardium. In addition to cardiac fatigue, a certain part in the pathogenesis of this form of arrhythmia is played by disturbances in conduction from the atria to the ventricles whose restorative functional period after increased systole is prolonged. The subsequent contraction of the atria evokes a weakened reaction of the ventricles. The mechanism of the alternating pulse is believed to consist in rhythmic changes in the strength of cardiac contractions due to diminished lability of impaired muscle fibres.

DISORDERS OF CORONARY CIRCULATION

Since coronary circulation ensures nutrition of the heart, disturbances in coronary circulation impair cardiac activity.

Disorders of coronary circulation—coronary insufficiency—may arise as a result of: 1) *disturbances* in vasomotor regulation of the *blood flow* in the vessels of the heart, in spasms of the coronary arteries of a reflex origin, or resulting from disorders in the subcortical region and higher parts of the brain; 2) *reduced arterial pressure*, especially in the aorta, as in cases of aortic insufficiency; 3) *atherosclerosis* of the coronary vessels, thrombosis and, less frequently, embolism; 4) oxygen deficiency in the blood, for example, in severe anemias, high-altitude disease and carbon monoxide poisoning.

In all these cases the blood supply to the heart is affected, the metabolism in the heart muscle is disturbed and the latter develops foci of ischemia, fatty degeneration and necrosis to the extent of myocardial infarction.



Fig. 106. Alternating pulse.

Experimentally disorders of coronary circulation may be produced by ligating the coronary vessels or by introducing small seeds of plants through the animal's carotid artery into the ascending branch of the aorta (Fig. 107). Experiments have shown that the effects on cardiac function depend on the branches of the coronary artery which are obstructed.

Obstruction or constriction of a large coronary vessel or of several of its branches may rapidly lead to death. Affection of smaller vessels causes development of an infarction in the corresponding part of the heart. Ligation of the left coronary artery in an animal causes disturbances in the cardiac rhythm manifested in extra contractions and periodic accelerations; these disturbances are followed by marked left ventricular failure, drop in blood pressure and, as a rule, death within 2-3 minutes. If the right ventricle continues to work, left ventricular failure results in engorgement of the pulmonary circulation and sometimes pulmonary edema. Ligation of the right coronary artery gives rise to right ventricular failure and engorgement of the veins of the liver, spleen, gastrointestinal tract and other branches of the venous system with venous blood.

After ligation of the right coronary artery the animals die in about 50 per cent of the cases. Ligation of even large cardiac veins does not produce such severe results because of the remaining collateral blood circulation.

One of the forms of disturbed coronary circulation in man is the heart disease known as *angina pectoris*. This disease is characterised by sudden attacks of intense pain in the region of the sternum and heart, the pain radiating to the left shoulder, arm, back and lower jaw; it is also marked by increased sensitivity zones in the skin—the Zakharyin-Head zones (Fig. 108).

The pain is due to the fact that the stimuli transmitted from the heart through sympathetic fibres and the stellate ganglion or sympathetic trunk to the spinal cord irradiate to the sensory cells of

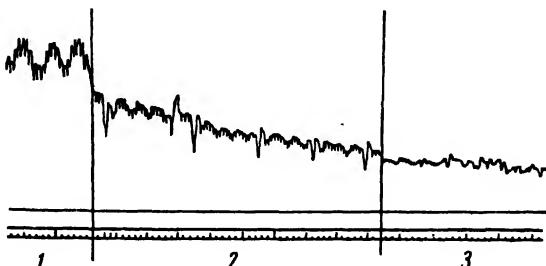


Fig. 107. Impairment of circulation caused by embolism of the coronary arteries.
1—pressure in the femoral artery before administration of lycopodium; 2 and 3—drop in arterial pressure after administration of lycopodium into the coronary arteries.

the given segment. The reflex contractions of the intercostal muscles give rise to a sense of constriction in the chest (*stenocardia*). Various vegetative reflexes arise, including tachycardia, elevated blood pressure, perspiration, salivation, and sometimes altered sensitivity and a drop in the temperature of the skin in the cardiac region. The patient develops a sense of apprehension of impending death. The attacks may end lethally, as a result of paralysis of the heart. Angina pectoris most commonly occurs in elderly people.

The anatomic changes in angina pectoris not infrequently consist in *atherosclerosis of the coronary vessels* with thickened arterial walls; the lumens of the arteries may be constricted or even obliterated. Angina pectoris is not always accompanied by atherosclerosis of the coronary arteries; there are cases in which autopsy shows the coronary arteries to be but very slightly sclerosed.

According to modern views, one of the important causes of angina pectoris is *neurogenic spasm of the coronary vessels*. For example, spasm of the coronary vessels may be produced by distension of the stomach (gastrocoronary reflex); it is experimentally produced in the dog by distension of the lower part of the esophagus.

Frequent emotional stress and abuse of nicotine may predispose the organism to attacks of angina pectoris. A number of clinical observations indicate that attacks of angina pectoris may arise as a conditioned reflex. The factors that cause development of angina pectoris may simultaneously lead to development of sclerosis, and sclerosed vessels are particularly subject to spasm.

Numerous brief spasms of the branches of the coronary artery may result in ischemia, atrophy and sclerosis of the corresponding parts of the myocardium, while long and repeated spasms of the coronary artery may produce *myocardial infarction*. In favourable cases the necrotic part is replaced by scar tissue. Sometimes, under the influence of intracardiac pressure the dystrophic part of the heart may rupture, or in the absence of continuous necrotisation may bulge out and give rise to *cardiac aneurysm*. Aneurysms are most commonly formed in the lower third of the anterior wall of the left ventricle; they may rupture and give rise to fatal hemorrhages.

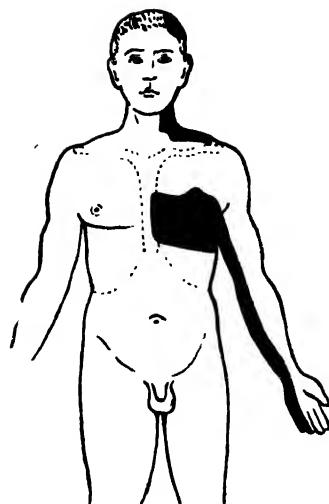


Fig. 108. Zakharyin-Head (cardio-cutaneous) hyperesthetic zones in angina pectoris.

In the picture of myocardial infarction certain consideration must be given to *changes in the conduction system* of the heart which is insufficiently supplied with blood.

The *pathogenesis* and possible results of *angina pectoris* (such as *myocardial infarction*) involve a number of other factors: hemodynamic disturbances (for example, hypertension and vascular spasm), thrombosis, embolism and metabolic disorders in the heart muscle, i.e., everything that leads to a lack of correspondence between the functional efforts of the myocardium, its oxygen requirements and the inflow of blood to it. This lack of correspondence occurs not only in primary constriction of the coronary vessels, but also in cases of increased activity of the myocardium.

The sensation of intense substernal pain in myocardial infarction is due to the stimulation of the sensory nerve fibres in the adventitia of the vessels.

Myocardial infarction and the inflammatory and necrotic phenomena in the heart muscle which accompany it are characterised by pyrexia, leukocytosis, accelerated erythrocyte sedimentation rate and changes in the electrocardiogram. A very important part in the origin of these phenomena is played by reflex reactions.

CIRCULATORY DISORDERS DUE TO DISTURBANCES IN VASCULAR TONE

The disturbances in vascular tone are based on changes in two factors—elasticity and resistance of the vascular wall—which in a large measure determine the extent of the obstruction to the work of the heart. The changes in these properties, capable of causing general circulatory disorders, may be of various origin.

Vasomotor disorders constitute a large group.

The vasomotor influences on blood circulation originate in the *central nervous system*. The vasomotor disorders are based on reflex disturbances.

Reflex influences on the vascular tone may originate in any organ.

The state of the blood circulation, blood supply and nutrition of various parts is also affected by the peculiarities of the vascular bed and the development of anastomoses in the corresponding vascular regions of the organism. In pathology the vascular tone may be either increased or decreased. These variations in the tone of the vessels are accompanied by changes in blood pressure.

Hypotension is a condition in which the arterial pressure in an adult is persistently diminished to 100/60 mm Hg and lower. The general diminution in vascular tone cannot be compensated by constriction of arteries in any part of the organism. This condition is marked by chronic circulatory insufficiency and is a result of diminished tone of small arteries, arterioles and capillaries.

Hypotension is characterised by general weakness, easy tiring, irritability, headaches, dizziness, pains in the region of the heart.

The persistent diminution in tone develops on the basis of nervous and neuroendocrine disorders. A prolonged drop in blood pressure is most commonly due to influences originating in the central nervous system. In such cases a diminished tone of small vessels is usually connected with a relative decrease in the function of the sympathetic division of the vegetative nervous system, especially in paralysis of vessels in the region innervated by the splanchnic nerve, and in affections of a number of endocrine glands which secrete pressor hormones. A decreased tone of small vessels is also observed in cachexia, acute infections, persistent intoxications and other diseases in which the reactivity of the nervous system is diminished. Shock is marked by the most strongly pronounced acute diminution in vascular tone involving a sudden drop in blood pressure.

Shock develops as a result of exposure of the organism to various stimuli, most commonly trauma (traumatic, postoperative or wound shock), burn, intoxication or infection, anaphylaxis or transfusion of heterogeneous blood. Each variety is characterised by its own peculiarities of origin and course. The mechanisms of the vascular disorders developing in shock are for the most part similar.

The pathogenesis of shock is based on a *disturbance in the function of the central nervous system* manifested immediately after the injury—primary shock and of developing gradually—secondary shock (see Chapter Three).

Collapse is characterised by a sharp and sudden diminution in all functions of the organism as a result of paralysis of the vessels and acute depression of cardiac activity. It occurs most commonly in acute infectious diseases (during the crisis), after massive hemorrhages and in cachexias. As a result of a sudden reflex dilatation of the vascular bed the blood pressure drops, the pulse becomes fast and weak, the flow of blood to the heart sharply diminishes and the supply of the vitally important centres (which are in a state of lowered excitability, as it is) is disturbed. It is impossible to draw a clear line between shock and collapse.

Hypertension is excessive arterial pressure. A persistent elevation of blood pressure is a sign of a general disease—*hypertensive vascular disease*. In this disease the tone of the entire vascular bed is increased, the small arteries tend to constrict and the arterial pressure is high (180-200-250 mm Hg and higher); not only the systolic, but also the diastolic pressure rises (80-90-100 mm Hg and higher). The rise in blood pressure creates an obstruction to the heart's action. The result is hypertrophy of the heart muscle, which always accompanies hypertensive vascular disease and not infrequently ends in cardiac insufficiency that resembles cardiac decompensation due to valvular defects.

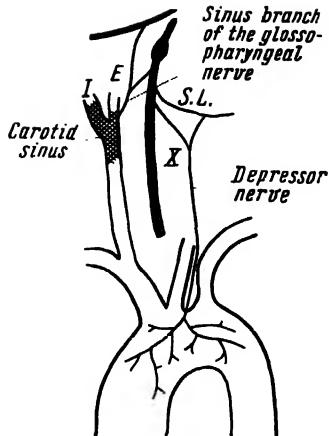


Fig. 109. Nerves of the sinus and aorta.

I—internal carotid artery; E—external carotid artery; X—vagus.

the increase in the tone of the peripheral vessels is played by constant neuropsychic factors, namely, an overstrain of the higher parts of the nervous system, especially, the cerebral cortex, by persistent negative emotions (G.F. Lang).

These factors may cause development of a stable focus of excitation in the vasomotor centres of the subcortical region responsible for the constriction of the peripheral vascular bed, the elevation of the blood pressure and the change in the vascular reaction. Disturbances in the function of the cerebral cortex in hypertensive vascular disease usually give rise to increased excitability of the sympathetic division of the nervous system, to an increased and even perverted reaction to the action of vasoconstrictors and vasodilators.

The recognition of the role of neurogenic factors in the genesis of hypertensive vascular disease is partly based on experimental observations.

Transection of the aortic depressors and sinus branch of the glossopharyngeal nerves (Fig. 109) produces in dogs and rabbits a rise in blood pressure which may persist for many months (Heimans). Experimental studies have shown such animals to exhibit persistent excitability of the bulbar vasomotor centre (N.N. Gorev).

Stimulation of the proximal end of one of the transected nerves reduces the blood pressure which rises again, however, as soon as the stimulation ceases (Fig. 110). A temporary elevation of blood pressure develops after anesthesia (cocaine) of the sinocarotid zone.

Hypertensive vascular disease was often ascribed to sclerotic changes in the vessels, which increase the resistance of the vascular wall to the blood flow. Hypertensive vascular disease is most commonly connected with atherosclerosis, although the latter does not always precede the development of hypertension and is not infrequently the result of it.

Today persistent vascular spasm in hypertension is explained not by organic, but mainly by functional disturbances due to disorders of the central nervous system, the sclerosis of the vessels offering favourable conditions for the development of spasm.

An important part in the dysfunction of the vasomotor centres and in

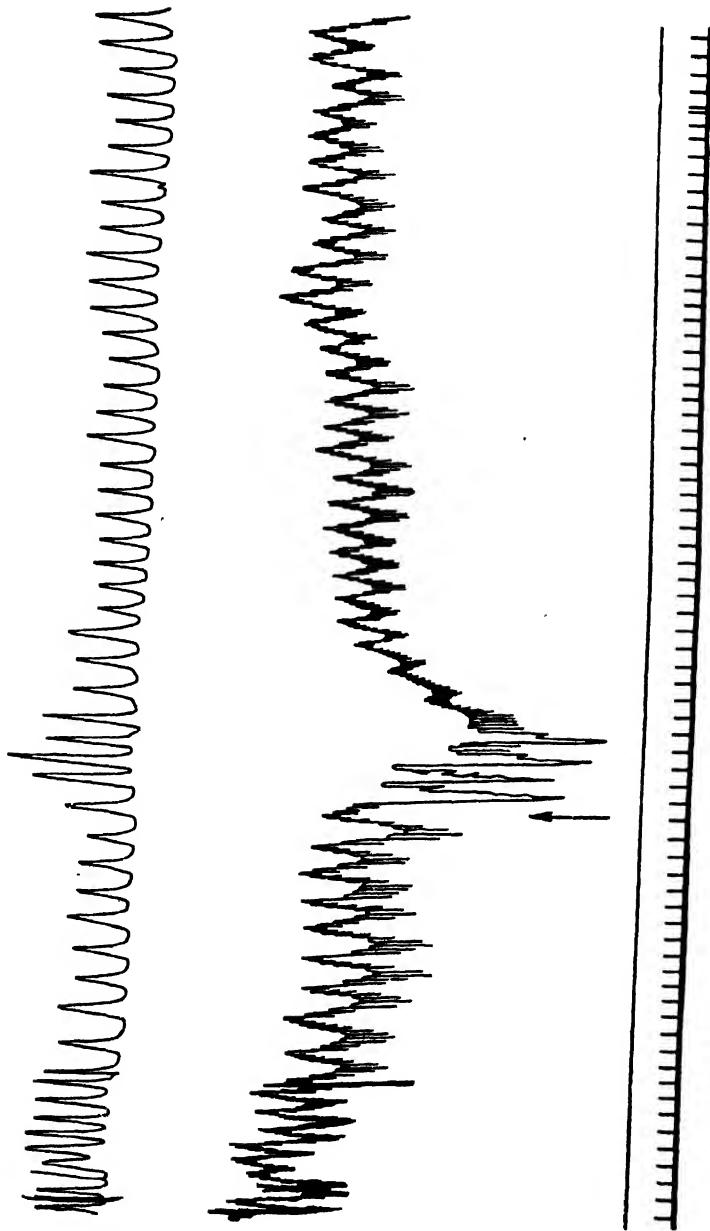


Fig. 110. Changes in arterial pressure (bottom) and respiration (top) in the dog in response to stimulation of the region of the carotid sinus with induction current. A drop in arterial pressure, and deepening and quickening of respiration are observed at the moment of stimulation (↑). Time intervals—5 seconds.

A prolonged rise in blood pressure can also be produced in dogs by injection of kaolin into the subarachnoid space. Kaolin, it appears, mechanically elevates intracranial pressure which in its turn leads to a reduced blood supply and causes ischemia in the diencephalon and the medulla oblongata. This explains the excitation of the vasoconstrictor centres and constriction of the peripheral vascular bed.

Lastly, it has lately been found possible to produce a persistent and relatively stable elevation of blood pressure in dogs in experimental neuroses caused by a "clash" of the excitatory and inhibitory processes.

Some role in the pathogenesis of hypertensive vascular disease is also played by disturbances in the *function of the endocrine glands*. Formerly vasopressin (a hormone of the posterior lobe of the hypophysis, which possesses vasoconstrictor action) was believed to play a certain part. Today greater importance is attached to changes in the function of the anterior lobe of the hypophysis. Thus basophilic adenoma of the anterior lobe usually shows a stable rise in blood pressure, the blood exhibiting an increase in the adrenocorticotropic hormone. The same thing is also observed in certain other cases of hypertension.

In the genesis of hypertension mention must also be made of the role played by the adrenal cortex.

It is well known that tumours of the adrenal cortex are accompanied by persistent hypertension. It is also well known that desoxy-corticosterone—one of the hormones of the adrenal cortex—increases the sensitivity of the peripheral vessels to certain vasoconstrictors, for example, adrenalin.

All the foregoing data indicate that disturbances in nervous and endocrine regulation play an important part in the pathogenesis of hypertensive vascular disease.

At one time hypertensive vascular disease was also believed to develop in primary affection of the kidneys. However, frequent cases of hypertensive vascular disease without any changes in the kidneys invalidate this point of view. The changes in the kidneys in hypertensive vascular disease may be regarded as subsequent phenomena which aggravate the main disease and stabilise the high blood pressure.

In addition to hypertensive vascular disease there are also *symptomatic hypertension*. These include *renal hypertension* in diffuse glomerulonephritis, secondarily contracted kidney, compression of renal vessels and certain other affections of the kidneys, *endocrine hypertension* arising in cases of hypophyseal lesions, adrenal tumours and hypogenitalism, and *hemodynamic hypertension*, for example, in atherosclerosis.

Chapter Thirteen

PATHOLOGY OF RESPIRATION

SIGNIFICANCE OF NERVOUS REGULATION IN RESPIRATORY PATHOLOGY

The respiratory centre is located in the medulla oblongata (in the region of the *reticular formation*). It is connected with the spinal cord, which regulates the function of the diaphragm and respiratory muscles, and with the higher parts of the hypothalamus and cerebral cortex which influence the excitability of the respiratory centre.

The respiratory centre may be stimulated and inhibited, and the respiratory movements may be accelerated, slowed down and even arrested reflexly from many parts of the organism—the nasal and laryngeal mucosa, the cervical sympathetic nerve and the internal organs—the liver, kidneys, spleen, gastrointestinal tract, uterus and ovaries. Affection of these organs, for example, by inflammation, may be accompanied by temporary disturbances in the rhythm and depth of respiration. But respiratory disorders are caused particularly frequently by changes in the system of permanent respiratory regulation. For example, stimulation of the pulmonary branches of the vagus nerve leads to premature inhibition of inhalation. There are apparently also afferent fibres of the vagus nerve, which stimulate respiration. Inhibitory impulses are also delivered to the respiratory centre along the afferent nerves of the respiratory muscles.

In pathology an important role is played by reflexes originating in the vascular reflexogenic zones of the carotid sinus and the arch of the aorta. The chemoreceptors of these zones react even to slight decreases in blood oxygen. Exclusion of the reflexogenic zones of the carotid sinus and the arch of the aorta in animals renders the latter insensitive to inhalation of an oxygen-deficient gaseous mixture. Elevation of the blood pressure in the region of the carotid sinus is accompanied by diminished pulmonary ventilation, whereas reduced pressure has the opposite effect.

A certain part in the pathogenesis of respiratory disorders is also played by affections of the higher parts of the central nervous system. This is attested by effects of psychic states on the res-

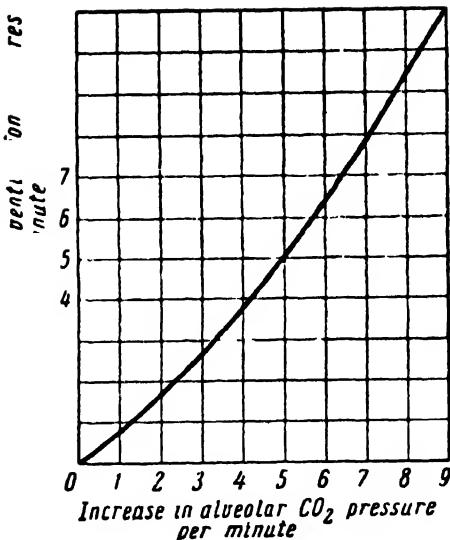


Fig. 111. Dependence of alveolar ventilation on carbon dioxide tension in the pulmonary alveoli.

piratory rhythm, for example, accelerated and deepened respiration under emotional stress.

Respiration is affected not only by reflex, but also by humoral influences on the respiratory centre. For example, the respiratory rhythm is altered by changes in the carbon dioxide and pH of the blood.

An increase in carbon dioxide in the alveolar air from 5.6 to 6.2 per cent causes an almost three-fold increase in pulmonary ventilation, while its decrease in the alveolar air leads to inhibition of the respiratory centre (Fig. 111). For example, respiration is arrested in hyperventilation (excessive deep breathing) as a result of excessive elimination of carbon dioxide by the lungs and its sharp decrease in the alveolar air and the blood.

A 0.012 decrease in the pH of the arterial blood causes a 100 per cent increase in respiration.

The excitability of the respiratory centre also decreases as a result of accumulation of metabolites in the blood, for example, in diseases of the kidneys, diabetes and various intoxications, under the action of morphine, hypnotics and carbon monoxide, and in cases of inadequate supply of the respiratory centre with oxygen (in severe anemias).

The regulation of respiration may be impaired by changes arising in the *central nervous system due to circulatory disturbances*. For example, in *sclerosis of the cerebral vessels* the respiratory centre is inadequately supplied with oxygen; on slowing of the blood

current the carbon dioxide in the blood increases, while the oxygen decreases; on the other hand, acceleration of the blood flow is accompanied by an increase in oxygen and decrease in carbon dioxide, since diffusion of oxygen into the tissue diminishes, while carbon dioxide is distributed over a greater amount of blood circulating per unit of time.

The respiratory centre may also be affected by *hemorrhages* into it in cases of pathologic changes in the vessels, for example, in sclerosis or degeneration of the vascular wall under the influence of toxic substances, in *thrombosis* and *embolism* or in cases of *compression* (by a tumour) of the respiratory centre or the vessels which supply it.

DISTURBANCES IN THE RESPIRATORY RHYTHM

Dyspnea. *Dyspnea is difficult or laboured breathing characterised by disturbances in the rhythm and strength of the respiratory movements.* It is usually accompanied by a distressing sensation of a lack of air. The mechanism of dyspnea consists in an impairment of the function of the respiratory centre due to: 1) stimulation arising predominantly in the pulmonary branches of the vagus nerve or the carotid zones; 2) influence of the blood resulting from a disturbance in its gaseous composition, its pH or accumulation in the blood of underoxidised metabolites; 3) metabolic disorders in the respiratory centre as a result of its injury or compression of its supplying vessels. Dyspnea is a protective physiologic mechanism by means of which the oxygen deficiency may be replenished and the excess carbon dioxide accumulated in the blood may be eliminated.)

In dyspnea the regulation of respiration is disturbed, this disturbance affecting the rate and depth of respiration. The respiration may be *accelerated* or *decelerated*, *shallow* or *deep*. Dyspnea may be *inspiratory*, i.e., long and difficult inhalations, *expiratory*, i.e., long and laboured exhalations, and *mixed*, in which case both respiratory phases are difficult.)

In experiments on animals artificial constriction of the upper air passage by compression or obstruction of the larynx, trachea or bronchi causes inspiratory dyspnea which is characterised by slow and deep breathing; in such cases the alveoli dilate slowly and stimulation of the peripheral ending of the vagus nerve is retarded with the result that the inhibition of the inhalation is late. Expiratory dyspnea arises after transection of the branches of the vagus nerve and sensory proprioceptive pathways originating in the respiratory muscles. Owing to the resultant absence of inhibition in the respiratory centre at the height of the inhalation a slowing of the exhalation is observed.

The character of dyspnea varies with its cause and mechanism. Dyspnea is most commonly manifested in the form of shallow and

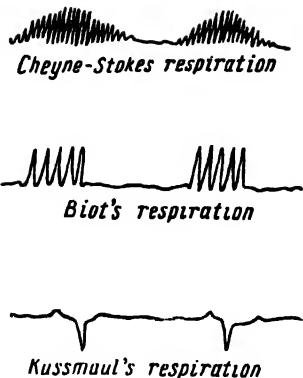


Fig. 112. Types of periodic respiration.

accelerated respiration, and less frequently as deep and slow breathing. Accelerated and shallow breathing involves a relatively greater expenditure of energy and insufficient utilisation of the respiratory surface of the lungs. Slow and deep respiration is more advantageous, not only because of the increased alveolar ventilation, but also because less energy is expended on the work of the respiratory muscles.

Rather long respiratory pauses or a temporary suspension of respiration (apnea) are observed in the newborn; they may also occur in other people after excessive pulmonary ventilation.

The appearance of apnea in the newborn is due to a carbon dioxide deficiency in their blood with a resultant diminished excitability of the respiratory centre. Apnea caused by increased pulmonary ventilation is also the result of a sharp decrease in carbon dioxide in the blood. Moreover, apnea may arise reflexly, for example, in response to stimulation of the afferent fibres of the vagus nerve.

Periodic Respiration. Periodic respiration includes Biot's, Cheyne-Stokes, and Kussmaul's types of respiration (Fig. 112). Cheyne-Stokes respiration is characterised by increasingly greater respiratory movements which reach their maximum and then gradually decrease, the respiration unnoticeably becoming shallow and ending in a pause which lasts up to 30 seconds; after the pause the same phenomena recur. This form of periodic respiration is sometimes observed in deep sleep (especially in old people); Cheyne-Stokes respiration is strongly pronounced in extreme cases of oxygen deficiency, for example, in severe pulmonary insufficiency, chronic nephritis, decompensated heart diseases, cerebral lesions (sclerosis, hemorrhages, embolisms or tumours), increased intracranial pressure and mountain sickness.

Biot's respiration is characterised by pauses in ordinary respiration, i.e., a series of respiratory movements are followed by a long pause, after which there is a new series of respiratory movements also followed by a pause, etc. This form of respiration is seen in meningitides, encephalitides, some cases of poisoning, and heat stroke. Kussmaul's respiration is characterised by long respiratory movements followed by long pauses. It may occur in uremia, eclampsia, diabetic coma and certain other diseases.

Periodic respiration, Cheyne-Stokes respiration in particular, is based on oxygen deficiency and reduced excitability of the respi-

tory centre which reacts weakly to the usual carbon dioxide concentration in the blood. During suspension of respiration carbon dioxide accumulates in the blood with the result that respiration is resumed, the excess carbon dioxide is eliminated from the blood and respiration is suspended again. Inspiration of an oxygen and carbon dioxide mixture eliminates periodic respiration.

It is now held that the impaired excitability of the respiratory centre is due to a discrepancy in time between the stimulation of the respiratory centre by carbon dioxide and the delivery of impulses from the periphery, the carotid sinus in particular. It is also possible that a certain role is played by variations in intracranial pressure, which affect the excitability of the respiratory and vasomotor centres.

In addition to the respiratory centre, the higher parts of the central nervous system also participate in engendering periodic respiration. This is evident from the fact that phenomena of periodic respiration are sometimes observed in connection with extraordinary excitation and transmarginal inhibition in the cerebral cortex.

A. Asphyxia. The condition characterised by insufficient delivery of oxygen to the tissues and accumulation of carbon dioxide in the latter is referred to as asphyxia. This condition is most commonly due to discontinued access of air to the lungs, as in strangulation, drowning, foreign bodies in the respiratory tract and laryngeal or pulmonary edema. Asphyxia may be experimentally produced in animals by compression of the trachea or administration of various suspensions into the respiratory tract.

In its acute form asphyxia presents a characteristic picture of respiratory, blood pressure and cardiac disturbances. The pathogenesis of asphyxia consists in reflex or direct action of the accumulated carbon dioxide on the central nervous system and a deficiency of oxygen in the blood.

Three indistinctly delimited periods may be observed in the course of acute asphyxia (Fig. 113).

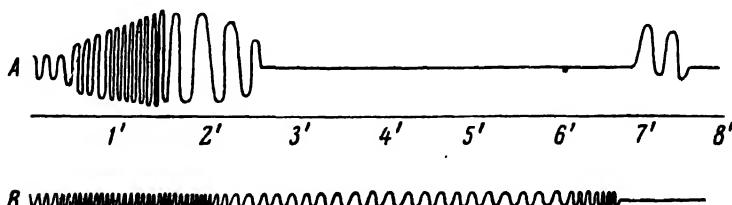


Fig. 113. Respiratory movements and cardiac activity in the dog in asphyxia. A—at first the respiratory movements become frequent and deep, then respiration slows down and, between the second and third minutes, is arrested; terminal respiratory movements are observed in the seventh minute and are followed by respiratory paralysis; B—cardiac activity is at first quickened, then sharply slowed; during the terminal period it is quickened again and is finally arrested.

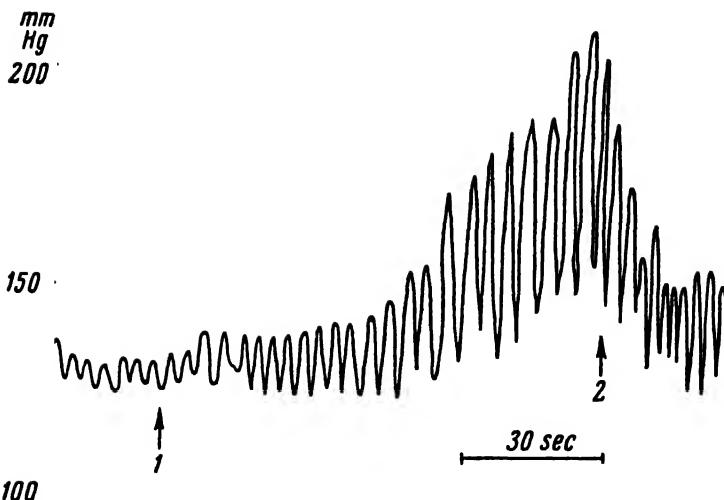


Fig. 114. Elevation of arterial pressure in asphyxia.
Arrows indicate beginning (↑ 1) and end of asphyxia (↑ 2).

The first period—*excitation of the respiratory centre* due to accumulation of carbon dioxide and oxygen deficiency in the blood. The respiratory disturbance is manifested in deepened and somewhat accelerated respiration involving increased inhalations (*inspiratory dyspnea*); *acceleration of the heart rate* and *elevation of arterial pressure* due to excitation of the vasoconstrictor centre are observed (Fig. 114); at the end of this period respiration slows down and is characterised by increased expiratory movements (*expiratory dyspnea*) accompanied by general clonic spasms and not infrequently by contractions of the smooth muscles, urination and defecation. The oxygen deficiency in the blood at first causes sharp excitation in the cerebral cortex which is soon followed by loss of consciousness.

The second period is characterised by a still greater slowing of respiration and *its temporary suspension*, *a drop in arterial pressure* and *a slowing of the heart's action*. All these phenomena are due to stimulation of the centre of the vagus nerves and reduced excitability of the respiratory centre resulting from excessive accumulation of carbon dioxide in the blood.

The third period is marked (owing to exhaustion of the nerve centres) by *extinction of the reflexes*, considerable dilatation of the pupils, relaxation of the muscles, *big drop in arterial pressure*, and infrequent but strong cardiac contractions; the period ends in a few terminal respiratory movements and respiratory paralysis. The *terminal respiratory movements* are most probably governed by

the lower weakly excitable parts of the spinal cord which take over the function of the paralysed respiratory centre.

In man acute asphyxia lasts a total of 3-4 minutes.

Observations show that in asphyxia the cardiac contractions continue some time after suspension of respiration. This is of great practical importance since it is still possible to revive the organism before complete cardiac arrest.

DISTURBANCES IN EXTERNAL RESPIRATION

Changes in the Thorax. Changes in the shape and size of the chest arise from diseases which lead to deformation of its framework of bones and cartilages, the pleura and lungs; sometimes these changes are a result of intrauterine disturbances. For example, extensive cicatrisation of the pleura and lungs leads to diminished mobility of the affected side of the thorax, a decrease in its size and curvature of the spine, which prevent restoration of the respiratory function. Accumulation of exudate or air in the pleural cavity or collapse of a lung may also cause a change in the size of the chest on the corresponding side.

In cases of considerable constriction of the chest (so-called paralytic thorax) the respiratory movements are somewhat decreased, the capacity of the lungs and the ventilation of the apices are diminished.

The opposite type of chest is one with an abnormally horizontal arrangement of the ribs, owing to which their movements are limited. This is particularly evident in sclerosis of the costal cartilages. In marked cases the ventilation of the pulmonary alveoli diminishes and the residual air in the lungs increases. In emphysema such changes in the thorax are sometimes very extensive.

The changes in the spine—lordosis (forward curvature of the lumbar spine), kyphosis (backward curvature of the thoracic spine) or scoliosis (lateral curvature of the thoracic spine)—may also cause a reduction in the size of the chest, constriction of the lungs, respiratory difficulties and a diminution in the volume of the air circulating in the lungs. Deformities of the chest are often the result of children's diseases, as pigeon breast in rickets and spinal curvatures in tuberculosis.

In view of the adaptability of the organism all these changes in the thorax have to be very extensive in order noticeably to affect respiration.

Changes in the Function of the Respiratory Muscles. In addition to the muscles which always participate in respiration (the external intercostal muscles and the diaphragm), there are also auxiliary muscles whose function is manifested in altered respiration connected with hard physical labour, infectious diseases and severe pulmonary and cardiovascular affections. The muscles taking part in

laboured and difficult inhalations include the *levatores scapulae*, *pectorales*, *trapezii*, etc., in laboured exhalations—mainly the muscles of the abdominal wall.

The function of the muscles participating in inhalations and exhalations may be impaired in muscular atrophies and dystrophies, but mainly in disorders of their innervation (in diphtheria, polio-myelitides, polyneuritides and certain other diseases).

Of the muscles taking part in respiration a very important part is played by the diaphragm, and disturbances in its function appreciably affect respiration.

The function of the diaphragm is disturbed as a result of lesions in its fibres and the diaphragmatic nerves which innervate them or in the centres of these nerves in the cervical part of the spinal cord. Lesions in the diaphragmatic nerves lead to paralysis of the diaphragm; the result of such paralysis is a function of the diaphragm which in this case assumes a position that leads to diminution in the internal size of the thorax (instead of descending the diaphragm is pressed upward).

A unilateral transection of the phrenic nerve sometimes performed to collapse and immobilise a lung in pulmonary tuberculosis does not cause any appreciable respiratory disturbances.

Respiration is also rendered difficult by a *high diaphragm and excessive intra-abdominal pressure* in cases of meteorism, ascites or tumours in the abdominal cavity, or by a *low diaphragm*, as in decreased intra-abdominal pressure and elevated pressure in the pleural cavity; the same difficulty arises in cases of reflex stimulation connected with pleurisy, peritonitis and other inflammatory processes in adjacent organs. Clonic spasms of the diaphragm causing *hiccups* are sometimes observed; in hiccups the inhalations are spasmotic. Hiccups occur as a result of reflexes originating in the abdominal organs, inflamed peritoneum, lesions in the phrenic nerve and certain diseases of the central nervous system.

Changes in the Upper Respiratory Tract. The most common affections of the upper respiratory tract are disturbances in its patency caused by inflammatory processes and, less frequently, by mechanical obstruction or constriction. Inflammatory processes are possible in any part of the respiratory tract. For example, inflammation of the nasal mucosa (acute and chronic rhinitis) makes respiration difficult because the air passing through the mouth into the trachea and bronchi is insufficiently heated and is not rid of the dust (normally almost 80 per cent of the dust inhaled with the air settles in the nasal cavity).

Inflammation of the larynx or trachea (laryngitis or tracheitis) also interferes with respiration. Diphtheritic inflammation of the larynx and trachea may give rise to constrictions which hinder inspiration; sometimes there is a danger of asphyxia, as in diphtheria or due to the effects of certain chemicals (vapours of ether).

chloroform, phosgene, mustard gas, etc.) which act mainly on the mucous membranes.

Inflammations of the mucous membrane of the bronchi—*bronchitides*—are accompanied by respiratory disorders whose extent depends on the character of the affection. The difficulty of the passage of air through the bronchi is due to tumefaction of the mucosa, accumulation of exudate and mucus in the bronchial lumens, and reflex spasm of the bronchial muscles.

Mechanical obstruction of the upper respiratory tract is commonly the result of foreign bodies gaining entrance into the bronchi and constricting or occluding their lumens. The penetration of foreign bodies is often due to paralysis of the epiglottis or diminished sensitivity of the mucosa, as in general anesthesia when inhalation of saliva and development of *aspiration pneumonia* are possible. The bronchi may also be compressed by a tumour growing from the mediastinum, an aortic aneurysm and a cicatricial contraction of the walls in peribronchial inflammation.

Constriction of the upper respiratory tract causes *slow* and *deep* (stenotic) respiration. The reason for the slowing of respiration is that in each inhalation the air passes with great difficulty into the lungs because of the obstruction in the upper respiratory tract (inspiratory dyspnea). The exhalation is retarded since the slow expansion of the lungs by the inhaled air impedes the stimulation of the endings of the pulmonary branches of the vagus nerves, which inhibit inhalation and stimulate exhalation. The inhalations are deep because the dilatation of the alveoli, which stimulates the endings of the pulmonary branches of the vagus nerves, is retarded by the slower passage of air into the alveoli.

A slight stenosis of the bronchi causes no perceptible disturbances in the organism because of the compensatory increase in respiration and gaseous interchange. Accumulation of carbon dioxide in the alveolar air and insufficient passage of oxygen into the organism are observed only in cases of considerable stenosis.

Occlusion of various bronchi results in a function of the corresponding parts of the lungs. In such cases no appreciable respiratory disturbances are observed because of compensatory hyperfunction of the remaining part of the lungs with the result that the gaseous interchange is unaffected.

Penetration of foreign bodies, food particles, mucus or saliva into the upper respiratory tract causes, in addition to laboured respiration, violent coughing (Fig. 115).

Coughing arises reflexly during irritation of the air passages, mainly the mucosa of the trachea and bronchi, but not the surface of the alveoli. It may arise as a result of stimuli originating in the pleura, the posterior wall of the esophagus, the peritoneum, liver, spleen, and directly in the central nervous system, for example, in the cerebral cortex (in encephalitis, hysteria). The stream of effe-

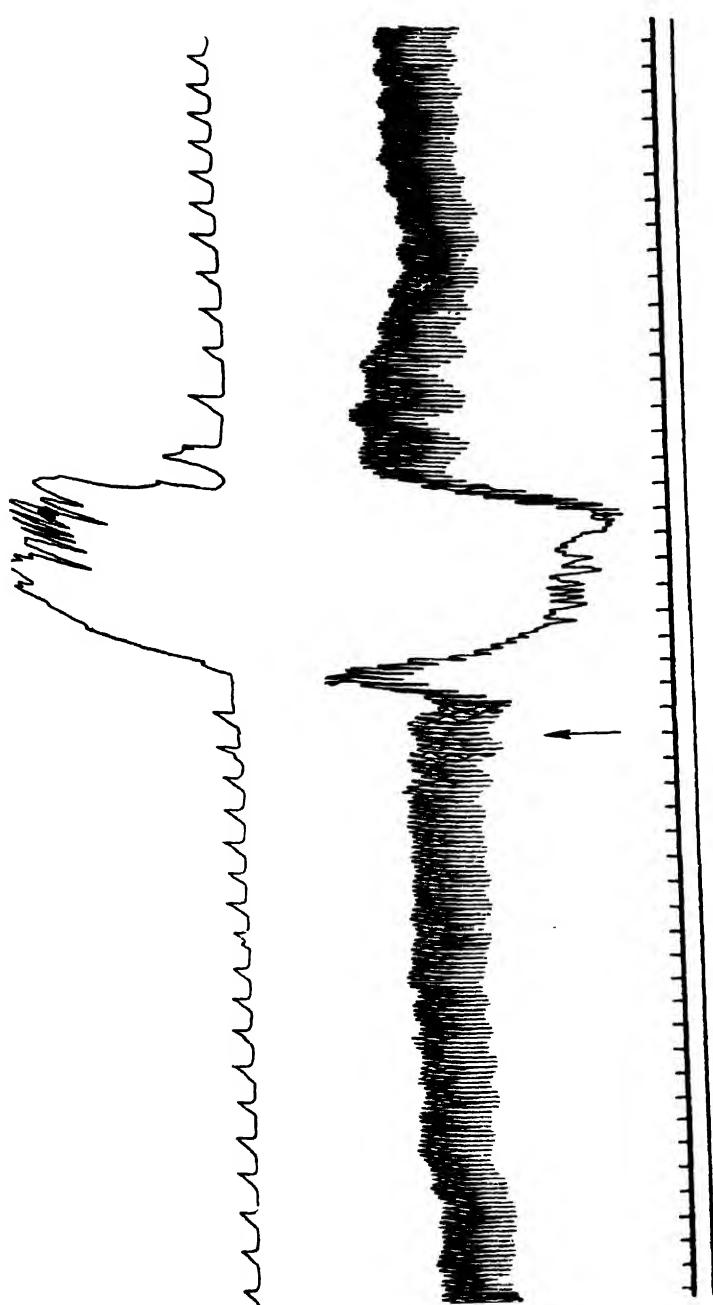


Fig. 115. Changes in respiration (top) and blood pressure (bottom) caused by air blown into the trachea. Arrow indicates beginning of blowing. Time markings—5 sec.

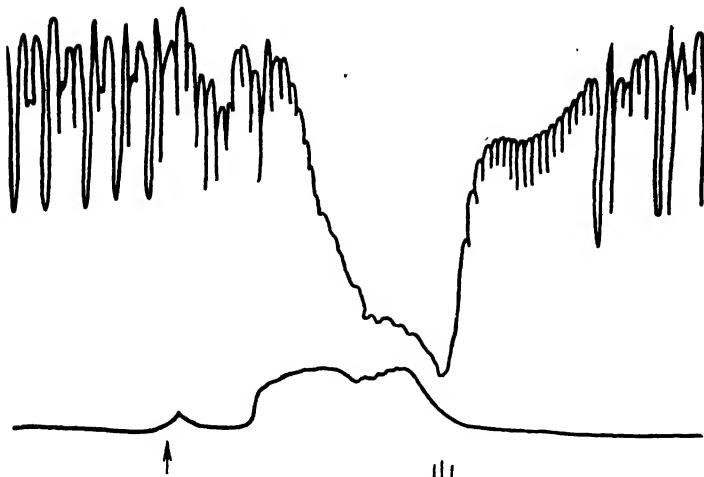


Fig. 116. Elevation of pressure in the femoral vein (lower curve) and drop in pressure in the carotid artery (upper curve) during increase in intra-alveolar pressure (\uparrow). Cardiac contractions are sharply weakened.

ent impulses from the central nervous system runs through the lower parts of the nervous system to the expiratory muscles, for example, the rectus abdominis and latissimus dorsi muscles, which in pathology participate in expiration. Deep inhalations are followed by spasmodic contractions of these muscles. With the rima glottidis closed the air pressure in the lungs noticeably increases, the rima glottidis opens and the air rushes to the exterior (in the main bronchus at the rate of 15-35 m per sec) under high pressure and with a characteristic sound. At the same time the soft palate closes the nasal cavity. The coughing expels from the air passages the mucus which has accumulated in them and which irritates the mucosa. This clears the air passages and eases respiration. Coughing plays a similar protective role when foreign particles gain entrance into the respiratory tract.

However, by causing elevated pressure in the thoracic cavity, violent coughing weakens its aspirating force. The outflow of blood through veins to the right heart may be impeded; the venous pressure is increased, the arterial pressure drops and the cardiac contractions become weaker (Fig. 116). The blood flow is disturbed, not only in the pulmonary, but also in the systemic circulation because the delivery of blood to the left atrium is hindered as a result of the elevated pressure in the alveoli and the compression of the pulmonary capillaries and veins. Moreover, there is a possibility of excessive dilatation of the alveoli and, in chronic coughing, of weakening of the elastic pulmonary tissue which, in old age, not infrequently leads to development of emphysema.

Sneezing is accompanied by the same movements as coughing, but it is the pharynx and not the rima glottidis that is compressed. The nasal cavity is not closed by the soft palate. The air is forced through the nose under high pressure. The stimulation originates in the nasal mucosa and is afferently transmitted through the trigeminal nerve to the respiratory centre.

Changes in the Lower Respiratory Tract. These include inflammatory processes—pneumonias and bronchopneumonias of various origin and capillary bronchitides which develop in the bronchioles and alveoli, compression of the lungs by an exudate (less frequently by tumours) and destruction of pulmonary tissue, as in tuberculosis.

All these changes are accompanied by dyspnea which is manifested the more sharply, the more lung surface is excluded from respiration and the sooner this exclusion occurs. These changes most commonly occur in acute pulmonary edema, embolism of a pulmonary artery and sudden compression of a lung, for example, by air penetrating into the pleural cavity. Severe exudative phenomena (in croupous and catarrhal pneumonia) may exclude from respiration an entire lobe of a lung or part of a lobe.

Affection of the bronchioles and lungs causes *accelerated and shallow respiration*. The air delivered from without stimulates the peripheral endings of the vagus nerve more strongly, the sensitivity of these endings in the affected parts of the lung being noticeably increased. This results in premature reflex inhibition of inhalation and gives rise to faster and shallow respiration. In cases of complete exclusion of part of the pulmonary tissue from respiration the inhaled air is distributed over fewer alveoli with the result that the latter sooner dilate to the limit which is necessary to inhibit inhalation and stimulate exhalation. In cases of faster inhalations the exhalations may be hindered because the air enters the large bronchi with difficulty through the constricted bronchioles (if the latter are inflamed). All these respiratory disorders due to diminution in the respiratory surface of the lungs give rise to oxygen deficiency and accumulation of carbon dioxide in the blood, which by stimulating the respiratory centre favour acceleration of respiration.

Moreover, exclusion of part of a lung from respiration may be accompanied by diminished circulation in it, for example, in cases of hepatisation of lobes of lungs in croupous pneumonia, or in compression of a lung by copious exudate from the pleural cavity. While not appreciably affecting the arterialisation of the blood, such exclusion of part of a lung is sometimes beneficial for the patient because in such cases less muscular energy is spent on respiration.

Atelectasis. Atelectasis is a collapsed state of all (or part) of a lung observed in cases of compression of the lung by air or exudate

from the pleural cavity and in occlusion of some part of the respiratory tract. The air present in this part of the lung is absorbed and its tissue becomes airless. Atelectasis may also arise as a result of increased contractile properties of pulmonary elements (muscle fibres and alveolar epithelium). The blood circulation through the vessels of the collapsed tissue of the lung diminishes, while in the remaining mass of the uncollapsed lungs it increases compensatorily, for which reason oxygenation of the blood flowing away from the lungs does not decrease despite the complete atelectasis of one lung.

By influencing the blood circulation in the lung the changes in the respiratory surface of the lung may affect cardiac activity. That is why in affections of the lower respiratory tract cardiac dyspnea is sometimes added to pulmonary dyspnea.

The disorders of the pulmonary apparatus include *bronchial asthma* and *emphysema* which are accompanied by development of pulmonary dyspnea (Fig. 117).

Attacks of *bronchial asthma* arise as a result of sudden spasm of the bronchi, especially of the bronchioles, and are due to increased excitability of the efferent fibres of the vagus nerve. These influences of the vagus nerve are under the control of the cerebral cortex, which is attested by the possibility of asthmatic attacks of a conditioned reflex character.

In cases of spasm of the bronchi and bronchioles respiration is very difficult and results in characteristic dyspnea. During attacks of bronchial asthma phenomena of asphyxia are observed. Exhalation is particularly laboured. Expiratory dyspnea in asthmatics is due to the resistance which has to be overcome by the air leaving the alveoli (in spasm of superior bronchioles). However, the respiratory movements are prolonged not only during exhalations, but also during inhalations. During exhalations the air is retained in the alveoli, the pressure in them rises and they dilate, the dilation affecting the capillary network of the lung. This in its turn influences the blood flow and pressure in the pulmonary circulation and, consequently, the work of the right heart.

One of the effects of bronchial asthma may be inflammation of

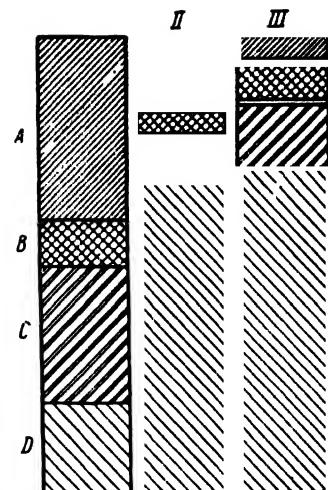


Fig. 117. Diagram showing distribution of pulmonary air.

Complemental (A), tidal (B), reserve or supplemental (C) and residual (D) air—normally (I), in asthma (II) and in emphysema (III). Horizontal lines in II and III above and below the space corresponding to tidal air indicate extent of respiratory movements.

the alveoli and, especially, of the bronchioles (*bronchiolitis asthmatica acuta*); this inflammation is accompanied by a discharge of phlegm containing thready structures of thick mucus, in the form of spirals, and eosinophils into the respiratory tract.

The development of an attack of bronchial asthma and the character of the disturbance in the morphological composition of the blood (eosinophilia) indicate that it is an allergic disease.

Respiratory disturbances are also observed in cases of diminished elasticity of the lungs. The elasticity of the lungs is altered the most in the disease known as *emphysema*. This disease is characterised by overinflation of the alveoli; in clearly marked cases the alveoli atrophy and the vessels are obliterated. The latter not only creates an obstacle to the work of the right heart and weakens the aspirating force of the thorax, but is also accompanied by impaired nutrition of the pulmonary tissue, which, in its turn, makes the lungs still less elastic and more distended.

Emphysema is characterised by incomplete inhalations due to the presence of a large amount of residual air in the alveoli, which means that less air is exhaled and the ventilation of the lungs is diminished. As a result the gaseous interchange in the blood is impaired, which gives rise to dyspnea of a predominantly expiratory character because the diminished elasticity of the pulmonary tissue noticeably hinders the exhalations. Respiration is effected with the aid of auxiliary muscles, which leads to an increased expenditure of energy. Oxygenation of the blood may diminish; cyanosis not infrequently develops and the oxidative processes in the tissues are disturbed.

The obstacles to exhalations leading to excessive dilatation of the alveoli most commonly arise as a result of chronic constriction of the lumens of bronchi in inflammatory processes, spasm of bronchioles and their compression by exudate. Not all forms of emphysema arise in this manner. There are forms of this disease which develop as a result of partial or complete ossification of the costal cartilages. The circulatory disturbances in the lungs, whatever their causes, also contribute to the development of emphysema.

Respiratory Disturbances Due to Affections of the Pleura and the Pleural Cavities. The respiratory disturbances due to changes in the pleura and pleural cavities are most commonly connected with inflammatory processes—pleurisies. Not infrequently they arise simultaneously with inflammation of the pulmonary tissue. Respiration becomes fast and shallow. Accumulation of exudate in pleural cavities hinders dilatation of the lungs during inhalations. The affected side takes but little part in the respiratory movements. Respiration is effected predominantly by the healthy side. In view of the reflexly increased work of the inspiratory muscles the volume of pulmonary ventilation may be restored by increased gaseous interchange in the healthy lung.

Clearly marked disorders of gaseous interchange occur only in cases of considerable accumulation of fluid in the pleural cavity (1.5-2 litres), crowding of the mediastinum to the opposite side and compression of the other lung with resultant circulatory disturbances. Circulatory disturbances are caused by compression of pulmonary vessels due to diminished aspirating action of the thorax (normally from —2 to —8 cm H₂O, during deep inhalations—up to —20 cm); they may also be caused by displacement of the heart, which hinders the blood inflow from the veins. During the period of compensation of the respiratory function the arterial pressure is either unaltered or is even somewhat elevated but, as the adaptability becomes impaired, the cardiac contractions weaken and the arterial pressure drops.

An important part in respiratory disorders in cases of pleural affections is also played by stimulation of the sensory nerve endings in the pleural leaves, which stimulates the respiratory centre and inhibits the respiratory movements on the affected side.

In experiment on dogs it may be observed that gradual injection of a poorly absorbable indifferent fluid (for example, 150-200 ml of vaseline or olive oil) produces dyspnea. The arterial pressure is almost unaffected, while the venous pressure somewhat rises. Continued injection crowds the mediastinum to the opposite side, compresses the heart and vessels, elevates arterial and venous pressure, and noticeably increases its respiratory variations due to dyspnea. The dyspnea, elevated arterial pressure and its respiratory variations indicate inadequate gaseous interchange in the lungs and stimulation of the respiratory and vasomotor centres by the carbon dioxide accumulated in the blood. Lastly, when the regulatory mechanisms fail, respiratory paralysis sets in; the paralysis is preceded by a drop in arterial pressure and a sharp weakening of cardiac contractions. Similar phenomena are observed after administration of large amounts of fluid (1 litre and more) into a pleural cavity, and in pneumothorax.

Pneumothorax is the presence of air or gas in a pleural cavity. It occurs whenever there is communication between a pleural cavity and the outside air. Air gains entrance into a pleural cavity mainly as a result of a traumatic injury (penetrating wound) to the chest, injury to pulmonary tissue (as in its destruction by tuberculosis, pulmonary abscess, emphysema and gangrene), and artificial administration of air into a pleural cavity in tuberculosis when it is necessary to exclude the affected lung from respiration, compress it and thereby hasten cicatrisation of the cavernous focus.

Pneumothorax may be *complete*, if an entire pleural cavity is filled with air, or *partial*, when the entire pleural cavity cannot be filled either because a small amount of air has been injected or because the cavity contains exudate or has adhesions.

Pneumothorax is satisfactorily tolerated by man if it is partial or unilateral; complete bilateral pneumothorax is always fatal.

Three forms of pneumothorax are distinguished: 1) *closed pneumothorax*—one having no opening through the chest wall; it may result from a sudden and very sharp elevation of intrathoracic pressure; 2) *open pneumothorax*—one in which the outside air freely enters the pleural cavity and leaves it through an opening during inhalations and exhalations; this form is particularly dangerous because, as a result of displacement of the mediastinum, the air which has gained entrance into the pleural cavity may compress the lung on the healthy side, owing to which the volume of inhaled air is sharply reduced, and severe dyspnea and circulatory disturbances develop; 3) *valvular pneumothorax*—one in which the orifice opens during inhalations and air is pumped into the pleural cavity until the pressure of the air in it equals that of the atmospheric air.

Unilateral pneumothorax, as well as accumulation of fluid in a pleural cavity, causes deeper and, usually, accelerated respiration on the healthy side. As soon as air enters a pleural cavity and a lung is compressed, respiratory and circulatory disorders—pallor, sometimes cyanosis, severe dyspnea, elevated venous pressure, and increased rate and amplitude of pulse waves—set in. The air entering a pleural cavity is gradually absorbed in the absence of communication with the outside air, the lung expands and respiration is restored. The respiratory and circulatory changes in pneumothorax are due to the same factors as in pleurisies.

Respiratory Disturbances Due to Circulatory Disorders in the Lungs. Circulatory disorders in the lungs give rise to disturbances in the gaseous interchange between the blood and the alveolar air and impair respiration. This may be occasioned by cardiac failure when the amount of blood circulating through the capillaries of the lungs diminishes or hemostasis develops in the pulmonary circulation (mainly in mitral failure). Diminution in pulmonary circulation causes retention of carbon dioxide in the blood and gives rise to dyspnea due to stimulation of the respiratory centre.

Hemostasis in the lungs leads to respiratory dysfunction of the alveoli, which is due mainly to a decrease in their dilatability and elasticity (they may subsequently become indurated), narrowing of their lumens and diminished permeability of their walls. The result is impaired pulmonary ventilation, diminished gaseous interchange, increased carbon dioxide in the blood and stimulation of the respiratory centre. At the same time the oxygen in the blood decreases (hypoxemia), which heightens the sensitivity of the respiratory centre to carbon dioxide.

These data on the nature of the respiratory disturbances resulting from circulatory disorders are not exhaustive. It has been discovered by direct determination of the gaseous composition of the

blood that diminished arterialisation of the blood in the lungs and the accumulation of carbon dioxide are not enough to explain the pathogenesis of dyspnea in cardiac disorders. It appears that the pathogenesis of cardiac dyspnea is based not so much on disturbed pulmonary gaseous interchange as on the circulatory changes in the systemic circulation and impaired oxygen interchange in the tissues. As a result of this the *nutrition of the respiratory centre is disturbed and acid metabolites accumulate in the blood*. Thus the origin of dyspnea in cardiac disorders is *centrogenic* rather than pulmonary. In accordance with the available data a particularly important role in the pathogenesis of cardiac dyspnea is also played by *excitation* of the respiratory centre originating in the interoceptors of the dilated atria and veins.

Several compensatory processes develop, including hypertrophy of the heart muscle in response to the weakening in its activity; the considerable area of the total cross-section of the pulmonary capillaries offers extensive possibilities for restoring the blood circulation. The establishment of new relations between respiration and the blood circulation in cardiac disorders is of enormous adaptive importance and is effected by the function of the central nervous system.

Pulmonary Edema. Pulmonary edema is an accumulation of transudate in the alveoli and a swelling of the alveolar septa. Circulatory changes in pulmonary circulation, congestive phenomena and impairment of the capillary network of the lungs are apparently the most important factors of the pathogenesis of *pulmonary edema* (in heart diseases, inflammatory processes in the lungs, and poisoning). The character of the edema depends on the relation between the hemodynamic and physicochemical factors in the pulmonary circulation and pulmonary tissue. The respiratory disturbances in pulmonary edema are due to a decrease in the respiratory surface of the alveolar apparatus.

Congestive edema in a lung must be distinguished in origin from toxic edema. Toxic pulmonary edema develops as a result of the action of various poisonous substances (for example, phosgene and diphosgene) on the pulmonary apparatus. It can be produced experimentally by intravenous administration of silver nitrate and Lugol's solutions, and by inhalation of phosgene. In the latter case toxic edema develops particularly rapidly with dyspnea, cyanosis, rales and a discharge of sanguineous sputum. In the origin of toxic edemas some part is apparently played, in addition to the altered blood circulation in the lungs, by affection of the pulmonary tissue and the walls of the vessels; increased permeability of the vessels and formation of exudate are the results. Disturbances in the respiratory function of the lungs (severe dyspnea) rapidly lead to development of hypoxemia, cardiac weakness, grave general circulatory insufficiency and not infrequently to death.

RESPIRATORY DISTURBANCES DUE TO CHANGES IN THE COMPOSITION OF THE BLOOD

A decrease in hemoglobin in the circulating blood due to a diminished number of erythrocytes or their insufficient saturation with hemoglobin is the cause of *hypoxemia—insufficient oxygen in the blood*. This occurs in severe anemias (for example, pernicious anemia), after considerable losses of blood (up to 70 per cent) or in marked functional disorders of the hematopoietic apparatus.

The organism tolerates a hemoglobin deficiency satisfactorily if it develops gradually and the organism has a chance to adjust itself to this disturbance. For example, in cases of blood losses the respiration becomes deeper and faster and the blood circulation is accelerated.

Dyspnea arises in the case of a blood loss as a result of stimulation of the respiratory centre, the stimuli originating in reflexogenic vascular zones, especially the carotid sinus and aorta (which are particularly sensitive to diminished oxygen in the blood); it may also be caused by changes in the composition of the blood, particularly accumulation of acid metabolites which stimulate the respiratory centre.

Blood circulation is accelerated as a result of faster heart action and increased aspirating force of the thorax associated with deeper and faster respiration. The same things occur in severe anemias. In cases of decreased hemoglobin in the blood accelerated blood circulation is conducive to better gaseous interchange; in anemia the coefficient of oxygen utilisation, i.e., the ratio of the oxygen absorbed by the tissues to its amount contained in the arterial blood, increases.

One of the mechanisms controlling the onset of grave signs of oxygen deficiency in severe anemia is a limitation of movements requiring expenditure of oxygen. Owing to hemoglobin deficiency (in marked anemias) any strain in work leads to respiratory disturbances which arise as a result of both hypoxemia and a direct stimulating effect on the respiratory centre by the carbon dioxide accumulated during work.

Respiratory disorders also arise in hypoxemias due to the loss of the hemoglobin's ability to combine with oxygen and are observed in cases of *poisoning with carbon monoxide* and *blood poisons* which transform hemoglobin into methemoglobin.

Carbon monoxide poisoning results from inhaling air containing this gas. Grave signs of poisoning appear when the inhaled air contains 0.1-0.2 per cent carbon monoxide; prolonged inhalation of air containing carbon monoxide is dangerous to life even when the concentration of this poison is as low as 0.05 per cent and lower.

Having gained entrance into the alveolar air carbon monoxide easily passes into the blood because its partial pressure in the blood is zero. Hemoglobin combines with carbon monoxide much more readily than it does with oxygen and forms carboxyhemoglobin. Carbon monoxide displaces oxygen from its hemoglobin compounds. A deficiency in the oxygen supply to the tissues arises. Elimination of carbon monoxide by the lungs is possible only in mild cases of poisoning, especially on inhalation of a mixture of oxygen and carbon dioxide (to stimulate the respiratory centre); in these cases CO-Hb is dissociated into CO and Hb. The reduced hemoglobin recombines with oxygen.

In cases of poisoning with blood poisons, for example, potassium chlorate, benzene compounds, phenylhydrazine and some arsenous compounds, hemoglobin is transformed into methemoglobin which combines with oxygen into a more stable compound. Methemoglobinemia therefore perceptibly affects the supply of the tissues with oxygen.

DISTURBANCES IN INTERNAL RESPIRATION

Internal respiration is tissue respiration, i.e., oxidative processes operating in the tissues and consisting in discharge of carbon dioxide into the blood and absorption of oxygen from the blood. Since the blood and lymph are the external environment of the tissues, a change in the gaseous composition of the blood due to disturbances in external respiration impairs tissue respiration. But pathologic phenomena may also originate in the tissues. Changes in intracellular respiration secondarily affect the function of the apparatus of external respiration.

The causes of impaired internal respiration may be *exogenous* and *endogenous*.

All the substances that affect the oxidative processes in the tissues by influencing the organs from without are exogenous causes. These substances include phosphorus, arsenic, cyanide compounds, narcotics and various toxic substances which gain entrance into the organism in infections and intoxications. The mechanisms of the action of these substances differ. Some of them depress the oxidative processes in the tissues by combining with oxygen (for example, phosphorus), others block various respiratory enzymes.

The endogenous causes of respiratory disorders are all the factors which, arising within the organism, disturb the oxidative processes in the tissues.

For example, disturbances in tissue respiration arise in cases of dysfunction of certain endocrine glands. Thus the oxidative processes in the tissues are depressed in hypofunction of the thyroid, hypophysis and gonads. Adrenalin, insulin and other hormones also exert a direct or indirect influence on tissue respiration.

Disturbances in tissue respiration arise in many pathologic processes both in individual organs and in all of the organism's tissues. This is observed, for example, in blastomatous growth, avitaminoses and severe cardiovascular disorders.

Lastly, disturbances in internal respiration may be the result of dysfunction of the nervous system, as in trophic ulcers of neurogenic origin.

HYPOXIA

Insufficient supply of the tissues with oxygen or inadequate utilisation of oxygen by the tissues is referred to as *hypoxia*.

Forms and Causes of Hypoxia

The following forms of hypoxia are now distinguished in accordance with the causes of their origin.

1. *Hypoxic hypoxia* in which the arterial blood is insufficiently oxygenated and the oxygen tension in it is low with the result that the saturation of hemoglobin with oxygen is also below normal. This form of hypoxia arises as a result of decreased oxygen in the inspired air, disturbance in *respiration and in ventilation of the alveoli* (due to disorders in the apparatus of external respiration, particularly diminished excitability of the respiratory centre, decreased patency of the air passages, etc.), or hindred passage of oxygen through the altered alveolar wall into the blood (in inflammatory pulmonary processes).

2. *Anemic hypoxia* in which the oxygen-carrying capacity of the blood is reduced due to a *decrease in hemoglobin* (in anemias) or to formation either of methemoglobin or carboxyhemoglobin. In this form of hypoxia the degree of saturation of the functioning hemoglobin is normal, but the total amount of oxygen in the blood is decreased.

3. *Stagnant or ischemic hypoxia* in which the circulation of the blood is slow. This form of hypoxia arises as a result of *general circulatory disorders* (in cardiac failure or shock) or in local circulatory disturbances (in venous congestion or ischemia). In these cases oxygenation of arterial blood is normal, but the total volume of oxygen carried to the tissues per unit of time is decreased. Diminished oxygen in the venous blood and an increased arteriovenous difference are observed.

4. *Histotoxic (tissue) hypoxia* in which, as distinct from all other forms, the transport of oxygen is undisturbed and its concentration in the blood is normal, but the *ability of the tissues to utilise the delivered oxygen is diminished*. This is due to a primary disturbance in the oxidative processes in the tissues, as in poisoning with cyanide compounds which paralyse the cytochrome oxidase (iron-containing enzyme), or under the action of narcotics which predominantly

depress the activity of diaphorases. Avitaminoses B₁, B₂ and PP, and endocrine disorders may also cause tissue hypoxia.

The foregoing classification must be supplemented by most frequently occurring forms of mixed hypoxias.

Mixed hypoxias include those occurring in traumatic shock and intoxications, and under the action of certain poisonous substances, when there are simultaneously cardiovascular and pulmonary insufficiency and disturbances in tissue metabolism. Of the disturbances characteristic of hypoxias it is not always possible to determine with sufficient certainty the symptom complex of the changes associated precisely with oxygen deficiency in the tissues. For example, in affections of the pulmonary apparatus, the blood or tissues, the phenomena of oxygen deficiency proper are overshadowed by phenomena of intoxication, metabolic disorders, signs of pulmonary disease, disturbances in the hematopoietic apparatus or dystrophic phenomena in various organs.

The most characteristic indications of inadequate supply of the tissues with oxygen are dyspnea and circulatory disorders (cardiac failure, drop in blood pressure and cyanosis).

Hypoxia causes a number of adaptive changes variously manifested in accordance with the extent of oxygen deficiency. The respiratory rate noticeably increases and, as a result, the blood flow is accelerated and the minute volume of the heart and mass of circulating blood increase (the latter is due to draining of the blood depots).

All these phenomena cause an increased inflow of blood to vitally important organs (heart and brain) thereby in certain measure compensating for the oxygen deficiency in the blood. The respiratory and circulatory changes in hypoxia arise in response to the stimulation of the chemoreceptors of the sinocarotid and aortic zones by the altered blood and to its direct influence on the central nervous system.

Effects of Decreased Partial Oxygen Pressure in the Air on the Organism and Processes of Adaptation

Hypoxia is most clearly manifest in a rarefied atmosphere where the partial oxygen pressure is decreased.

In experiment oxygen deficiency may occur under relatively normal atmospheric pressure with decreased oxygen as may be the case in a closed space. Phenomena of oxygen deficiency may be observed in mountain climbing and high altitude flying—*mountain and altitude sickness* (Fig. 118).

The first signs of acute mountain sickness may sometimes be observed already at an altitude of 2,500-3,000 m. In most people they manifest themselves at an altitude of 4,000 m. At this altitude the partial oxygen pressure of 159 mm (at an atmospheric pres-

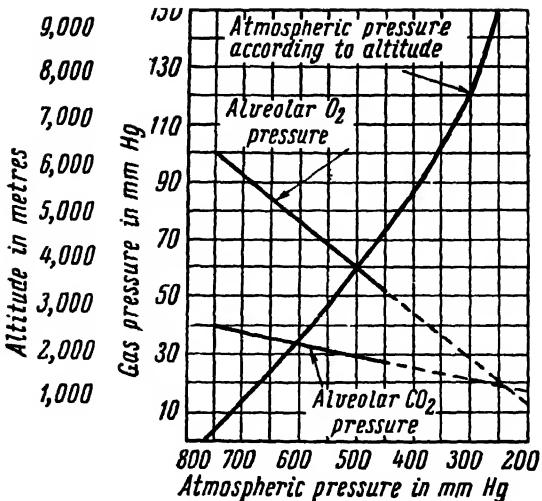


Fig. 118. Pressure of gases in the alveoli of persons living at different altitudes.

sure of 760 mm Hg) drops to 89 mm (at an atmospheric pressure of 430 mm Hg), and the oxygen content of the arterial blood begins to decrease. Symptoms of hypoxia usually appear when oxygenation of the arterial blood drops to 85 per cent of its oxygen-carrying capacity; death may occur when it drops below 50 per cent.

Mountain climbing is accompanied by characteristic phenomena which are also due to temperature conditions, wind and muscular work done during the climbing. The higher the metabolism caused by muscular effort and drop in the temperature of the air, the sooner the signs of the sickness appear.

The disorders arising during the ascent to a high altitude occur the sooner, the faster the ascent. In such cases training plays a very important part.

Oxygen deficiency which accompanies high altitude flying has its own distinctive features. Mountains are climbed slowly and the climbing requires strenuous muscular effort, while aircraft may reach high altitudes within very short periods of time. Flying at an altitude of 5,000 m without adequate training is accompanied by headache, dizziness, a feeling of heaviness in the chest, palpitation, and expansion of gases in the intestines, owing to which the diaphragm is crowded upward and respiration is rendered still more difficult. Use of an oxygen mask eliminates all these phenomena (Fig. 119).

The effect of decreased oxygen in the air on the organism is manifested in nervous, respiratory and circulatory dysfunction.

A certain period of excitement is followed by fatigue, apathy, somnolence, heaviness in the head, psychic disturbances in the form of irritability and subsequent depression, partial loss of orientation, disorders of the motor function and disturbances in higher nervous activity. Internal inhibition in the cerebral cortex weakens at middle altitudes, while diffuse inhibition develops at high altitudes. The condition also involves disturbances in the vegetative functions as dyspnea, accelerated heart rate, circulatory changes and digestive disorders.

Acute oxygen deficiency is marked by *respiratory* disturbances. Respiration becomes fast and shallow as a result of stimulation of the respiratory centre. Some cases are accompanied by peculiar, intermittent, so-called periodic respiration (Cheyne-Stokes type) in which pulmonary ventilation is perceptibly affected. In gradually developing oxygen deficiency respiration becomes fast and deep, the circulation of air in the alveoli appreciably improves, but the concentration and tension of carbon dioxide in the alveolar

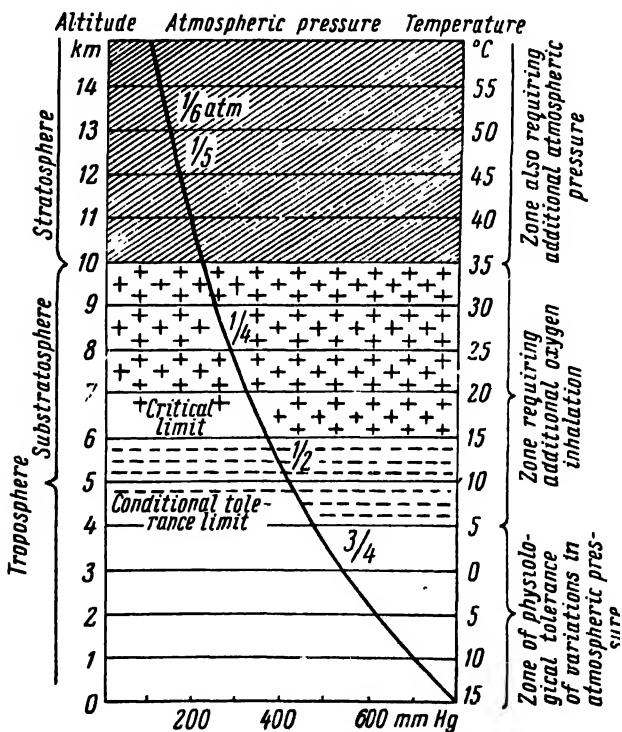


Fig. 119. Vertical section of the atmosphere offering an idea of flying conditions.

air decrease, i.e., hypocapnia, which aggravates the course of hypoxia, develops. The respiratory disturbances may lead to loss of consciousness.

Acceleration and intensification of the heart's action arise as a result of hyperfunction of the accelerator nerve of the heart and hypofunction of the vagus nerves. Acceleration of the pulse in cases of oxygen deficiency is therefore one of the indications of the reaction of the nervous system which regulates the blood circulation.

Several other circulatory disorders arise at high altitudes. The arterial pressure at first rises, but subsequently begins to drop in accordance with the state of the vasoconstrictor centres. With a very low oxygen concentration in the inspired air (7-6 per cent) the heart's action noticeably weakens, the arterial pressure drops, while the venous pressure rises, cyanosis develops and arrhythmia results.

Bleeding from the mucous membranes of the nose, mouth, respiratory tract, gastrointestinal tract, and from the conjunctiva is also sometimes observed. This is largely ascribed to dilatation of superficial blood vessels, especially the vessels in the mucous membranes, and their increased permeability. Action of toxic metabolites on the capillaries is another factor.

The dysfunction of the nervous system in a rarefied atmosphere is also manifested in *gastrointestinal disorders*, usually as anorexia, inhibition of the function of the digestive glands, diarrhea and vomiting.

Altitude anoxia (hypoxia) is characterised by *metabolic* disturbances. Consumption of oxygen at first increases and then, in cases of marked oxygen deficiency, falls; the specific dynamic effect of protein diminishes and the nitrogen balance becomes negative. The nonprotein nitrogen in the blood increases and ketone bodies, especially acetone, accumulate and are excreted in the urine.

Until a certain limit is reached a decrease in oxygen in the air barely affects the formation of oxyhemoglobin, but with the subsequent diminution in oxygen to 12 per cent the oxygen concentration in the blood drops to 75 per cent of the normal and, when the oxygen in the air decreases to 6-7 per cent, its concentration in the blood goes down to 50-55 per cent of the normal. The tension of the oxygen diminishes particularly in the capillary blood and appreciably affects oxygen diffusion into the tissues.

The increase in the respiratory capacity of the lungs and the greater pulmonary ventilation in hypoxia give rise to a carbon dioxide deficiency in the alveolar air and the blood (hypocapnia) and to relative alkalosis, owing to which the respiratory centre may be temporarily inhibited, while the heart's action is weakened. Inspiration of carbon dioxide at high altitudes therefore leads to increased excitability of the respiratory centre, aids in increas-

ing the oxygen in the blood and thereby improves the state of the organism.

However, the continued decrease in partial oxygen pressure during ascent to a high altitude is conducive to further development of hypoxemia and hypoxia. The phenomena of insufficiency of oxidative processes increase. Alkalosis is again replaced by acidosis which in its turn somewhat diminishes owing to the acceleration of the respiratory rhythm and diminution in the oxidative processes and partial carbon dioxide pressure.

During ascent to a high altitude the *heat exchange* is also noticeably altered. The heat loss increases mainly by evaporation of water from the body surface and through the lungs. Heat production gradually begins to lag behind heat loss with the result that the body temperature, which at first somewhat rises, then drops.

The manifestations of oxygen deficiency very largely depend on the characteristics of the organism, i.e., the state of its nervous system, lungs, heart and vessels, which determine the organism's ability to tolerate a rarefied atmosphere.

The effect of rarefied air also depends on the rate of development of oxygen deficiency. In cases of acute oxygen deficiency dysfunction of the nervous system comes to the foreground, whereas in chronic cases pathologic nervous phenomena do not appear for a long time because of the gradual development of compensatory processes.

A healthy person generally tolerates a certain decrease in barometric pressure and partial oxygen pressure satisfactorily, and copes with it the better, the slower the ascent and the easier the adjustment of the organism. A drop in atmospheric pressure to one-third the normal, which is 250 mm Hg and occurs at an altitude of 8,000-8,500 m, the air containing 4-5 per cent oxygen, may be considered the human tolerance limit.

It has been established that at high altitudes with insufficient oxygen supply to the tissues the organism *adapts* or acclimates itself, the adaptation ensuring compensation for the respiratory disorders. Mountaineers and trained mountain climbers may not develop the mountain sickness even at an altitude of 4,000-5,000 m, while well-trained flyers can fly without an oxygen mask at 6,000-7,000 m and even higher.

Adaptive Mechanisms in Altitude Anoxia

Dyspnea in the form of *deeper and faster* respiratory movements arises in hypoxia as a result of oxygen deficiency and accumulation of carbon dioxide and underoxidised metabolites in the blood. The blood stimulates the chemoreceptors in the carotid sinus, the arch of the aorta, the vessels of the pulmonary circulation and directly the respiratory centre. Dyspnea leads to an increase in the pul-

monary ventilation and functioning respiratory surface of the lungs with the result that the gaseous interchange in the pulmonary alveoli increases, more oxygen is delivered to the organism and the excess carbon dioxide is eliminated.

The *accelerated circulation* in hypoxia is due to the increased aspirating action of the thorax, which accompanies dyspnea. The insufficient inflow of oxygen reflexly increases the function of the accelerator nerve of the heart and the peripheral circulation. All these factors combine to increase the minute volume of the heart with the result that circulation is improved and more oxygen is delivered to the tissues. Lastly, the increased excursions of the diaphragm force the blood from the visceral vessels into the general circulation.

The *increase in erythrocytes* observed during the very first stage of oxygen deficiency is due to their mobilisation from the blood depots. This phenomenon is a result of a reflex contraction of the spleen and ejection of a large number of erythrocytes into the blood current. Hemoconcentration caused by extensive evaporation of water from the body surface is apparently also of some significance. Somewhat later the *function of the bone marrow increases* with a resultant absolute increase in the number of blood cells. Already 24 hours after the ascent to a high altitude the number of erythrocytes in the blood noticeably increases above normal. Changes in the blood manifested in the appearance of polychromatophilic erythrocytes, reticulocytes and sometimes normoblasts are indicative of increased hematopoiesis. Development of hyperglobulia helps to maintain the oxygen exchange on the normal level.

The property of the blood hemoglobin to combine with oxygen within limits close to normal despite the altered oxygen tension in the alveolar air is also ascribed to the aforesaid changes. This is feasible because the connection between oxygen and hemoglobin is chemical, and the ability of hemoglobin to combine with oxygen in oxygen deficiency may long persist on a high level. For example, at a partial oxygen pressure of 60 mm Hg the hemoglobin contains about 80 per cent oxygen. Only with a further drop in partial oxygen pressure does the oxygen exchange between the blood and the alveolar air begin perceptibly to decrease.

In altitude hypoxia the *ability of the tissues to absorb oxygen increases*, a certain intensity of the oxidative processes thus being ensured.

Owing to the adaptive mechanisms, respiration and blood circulation, impaired by the oxygen deficiency, gradually return to normal.

Slightly rarefied air, for example, at an altitude of 1,500-2,000 m is often even beneficial for the organism; it improves the blood circulation, the blood supply to the lungs, pulmonary ventilation

and erythropoiesis. This accounts for the favourable influence of a mountain climate on anemia patients, provided they are not affected with any respiratory or circulatory diseases.

In cases of slight oxygen deficiency the defensive physiologic functions of the organism ensure an increased inflow of oxygen to the tissues and the processes of oxidation therein. An increase in oxygen deficiency gives rise to sluggishness, apathy and depression of nervous activity. In such cases inhibitory reactions in the cortex are observed; these reactions may be regarded as a manifestation of transmarginal inhibition aimed at preservation of the efficiency of the cortical cells. Such inhibition may be characterised as protective. As a matter of fact, experimental observations have shown that inhibition in the cerebral cortex due to the effects of hypnotics and closely resembling natural sleep renders animals temporarily more resistible to hypoxia.

However, the ability of the organism to adapt itself to reduced partial oxygen pressure is not unlimited and may be particularly impaired by the action of additional factors, as infection, intoxication and increased physical work, with the result that pathologic phenomena, unified under the designation of chronic mountain sickness, develop. The latter is characterised by erythremia, hemorrhages, emphysematous phenomena with marked dyspnea, cyanosis, signs of cardiac insufficiency, nervous and mental disorders, and culminates in death (if the patient remains in the rarefied atmosphere).

EFFECTS OF ELEVATED PARTIAL PRESSURE OF OXYGEN, CARBON DIOXIDE AND NITROGEN ON THE ORGANISM

The *effect of increased oxygen on the organism* may be observed not only under artificial conditions (inhalation of oxygen, especially under conditions of increased pressure), but also at great depths, in caissons, i.e., chambers in which work is done under elevated atmospheric pressure. In these cases the organism is under elevated pressure in general and increased partial oxygen pressure in particular. *Increased partial oxygen pressure* is tolerated by the organism much better than below-normal pressure. In cases of elevated partial oxygen pressure the delivery of oxygen to the lungs is accelerated and the amount of oxygen dissolved in the plasma increases. An elevation of atmospheric pressure to 2 atm usually causes an intensification of the oxidative processes.

Pathologic phenomena in the organism begin to be observed after 4-5 hours under a pressure of 2 atm and after 2 hours under a pressure of 3 atm. These phenomena include respiratory disturbances (deeper and slower respiration), slowing of the heart's action and of the pulse, engorgement of the internal organs with blood and inhibition of the function of the central nervous system;

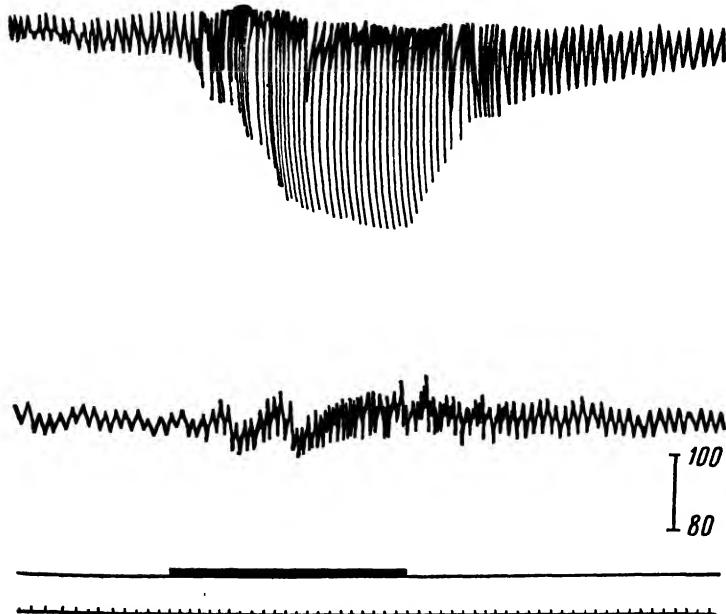


Fig. 120. Pulmonary ventilation when the inhaled air contains 6 per cent carbon dioxide.
of inhalation of carbon dioxide is marked by the black line. Upper curve—respiratory record, lower curve—arterial pressure (G. P. Konradi).

these may be followed by general convulsions and loss of consciousness. The amount of gases dissolved in the blood increases and the metabolism is impaired, i.e., there is greater disintegration of albuminous substances and accumulation of underoxidised metabolites. At a very high partial pressure oxygen loses its property to increase the oxidative processes and may even become a poison to the organism.

The return from an atmosphere with an elevated pressure to one with normal pressure must be gradual and must include rather long intermissions. Rapid transition from high to normal pressure may give rise to *caisson disease*. Mild cases of the latter are characterised by pain in the muscles and joints, itching of the skin, disturbed heat exchange which leads to cooling and sometimes penetration of air under the skin (cutaneous emphysema); severer cases are marked by unconsciousness, convulsions, pareses and paryses. The gases dissolved in the plasma (mainly nitrogen) are liberated in the form of bubbles giving rise to gas emboli. The results of embolisms vary with the size of the emboli, the rapidity of their formation, the site of vascular occlusion, etc. Gas emboli are eventually resorbed and these phenomena in most cases disap-

pear, but in cerebral and cardiac vessels they are very dangerous for they may cause instant death.

Increased carbon dioxide in the surrounding atmosphere primarily causes greater pulmonary ventilation and an increase in the respiratory capacity of the lungs due to stimulation of the respiratory centre (Fig. 120). A slight increase in the concentration of carbon dioxide in the blood dilates the coronary and cerebral vessels and alters the distribution of the blood. Carbon dioxide acts through the reflexogenic zones of the lungs, upper respiratory tract and vascular walls, but particularly through the blood directly on the respiratory centre. In cases of hypofunction of the respiratory centre clinical practice makes use of the stimulating effect of a slight increase in carbon dioxide in the blood on the respiratory centre.

The first mild subjective sensations of disturbed respiration are observed when the air contains 2 per cent carbon dioxide (instead of the normal 0.04 per cent). If the carbon dioxide in the air increases simultaneously with a decrease in oxygen the respiratory centre becomes noticeably more sensitive to carbon dioxide.

An increase in carbon dioxide in the air to 8-9 per cent leads to dyspnea and slowing of the cardiac rhythm, drop in blood pressure, weakness, apathy and a narcotic state. All of the organism's functions are depressed. Signs of intoxication occur as a result of disintegration of the albuminous substances of the tissues; more sulfur and phosphorus and relatively less sodium chloride are eliminated in the urine. An increase in carbon dioxide in the air above 10-15 per cent intensifies the aforesaid phenomena and leads to loss of consciousness and death due to respiratory paralysis.

Under pressure *nitrogen* produces a narcotic and toxic effect on man and animals. It dissolves in the blood and tissues, mainly in fats. The effects of nitrogen are manifested in such nervous disorders, as tremor capitis, disturbances in standing and walking, automatic movements and convulsions. Some pathologic phenomena resulting from working in caissons are apparently also due to elevated partial nitrogen pressure.

PATHOLOGY OF DIGESTION

Functionally the various parts of the gastrointestinal tract constitute a single system. As the classic studies of Pavlov and his school have shown, this unity is determined mainly by the regulatory activity of the nervous system.

The gastrointestinal tract may suffer from disturbances in its basic functions—motor, secretory, absorptive and excretory—as well as from intestinal fermentation and putrefaction. These disturbances are also associated with disorders of the sensations of hunger and thirst, metabolism and hematopoiesis.

DISTURBANCES IN THE SENSATIONS OF HUNGER AND THIRST

The sensation of hunger and the associated increase in appetite are determined by periodic contractions of the empty stomach and the transmission of the excitation caused by these contractions along afferent nerve fibres to the brain. The sensation of hunger arises as a result of a change in the functions of the diencephalon. Stimulation of its corresponding part may be produced not only by afferent impulses originating on the periphery, but also by the effect of the altered composition of the blood.

Certain diseases are attended with insatiable hunger—*bulimia*—which is accompanied by headache and general debility. The result of the insatiable hunger is a sharp increase in food consumption—*polyphagia*. It is observed in neuroses, certain lesions in the subcortical region, as a result of increased or perverted metabolism (exophthalmic goitre, diabetes mellitus) and in cases of accelerated evacuation of the stomach contents.

A lack of appetite—*anorexia*—is observed in infectious diseases, gastroenteritides, emaciating diseases and avitaminoses. In anorexia the secretion of digestive juices is perceptibly diminished.

Perverted appetite—*parorexia*—is characterised by the patient's tendency to consume nonalimentary substances, for example, vinegar, chalk.

Thirst is a sensation associated with the need of the body for water or with its excessive excretion. It is particularly pronounced in cases of excessive consumption of sodium chloride or considerable dehydration of the organism by profuse sweating, vomiting, diarrhea, excessive urination or bleeding. Excessive thirst as a pathologic phenomenon—*polydipsia*—is observed in diabetes insipidus and diabetes mellitus and is accompanied by polyuria (excessive passage of urine) which is characteristic of these diseases. The sensation of thirst is explained in two ways. Some hold the main factor to be a general dehydration of the organism with a resultant stimulation of sensory nerve endings reflexly projected to the region of the pharynx. From this point of view the sensation of dryness in the mouth and pharynx in thirst is a secondary phenomenon. According to others, the sensation of thirst arises only in connection with the primary appearance of dryness in the oral and pharyngeal mucosa. Thirst therefore arises from the action of such factors as produce dryness in the mouth, for example, inhalation of warm air, prolonged speaking, depression of the salivary secretion by strong emotions (fear). The origin of thirst is apparently based on both factors—the reflex from the oral and pharyngeal mucosa, and diminished water in the tissues, while the sensation of thirst is always formed in the central nervous system.

DISTURBANCES IN DIGESTION IN THE ORAL CAVITY

Disturbances in digestion may begin in the oral cavity with disorders of mastication. Normally mastication of food reflexly causes secretion of gastric and pancreatic juices, for which reason disturbances in mastication and in the processing of food in the oral cavity affect the function of the lower parts of the digestive tract.

Disturbances in mastication arise as a result of affections of the teeth. The absence of a large number of teeth or inflammation of the dental pulp hinders the grinding of food. Gaining entrance into the stomach poorly ground food causes disorders of gastric digestion, which not infrequently give rise to inflammation of the gastric mucosa (*gastritis*). Disorders of mastication may be the result of central paralyses and inflammatory processes in the mucosa of the mouth (*stomatitides*) and the gums (*gingivitides*). Stomatitides and gingivitides are most commonly the results of the action of infections and traumatic factors or of the secretion by the oral mucosa of mercury and lead salts which have gained entrance into the organism. Lastly, mastication is impaired by inflammatory processes in the muscles participating in mastication.

Disorders of salivary secretion may manifest themselves as hypersalivation.

Hypersalivation, or increased secretion of saliva, is observed as a result of reflex stimulation of the secretory nerves of the salivary glands in pregnancy, vomiting, certain inflammatory processes in the oral mucosa, lesions in abdominal organs, after bulbar paralyses (in association with disturbed swallowing of saliva) and under the action of parasympathomimetic substances (physostigmine, muscarine, pilocarpine, etc.).

Increased salivation overlubricates the alimentary bolus; the swallowed saliva neutralises the gastric juice with the result that digestion in the stomach diminishes and processes of fermentation and putrefaction develop. Losses of large amounts of saliva (sometimes up to 12 litres instead of the normal 1-2 litres a day) lead to emaciation of the organism.

Hyposalivation, or depression of salivary secretion, arises as a result of a reflex disturbance in the function of the salivary glands and disorders of water metabolism, as in cases of infectious and febrile processes, excessive sweating, massive hemorrhages, or protracted diarrheas; it may also be produced by substances which suppress parasympathetic innervation of salivary glands (for example, under the action of atropine).

Decreased salivation hinders mastication and swallowing, is conducive to processes of fermentation and putrefaction in the oral cavity, and is accompanied by retention in the organism of the metabolites which are usually secreted in the saliva, for example, rhodanates or salts of mercury, lead and copper which have gained entrance into the organism.

Pathologic processes may also affect the *tonsils*. These are in most cases inflammations of an infectious character, for example, tonsillitis and abscesses, which hinder swallowing and affect the secretory processes in the oral cavity.

The teeth (in cases of alveolar granulomas) and tonsils may be foci of latent infection which spreads all over the organism. From these foci the organism may be invaded with toxins and waste products of infectious agents which sensitise the organism to subsequent penetration of the same substances from the foci of infection into the general circulation. This gives rise to the allergic state which underlies the pathogenesis of a number of diseases (for example, rheumatism, chronosepsis, etc.). Moreover, the affected tonsils may reflexly affect the coronary vessels and heart.

DISTURBANCES IN DEGLUTITION

From the oral cavity the food enters the pharynx. The passage of the food into the pharynx may be hindered by paralysis of the tongue (mainly of bulbar origin). The deglutition reflex is absent

in cases of poisoning with narcotics, in diabetic coma, uremia, affections of the arches of the soft palate and of the tonsile (tonsillitis and abscesses). As a result food may gain entrance into the respiratory tract with subsequent development of aspiration pneumonia.

Inhibition of deglutition is also observed in spastic contractions of the pharyngeal muscles due to tetanus, rabies and sometimes hysteria.

DYSFUNCTION OF THE ESOPHAGUS

Pathologic phenomena in the esophagus for the most part consist in impeded movement of the alimentary bolus towards the stomach. This state is usually the result of a *constriction of the esophagus* due to anatomic changes in the wall of the esophagus, its mechanical compression or spastic contraction. The esophagus is usually constricted by tumours and scars following inflammatory processes, the esophagus becoming dilated above the site of constriction, due to accumulation of food hindered from passing into the stomach. Tumours, aneurysm of the aorta and abscesses in the tissues surrounding the esophagus may mechanically compress the esophagus and hamper the movement of the alimentary bolus.

Spasm of the esophageal muscles is most commonly observed in the cardia and is due to neurogenic causes. In experiment stimulation of the vagus nerve in the neck causes relaxation of the cardiac sphincter, while stimulation of the sympathetic nerve causes its spasm. Acid reaction of gastric juice reflexly produces contraction of the cardiac sphincter, while alkalinisation of the juice favours opening of the cardia. Spasm of the esophagus in hysteria is subjectively manifested in the sensation of a lump coming into the throat. Protracted constriction of the esophagus leads to death from starvation.

Paralysis of the motor activity of the esophagus arises as a result of affection of the nerves which innervate it. A dilatation of the esophagus combined with spasm of the cardia presents difficulties to the movement of the bolus toward the stomach.

There are also local dilatations of the esophagus in which the part of the wall protruding like a hernia consists of the mucosa and submucous tissue with a thinned muscular layer; the latter may even be totally absent. These so-called diverticula are formed as a result of stretching of the esophageal wall by a foreign body or trauma. Diverticula are most commonly located in the posterior wall of the esophagus. Food is retained in the protruding part and an inflammatory process arises; the process is accompanied by regurgitation and pain sensations. The diverticula sometimes rupture, in which case their contents come in contact with the surrounding tissues; the result is ichorous mediastinitis which not infrequently ends lethally.

DISTURBANCES IN GASTRIC DIGESTION

Both secretory and motor disturbances may be observed in the stomach. Digestive afunction of the stomach or of its various parts does not kill the organism but affects digestion. The attitude of the gastrectomised dog to food varies with whether the cardia has been removed or retained; in cases where the cardia has been retained the dog takes food in small portions, whereas removal of the cardia is accompanied by ingestion of large portions followed by their ejection (Y. S. London).

In gastrectomised cases the digestion of certain food constituents, for example, proteins of connective tissue, is particularly affected, the latter swelling and dissolving precisely in gastric juice.

Secretory Dysfunction of the Stomach

Several types of gastric secretion in dogs have long since been established in Pavlov's laboratory in both normal and pathologic digestion. These types have served as the basis for classification of types of gastric secretion in man. The following types have been established: *normal type* characterised by moderate excitability of the glands during the different phases of secretion and by intact motor reaction; *excitable type* with excessively excitable glands, increased secretion and acidity, as well as increased gastric tone; *inhibited type* with diminished excitability of the glands and noticeably decreased gastric acidity, tone and peristalsis; *asthenic type* with a clearly marked glandular reaction in the first, neuro-reflex phase, diminished glandular excitability during the second, chemical phase, and increased motor reaction; *inert type* with diminished glandular excitability in the first phase and normal or increased secretory reaction in the second; motor reaction is at first decreased and then increased.

To determine the character of the secretion, the gastric juice is obtained by means of a stomach tube on an empty stomach and during different phases of digestion after alimentary (test breakfast) or chemical tests (histamine, alcohol, caffeine). The state of gastric secretion is established mainly on the basis of acidity (total acidity and free hydrochloric acid), amount and enzymatic composition of the secreted juice.

Excessive acidity of gastric juice (hyperacidity) occurs in cases where instead of the normal 0.15-0.20 per cent hydrochloric acid the chyme contains up to 0.5 per cent acid (at the height of digestion). In these cases, in terms of units, i.e., number of ml of a 0.1 N solution of NaOH which neutralises 100 ml of gastric juice the total acidity rises above 60 and the free hydrochloric acid above 50, whereas under physiologic conditions the total acidity figures range from 40 to 60 and those of free hydrochloric acid from 20

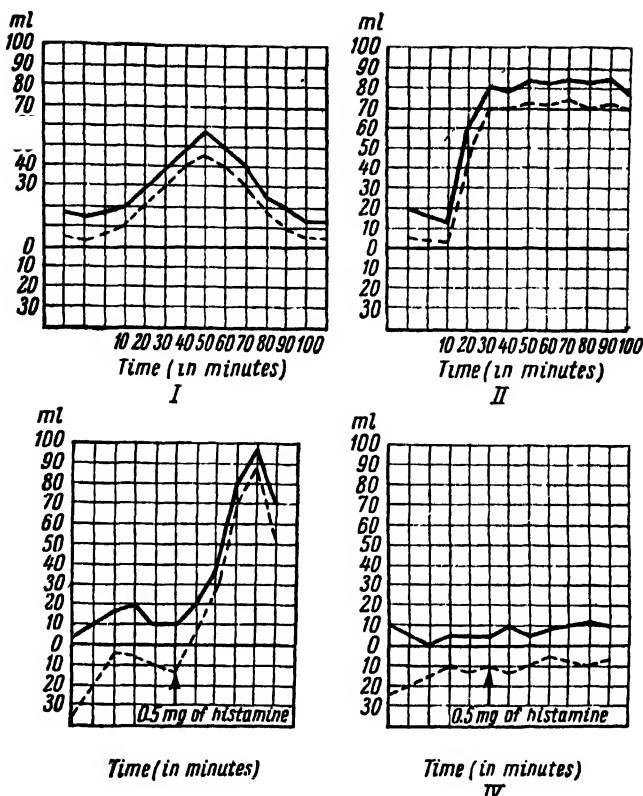


Fig. 121. Curves of gastric juice acidity (stimulus—alcohol solution).
I—normal acidity; *II*—hyperacidity; *III*—anacydity (resistless to histamine); *IV*—anacydity (histamine-resistant). Continuous line—general acidity; dotted line—free hydrochloric acid. Axis of abscissus—time in minutes, axis of ordinates—acidity in titer units.

to 40. The pH of normal gastric juice varies between 1.2 and 2.2. This acidity is optimum for the action of pepsin.

Excessive acidity of gastric juice is usually concurrent with increased secretion—*hypersecretion*. Hypersecretion is characterised by acid juice on an empty stomach, i.e., when there are only traces of hydrochloric acid under physiologic conditions. The hydrochloric acid curve after a test breakfast varies with the character of the secretory disorder and is steep, gentle or stepped (Fig. 121).

Increased acidity develops mainly on the basis of functional disorders of the nervous system, particularly reflex influences on gastric secretion from other organs, for example, the intestines and liver. Hyperacidity and hypersecretion are also observed in cases of organic changes in the gastric mucosa, as in peptic ulcer, chronic hypertrophic gastritis and certain forms of acute gastritis.

Experimentally it may be produced by injections of acetylcholine and histamine, which, in their effect on gastric secretion, are analogous to gastrin originating in the wall of the stomach.

In *decreased acidity of gastric juice* or complete absence of hydrochloric acid (*anacidity* or *achlorhydria*) the total acidity is below 30 and may drop to 20-10 u, while free hydrochloric acid is absent. In these cases, not only hydrochloric acid, but also the enzymes may be absent (*achylia gastrica*).

Lowered acidity is usually concurrent with diminished secretion—*hyposecretion*. Lowered acidity and hyposecretion are often due to dysfunction of the nervous system. Psychic trauma depresses secretion and reduces acidity. After transection of the vagus nerves in dogs the latter completely lose the neuroreflex phase, while the chemical phase of gastric secretion diminishes, the latent period of secretion grows longer and the effect of the conditioned stimulus ceases. Achylia gastrica is often observed in organic affections of the gastric mucosa, for example, in its atrophy due to pernicious anemia and in cancer of the stomach; atrophic gastritis is characterised by histamine-resistant achylia.

In functional disorders it is sometimes impossible to detect variations in the quantitative content of pepsin in gastric juice because the enzymatic effect of pepsin depends on the acidity of gastric juice. In achlorhydria it is enough to introduce into the stomach the normal amount of hydrochloric acid for the effect of pepsin to become manifest. The gastric glands completely fail to produce pepsin only in marked pathologic states of the stomach.

Experimental observations have shown that in cases of gastric juice deficiency the food is digested mainly in the intestinal tract. In these cases digestion of connective tissue noticeably diminishes, anaerobic putrefaction increases, and the feces are usually fetid, gluey, of soft consistency and alkaline reaction.

Motor Dysfunction of the Stomach

Disorders of the motor activity of the stomach may manifest themselves as *changes in muscular tone and changes in peristalsis*.

Increased or decreased muscular tone is usually manifested in increased or diminished ability of the stomach to clasp and compress the food masses. It depends on the tone and elasticity of the muscular wall, especially its fundic part (Fig. 122).

The impulses increasing the tone of the stomach usually come through the vagus nerve, while those decreasing the tone come through the sympathetic nerve.

An *increase in the tone of the stomach* is sometimes observed in physically well-developed people and is manifested in a shortened stomach with an increased diameter of the upper part and deepest location of the pylorus.

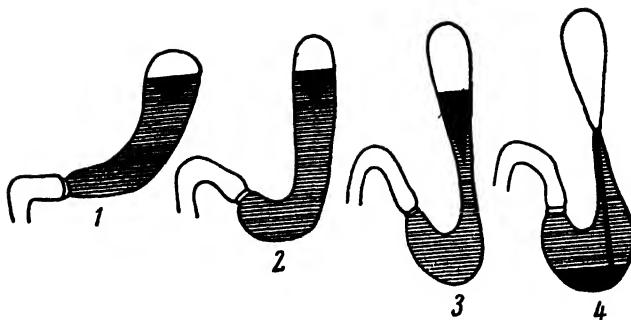


Fig. 122. Various shapes of the stomach.
1—hypertonic; 2—normotonic; 3—hypotonic; 4—tonic.

Atonia, or relaxation of the stomach (hypokinesis) may arise as a result of paresis of the muscular layer and reflexly when obstructions to the movement of the chyme toward the pyloric end of the stomach appear locally (neoplasms, scars). A decrease in the tone of the stomach may be caused by psychic factors (various emotions) which act through the diencephalon.

Atonia may lead to *dilatation of the stomach*. For example, a sharp dilatation of the stomach results from paralysis of the neuromuscular apparatus of the stomach due to lesions in the splanchnic nerves, surgical trauma or infection. In such cases the evacuation of the stomach contents ceases and the chyme undergoes fermentative and putrefactive decomposition. The sharply dilated stomach presses on the functionally important nervous plexuses in the abdominal cavity.

Weakened gastric peristalsis is most commonly observed in cases of an atonic stomach, disturbances in the nervous system and in marked inflammatory processes (gastritides and perigastritides), when the walls of the stomach become less elastic, in cachexias and severe (calloused) ulcers.

The motoricity of the stomach is sharply weakened in the dog after resection of the pyloric part or establishment of an anastomosis between the stomach and a loop of the small intestine (the operation known as gastroenteroanastomosis is sometimes performed in man in connection with ulcer or cancer of the stomach). At the same time this operation facilitates delivery of duodenal juice to the stomach. In such cases it takes 2 or 3 times as long for the chyme to move into the duodenum as usual.

Excessive gastric peristalsis (hyperkinesis) or so-called peristaltic rush is due mainly to nervous impulses, those originating in the brain and spinal cord in particular. The intensified peristalsis is associated with an increase in the excitability of the vagus nerve.

Tabetic crises (in tabes dorsalis) are accompanied by increased peristalsis apparently due to stimulation of the vegetative centres of the spinal cord.

Spastic contraction of the stomach—a form of hyperkinesis—may be due to the general state of the nervous system or stimulations of an inflammatory character. Increased gastric peristalsis with subsequent hypertrophy of the stomach muscles is observed in cases of organic or functional constriction of the pyloric opening. Coarse food, alcohol, lactic acid, histamine and choline substances increase gastric peristalsis and thus ensure the timely passage of the stomach contents into the duodenum.

The movement of the chyme towards the duodenum depends mainly on the motor activity of the pylorus.

Accelerated evacuation of the stomach contents is in most cases due to *decreased acidity of gastric juice* and is particularly pronounced in achlorhydria or achylia. The reason is that the *contractions of the pylorus are functionally connected with the rate of neutralisation of the portions of gastric juice in the beginning of the duodenum*. If the acidity is diminished, the chyme is rapidly neutralised by the duodenal contents and conditions are created for reflex inhibition of the contractions of the pylorus; the pylorus opens and the chyme easily passes into the duodenum.

A motor insufficiency of the pylorus may of itself lead to accelerated evacuation, as in inflammatory processes, or as a result of cancer of the pylorus. Moreover, an excessively filled duodenum favours prolonged closure of the pylorus, an empty duodenum—its opening.

A slowing in the evacuation of the stomach contents is observed more commonly. Here the most important part is played by *mechanical obstructions* to the movement of the food; these obstructions may occur in cases of pyloric dysfunction or in organic changes in the pylorus (constriction of its lumen by scars, tumours, compressions). A considerable role is also played by *hyperacidity of the gastric juice* and slow neutralisation of the portions of food passing into the duodenum, which reflexly retards the opening of the pylorus.

Nor can the possibility of retarded movement of the food in the stomach due to a *general spastic condition of the stomach or spasm of its pylorus* be denied; this condition may arise as a result of disturbances in nervous regulation.

Pyloric spasm is of neurogenic origin. It is not infrequently due to ulcer in the pylorus or to reflex stimulation originating in other organs.

As a result of motor dysfunction of the stomach, especially its pyloric part, the food in the stomach stagnates.

The effects of disorders of gastric digestion vary. Disturbances in gastric digestion lead to weakening of intestinal digestion.

In cases of food retention in the stomach and retarded evacuation of the food into the intestine abnormal processes of gastric digestion develop. Stagnation of the food gives rise to processes of their bacterial decomposition, accumulation of disintegration products and gases which irritate the gastric mucosa and cause heartburn, pain, nausea and vomiting.

Motor and secretory disorders of gastric digestion affect the properties of the gastric juice. Here it is necessary to bear in mind its *antiseptic action*. It is well known that normal gastric juice possesses bactericidal action, for example, with respect to the pathogenic microbes of cholera and typhoid fever. It prevents the development of the processes of putrefaction and fermentation. These properties of the gastric juice may be impaired in connection with changes in the secretion and the rapidity of evacuation of the stomach. The *content of mucus in the stomach* also changes; it is decreased in cases of hyperacidity and increased in hypoacidity.

Secretory dysfunction of the stomach affects the *entire organism*. An increased secretion of juice causes a deficiency in chlorine and acid radicals in the organism. As a result the acid-base balance shifts towards alkalinity. The changes in the acid-base balance are compensated for by reabsorption of gastric juice in the intestinal tract. But in cases of pyloric stenosis reabsorption of gastric juice is insufficient or absent.

Gastric stenosis and irritation of the mucosa may give rise to vomiting which also causes development of alkalosis due to the loss of hydrochloric acid by the organism. Pathologic respiratory and urinary phenomena are the result; signs of incipient tetany are sometimes observed as a result of development of alkalosis.

The motor disorders include *eructation, heartburn and vomiting*, which not infrequently accompany digestive disorders.

Eructation is ejection of swallowed air from the stomach (particularly in cases of closure of the larynx) and gases (hydrogen sulfide, carbon dioxide, methane) if they have formed in the stomach as a result of impaired digestion. Eructation occurs as follows: in case of an open cardia and spasm of the pylorus the diaphragm, which lowers on inhalation, and the tense abdominal muscles press on the stomach; some part is also played by the contraction of the stomach walls. These phenomena are most probably produced by reflexes originating in the stomach or the peritoneum.

Heartburn, a burning sensation, arises when the acid content of the stomach is forced into the esophagus by gastric antiperistalsis.

Vomiting is a complex disturbance in the motor function of the stomach and respiration accompanied by involuntary ejection of food from the stomach to the exterior (Fig. 123). It begins with a feeling of weakness, dizziness, pallor of the face and nausea, and ends in the act of vomiting—a deep inhalation, strong contraction of the abdominal muscles, sharp descent of the diaphragm (with

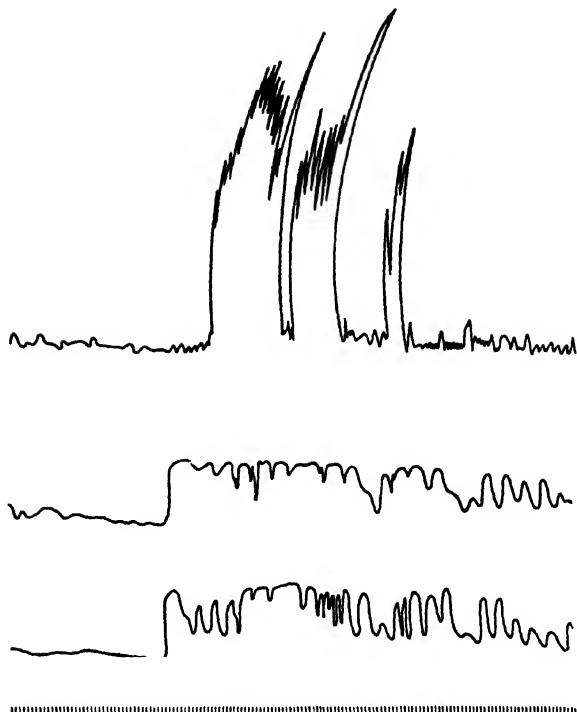


Fig. 123. Curves of vomitory movements: stomach (upper curve), duodenum (middle curve) and small intestine (lower curve) (Y. B. Babsky).

closure of the pylorus, contraction of the stomach and opening of the cardia) and ejection of the food from the stomach through the esophagus into the oral cavity and to the exterior. The lowering of the epiglottis, rise of the larynx and closure of the rima glottidis prevent the vomit from gaining entrance into the respiratory tract. Contraction of the muscles which raise the soft palate prevent the vomit from entering the nasal cavity. Moreover, severe vomiting is accompanied by excessive intestinal peristalsis, sometimes in the opposite direction (antiperistalsis). In such cases the ejected food may contain bile from the duodenum where it is delivered in excessive quantities as a result of compression of the gallbladder and bile ducts.

The act of vomiting is effected as a result of stimulation of the vomiting centre in the medulla oblongata. The vomiting centre is connected with the functions of the apparatus which participate in effecting the act of vomiting. Certain poisons (apomorphine), intoxications (for example, in infections, uremia) and pathologic phenomena in the medulla oblongata (as in meningitis, compres-

sion of the brain by tumours or concussion of the brain) may cause vomiting. Most commonly, however, vomiting is of reflex origin and is stimulated from the branches of the vagus nerve of the cardia, from the glossopharyngeal nerve, from the intestinal mucosa, the peritoneum, the liver, uterus and other organs. Hypersalivation and excessive sweating which may be observed simultaneously with vomiting indicate that the act of vomiting is accompanied by general excitation of the central nervous system.

Vomiting is usually preceded by a feeling of *nausea* which is characterised by unpleasant sensations in the region of the pharynx and stomach and is accompanied by pallor, perspiration, accelerated heart rate, slowing of respiratory movements and salivation. At the same time the contractions of the esophagus and stomach cease, and the pylorus is closed. This phenomenon is probably due to stimulation of the thalamic region by afferent impulses arising in various parts of the gastrointestinal tract.

GASTRIC AND DUODENAL ULCERS

Gastric ulcer implies a *round peptic ulcer of the stomach (ulcus rotundum pepticum ventriculi)*; this ulcer has a definite shape with rounded edges which descend terracelike to the base of the ulcer; peptic ulcers heal with difficulty.

Ulcers are most commonly localised along the lesser curvature or in the region of the pylorus, much less frequently—in the fundus. The predominant localisation along the lesser curvature or in the pylorus is due to the physiologic and partly anatomic peculiarities of these parts. The most important factor is apparently hyperfunction of these parts, their greater vulnerability and sensitivity due to abundant innervation.

Very closely related in origin to gastric ulcer is *duodenal ulcer* which is usually localised near the pylorus.

Peptic ulcer involves digestion of part of the mucosa, which gives rise to a defect of the mucosa, sometimes involving bleeding. In such cases the blood effuses into the stomach, and the gastric juice mixed with it assumes the appearance of coffee grounds, which is characteristic of the vomit of ulcer patients. This colour of the vomit is due to the fact that hematin splits off from hemoglobin as a result of contact with the hydrochloric acid of the gastric juice.

Deeper ulceration of the mucosa may lead to perforation of the gastric wall with all the usual consequences, such as peritonitis and intra-abdominal hemorrhages.

In *gastric ulcer the motor and secretory dysfunction of the stomach* most commonly consists in hypersecretion and increased acidity of the gastric juice, and excessive motor reaction. There are also ulcers with relatively normal gastric juice and even with diminished acidity and diminished motor function (in 15-30 per

cent of gastric ulcer cases and in up to 7 per cent of duodenal ulcer cases).

Etiology and Pathogenesis of Gastric and Duodenal Ulcers. Of the numerous theories and hypotheses concerning the origin of ulcers several theories competed with each other for a long time. These were: the mechanical theory which believed an interruption of the continuity of the mucosa to be the cause of ulcers; biochemical theories which at different times attached the greatest importance either to the hyperacidity of the gastric juice or to changes in its chemical properties, to a change in the acid-base balance in the blood or to the ejection of trypsin-rich intestinal juice from the duodenum into the stomach; the vascular theory which considered ulcers to be caused by changes in blood circulation; and, lastly, the still rather widely accepted gastritic theory which regards ulcers as due to chronic inflammatory processes in the gastric mucosa.

None of the aforesaid theories is able to uncover the pathogenesis of peptic ulcer, although in its origin some part is, indeed, played by local circulatory disturbances, inflammation of the mucosa and the digestive action of the gastric juice.

Neurogenic theories come closest to truth. One of them attaches the prime importance to vegetative-nervous disturbances in the organism (Bergman). The decisive importance in the origin of ulcer is attached to vegetative "disharmony" which, under the influence of stimuli acting for a long time, leads to dysfunction of the vegetative nervous system. Persons with such dysfunction of the vegetative nervous system have a tendency to spasm of the gastric muscles, which leads to compression of the vessels and ischemia. The result is impaired nutrition of the gastric mucosa, lowering of its resistance, and its digestion with subsequent formation of an ulcer. However, this view is one-sided since it bases the pathogenesis of the ulcerative process entirely on disturbances in the vegetative nervous system without taking sufficient account of the role played by the higher parts of the central nervous system.

Experimental studies have shown that changes in the secretory and motor functions of the stomach and development of such pathologic phenomena as ulcerative processes may actually be the result of artificially produced disturbances in the central or peripheral nervous systems. The same mechanism apparently underlies ulcer produced by the action of histamine used in experiment to provoke peptic ulcer. Experimental ulcer has lately been produced by administration of atophan (cichophen) per os. Administration of atophan to dogs causes vomiting, diarrhea, a tarry stool and development of peptic ulcer along the lesser curvature. The development of ulcer after administration of atophan is probably due to the action of the latter on the gastric mucosa and the neural elements in the gastric wall. Moreover, in the pathogenesis

of ulcer a considerable part is also played by pathologic reflexes originating in inflamed abdominal organs (for example, in appendicitis) or in the ileocecal region which abounds in receptor structures.

The shortcoming of the aforesaid views consists in underestimation of the role of the cerebral cortex in the pathogenesis of gastric and duodenal ulcers.

K. M. Bykov and T. I. Kurtsin have found disturbances in corticovisceral relations to play a certain part in the pathogenesis of ulcers. As a result of protracted and repeated unconditioned and conditioned intero- and exteroceptive impulses reaching the central nervous system from dysfunctioning organs, the ratio of the processes of excitation to those of inhibition in the cortex and the subcortical structures is disturbed with the result that processes of inhibition predominate. In cases of relative stability of these phenomena the hypothalamic region becomes disinhibited and develops a focus of inert excitation which leads to dysfunction of the vegetative nervous system. This gradually gives rise to the "disharmony" of the vegetative functions against the background of which prolonged spasm of the vessels and the muscular layer of the stomach wall, the excitable type of gastric secretion and trophic disorders, which lower the resistance of the mucosa, may develop. Interoceptive impulses reaching the cerebral cortex from the affected stomach establish new relations between the cerebral cortex and subcortex, on the one hand, and the affected organ—the stomach or duodenum—on the other.

This corticovisceral connection is maintained through intermediate links, which are not only the lower parts of the nervous system, but also the humoral substances participating in the mechanism of the nervous impulse. Research (Alpern) has shown that the blood of ulcer patients, especially the blood in the gastric veins, contains acetylcholine and that cholinesterase, the enzyme that splits acetylcholine, is more active. Accumulated acetylcholine apparently causes the stomach muscles to contract with the result that the vessels are compressed, anemia develops and the affected part is digested.

Ulcer patients show functional disorders of the entire nervous system. As is well known, the psychogenic factor often plays an important part in the development of ulcer.

In the light of neurogenic theories gastric and duodenal ulcers must be regarded as a local manifestation of a general state of the organism. Peptic ulcer must therefore be considered a disease of the whole organism, an *ulcer disease*.

DISORDERS OF INTESTINAL DIGESTION

The disorders of intestinal digestion include those of *secretion*, *motorium*, *excretion*, *absorption* and changes in the *microbial flora*. The duodenum receives juices produced by the glands imbedded in

its wall, the secretion of the pancreas and bile. Intestinal juice has an alkaline reaction and contains enterokinase, the enzyme that activates trypsinogen. Processes of digestion operate all along the small intestine. In the upper parts of the duodenum and of the remainder of the small intestine digestion is the most intensive, and all the main nutritive substances—proteins, fats and carbohydrates—undergo digestion there. Absorption takes place mainly in the small intestine. The absorbed sugar and amino acids pass into the blood, fats and products of their conversion—mainly into the lymphatic vessels.

Secretory Dysfunction of the Intestines

Secretory disorders are caused by disturbances in the activity of the central nervous system and resultant dysfunction of the *innervation apparatus* of the intestines. Stimulation of the vagus nerve evokes an increase in the amount and enzymatic activity of the intestinal juice.

The secretory disorders of reflex origin include those which arise as a result of *disorders of gastric secretion*. The composition of the gastric juice, as well as the extent to which the food has been digested in the stomach and prepared for intestinal digestion affect the secretory function of the intestine. For example, digestive disorders in the duodenum are associated with hyperacidity of gastric juice and retarded evacuation of the food from the stomach. Accelerated passage of the chyme into the duodenum in achylia causes overloading and increased peristalsis of the small intestine.

The secretory function of the intestines is altered also during *inflammatory processes*, for example, duodenitis, enteritis, colitis and duodenal peptic ulcer.

Inflammatory processes are also characterised by secretion of mucus all along the intestine. The inflammatory phenomena in the intestinal mucosa must not be considered apart from intestinal dysfunction caused by disorders of the nervous system, since they are closely interrelated. Disorders of the secretory and motor functions of the intestines due to dysfunction of the nervous system may, in view of disturbed intestinal digestion, lead to development of inflammatory phenomena in the mucosa.

Normal digestion in the small intestine depends mainly on delivery of pancreatic juice and bile.

The *disturbances in the secretion of pancreatic juice and bile* may be both quantitative and qualitative.

Absence or insufficient delivery of bile to the duodenum (*acholia* and *hypocholia*) are most frequently the result of a mechanical closure of a bile duct by a calculus, a growing tumour or an inflammatory swelling of the mucosa of the bile ducts. Bile secretion may also be diminished because of dysfunction of the innervation mechanisms of the gallbladder and disease of the liver itself.

Acholia and hypocholia appreciably affect the entire process of intestinal digestion. They affect most of all the digestion and absorption of fats, more than 60 per cent of which fails to be assimilated. Absorption of fatty acids formed in the intestine by the splitting of fats is particularly disturbed. The reason for it is that in the absence of bile acids the fats are not sufficiently emulsified and not enough water-soluble complexes of bile acids and fatty acids required for their absorption are formed.

The digestion of proteins is also somewhat disturbed in hypocholia since the unabsorbed fats, by enveloping the intestinal contents, block the action of trypsin. Moreover, in the absence of bile the intestine offers favourable conditions for the development of a bacterial flora which intensifies the processes of putrefaction and fermentation. Intestinal peristalsis also diminishes with the result that gases accumulate and constipation develops. The feces assume the colour of white clay and contain a large amount of unabsorbed fat, fatty acids and soaps. Such feces are fetid. Absorption of vitamin K is sharply diminished and blood clotting is impaired as a result.

Calculi situated in the pancreatic duct and obstructing it, inflammatory phenomena in the pancreas and in the duodenal mucosa, and disturbances in innervation also cause digestive disorders associated with an *absence or deficiency of pancreatic juice*. Similar phenomena may be observed in experiment after ligation of the pancreatic duct.

A *deficiency of pancreatic juice* affects the digestion of fats. In such cases fats are only partly split by the intestinal lipase, while the greater part of it (60-80 per cent) fails to be digested in the intestine and is excreted in the feces. Absence or deficiency of trypsin in the pancreatic juice impairs the digestion of proteins, although to a lesser extent than that of fats (30-40 per cent).

In cases of inadequate delivery of pancreatic juice the feces contain a large amount of undigested muscle fibres, especially undigested nuclei, since nucleoproteins are split predominantly under the influence of trypsin.

The absence of amylase makes digestion of starch impossible. Large number of starch grains appear in the feces.

Absence of pancreatic juice affects not only digestion, but also absorption of fats, proteins, salts and vitamins through the intestinal wall.

Little is known about disturbances in the *secretion of intestinal juice* in man because of the difficulty of obtaining it in pure form without admixtures of pancreatic juice and bile. It is known that intestinal juice does not play so important a role in the processes of digestion as does pancreatic juice. Removal of relatively large portions of the small intestine (even up to two-thirds of it) may not involve appreciable digestive disorders.

Absence of intestinal juice particularly affects nurslings, since failure of lactase to be delivered to the intestine prevents assimilation of milk sugar. But the secretory function of the small intestine is so closely connected with its absorptive and motor functions that it is very difficult to evaluate separately the role of the secretion of the small intestine in digestion.

Motor Dysfunction of the Intestines

The disorders of the motor function of the intestines vary in origin and are discovered in different parts of the intestines. They consist in excessive or diminished peristalsis.

Excessive peristalsis arises as a result of various inflammatory processes in the intestinal mucosa, as well as of mechanical or chemical irritations produced by coarse and barely digestible parts of food, accumulated decomposition products, acids and toxic substances. Not infrequently motor disorders may also be the result of dysfunction of the nervous system. For example, increased peristalsis is observed in connection with strong emotions (fear) which cause stimulation of the vegetative nervous system (Fig. 124)

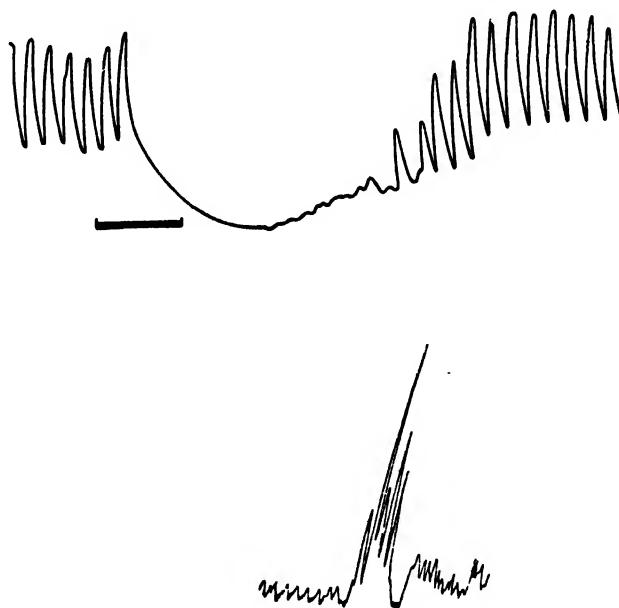


Fig. 124. Depression of the motor function of the small intestine caused by stimulation of the splanchnic nerve (upper curve). Excitation of the motor function of the small intestine due to stimulation of the vagus nerve (lower curve).

Black line indicates time of stimulation.

and in cases of hypersensitivity of the receptor apparatus, as in association with inflammation of the mucosa. The waves of contraction very easily arise in the most excitable and mobile parts of the intestines and spread in the direction of the more sluggish parts, for example, from the pylorus and duodenum in the direction of the large intestine.

Excessive intestinal peristalsis results in *diarrhea*—increased frequency of the stool. In diarrhea caused by changes in the motor properties of the small intestine the feces contain barely digested particles of food. In addition to excessive peristalsis, increased secretion of the mucosa and diminished absorption of water also play some part in the increased frequency of the stool.

Diarrhea is usually caused by excessive peristalsis of the large intestine, especially when associated with similar phenomena in the small intestine. The reason for excessive peristalsis of the large intestine, in addition to neurogenic factors, is poorly digested contents of the small intestine, which irritate the large intestine.

Products of fermentation and putrefaction (indole, skatole, phenol, ammonia, methane, hydrogen sulfide), when abundantly formed, infectious agents and toxins, as well as adrenal insufficiency and the resultant diminished tone of the sympathetic nervous system, may be causes of diarrhea. Diarrhea is often accompanied by decreased absorption and considerable discharge of water into the lumen of the intestine (especially in certain inflammatory processes), as a result of which the intestinal contents become still more diluted. Increased secretion of mucus may simultaneously occur in the intestine; sometimes the secretion comes out to the exterior in layers whose shape is determined by the intestinal lumen, as in cases of membranous colitis (*colitis membranacea*). Frequent diarrheas lead not only to digestive disorders, but also to general nutritional disturbances.

Diminished peristalsis is not a rare phenomenon in disorders of the intestinal function. It is due to the absence or inadequate action of the mechanical and chemical factors which maintain normal peristalsis. Peristalsis diminishes in connection with neurogenic disorders, for example, decreased excitability of the receptor apparatus of the intestines, and inflammatory processes (especially of a chronic character) which, depending on their course, may give rise to either diarrhea or constipation. In inflammatory processes the diminution in peristalsis may also be due to dysfunction of the nervous system.

Diminished intestinal peristalsis, of whatever character, causes *constipation*.

The small and large intestines participate in the origin of constipation to various extents. An important part in the pathogenesis of constipation is played by the large intestine where the fecal

masses are consolidated and formed. *Constipation may be atonic and spastic*, depending on the mechanism of its origin.

Atonic constipation is due to relaxation of the muscular layer of the intestinal wall and diminution in peristalsis in the upper parts of the large intestine. .

Spastic constipation is the result of prolonged spasm of the circular muscles of the intestinal wall, which obstructs the movement of the intestinal contents. At the same time the density of the feces is increased and the feces are sometimes eliminated in lumps.

Constipation arises as a result of general dysfunction of the nervous system, the vegetative innervation of the intestines in particular. A certain part is also played by decreased stimulation of the receptors of the mucosa, especially when there is no cellulose in the intestinal contents or there is too much fat or too little organic acids and monosaccharides which stimulate peristalsis. As a result of constipation the intestine absorbs more water, the fecal masses become consolidated, the appetite diminishes, general weakness develops and meteorism occurs.

Meteorism is the result of diminished intestinal peristalsis, increased processes of fermentation and putrefaction, and accumulation of gases (methane, hydrogen sulfide, carbon dioxide, ammonia, etc.) in the intestines. In severe meteorism the venous pressure rises, the arterial pressure at first rises and then drops, respiration is disturbed, the pulse grows weak, the secretory function of the digestive glands diminishes, and painful sensations in the region of the intestines appear. All these phenomena are due to mechanical compression of the vessels, the high position of the diaphragm and stimulation of the mechano- and chemoreceptors in the intestinal wall.

The foregoing disturbances in intestinal function are particularly marked in *ileus (intestinal obstruction)*. Two main forms of ileus are distinguished: mechanical ileus caused by mechanical closure of the intestinal lumen (obstruction by extrinsic pressure, volvulus, intussusception) and dynamic ileus caused by paralysis or, less frequently, spasm of the intestinal muscles. The part of the intestine situated above the obstruction becomes considerably dilated. Antiperistaltic movements appear and lead to vomiting, sometimes stercoraceous.

Volvulus, strangulation or intussusception are characterised, in addition to the aforementioned phenomena, by circulatory disturbances as a result of compression of the mesenteric vessels with subsequent mortification of the corresponding portion of the intestine.

Intestinal obstruction leads to development of deep general changes in the organism particularly manifested in general circulatory disturbances and characteristic alteration of the blood composition. The organism becomes dehydrated, and hemoconcentration, hypochloremia, azotemia and alkalosis develop. These

changes are in large measure due to increased secretion of digestive juices and their discontinued reabsorption, intractable vomiting and corresponding disturbances in renal function.

In the pathogenesis of the disorders observed in ileus an important part is played by intoxication due to absorption of the poisons formed and retained in the intestines; of some importance also are the reflex influences produced by the affected intestine on the blood circulation and other vitally important functions.

Disturbances in Defecation

Defecation is essentially a reflex act. The following defecation centres are known: the *higher centre*—diencephalon and ascending frontal gyrus, and subsidiary *spinal centre*—lumbar segments of the spinal cord (relaxation of sphincters) and sacral segments of the spinal cord (contraction of sphincters).

Disorders of defecation arise as a result of affection of the centres which control this reflex. Defecation may be hindered as a result of contraction of the sphincters, levator ani muscles and a number of voluntary muscles of the perineum due to excitation of corresponding centres. Rectal incontinence is observed in paralysis of the sphincters resulting from dysfunction of the centres, for example, in advanced age, tumours, epilepsy, fear.

The mechanism of defecation disorders sometimes consists in a weakening of the sensory nerves in the rectum, the nerves perceiving the stimulation by fecal matter, with the result that the defecation reflex is inhibited. In other cases the sensitivity of the mucosa, on the contrary, increases, increasing the urge to defecate, as in inflammation of the mucosa in the region of the sphincters.

Lastly, defecation may be hindered as a result of diminished intestinal peristalsis or flabbiness of the abdominal muscles, as in women after childbirth or in old people.

Disturbances in the Absorptive and Excretory Functions of the Intestines

Disturbances in *absorption* are an important form of gastrointestinal dysfunction. They are observed in connection with disorders of the secretory and motor functions of the gastrointestinal tract, especially resulting from deficiency in bile secretion and in the secretory function of the pancreas. Absorption is diminished in diarrhoeas when the intestinal contents are quickly expelled to the exterior.

Absorption is also disturbed as a result of *changes in intestinal blood circulation*. Diminished blood circulation due to general circulatory disorders, congestion in the portal vein or massive loss of blood decreases the processes of absorption. Disorders of the lymph

circulation in the intestines (for example, in inflammation of lymph nodes) are responsible for diminished fat absorption. Lastly, *inflammatory changes* in the intestinal mucosa also cause disorders of absorption. Absorption takes place mainly in the small intestine. If the absorptive capacity of the small intestine is greatly decreased, the absorption in the lower parts of the intestines increases.

The absorptive capacity of the intestines may be disturbed experimentally by injury to the intestinal mucosa with sodium fluoride. The animal dies soon after administration of sodium fluoride.

In certain acute inflammations of the intestinal mucosa fats and coarser complexes of proteic substances begin to be absorbed and on gaining entrance into the organism play the role of antigens, sensitising the organism. In chronic atrophic inflammation absorption is diminished.

Disorders of gastrointestinal digestion cause disturbances not only in the absorptive capacity. They also affect the *excretory function of the intestinal wall*. In some measure the secretory and excretory functions are independent of each other. This is evident from the fact that an increase in one may be accompanied by a depression or lack of change in the other.

The main causes of the excretory dysfunction of the small intestine are organic and functional changes in the intestinal wall.

Abnormal excretion of water through the intestinal wall causes dilution of the intestinal contents and hastens development of diarrhea. It is difficult to distinguish this phenomenon from the increased excretion of digestive juices into the intestinal lumen, which is observed in certain secretory dysfunction of the digestive glands.

Processes of Fermentation and Putrefaction

The small intestine contains few microbes, whereas the number of microbes in the large intestine is very great. Bacteria participating in processes of fermentation predominate in the upper part of the large intestine. Lactic and acetic acids, carbon dioxide and methane are formed in the process of fermentation. The intestinal flora helps to split cellulose which makes its assimilation possible. Microorganisms also synthesise certain vitamins, for example, vitamin K, eneurin, biotin, folic acid. The lower part of the large intestine contains *Escherichia coli*, *Aerobacter aerogenes* and some other bacteria. The large intestine contains anaerobes which participate in the processes of putrefaction of proteic substances.

The contents of the different parts of the intestines possess poisonous properties variously manifested in accordance with the character of the processes of fermentation and putrefaction operating in them. The most poisonous, for example, are the contents of the large intestine. Intravenous administration of extracts from the contents of the large intestine poisons the animal 2-3 times as fast

as does that of extracts from the contents of the lower part of the small intestine. Poisoning with products of putrefaction is accompanied by a drop in blood pressure. No poisoning takes place in the organism because of the barrier properties of the intestinal wall and the liver.

Changes in the processes of *fermentation* and *putrefaction* are observed in cases of disturbed digestion. These processes operate more intensely and do so in such parts of the intestines where they are not normally observed, for example, the jejunum and even the duodenum.

Absorbed and gaining entrance into the liver the products of putrefaction are usually rendered harmless because of the formation of paired compounds. But in pathology they may accumulate to such an extent as to make it impossible for the liver to detoxicate them. Of these substances special mention must be made of certain aromatic compounds formed from amino acids by a splitting off of ammonia and further transformations (phenol, cresol, skatole and indole). Decarboxylation of amino acids leads to formation of a number of amines—putrescine, cadaverine, histamine, tyramine, etc.

On being absorbed the foregoing substances may produce phenomena of *intestinal autointoxication*. Intestinal autointoxication manifests itself with greater intensity not only in cases where more products of putrefaction are formed and absorbed (as in inflammation of the mucosa), but also where intestinal peristalsis is weakened, the barrier role of the liver is decreased and the excretory capacity of the kidneys is diminished.

Phenomena of intoxication may arise in inflammatory processes in the intestines, especially in intestinal obstruction. In such cases intoxication leads to impaired metabolism and not infrequently to dysfunction of the nervous system. The patient's general condition changes for the worse, headaches and increased irritability appear, lack of appetite and insomnia are observed.

The phenomena ascribed to autointoxication are today believed to arise as a result of reflexes originating in the intestines abnormally distended by gases.

PATHOLOGY OF THE HEPATIC FUNCTION AND OF BILE SECRETION

The liver plays a very important part in various functions of the organism, especially in processes of intermediate metabolism. Moreover, by producing bile it participates in the digestion and assimilation of food and excretion of a number of metabolites. The liver possesses a barrier function. It detoxicates toxic substances which form in the organism, especially in pathology and find their way into it from the gastrointestinal tract. Together with other organs the liver plays an important role in immune reactions.

GENERAL ETIOLOGY AND PATHOGENESIS OF DISEASES OF THE LIVER

Harmful agents gain entrance into the liver in various ways. Poisonous metabolites, infectious agents and their toxins, narcotics (for example, alcohol), phosphorus, as well as indole, skatole and proteinogenic amines enter the liver from the gastrointestinal tract and spleen *through the portal vein system*. The liver may also be reached through the *arterial system* (hepatic artery) and *bile ducts* (Fig. 125). For example, the liver may be invaded through the arterial current by microbes and toxins (as in syphilis and tuberculosis). Not infrequently infection spreads along ascending paths—through intrahepatic ramifications of the bile ducts. This may give rise to inflammatory processes in the bile ducts (*cholangitis*) and dystrophic phenomena in the liver cells.

Lastly, harmful agents penetrate into the liver through *lymphatics* from the region of the diaphragm and the abdominal coats.

The hepatic function may also be affected by harmful agents reflexly from various receptor fields, especially the gastrointestinal tract.

Diseases of the liver vary in character and course. The acute and chronic pathologic processes in the liver may be of a *dystrophic* as well as *inflammatory* character. Liver diseases cannot be strictly divided into dystrophic and inflammatory because the most common

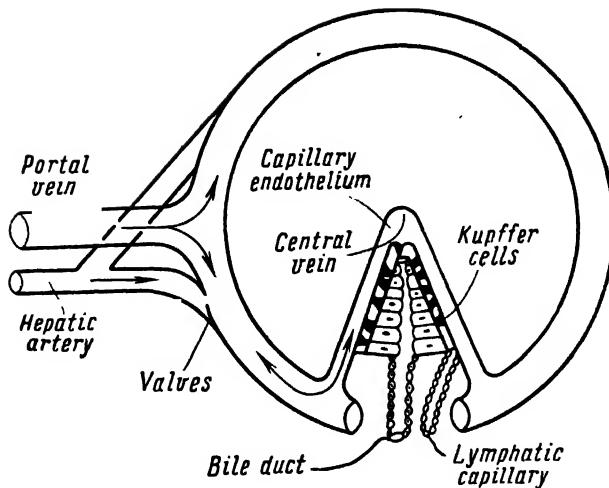


Fig. 125. Diagram showing structure of a lobe of the liver and its relation to the blood, lymph and bile ducts.

forms are mixed. Dystrophic changes in the epithelium are usually combined with infiltrative changes in the mesenchymal elements of the liver.

According to their course, acute and chronic inflammatory processes are distinguished in the liver.

The most common forms of *acute processes* are *diffuse affections* (acute parenchymatous hepatitides) with a predominance of either dystrophic or inflammatory phenomena.

Such affections of the liver are caused by intoxications of an infectious, mainly viral, origin; the most common of these is epidemic hepatitis (Botkin's disease). Acute hepatitis may be of noninfectious origin, as in cases of administration of mercurial preparations.

The clearest manifestation of the severe form of diffuse dystrophic affection of the liver is *acute yellow atrophy* characterised by clearly marked intoxication, severe jaundice and phenomena of tissue autolysis.

Cirrhoses constitute an important group of *chronic diffuse affections* of the liver. These affections differ very greatly in their etiology but have one common characteristic—diffuse inflammatory proliferation of mesenchymal tissue.

So-called *primary cirrhoses* must be regarded as classic forms of chronic diffuse affections of the liver. *Atrophic* and *hypertrophic cirrhoses* have long been distinguished as primary forms of cirrhosis of the liver. The former is characterised by interlobular proliferation of connective tissue accompanied by contraction of the liver

with subsequent phenomena of cellular atrophy. The results are congestion in the portal vein system with subsequent development of hepatic insufficiency and transudation of fluid into the peritoneal cavity (ascites). Hypertrophic cirrhosis of the liver is characterised by proliferation mainly of intralobular connective tissue and enlargement of the liver. It is accompanied by icterus and enlargement of the spleen; in this form of cirrhosis there is no ascites. It is now believed that these two forms cannot be strictly differentiated since they are essentially two varieties of the same cirrhosis of the liver.

Hypertrophic cirrhosis is usually accompanied by a reaction of the reticuloendothelial elements, especially of the spleen. Hypertrophic cirrhosis is therefore considered a manifestation of a single *hepatolienal* disease.

There are also other forms of chronic diffuse affection of the liver—secondary cirrhoses, namely: *infectious cirrhoses* which are a result of acute dystrophic and inflammatory changes in the liver in acute infectious diseases and in a number of chronic infections (tuberculosis, syphilis, malaria); *parasitic cirrhoses* as in multicystic echinococcosis; *toxic cirrhoses* in certain metabolic diseases, hemolytic jaundice, etc.; *cardiac and vascular cirrhoses* in heart disease and chronic congestion in the liver, obliterating hepatic phlebitis and sclerosis of hepatic arteries; *biliary cirrhoses* in cases of obstruction of bile ducts and in angiocholitis. Some part in the pathogenesis of cirrhoses may also be played by nutritional disturbances and absence of lipotropic substances (choline and methionine) in the food.

The mechanism of action of the aforementioned factors in the origin of chronic diffuse affections and cirrhoses of the liver has not been fully elucidated as yet. Some investigators consider them the result of affection of connective tissue. Others hold that the proliferation of connective tissue is the result of atrophy or dystrophy of hepatic cells. The development of the basic forms of cirrhosis of the liver may apparently be due to both afflictions of the parenchyma and inflammatory changes in the mesenchymal tissue.

Attempts have also been made to provoke cirrhosis by *alcohol* which in the opinion of some investigators is a frequent cause of cirrhosis of the liver in man. However, no typical forms have been produced even in cases where very large amounts of alcohol were administered. It is suggested that in *chronic alcoholism* cirrhosis is not produced by the direct effect of alcohol on the hepatic function, but is the result of primary gastrointestinal indigestion caused by alcohol and the subsequent absorption and effect on the liver of the products formed in the process of impaired digestion.

Experimental cirrhosis of the liver (through the stage of fatty infiltration) was provoked in animals (rats) by feeding them for a long time protein-deficient food lacking in cystine and methionine.

These experiments suggest the importance of metabolic disturbances in the pathogenesis of cirrhosis of the liver.

Continuous administration of carbon tetrachloride, silicon dioxide or tannic acid to animals (mainly dogs and rats) may cause affection of the liver, most commonly necrotic phenomena with subsequent fibrosis. The resultant cirrhoses were in most cases of a marked atrophic character. Experimental cirrhoses to a greater or lesser degree resemble those in man.

Ascites which in some cases accompanies cirrhosis of the liver in man may be one of the results of experimental cirrhoses. A certain role in the development of ascites is played by: 1) venous congestion with elevated pressure in the portal vein and often obliterating fibrosis of the hepatic veins, 2) development of obstacles to the outflow of the lymph, 3) hypoproteinemia as a result of reduced albumin in the serum, and 4) retention of sodium because of increased activity of mineralocorticoids, mainly aldosterone in virtue of its slow inactivation by the liver.

The importance of each of the aforementioned factors and their combinations differs in different experimental cirrhoses.

A special form of cirrhosis of the liver develops as a result of lesions in the basal ganglia of the diencephalon (for example, in encephalitides).

EXPERIMENTAL STUDIES OF HEPATIC DYSFUNCTION

An important part in the studies of the hepatic function under physiologic and pathologic conditions was played by experimental influences exerted on the liver.

The *Eck's fistula* (Fig. 126) is an experimental procedure of anastomosing the portal vein to the inferior vena cava, which ensures a free flow of blood from the former to the latter. Above the anastomosis the portal vein is ligated, whereby the liver is excluded from the vascular system of the digestive organs. In such a case the substances passing into the portal vein from the intestines bypass the liver, enter the inferior vena cava and then the general blood flow whence they may but gradually gain entrance into the liver through the hepatic artery.

During the first days following the operation the condition of the animals is satisfactory provided they are fed dairy and vegetable food. Then for a period of 10-12 days (sometimes longer) the animals show periodically occurring and increasing motor disorders, rigidity of the hind limbs, tonic and clonic spasms. If fed raw meat the animals show all these phenomena already 3-4 days after the operation. At the same time a considerable increase in ammonia and its salts (which are normally rendered harmless by the liver) is observed in the blood (Pavlov and Nentsky).

The experiments on dogs with an Eck's fistula have helped not

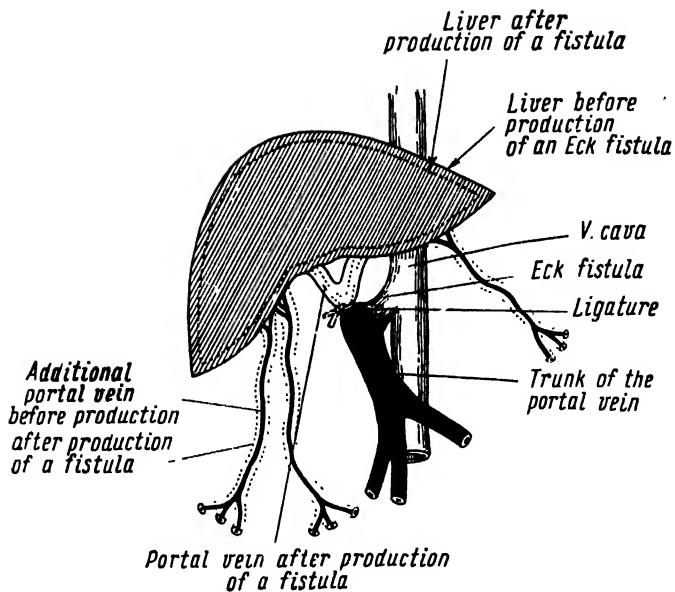


Fig. 126. Effects of an Eck's fistula.

only to study the detoxicating and urea-producing function of the liver, but also to establish a number of factors demonstrating the role played by hepatic insufficiency in the processes of digestion and intermediate metabolism.

In addition to the regular Eck's fistula, an *Eck in reverse fistula* is produced for the purpose of studying the function of the liver; by means of this fistula the blood is directed from the inferior vena cava into the portal vein. This is achieved by anastomosing these two vessels and subsequent ligation of the inferior vena cava above the anastomosis. The function of the liver can be studied on dogs with such a fistula under various conditions of feeding.

The operation of producing an Eck in reverse fistula served as the basis for elaborating the operation of complete removal of the liver in dogs.

The *operation for complete removal of the liver* (Mann-Magath) is performed in two stages, the first stage consisting in production of the Eck in reverse fistula. As a result of this operation all the blood of the lower part of the body and the intestines is directed into the portal vein and the liver. The second operation is performed four weeks after development of powerful collaterals which ensure the outflow of part of the venous blood, by-passing the liver, into the superior vena cava (through a thoracic and an internal mammary

veins); the operation consists in ligation of the portal vein above the anastomosis and removal of the liver.

No specific disturbances are observed during the first few hours following the operation: the animal can stand and drink water. Within 4 to 8 hours after a satisfactory outcome of the operation the animal develops increasing muscular weakness, adynamia and convulsions. The convulsions are soon followed by hypothermia, coma and death from respiratory arrest. The blood sugar diminishes. After injections of glucose the hepatectomised animals may live on for 16-34 hours. Excision of the liver causes an increase in the content of ammonia and amino acids and a decrease in the amount of urea (Fig. 127). Deamination of amino acids sharply diminishes. Uric acid continues to form, but its conversion into allantoin is impaired.

Despite the early death of the animals the experiments with allatoxin of the liver have also made it possible to elucidate the role of the liver in bilirubin production, the possibility of extrahepatic bilirubin production, and the participation of the liver in cholesterol metabolism, regulation of the acid-base balance, formation of paired compounds, heat regulation, blood clotting, detoxication of poisonous metabolites, etc.

An *angiotomy* (London) consists in suturing cannulas to the walls of the large veins of the liver—portal and hepatic—so that it is possible to get the blood flowing to and away from the liver. By this method it has been possible to investigate the participation of the liver in the different disturbances in intermediate protein, carbohydrate and fat metabolism, bilirubin production and salt metabolism, as well as the role played in these processes by other

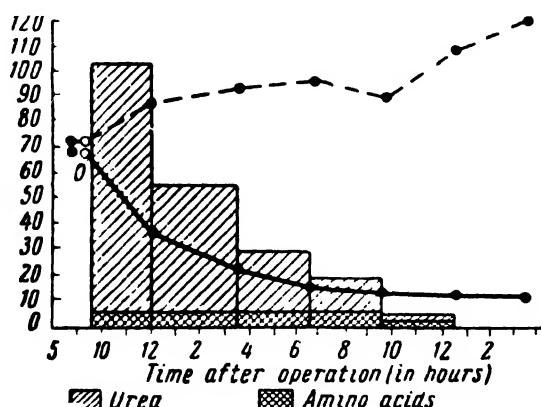


Fig. 127. Effect of removal of the liver (O) in the dog on the content of N-amino acids (—) and N urea (—) in the blood (in mg/l) and in the urine—columns (in mg·hr) (Mann).

organs, since vascular cannulas can be simultaneously applied to other large vessels.

Ligation of the portal vein (Fig. 128) causes death from extensive hemorrhages into the abdominal cavity already within 1-2 hours. The spleen and entire gastrointestinal tract are extremely hyperemic. The speedy death is to be explained not so much by a function of the liver (in cases of hepatectomy the animal lives longer) as by a sharp disturbance in circulation.

Ligation of the hepatic artery also gives rise to phenomena of marked intoxication. The period of survival of the operated animal depends on the completeness of the ligation and the presence of arterial collaterals.

The speedy death after ligation of the hepatic artery is apparently due to development of infection. If infection is prevented by antibiotics, ligation of the hepatic artery does not rapidly kill the animal, and the blood circulation in the liver is gradually restored. The amount of urea excreted in the urine somewhat diminishes. Autopsy reveals phenomena of parenchymatous dystrophy and sometimes necrosis.

Ligation of the hepatic artery in dogs after production of an Eck's fistula soon results in the animals' death. Before death the animals lapse into a comatose state, the amount of ammonia in the serum greatly increases and that of serum albumin decreases.

Analogous phenomena may be observed in man in cases of thrombosis of large hepatic vessels.

Lastly, various manifestations of hepatic insufficiency and the role of the liver in metabolism have been established in experiments

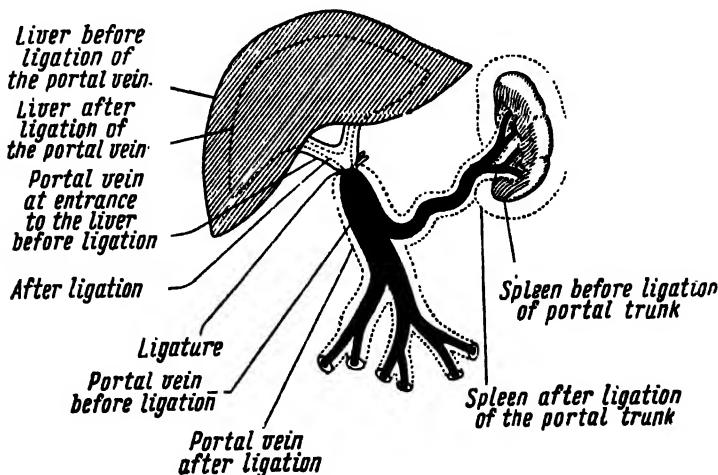


Fig. 128. Effects of ligation of the portal vein.

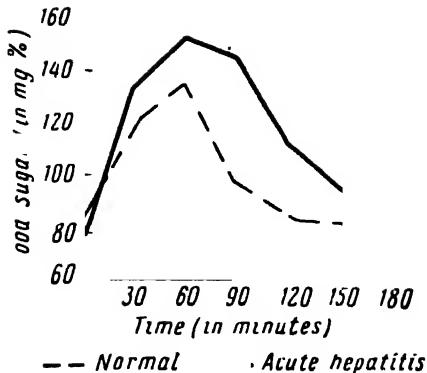


Fig. 129. Galactose test in healthy people and in patients with liver disease.

on animals with biliary fistulas in intoxication with hepatic poisons and in cases of artificial administration of substances whose assimilation requires participation of the liver.

MANIFESTATIONS OF HEPATIC INSUFFICIENCY

Metabolic Disturbances

The reaction of the liver to stimuli manifests itself primarily in changes in carbohydrate metabolism. Experiments on animals deprived of the liver have shown that the content of glucose in the blood depends on the function not only of the liver, but also of other organs. More specific is the metabolism of *levulose*, but it, too, undergoes transformations not only in the liver, but also in the intestinal epithelium and the muscles. Only galactose fails to be assimilated in the absence of the liver. The *galactose tolerance test*, i.e., the test of the glucogenic function of the liver by the amount of galactose excreted in the urine after its administration to the subject, has therefore become very popular in the clinic, although it does not always make it possible to differentiate the various forms of liver disease; this test produces more definite results in cases of diffuse affection of the liver. The elimination of more than 3 g of galactose over a 5-hour period after administration of 40 g of it indicates hepatic dysfunction.

Demonstrative results are also obtained by examination of the blood sugar curve after administration of galactose (Fig. 129).

The liver also plays a considerable part in the disturbances in *fat* and *lipoid metabolism*. As a result of deficient carbohydrate metabolism, for example, in diabetes and liver intoxications the liver loses

glycogen which is replaced by fat. In such cases lipemia and ketonemia develop. Fat metabolism is also disturbed when bile production and bile secretion are impaired, since bile plays an important part in fat absorption.

Hepatic dysfunction greatly impairs cholesterol metabolism. For example, owing to disturbed bile secretion the *total cholesterol* in the blood increases, while in parenchymatous affections of the liver it noticeably diminishes, the *ratio of cholesterol to cholesterol esters* increases because esterisation of cholesterol perceptibly decreases (from 60 per cent of total cholesterol to 40 and sometimes even to 5 per cent). The extent of these changes does not always correspond to the severity of the liver disease. The content of phosphatides in the blood is maintained at a definite ratio to that of cholesterol and also depends on the functional state of the liver. Affections of the liver are usually accompanied by a certain disturbance in the *ratio of the phosphatides to cholesterol*.

Nitrogen metabolism is appreciably impaired. The experiments with excision of the liver or production of an Eck's fistula have clearly shown the importance of the liver in nitrogen metabolism.

After removal of liver the production of *urea* in dogs noticeably decreases and does not increase from subsequent administration of ammonia salts (ammonium carbamate) and amino acids to these animals. But even in cases of relatively severe affections of the liver excretion of amino acids and production of urea may not be impaired because this function is performed even when the organism has retained but a very small part of the liver. The increased excretion of ammonia compounds sometimes observed in disorders of the hepatic function cannot be explained solely by a weakening of the urea-producing function of the liver. Ammonia is used to neutralise the acids (for example, volatile fatty acids and lactic acid) accumulating in the organism owing to impairment of the hepatic function.

Diminished urea in the urine is observed only in severe cases of jaundice, congested liver, fatty degeneration, etc. Acute yellow atrophy of the liver causes the content of urea in the daily amount of urine to decrease to 0.5 g.

The *accumulation of amino acids in the blood* and their increased excretion in the urine are only partly due to the weakened deaminising function of the liver. They are to a no lesser extent connected with concurrent changes in the functions of the kidneys and intestines. The increase in the content of amino acids (tyrosine, leucine, etc.) in the blood and their elimination in the urine may also be the result of autolysis of liver tissue.

An increase in nonprotein nitrogen—*azotemia* and *azoturia*—is observed in the blood and urine in diffuse parenchymatous affections of the liver. But the kidneys may also take part in the development of these phenomena.

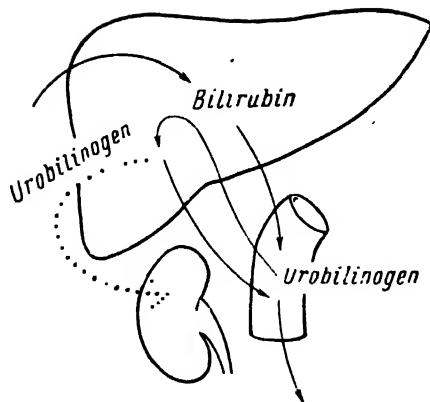


Fig. 130. Diagram showing formation of urobilinogen from bilirubin in the intestines and its circulation. Dotted line shows passage of urobilinogen into the blood and its excretion by the kidneys in hepatic dysfunction.

The *protein content of the blood is also altered* since the liver actively participates in protein metabolism. In liver affections the *content of serum albumin decreases, while that of γ -globulin and its concomitant lipoprotein increases*. To reveal this, electrophoretic studies of proteins in the blood plasma or serum and their ability to form flakes are conducted, and the albumin/globulin ratio is determined.

Lastly, in diseases of the liver there is a possibility of a *diminution in the blood prothrombin* in connection with the decreased absorption of vitamin K (due to insufficient bile secretion) or as a result of affection of the parenchyma of the liver, as in acute yellow atrophy and phosphorus and chloroform poisoning.

Disturbances in pigment metabolism are considered to be directly connected with hepatic insufficiency. This view is based on participation of the reticuloendothelial elements of the liver in bilirubin production, and the fact that liver cells, as the site of bilirubin secretion, may play some role in its final shaping. *Bilirubinemia*—accumulation of bilirubin in the plasma—is therefore a sign of parenchymatous affections of the liver and congestive phenomena therein.

In connection with bilirubin metabolism it is also necessary to mention the changes in *urobilin* metabolism. In its chemical structure urobilin very closely resembles bilirubin. Urobilin is formed as a result of oxidation of urobilinogen, while urobilinogen is produced in the intestines by reduction of bilirubin due to the action of intestinal bacteria.

Part of the urobilinogen forming in the intestines is eliminated in the feces as stercobilin formed by reduction, while the other

part is absorbed and re-enters the liver where it is transformed into bilirubin or its derivatives. In *affections of the liver* the metamorphosis of urobilinogen is inhibited or discontinued and its amount in the blood and urine increases (Fig. 130).

The content of urobilin in the urine may also increase as a result of too much urobilinogen passing into the urine from the intestine (for example, in hemolytic jaundice). There is also another not ungrounded assumption that urobilinogen is formed in the liver itself by fermentative reduction of bilirubin, especially in cases of congestion. In such cases urobilinogen enters the intestine with the bile and, in virtue of resorption, re-enters the liver from the intestine. In liver affections urobilinogen and urobilin pass into the urine.

The *acid-base balance* in the blood in certain measure depends on the functional state of the liver. Disturbances in the hepatic function accompanied by glycogen deficiency of the liver cells are simultaneously characterised by acidosis. In addition to keto acids, diseases of the liver are also responsible for accumulation of other acid metabolites (for example, volatile fatty acids, lactic acid) which cause a change in the alkali reserves of the blood. Such a phenomenon may be observed in diabetes, avitaminoses and anaphylaxis in whose pathogenesis the liver undoubtedly plays an essential part. The significance of the liver in the acid-base balance is that along with other organs the liver plays an important role in regulating *salt metabolism*.

Water metabolism is also connected with the function of the liver. Contraction of the hepatic veins causes an elevation of pressure in the hepatic capillaries with the result that lymph formation is increased and water is retained. Excitation of the sympathetic division of the vegetative nervous system which innervates the liver opens the "muscle sluices", the pressure in the capillaries drops, and the greater part of the fluid rushes into the blood current again. Production of an Eck's fistula is accompanied by development of hydremia and increased excretion of urine... In severe cases the *excretion of urine not infrequently decreases and hydremia develops*; the latter disappears upon improved hepatic function.

The diminished excretion of urine in severe affections of the liver may be due to the weakened ability of the liver to inactivate and split the steroids of the adrenal cortex, which may lead to retention of sodium and water.

Disturbances in the Detoxifying Function of the Liver

In diseases of the liver the detoxifying and excretory role of the liver is also disturbed. Observations of dogs with an Eck's fistula have established that the liver renders harmless the toxic products formed in the processes of normal and impaired protein metabolism. Methyl-

ated bases are discovered in the organism of such dogs. These are ammonium carbamate and methylated betaine-type products. In diseases of the liver caused by phosphorus poisoning compounds homologous to betaine may be found in the urine. The toxic products rendered harmless by the liver include proteinogenic amines (tetramethylenediamine, pentamethylenediamine, etc.) formed as a result of decarboxylation of amino acids in the intestine and found among products of putrefaction. The liver also detoxifies exogenous toxic substances, such as menthol, camphor and salicylic acid.

The detoxifying function of the liver is based on chemical processes operating in it. A particularly important aspect of the detoxifying role of the liver is its ability to *synthesise paired* ether-sulfur and glucuronic compounds. The formation of paired compounds in the liver increases under the influence of substances containing organically bound sulfur (for example, methionine and cysteine).

Observation of people affected with liver disease shows that *the synthesis of paired compounds* in the organism is *not infrequently diminished*. The detoxifying function of the liver is evaluated on the basis of a test involving administration of sodium benzoate and subsequent determination of hippuric acid in the urine, formed from benzoic acid and glycocoll. A decrease in the synthesis of hippuric acid and in its elimination in the urine attests a disturbance in the detoxifying function of the liver (Quick's hippuric acid synthesis test).

Accumulation of poisons in the organism is in large measure prevented by the *excretory function* of the liver. Various metabolites and foreign substances which have gained entrance into the liver through the blood are excreted into the bile, namely, bacteria, organic and inorganic poisons, salts of metals (iron, copper, manganese, mercury, aluminium), a number of medicinal substances administered into the organism (salicylic acid, urotropin, terpenes) and dyes (methylene blue, Congo red, sulfobromophthalein, tetrabromophenolphthalein, etc.). The content of the bile components gives an idea of the excretory function of the liver. This underlies the so-called chromodiagnosis which helps to determine the state of the excretory function of the liver by the rapidity with which the foreign dyes are eliminated in the bile.

DISTURBANCES IN BILE SECRETION AND BILE PRODUCTION

The secretion of bile begins in intercellular bile ducts; this is indicated in the diagram shown in Fig. 131.

The *secretion of bile may be hindered by functional disorders*, such as disturbances in the contractions of the muscles of the gallbladder, ducts and sphincter of Oddi (dyskinesias) and by

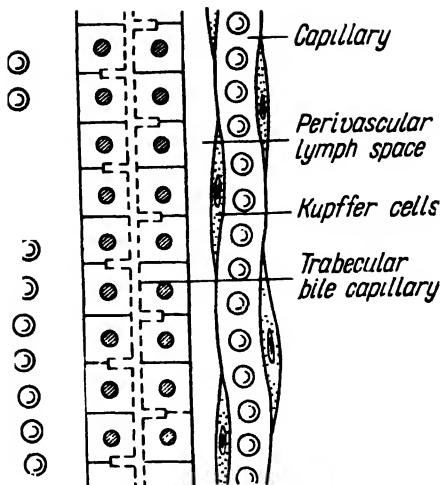


Fig. 191. Diagram showing structure of a trabecula of a liver lobe.

organic lesions in the mucosa of the bile ducts due to obstruction of the ducts by products of inflammation, a calculus or compression by a tumour. The dyskinesias include a special *hypertonic form* arising as a result of stimulation of the parasympathetic fibres which innervate the bile ducts. The result is a strong contraction of the sphincter of Oddi and a weaker contraction of the gallbladder which is unable to overcome the obstacle offered by the sphincter; this is sometimes observed during pregnancy. Another form of dyskinesia—*hypotonic*—is due to stimulation of the sympathetic division of the nervous system and inhibition of the vagus nerve. As a result the gallbladder relaxes, the pressure in the gallbladder drops and the egress of bile is impeded.

Disorders of bile secretion are observed under emotional stress in virtue of the changes in the functional state of the cerebral cortex. A possibility of conditioned reflex bile secretion has also been established.

Secretion of bile is accelerated by the action of a number of substances—magnesium sulfate, egg yolk, fats, peptone and hypophysin. Most of these substances exert an influence on bile formation, but in the main they affect the contractility of the gallbladder, the pressure in the bile ducts or the relaxation of the sphincter of Oddi. Thus, the amount of bile secreted into the duodenum depends not only on the secretory activity of the liver, but also on the regulation of bile secretion.

Jaundice is one of the important manifestations of impaired bile secretion and bile production.

Jaundice

Jaundice (*icterus*) is a pathologic condition characterised by pigmentation of the integuments due to deposition of bile pigments. Jaundice may also be accompanied by accumulation of bile acids and other bile components in the blood (*cholemia*). Bile pigments are deposited in the cells of the Malpighian layer of the skin, which remain pigmented for a long time even after bilirubin has ceased to be retained in the blood. The icteric pigmentation is also observed in the mucosa, sclera and internal organs; the skin and mucosa are pigmented the most, the parenchymal organs—less, the peritoneum and muscles—still less; the cerebral tissue is barely pigmented because the hematoencephalic barrier is impermeable to bile pigments. Bile pigments are also excreted into the urine and impart to it a corresponding colouring. Other bile constituents, for example, bile acids, may be excreted into the urine together with bilirubin. In such cases the blood of jaundice patients is toxic for the organism. This toxicity is due to accumulation in the blood not only of bile acids, but also of intermediate metabolites formed in liver affection. The toxic manifestations of jaundice vary and affect all the basic functions of the organism.

Van den Bergh's method is used for a quantitative determination of bilirubin in the serum. This method makes it possible qualitatively to distinguish two reactions to bilirubin—direct and indirect reactions. The reaction is called direct if the reagents (solutions of sulfanilic acid and sodium nitrite) produce a characteristic pink pigmentation after their direct addition to the serum. An indirect reaction occurs only after preliminary treatment of the serum with alcohol.

Jaundice accompanies a number of diseases of the liver and bile ducts, resulting from intoxication or infectious diseases and from certain diseases of the blood. There are also physiologic forms of jaundice (jaundice of the newborn, jaundice of pregnancy and menstrual jaundice).

Three main groups of jaundice may be distinguished according to pathogenesis: 1) due to impaired bile secretion caused by mechanical obstruction in the extrahepatic bile ducts (mechanical, congestion or resorption jaundice); 2) due to impaired function of the hepatic parenchyma (hepatic, parenchymal or retention jaundice); 3) due to intensified breakdown of blood erythrocytes and increased bile production (hemolytic or dynamic jaundice).

1. *Mechanical, congestion or resorption jaundice* arises as a result of some obstruction to the bile secretion. Such an obstruction may be created by an inflammatory process in the duodenum and the bile passages, a passing calculus (in cholelithiasis), sharply condensed bile or compressing tumour. Above the obstruction the bile ducts are distended by bile. Owing to the proximity of their terminal parts to

the walls of the lymph capillaries of the liver, bile begins to be absorbed into the lymphatics, then bile constituents gain entrance into the general circulation through the thoracic duct with resultant phenomena of general intoxication.

However, the onset of congestion jaundice cannot be explained by mechanical causes alone; reflexly arising functional disturbances, such as spasm of bile ducts, may also take place. Changes in the hepatic cells and disturbances of an infectious-toxic origin, which of themselves lead to disorders of bile secretion are also possible. The possibility of discovering hepatitis in this form of jaundice was already mentioned above.

2. *Hepatic or retention jaundice* owes its onset to a disturbance in the function of the hepatic cells due to various causes—*infections, toxins and poisons*. Bilirubin and other bile constituents are retained either because of the inability of the hepatic cells to secrete the bile or because the bile is directed not only along the usual passages into the gallbladder but also into the blood. In such cases not only the ability to secrete bilirubin, but also the protein and fat metabolism are impaired, and a dissociation of the hepatic functions is observed, either bilirubin or bile acids being retained in the blood.

3. *Hemolytic jaundice* arises as a result of hemolysis of erythrocytes, increased production of bilirubin and its passage into the blood. The disease may arise in cases of hemolysis, for example, in connection with diminished resistance of erythrocytes in hemolytic anemia or as a result of the action of certain drugs (phenylhydrazine, hydrogen arsenide). The hemoglobin liberated in hemolysis is transformed into bilirubin which forms in so large an amount that it fails to be excreted by the liver, is retained in the blood, passes into the tissues and is responsible for the appearance of jaundice.

The pure form of hemolytic jaundice, unlike other forms of jaundice, is not accompanied by retention of bile acids and cholesterol in the blood. The reason for it is that in hemolytic jaundice there is only increased production of bile pigments and no retention of all the bile constituents; bilirubin is not usually excreted into the urine, because it is produced in some less oxidisable form which yields an indirect reaction, and does not pass through the kidneys. In this case the bile which pours into the duodenum is usually rich in bilirubin, and the urine therefore contains an excess of urobilin. Hemolytic jaundice is sometimes complicated by formation of bile thrombi in the bile ducts because of secretion of thick bile and plugging of the ducts. In the latter case mechanical jaundice simultaneously sets in. Jaundice of the newborn also belongs to the group of hemolytic jaundices.

The following forms of *jaundice of the newborn* are distinguished: *simple jaundice* which passes during the first days of life and is

characterised by an excess of erythrocytes and their partial destruction in the blood, and *erythroblastosis foetalis*—a disease marked by severe erythroblastic anemia and accompanied by icterus. The latter disease is due to the fact that during pregnancy the erythrocytes of the fetus containing *Rh agglutinogens* immunise the *Rh negative* mother and cause accumulation of *anti-Rh agglutinins* in the mother's blood; the anti-Rh agglutinins pass through the placenta into the organism of the fetus, agglutinate and destroy its erythrocytes, thereby causing icterus and impairing the function of the hematopoietic apparatus.

The *effects of jaundice on the organism* vary with the basic liver disease which is accompanied by this symptom. Phenomena of intoxication are observed when bile acids are retained. Hemolytic jaundice is an exception since in this disease only bilirubin is retained in the blood and tissues.

Toxic phenomena can be easily observed in experimental jaundice. If the bile duct is ligated in the dog, signs of jaundice and intoxication are noted already on the 4th or 5th day. Pigments appear in the urine, the feces are colourless and the scleras acquire the colour of jaundice. The animal becomes irritable during the very first days after ligation of the duct; this is followed by depression of the nervous function and diminished blood clotting.

Accumulation of bile in the blood in jaundice pathologically affects the *nervous system*; it gives rise to depression, headache, fatigue, and sometimes increased neuromuscular excitability. Particularly characteristic is the itching of the skin, which sometimes appears long before the signs of the disease. The itching is due to stimulation of the sensitive nerve endings in the skin by bile acids.

The *circulatory disorders* produced by bile acids in jaundice are *bradycardia, drop in blood pressure and a slowing of respiration* (Fig. 132). The slowing of the pulse is a result of *stimulation of the vagus nerves of the heart*. Jaundice also affects the neuromuscular elements of the myocardium itself.

Blood clotting is diminished and phenomena of hemorrhagic diathesis with bleeding from the nose, stomach and intestines develop. A tendency to postoperative hemorrhages is observed. The reason for diminished blood clotting is impaired absorption of vitamin K (due to the lack of bile in the intestines) with a resultant decrease in production of prothrombin (which is necessary for blood clotting) in the liver.

Insufficient delivery of bile to the intestines is accompanied by *digestive disturbances*. In cases of hemolytic jaundice the bile secreted into the intestines is thick and abounds in pigments. Such bile imparts to the fecal masses a very dark colour.

The congestion and retention forms of jaundice are not infrequently accompanied by *parenchymatous disturbances* in the

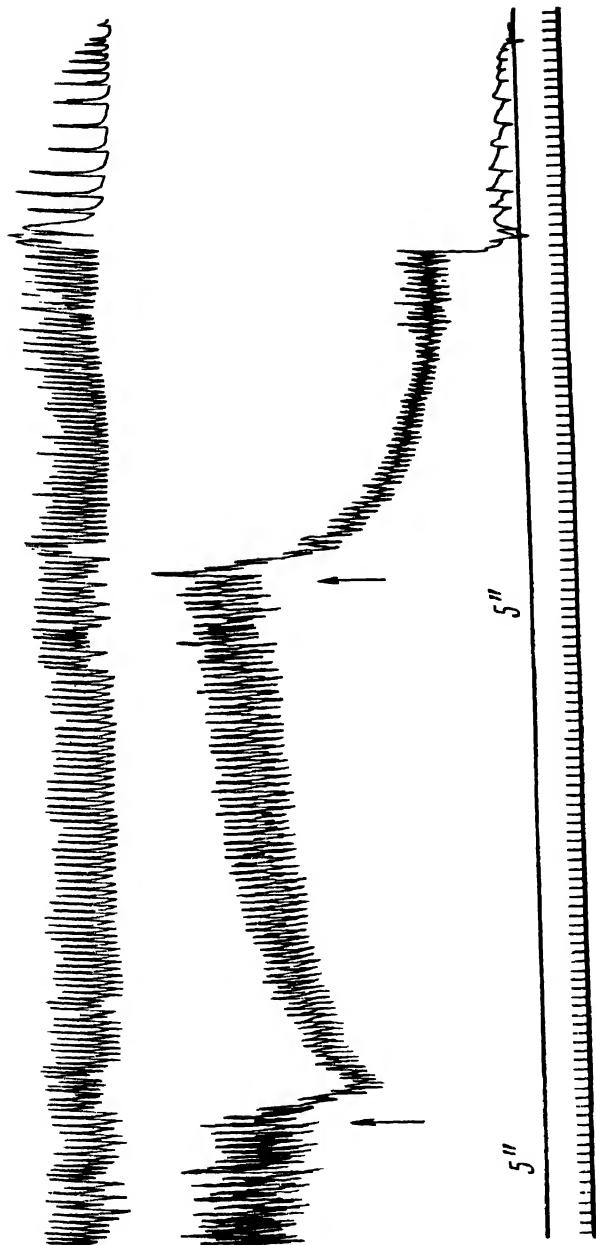


Fig. 132. Changes in the blood pressure (bottom) and respiration (top) in the dog after intravenous administration of 20 ml of ox bile (first arrow). Repeated administration of 40 ml (second arrow) was followed by sharp drop in blood pressure, slowing of respiration and the animal's death.

kidneys, spleen and pancreas, and changes in metabolism, such as accumulation of cholesterol in the blood and tissues because the synthesis and excretion of cholesterol are impeded by the affected liver.

Cholelithiasis

Cholelithiasis is characterised by formation of stones in the gall-bladder and bile ducts.

Several kinds of stones are distinguished according to their composition (Fig. 133).

1. *Radiating cholesterol stones* composed of cholesterol. Usually one round or oval stone is found in the gallbladder. In section the peripheral part of the stone has rough radiating lines. In the centre of the stone the trabeculae are arranged less regularly; sometimes they cross around a crystallisation centre consisting of pigment and calcium salts. Most commonly, however, there is no crystallisation centre.

2. *Large combined stones* composed of a cholesterol radiating nucleus and cholesterol-pigment-salt layers. They form from radiating cholesterol stones when cholesterol, pigment and salt settle out of the bile and become stratified.

3. *Mixed cholesterol-pigment-salt stones* are the most numerous and occur the most commonly. They are of different sizes (usually there are several stones in the gallbladder), from that of a millet grain to that of a hazelnut, and may be polished as a result of mutual friction. They are so-called *faceted stones* (with a predominance of cholesterol). A section shows a loose centre consisting of pigment with an admixture of scraps of epithelium, mucus or blood clots; the centre is covered with layers of cholesterol in the form of a dense mass with an admixture of pigment and salts.

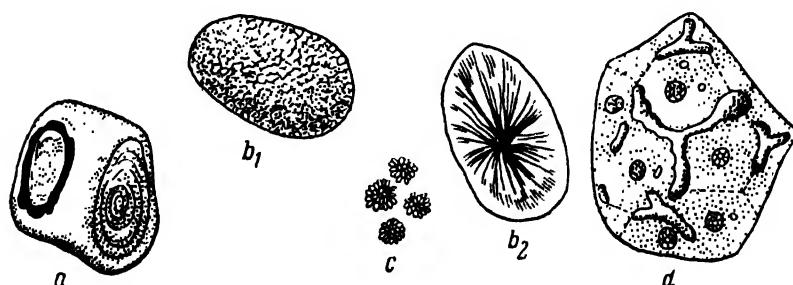


Fig. 133. Gallstones.

a—faceted mixed stones (cholesterol-lime-pigment); b₁—pure cholesterol stone; b₂—radiating cholesterol stone with pigment nucleus; c—pure pigment stones; d—bile capillaries dilated after obstruction.

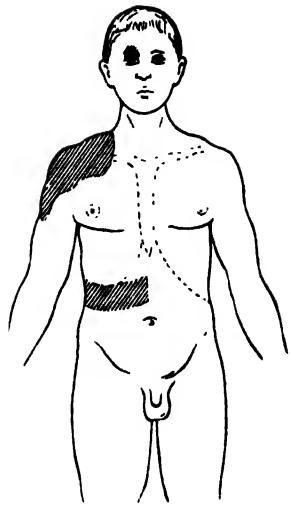


Fig. 134. Typical hyperalgesic (painful) zones after attack of gallstone colic.

4. *Pigment stones*, blackish, of small size, are found in the gallbladder, as well as the bile ducts. They consist mainly of bilirubin and sometimes contain salts, copper salts in particular.

The stones in the gallbladder may be either of an *inflammatory or non-inflammatory origin*.

Botkin was the first to suggest that the main cause of stone formation is infection which is responsible for the development of *inflammatory phenomena* in the mucosa of the ducts and bladder (angiocholitis, cholecystitis). Considerable importance is attached to desquamation of the epithelium. However, not only epithelium, but also mucin, products of inflammation and fibrin threads may serve as the crystallisation centres around which layers are deposited, leading to formation of stones. Typical stones of infectious-inflammatory origin are cholesterol-pigment-salt stones.

Purely cholesterol stones (of noninflammatory origin) form as a result of impaired cholesterol metabolism with cholesterol accumulating in the bile and settling out of the colloid solution about a crystallisation centre which may be desquamated epithelium of the bladder, mucin, et. However, there must not necessarily be a crystallisation centre for formation of cholesterol stones. Disturbances in general metabolism may give rise to increased production of bile acids, which leads to diminished solubility of cholesterol and its precipitation. Such aseptic, primary stones may secondarily cause inflammation of the gallbladder. Purely pigment stones also belong to the group of stones arising as a result of metabolic disturbances.

Lastly, stones of bilirubin calcium are found in bile ducts; an important role in their origin is played by stasis.

Thus there are various reasons for the appearance of gallstones: 1) impaired metabolism (cholesterol, pigment stones), 2) infectious-inflammatory processes (mixed stones) and 3) stasis (bilirubin-calcium stones and pigment concretions in the bile ducts). A combination of the different factors with predominance of one of them is also possible.

The effects of stone formation vary. In some cases the formation of a stone in the gallbladder may not produce any noticeable phe-

nomena. In other cases, in the presence of cholecystitis a stone causes colic—paroxysmal pain with characteristic irradiation (Fig. 134) due to spastic contractions of the bile ducts—and not infrequently elevation of temperature. The colic is particularly painful when a stone obstructs the neck of the gallbladder. Stones passing through biliary passages may obstruct a bile duct and cause development of jaundice. Such jaundice may disappear and reappear, depending on the position of the stone and the extent to which it has obstructed the biliary passage. In cases of latent infection the injury inflicted by a stone is often responsible for the spread of the infection along the biliary passages, its penetration into liver tissue, damage to the tissue and development of hepatic jaundice.

PATHOLOGY OF URINE SECRETION

Normally the kidneys perform *concentrating and diluting functions*. Concentrations of solids in various portions of urine excreted in the course of a day vary within narrow limits. Usually the daily amount of excreted urine does not exceed 1.5 litres, while the content of solids in the daily urine remains more or less constant.

Disturbances in urinary output are due to changes in the renal function and general organic disturbances, especially circulatory and metabolic. Owing to this, renal and extrarenal uropoietic disorders are distinguished, although it is impossible to draw a clear line between them.

EXTRARENAL FACTORS DISTURBING URINE SECRETION

The following extrarenal disturbances in urine secretion are distinguished:

1. *Disturbances in nervous and neuroendocrine regulation* which physiologically ensures normal relations between the tissues, blood and the uropoietic apparatus.

It has been experimentally demonstrated that disturbances in uropoiesis may be provoked by dysfunction of the central nervous system, the medulla oblongata and tuber cinereum in particular. A needle puncture in the medulla oblongata (between the nuclei of the vagus and acoustic nerves) causes increased excretion of water through the kidneys. A puncture in the region of the *funiculus teres* leads to increased concentration of sodium chloride in the urine as a result of a change in the renal function. Increased excretion of urine is also observed after a puncture in the region of the tuber cinereum on both sides of and somewhat behind the hypophysis. Uropoiesis is not infrequently increased in cases of tumours of the diencephalon.

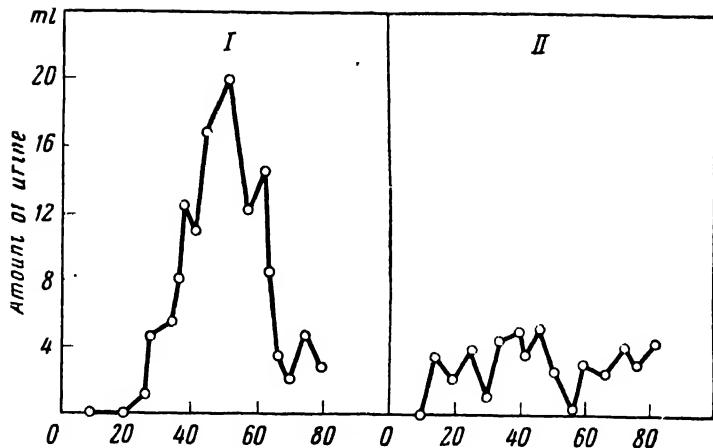


Fig. 135. Level of urinary output in normal activity of the cerebral cortex (I) and against the background of developing inhibition (II) (M. A. Usiyevich).

Some data also indicate cortical regulation of the renal function, for example, increased uropoiesis in cases of fright, hypnotic suggestion of drinking or the effect of a conditioned stimulus (Fig. 135).

Cortical influence on excretion of urine is effected through lower parts of the central nervous system, the hypothalamus, the vegetative and vegetative-endocrine systems. For example, stimulation of the splanchnic nerves causes a decrease in excretion of urine, transection of both splanchnic nerves—plentiful excretion of urine and a decrease in the concentrating capacity of the kidneys. Transection of the vagus nerves on the neck is followed by increased uropoiesis and greater concentration of chlorides in the urine, while stimulation of these nerves leads to a decrease in the concentration of chlorides. A completely denervated kidney in a large measure loses its adaptability to the altered conditions of both the external and internal environment and its ability to concentrate and dilute the urine.

Disturbances in renal secretion often arise *reflexly*. Intense pain stimulation may cause complete cessation of uropoiesis. Cooling of the skin produces a temporary spasm of the renal vessels and a decrease in urinary output, while heating increases the production of urine. Various parts of the intestines and the lower urinary passages—ureters and bladder—are reflexogenic zones with respect to excretion of urine.

The nervous regulation of the renal function consists in its influence on renal circulation and the process of filtration in the glomeruli.

Disorders of *neuroendocrine regulation* of urine excretion, especially diencephalohypophyseal disturbances, are also observed in pathology; these disturbances lead to a decrease in the antidiuretic hormone (secretion of the posterior lobe of the hypophysis) which intensifies reabsorption of water and inhibits reabsorption of sodium chloride. Insufficient secretion of this hormone causes increased production of urine of low specific gravity and a decrease in its sodium chloride.

2. *Changes in the chemical composition and physicochemical properties of the blood* caused by metabolic disturbances which alter the composition of the blood so that the amount of substances that have to be excreted in the urine may increase, or substances normally absent may appear, for example, an increase in sugar in diabetes and bile acids and bilirubin in jaundice, an appearance of hemoglobin in the plasma in cases of hemolysis of erythrocytes, and increased concentration of sodium chloride and other salts in disturbances in mineral metabolism.

A drop in the osmotic and oncotic pressure of the plasma leads to increased production of urine of low specific gravity, as in cases of copious administration of fluid or intravenous infusion of hypotonic solutions.

Renal insufficiency in its turn effects the chemical and physicochemical properties of the blood.

3. *Changes in the general circulation* and, accordingly, in renal circulation. A slowing or acceleration of circulation and changes in blood pressure in circulatory disorders affect the excretion of urine which may increase, decrease or even cease.

Disturbances in the renal function due to a slowing of the general and renal circulation may be observed in an experiment in which glass tubes are inserted into the dog's ureters. From each ureter urine is delivered through a tube into a cylinder. The renal function is judged by the amount of excreted urine and its properties (specific gravity, colour, presence of protein, etc.) Then the vein of one of the kidneys is clamped for a few minutes. Venous congestion leads to diminished secretion of urine and its subsequent cessation. At this time the unaffected kidney may increase excretion of urine. After removal of the clamp the blood circulation is resumed and the urinary output is restored. The urine excreted by the congested kidney contains protein. The urine of the control, unaffected kidney contains no protein. Similar results are obtained by compression of the abdominal aorta above the site of origin of the renal arteries; in this case the filtration pressure in the glomeruli drops. Experiments with an isolated kidney have established a direct dependence of the amount of primary urine on the level of arterial pressure. At an arterial pressure below 40-50 mm Hg uropoiesis ceases completely (Starling).

RENAL FACTORS DISTURBING URINE SECRETION

Of the renal factors disturbing the urine secretion an important part is played by inflammatory processes in the kidneys—*nephritides*, especially glomerulonephritides, and less frequently—focal nephritis with partial affection of the glomeruli. Glomerulonephritis is characterised by a bilateral diffuse affection of the renal parenchyma with pathologic phenomena mainly in the glomeruli. The changes in the glomeruli consist in a combination of exudative and proliferative processes which develop both inside the glomerular capillaries and outside, i.e., in the cavity of the glomerular capsule.

In the etiology of acute diffuse nephritis an important part is played by infections, mainly streptococcal, especially in combination with cooling. Nephritis also arises in cases of influenza, malaria and a number of other diseases.

Studies of the condition of the vascular system and experimental observations have shown that primary changes in the functions of the capillaries—vascular spasm—throughout the organism also play an important part in the pathogenesis of glomerulonephritis. Acute glomerulonephritis is marked by decreased uropoiesis, appearance of erythrocytes in the urine and impeded excretion of nitrogenous products. Due to increased reabsorption in the tubules the specific gravity of the urine increases, although it may also be normal. The arterial pressure rises, cardiac insufficiency often develops, a certain amount of protein appears in the urine, and edema, especially of the face, is observed. The retention of nitrogenous products in the organism may cause uremia.

Acute glomerulonephritis may become chronic with characteristic alterative and proliferative phenomena in the glomeruli and tubules. Proliferation of connective tissue between the glomerular vessels and between the tubules gives rise to phenomena of obliteration in the glomeruli and tubules (so-called secondary contracted kidney).

Chronic forms of nephritides are characterised by high arterial pressure, hypertrophy of the heart, and erythrocytes, casts and epithelium in the urine. In the beginning the amount of urine is increased and its specific gravity is low. In the terminal stage of its development chronic nephritis may lead to uremia.

Nephroses, another group of renal diseases, arise under conditions of disturbed protein and fat-lipoid metabolism and are accompanied by development of dystrophic phenomena in the epithelium of the uriniferous tubules and deposition of doubly refracting lipoid substances and amyloid. They are most commonly due to protracted purulent processes or chronic emaciation of the organism (in syphilis, tuberculosis, dysentery).

Marked cases of nephrosis, especially chronic (lipoid) nephrosis, are usually characterised by considerable albuminuria, a decreased amount of urine of increased specific gravity, a plentiful sediment,

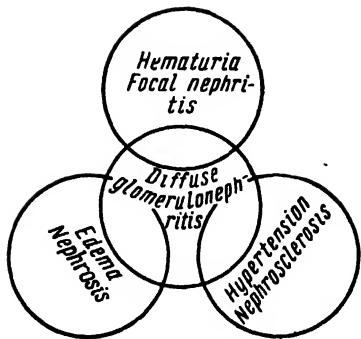


Fig. 136. Diagram showing the most characteristic symptoms of the main renal diseases. Each of the three outer circles indicates one of the main diseases with its characteristic symptom. The central circle crossed by the other three indicates the disease characterised by all three symptoms.

the size and shape of the kidneys (so-called *primary contracted kidney*). The causes of this disease are as yet insufficiently clear. Hypertensive vascular disease must be considered one of the causes. The disturbances in urine secretion developing in nephroscleroses resemble those in chronic glomerulonephritides.

Secondary contracted kidney develops as a result of chronic diffuse nephritis. This condition is marked by sclerosis of the blood vessels, induration and contraction of the kidney, obliteration of a considerable number of glomeruli, diminished filtration and reabsorption, and development of azotemia which may lead to uremia and hypertension. A contracted kidney may be produced experimentally in rats by feeding them cholesterol, especially after preliminary removal of the spleen. The symptoms of renal lesions vary, but they have many features in common (Fig. 136).

Experimentally it is possible to produce disturbances in the renal function, but these disturbances usually differ from those occurring in man. Chromium and uranium salts and mercury bichloride administered to animals cause damage mainly to the tubules; cantharidin, arsenic and toxins (diphtheria and streptococcal) affect the glomeruli. The severe changes produced in the kidneys in these cases are manifested in coarse dystrophic and necrotic phenomena and are not accompanied by hypertension or edema, as is frequently the case in man. It is sometimes possible to produce in rabbits changes in the glomeruli more closely resembling glomerulo-

impeded excretion of chlorides, a diminished ability of the kidneys to dilute the urine, a decrease in blood albumin (to 1-2 instead of 4-6 g%) and increase in fatty acids and cholesterol (to 500-1000 instead of 150-180 mg% under physiologic conditions) in the blood. Hypoproteinemia gives rise to a drop in oncotic pressure, decreased dispersion of the plasma colloids, and considerable edema.

In addition to nephritides and nephroses, kidney diseases include *nephrosclerosis*, i.e., sclerotic changes in the small renal arteries. The changes in the vascular system lead to impairment of nutrition of renal tissue, destruction of specific elements, and proliferation of connective tissue. The proliferated connective tissue shrivels and alters

nephritides by injecting endotoxin from streptococci isolated from scarlet fever patients.

Glomerulonephritis produced by sensitisation of rabbits with protein from a chicken egg and subsequent injection of the same protein directly into the renal artery occupies a special place among experimentally produced renal diseases. It has also been possible to provoke glomerulonephritis by sensitisation of animals with streptococci. The course of experimental streptococcal glomerulonephritis and the concomitant morphological changes in the kidneys bring it very close to glomerulonephritis in man. This is also attested by clinical observations of the onset and course of glomerulonephritis. Great importance in the pathogenesis of glomerulonephritis is therefore attached to allergy.

The allergic origin of glomerulonephritis is conceived as follows: infection, mainly streptococcal, sensitises the organism; subsequent penetration of antigen into the organism or the action of a non-specific factor, for example, cooling, gives rise to hyperergic inflammation in the kidneys, affecting mainly the glomeruli. The cooling may itself be a sensitising factor causing formation of antigen in the organism. Development of allergic nephritis in man is apparently the result of two processes: formation of autoantibodies against renal tissue in its affection by bacterial toxins and the pathogenic effect of these antibodies on renal tissue.

RENAL INSUFFICIENCY

Impairment of the Diluting and Concentrating Ability of the Kidneys

The kidneys have *an ability to excrete water* (diluting ability) and *to concentrate the solid constituents of the urine*. This ability may be judged by the freezing point of urine and its specific gravity after water intake or in xerophagia. In cases of plentiful intake of water healthy kidneys excrete large amounts of thin urine of low specific gravity (1.001); in cases of limited water intake or total deprivation of water the specific gravity of the urine reaches 1.035.

The *dilution test* consists in the following:

The subject drinks 1.5 litres of water on an empty stomach. The urine is collected at first every half hour and then every hour, and the amount of urine and its specific gravity are determined. Healthy kidneys excrete this amount of water in about 4 hours, the specific gravity of the urine dropping to 1.001-1.002. The dilution test makes it possible to evaluate the ability of the kidneys to excrete water or their ability to dilute the constituents of urine. The test may depend not only on the renal function, but also on the state of water metabolism in the entire organism, for example, on cir-

culatory disorders, physicochemical changes in the tissues and the retention of water therein, and the excretory activity of the intestines, skin and lungs which under physiological conditions maintain the physicochemical balance in the tissues.

The concentrating ability of the kidneys depends much less on extrarenal factors than does their diluting ability. The concentration test is therefore of greater importance for evaluating the state of the renal function. It reflects the processes of reabsorption in the kidneys.

The *concentration test* consists in the following: the urine of the subject who is given no fluid with the food is collected and analysed every hour or every 2 hours, the amount of urine excreted by healthy kidneys regularly diminishing in the course of the day and its specific gravity increasing to 1.030-1.035. This test makes it possible to evaluate the concentrating function of the kidneys (Fig. 137).

In cases of affected renal parenchyma (for example, in chronic glomerulonephritis) the ability of the kidneys to concentrate the urine diminishes; in such cases depriving the organism of water does not cause any appreciable increase in the specific gravity of the urine because tubular reabsorption is diminished.

The diminished ability of the kidneys to concentrate urine is called *hyposthenuria*. This condition is characterised by excretion of urine of low specific gravity which varies but slightly. The total daily excretion of urine is increased and its specific gravity is not above 1.012-1.014. Hyposthenuria is frequently observed in chronic glomerulonephritides.

In cases of deeper affections of the kidneys the latter may completely lose their ability to concentrate urine, the specific gravity of the urine remaining almost on the same low level under all conditions of water intake or xerophagia and the concentration of the urine being about equal to that of protein-free plasma. The inability of the kidneys to concentrate or dilute urine is called *isosthenuria*. It indicates the inability of the kidneys to adjust themselves to changes in metabolism and composition of the blood (mainly with respect to proteins and salts).

Disturbances in the concentrating ability of the kidneys are also investigated by administration of sodium chloride, urea and creatinine. Retarded excretion of these substances indicates renal insufficiency.

Changes in the Amount of Urine

The changes in the concentrating and diluting ability of the kidneys are often combined with differences in the *daily amount of urine excreted by the kidneys*.

Oliguria—diminished excretion of urine—may be of both renal and extrarenal origin.

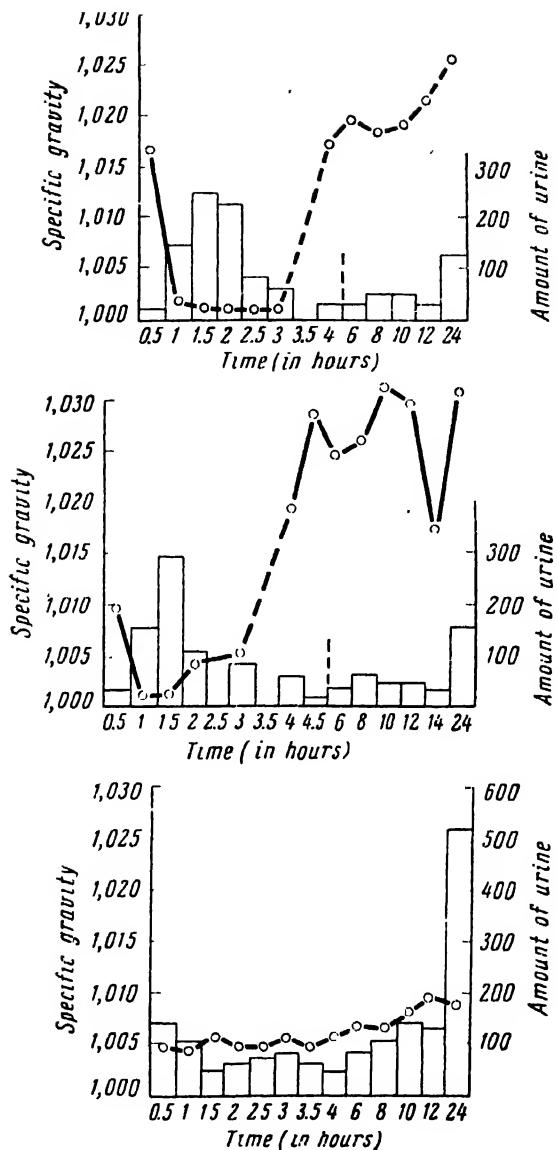


Fig. 137. Dilution and concentration test (Volhard). Dilution test during the first four hours is followed by concentration test.

Upper curve—urinary output of normal kidneys; middle curve—urinary output in nephrosis; lower curve—urinary output in chronic nephritis.

Oliguria of extrarenal origin may be traced to several causes:

- 1) *general impairment of blood circulation* accompanied by diminution in the minute volume of the heart, drop in blood pressure, congestive phenomena and resultant slowing of circulation in the kidneys;
- 2) *loss of a large amount of water by the organism* due to profuse sweating, accelerated respiration, excessive vomiting, and diarrhea;
- 3) *retention of water in the organism*, for example, at the height of fever or in edema;
- 4) *reflex influences* from various parts of the gastrointestinal tract and skin, certain lesions in the nervous system, particularly in the region of the hypothalamus and medulla oblongata, and psychic trauma.

Oliguria of renal origin may occur in kidney disease of inflammatory and dystrophic character and is due to changes in renal tissue responsible for slower elimination of water and intensified reabsorption of water excreted by the glomeruli. In these cases the urine is of higher specific gravity in virtue of the increased concentrating ability of the renal filter.

In inflammation of the kidneys the lumens of the tubules may become obstructed by casts or products of inflammatory infiltration, the tubules may become compressed as a result of edema of interstitial tissue, and the renal vessels may be compressed by a tumour; the inflammation may also give rise to a thrombus or to vascular spasm. Considerable oliguria and even anuria (total arrest of urinary output) may be observed in all these cases.

Anuria is a temporary or protracted total arrest of urinary secretion. It occurs in acute glomerulonephritides and nephroses. The character and duration of its course, as well as the functional restorability of the kidneys, vary; the renal function is restored sooner in cases of nephrosis than it is in cases of vascular inflammation. Such anuria may be produced experimentally by poisoning an animal with mercury bichloride or lead.

In addition to the purely *renal form* of anuria there is also anuria of extrarenal origin, namely, *prerenal anuria*—in cases of diminished blood supply to the kidneys (due to reduced arterial pressure, thrombosis or compression of renal arteries or veins), *subrenal anuria*—in cases of obstruction or compression of the ureters (by stones or a tumour), and *reflex anuria*—in cases of trauma, contusion or operations in the urinary tract, etc.

Polyuria—pathologic increase in urinary output—may be caused by extrarenal factors: 1) *changes in the general circulation*, as elevated arterial pressure and increased blood flow with a resultant change in renal blood circulation and increased urinary output; 2) *metabolic disturbances and accumulation in the blood of compounds conducive to excessive urinary output*, for example, glucose in diabetes, and nonprotein nitrogen in disorders of protein metabolism.

ism connected with liver disease; 3) *abundant fluid intake by the organism*, leading to a drop in the osmotic and oncotic pressure of the blood; 4) *stimulation of certain parts of the brain*—the hypothalamus, medulla oblongata and cortex, or elaboration of a reflex to increased urinary output.

Diabetes insipidus is a peculiar disturbance in urinary output of neuroendocrine character. This disease accompanied by protracted polyuria is mainly a result of impaired water metabolism and concentrating ability of the kidneys with respect to sodium chloride. In this disease ingestion of sodium chloride increases polyuria which is quite pronounced as it is (5-20 litres per day). Polyuria is accompanied by polydipsia (excessive thirst) which is a result of developing polyuria. Diabetes insipidus is due to disturbances in the region of the diencephalon and insufficient production of the antidiuretic hormone in the hypophysis.

Increased excretion of urine occurs in cases of *secondary and primary contracted kidney*. Fluctuations in the concentrating ability of the kidneys—from its increase in the very beginning with a gradual subsequent decrease to a sharp drop with the transition of the process to the chronic stage—may be observed in the former case as the process progresses from the acute stage (glomerulonephritis) to the condition of contracted kidney.

The weakening of the concentrating ability of the kidneys leads to retention of urea and other nitrogenous substances or sodium chloride in the blood; these substances can be eliminated from the organism only by increased urinary output. This form of *polyuria* is called *compensatory* because it compensates for the impaired ability of the kidneys to excrete the solid substances. It is characterised by excretion of urine of low specific gravity—*hyposthenuria*—and is due to the fact that the water excreted by the glomeruli is not sufficiently reabsorbed in the tubules because of the atrophic processes developing therein (in cases of contracted kidney). The concentration of sodium chloride in the urine in cases of contracted kidney is about equal to its concentration in the blood and may be even lower. The concentration of urea in the urine is also decreased, but compared with the concentration of sodium chloride this decrease is not so pronounced. In the incipient stages of development of contracted kidney polyuria compensates, mainly by decreased reabsorption, for the impaired ability of the kidneys to excrete solid substances.

Blood Changes in Disorders of the Renal Function

Disorders of the renal function may lead to changes in the *quantity* as well as *composition* of the blood.

The determining factor with respect to the *amount of blood* is the *condition of the tissues*—the more pronounced the edema and

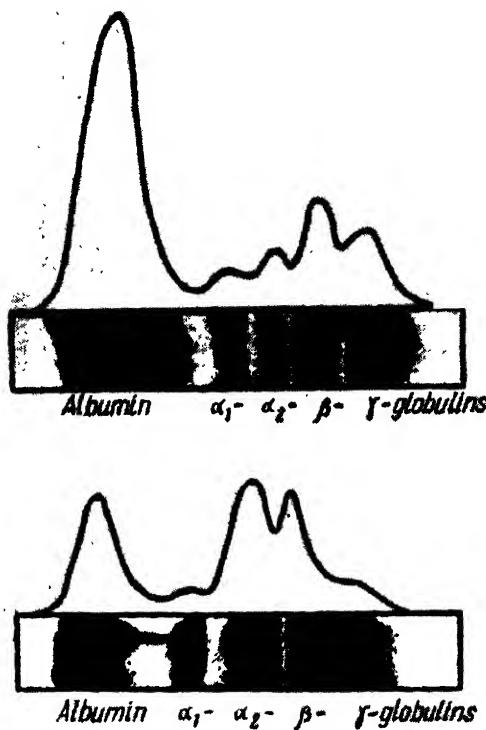


Fig. 138. Changes in the proteins of the blood serum in nephrosis found by means of electrophoresis. Top—normal; bottom—diminution of albumin (Alb) and increase in α_2 - and γ -globulins (Hoff).

retention of water in the tissues, the more appreciable the decrease in the mass of the blood. The development of hydremia and the tendency to edemas in nephritides are inversely proportional to each other. Hydremia with subsequent changes in the properties of the blood not infrequently arises in cases in which edema cannot develop.

In disorders of the renal function the amount of protein, especially the albumin fraction, in the plasma diminishes. The greatest drop in plasma albumin is observed in chronic (lipoid) nephrosis which is accompanied by considerable albuminuria. However, the drop in plasma albumin is far from proportional to its excretion in the urine, and the increased excretion of albumin in the urine cannot therefore be considered the only cause of this drop. In renal disease restoration of proteins is also impaired.

The globulin content somewhat increases. The albumin-globulin coefficient drops (Fig. 138).

Renal insufficiency in some measure leads to retention of metabolites in the organism. Most commonly *nonprotein nitrogen is retained in the blood*, and *hyperazotemia* develops.

Retention of nitrogenous products in the blood is observed in the chronic stage of diffuse glomerulonephritis when a considerable number of glomeruli become obliterated; hyperazotemia is also found in far advanced nephrosclerosis. Hyperazotemia may arise not only from functional insufficiency and diminished concentrating ability of the kidneys, but also from impaired protein metabolism due to concurrent changes in the hepatic function. Hyperazotemia may be extrarenal and unconnected with pathologic phenomena in the kidneys. For example, increased nonprotein nitrogen in the blood is observed in infectious fevers (such as pneumonia), massive hemorrhages, extensive burns, hypochloremia and primary diseases of the liver. Hyperazotemia is therefore not always connected with impairment of the renal function.

Owing to renal insufficiency, *urea*, the principal constituent of nonprotein nitrogen accumulates in the blood. Instead of the normal 50 per cent it may constitute 70-90 per cent of the nonprotein nitrogen. An excess of urea in the blood is observed when the ability of the kidneys to concentrate urine is impaired and the specific gravity of the urine is already lowered.

The earliest blood changes to appear in renal disease are those in the content of *uric acid*. All cases of excess uric acid in the blood except when uric acid accumulates in the blood and tissues as a result of changes in nuclein metabolism (leukemia, fever, gout) are due to renal disease.

Renal insufficiency is also marked by accumulation of *indican* and *phenol compounds* in the blood; these substances pass into the blood from the intestines and are normally excreted through the kidneys. The indican content in the blood often increases in chronic nephritides and indicates protracted disease.

Creatinine is another nitrogenous substance retained in the blood in renal insufficiency: the increase in this substance in the blood indicates mainly an impaired filtering ability of the kidneys since endogenous creatinine is not reabsorbed in the tubules.

The table following offers an idea of the limits within which the various nitrogenous constituents of the blood vary normally and in renal insufficiency.

Renal dysfunction is often marked by changes in the *ionic composition of the blood and tissues*. The relations between the content of *chlorine* in the erythrocytes and the plasma are altered. An important part in this distribution of chlorine is played by *carbon dioxide tension in the blood*. An increase in carbon dioxide tension causes increased passage of chlorine from the plasma into the red blood cells. In renal dysfunction changes in carbon dioxide tension affect the chlorine content in the plasma and its excretion into

**Variations in Nonprotein Nitrogen and Its
Constituents in the Blood Normally and in Renal
Insufficiency (in mg %)**

Nitrogenous substances	Normally	In renal insufficiency
Nonprotein nitrogen	20-40	400-500
Uric acid	2-4	10-20
Urea	20-30	500-700
Indican	0.04-0.107	6-7
Creatinine	0.6-2	30-40

the urine. These interrelations are actually still more complicated because bicarbonates also affect the permeability of erythrocytes.

Renal insufficiency usually gives rise to an increase in *inorganic phosphorus* in the blood; its concentration goes up to 6-8 mg% instead of the normal 3-4 mg%. In its turn the increase in blood phosphorus is in many cases connected with a diminution in the concentration of calcium in the blood (to 7-8 mg%). The decrease in ionised calcium is responsible for the condition which resembles parathyroid tetany and is characterised by a tendency to convulsions. Phenomena of acidosis were mentioned above in the general description of the disorders connected with renal dysfunction.

Hemorenal Indices of Changes in Renal Functions

Hemorenal indices show the relations between the same constituents of the blood and the urine.

The renal function is most commonly determined by glomerular filtration and tubular reabsorption (Fig. 139).

Impairment of glomerular filtration and tubular reabsorption can be established by simultaneous determination of the relations between the concentrations of certain substances in the blood and urine.

The filtration and reabsorption indices are affected in renal insufficiency, especially in chronic nephritis and nephrosclerosis. The glomerular filtration of certain substances can be established by the clearance coefficient. The clearance coefficient is the volume of blood plasma (in ml) which filters through the kidneys and is cleared of a given substance in 1 minute. Determination of the creatinine content in the blood and urine is used to establish the filtering and reabsorbing function of the kidneys.

Creatinine is completely filtered by the glomeruli, is not reabsorbed in the tubules and is not excreted by them. Assuming that

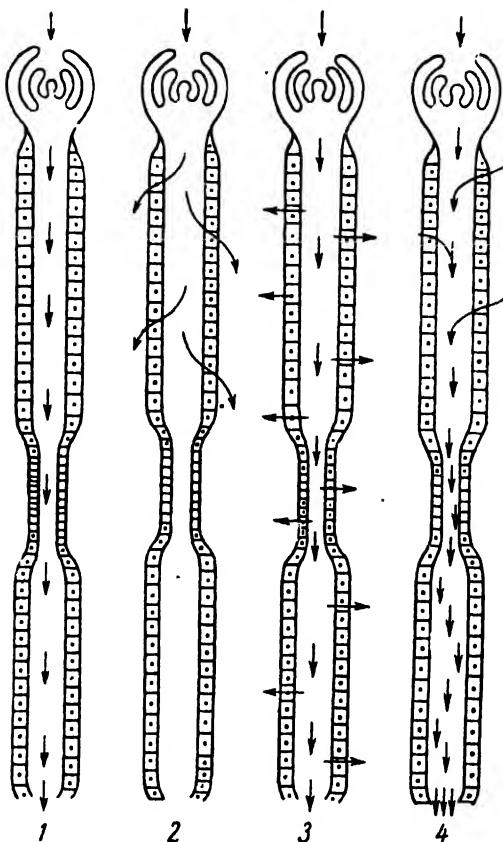


Fig. 139. Excretion of various substances by the kidneys.

1—endogenous creatinine and inulin are excreted into the urine by glomerular filtration and are not reabsorbed in the tubules; 2—after glomerular filtration glucose is fully reabsorbed in the tubules and normally does not pass into the urine, 3—urea, uric acid and chlorides are filtered in the glomeruli, are partly reabsorbed in the tubules and partly excreted in the urine; 4—diodrast, phenol red and para-aminonhippuric acid are excreted by glomerular filtration and tubular secretion.

the creatinine concentration in the blood plasma and in the glomerular filtrate is equal and measuring the urinary output for a definite period of time, the concentration of glomerular filtration during the passage of creatinine through the tubules is calculated (index of creatinine concentration). The reabsorption of water in the tubules equals the difference between the filtration and excretion of urine for the same period of time.

Glomerular filtration (F) is calculated by the formula

$$- \frac{E_u \cdot C_{cu}}{C_{cb}}$$

where E_u is excretion of urine in 1 minute, C_{cu} is the creatinine concentration in the urine, and C_{cb} is the creatinine concentration in the blood.

Tubular reabsorption (R) is calculated by the formula

$$R = \frac{F - E_u \cdot 100}{F}$$

Since it has now been demonstrated that creatinine may be secreted in the tubules, inulin (levulose polysaccharide) is injected to determine the filtering and reabsorbing function of the kidneys. According to experimental data, inulin is filtered only in the glomeruli and is not reabsorbed in the tubules.

The clearance coefficient makes it possible to determine the renal blood circulation which also frequently changes in connection with renal insufficiency.

To calculate the renal blood flow, such substances are used as are completely eliminated from the plasma during a single passage through the kidneys. At first this was done with phenol red which is excreted into the urine mainly by the renal tubules (94 per cent of the administered dye). It has been established that at a low phenol red concentration in the blood (not above 2 mg%) the phenol red clearance coefficient averages 400 ml a minute, which corresponds to the amount of plasma flowing through the tubules, since phenol red is present only in the plasma. In terms of the blood the renal blood flow, according to phenol red, is 700 ml per minute. The state of the renal blood circulation is determined more precisely yet by means of diodrast or para-aminohippuric acid—substances which are most completely eliminated during a single passage through the kidneys.

Uremia

Uremia must be considered one of the most clearly pronounced manifestations of renal insufficiency.

Uremia is a symptom complex showing autointoxication of the organism with nitrogenous products which should be eliminated with the urine but are retained in the blood and urine as a result of renal insufficiency. In uremia nitrogenous metabolites accumulate in the blood and tissues. Such uremia is called azotemic or true uremia.

Azotemic uremia develops at the terminal stage of renal insufficiency resulting from advanced diffuse lesions of the kidneys, especially their vascular apparatus, as in chronic glomerulonephritis. It may also arise as a result of impaired excretion of urine caused by affection of urinary passages as in cases of bilateral obstruction of the ureters by stones or compression of the urethra by a tumour. Azotemic uremia is characterised by a decrease in all clearance coefficients and resultant extreme intoxication. In some cases the

intoxication is manifested mainly in the central nervous system, i.e., drowsiness, headache, apathy, pruritus and convulsions; in other cases it is marked by gastrointestinal phenomena—vomiting, dyspepsia and diarrhea, and in still other cases—by respiratory disturbances (periodic respiration) and a comatose state due to development of acidosis and accumulation of organic acids.

The manifestations of uremia are extraordinarily varied: there are mild and severe forms with various combinations of symptoms.

Uremia cannot be experimentally produced in the form in which it is observed in man. The closest to uremia is the condition produced in animals by ligation of the ureters, which causes retention of already secreted urine; in this condition either the urine itself or the products of its decomposition produce similarly severe toxic effects on the organism. The mechanism of intoxication following removal of the kidneys is different; here the principal role is played by retention of the usual metabolites and partly by the absence of the kidneys as organs not only producing urine, but also participating in processes of tissue metabolism.

The development of azotemic uremia is believed to be due to retention of nitrogenous metabolites—nonprotein nitrogen—in the organism.

However, the amount of nonprotein nitrogen in the blood does not strictly correspond to the character of uremia. Urea does not play a decisive part in the pathogenesis of uremia. It is more probable that in kidney patients urea passes into the intestines where it is transformed by bacterial action into toxic substances—ammonium carbonate and ammonium carbamate which are very toxic.

Phenol compounds, poisons which form in the intestines and are normally easily excreted by the kidneys are also considered responsible for development of uremia. *Phenol, cresol, indole, acetic acid and other oxyacids* are actually found in the blood in azotemic renal insufficiency. The severity of uremia corresponds to the content of these substances in the blood to a greater extent than it does to the content of nitrogen. The role of phenol compounds in the origin of azotemic uremia is demonstrated by the uremic phenomena sometimes observed in persons who in virtue of their occupation have to do with carbolic acid (in cases of carbolic acid poisoning).

Unlike azotemic uremia, *uremic eclampsia*, another complication of renal insufficiency, arises suddenly and is characterised by violent convulsive seizures. It does not involve appreciable azotemia and is marked by headache, vomiting, epileptiform clonic and tonic convulsions, delirium and paralyses. The picture of an attack largely resembles the phenomena observed in eclampsia, the disease developing in connection with pathologic pregnancy.

An important part in the pathogenesis of uremic eclampsia is played by spasm of cerebral vessels and resultant cerebral anemia.

Only this can explain the suddenness of the attacks and the periodicity of the developing phenomena.

A picture resembling uremic eclampsia can be experimentally produced by ligation of four cerebral arteries and the resultant increase in intracranial pressure. Experimental observations warrant the assumption that uremic eclampsia is due to ischemia of cerebral tissue and concurrent oxygen deficiency in various areas of the brain. Cerebral ischemia apparently develops in connection with spasm of the vessels. On the other hand, spasm of the cerebral vessels, which leads to development of ischemia, is apparently of a *toxic origin* and is a result of accumulation of toxic substances in the blood due to renal insufficiency.

Pseudourencias also include the effects of vascular spasm of extrarenal origin, which sometimes arises in patients suffering from hypertensive vascular disease; in these cases phenomena resembling those of eclampsia—headaches, convulsions, paralyses, temporary unconsciousness and delirium—are observed.

Changes in Composition of the Urine

Renal disease is not infrequently accompanied by excretion of protein into the urine. The condition in which the urine contains protein is called *albuminuria* or *proteinuria*. Protein is most commonly excreted by glomeruli.

The amount of protein in the urine is not an index of the severity of renal disease: for example, even relatively severe cases of acute nephritis are not accompanied by excretion of any appreciable amount of protein, whereas benign lipid nephrosis is characterised by appearance of a considerable amount of protein in the urine (10-30-50%).

Protein may appear in the urine in different cases of affection of the renal epithelium, mainly in nephrosis and to a lesser extent in nephritis.

According to modern views, protein is filtered by the glomeruli because of the increased permeability of their capillaries. The presence of protein in glomerular capsules in renal disease involving albuminuria is usually adduced as proof. Experimental studies of rabbits have shown that protein first appears in glomerular capsules and only after that in the lumens of the tubules. However, some investigators explain the appearance of protein in the urine also by affection of the tubular epithelium. This is confirmed, in particular, by the fact that, while protein is excreted in the urine, products of protein disintegration are often retained in the blood, whereas, as smaller molecules, the products of protein disintegration should particularly easily penetrate through the impaired glomeruli.

There is also an assumption that the protein in the urine origi-

nates from the disintegrating tubular epithelium. This view is hardly correct, however, for it is difficult to conceive that the epithelium of the tubules is the only source of origin of so large an amount of protein as is sometimes excreted in the urine in 24 hours. If this point of view were accepted, it would be necessary to assume that the tubules have to be destroyed in a short period of time or that their epithelium possesses enormous regenerative ability; but the existence of such regenerative ability has in no way been demonstrated. It is thus more correct to assume that protein does not appear as a result of tubular affection, but is due to *increased glomerular permeability*.

Protein may appear in the urine not only in organic lesions in the kidneys, but also in cases of dysfunction of the renal filter.

This is attested by so-called *physiologic albuminuria* observed in cases of intense muscular effort, cold bathing, during the last months of pregnancy and during menstruation. In all these cases the albuminuria is transitory and is, in all probability, conditioned by changes in renal circulation. A certain part may also be played by physico-chemical and chemical changes, as well as changes in the state of blood proteins.

Albuminuria observed in cases of dysfunction of the nervous system (epilepsy, certain psychoses, in experiment after a puncture in the floor of the fourth ventricle, etc.) is most probably also connected with disturbances in renal circulation.

Orthostatic albuminuria, also called albuminuria of adolescence, is sometimes observed in children and adolescents, especially after they have long been in an upright posture. Cessation of albuminuria when the subject is in a horizontal position, its increase in cases of marked lordosis and its cessation when the body is in a position in which lordosis exerts the least pressure on the lumbar venous vessels support the assumption that orthostatic albuminuria involves changes in renal circulation.

The more protracted forms of albuminuria, which are not due to primary renal lesion, include *congestive albuminuria*. It is observed in cardiac decompensation and is due to renal hemostasis which is responsible for the inadequate supply of oxygen to the kidneys.

Hematuria is a condition characterised by discharge of urine containing blood; in strongly pronounced cases the urine is blood-stained. Blood may appear in the urine not only as a result of lesions in the kidneys, but also in cases of hemorrhages in the lower urinary tract, for example, in inflammatory and ulcerative processes in the kidney pelves, ureters and bladder.

Hematuria of renal origin arises in diffuse (especially acute) and focal glomerulonephritides, renal embolism and infarction, extreme renal congestion, neoplasms, tuberculous and syphilitic infiltrates. The discharge of blood into the urine is due to affection

of the vascular network. Acute glomerulonephritides are usually accompanied by considerable hematuria, chronic—by lesser hematuria.

Hemoglobinuria, i.e., the presence of hemoglobin in the urine, is due to hemolysis, when hemoglobinemia has reached a definite limit. It may occur already at disintegration of 70-80 ml of blood, i.e., approximately 1/60 of its total mass.

Hemoglobinuria is observed in cases of transfusion of heterogeneous blood. It also appears as a result of the action of poisonous substances—arsenic, hydrogen sulfide, acetylene, aniline and sulfonal; it may likewise be seen in severe infections (syphilis, malaria, scarlet fever), burns, hypothermia and eclampsia. An important part is played by violation of the excretion threshold so that even slight hemolysis is accompanied by discharge of hemoglobin into the urine.

Hemoglobinuria is also possible in the absence of hemoglobinemia; in this case hemolysis occurs in the kidneys owing to their affection by toxins or poisonous substances.

Paroxysmal hemoglobinuria is a special form which occurs in some people usually under the influence of extreme cooling or muscular strain. It occurs in paroxysms and is accompanied by pyrexia and pain in the joints, muscles and region of the kidneys. The erythrocytes of healthy people are hemolysed by the serum of paroxysmal hemoglobinuria patients. Heating the serum for 15 minutes at 45°C is enough to render it inactive; addition of even a very small amount of fresh serum may reactivate the patient's serum. The hemolysing serum of the patient apparently contains hemolysin.

Protracted hemoglobinuria may of itself damage the renal epithelium and, as a result, cause noticeable albuminuria. Such damage is due to the poisonous properties not so much of the hemoglobin itself, as of the products of disintegration of the framework of hemolysed erythrocytes. It may also be assumed that the cause of hemoglobinuria simultaneously leads to affection of the renal epithelium.

Cylindruria is the presence of casts, special structures of albuminous nature, in the urine. There are hyaline, granular, epithelial, waxy and other *casts* (Fig. 140).

Hyaline casts occur most commonly. They have a homogeneous hyaline structure and reproduce the form of the renal tubules. In addition to renal disease, hyaline casts occur in stasis, fevers and sometimes in physiologic albuminurias. They often seem to be covered with a fine dust consisting of urates, protein grains and products of cell disintegration.

Epithelial casts consist of desquamated tubular epithelium. They are observed in affections of the renal parenchyma.

Granular casts have a coarser granular appearance and are

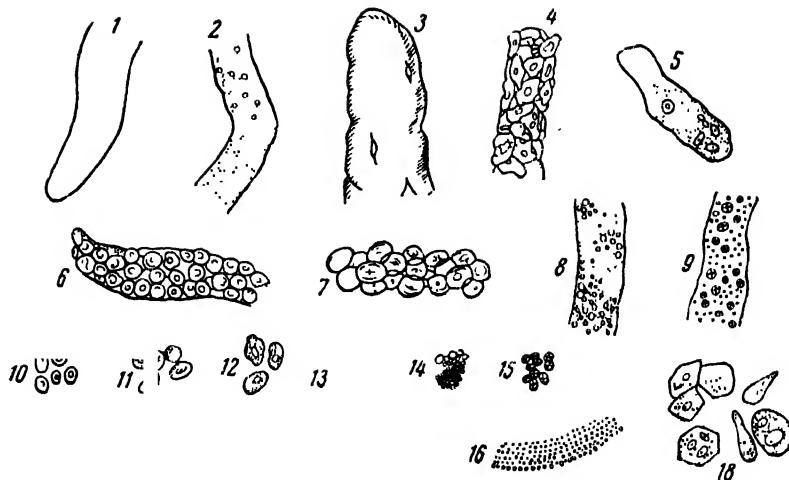


Fig. 140. Organised formed elements in the urinary sediment.

1-hyaline cast; 2-granular cast; 3-waxy cast; 4-epithelial cast; 5-mixed casts; 6-blood cast; 7-purulent casts; 8-fatty casts; 9-lipoid casts; 10-red blood corpuscles; 11-white blood corpuscles; 12-renal epithelium; 13-spheres with fatty granularity; 14-fatty droplets; 15-lipoid droplets; 16 and 17-cyldnroids; 18-epithelium of the urethra.

covered with grains, which are products of cell disintegration, and drops of fat; sometimes this granularity increases by addition of leukocytes loaded with fat. Granular casts probably arise from epithelial casts whose cells have undergone degenerative changes.

Hemoglobin casts may appear as a result of hemoglobinuria. *Waxy casts* form in chronic degenerative processes in the kidneys.

The appearance of casts in the urine, especially epithelial casts, is one of the signs of dystrophic processes in the renal epithelium.

Most casts, hyaline casts in particular, are products of coagulation of protein, mainly globulin and cellular detritus, in the tubules. The amount of casts, it would seem, should correspond to the degree of proteinuria, but experience has shown that hyaline casts are found in the urine independent of protein urea, for example, in subsiding acute nephritis; on the contrary, abundant proteinuria is not infrequently accompanied by a very small amount of casts in the precipitate (in amyloid nephrosis). Coagulation of uric protein apparently requires special conditions which arise directly in the tubules. An important part in coagulation of protein is played by the acid reaction of the urine; in cases of alkaline reaction no casts are usually formed in the tubules, nor is there any precipitation of protein. Moreover, precipitation of protein requires a definite relation between the concentrations of the precipitated and precipitating colloids; too much of either may lead to diminished coagulation and precipitation. The altered relations between the



Fig. 141. Unorganised formed elements in the urinary sediment.

1—various forms of uric acid crystals; 2—urate, brick sediment; 3—magnesium ammonium phosphate; 4—calcium sulfate; 5—calcium carbonate; 6—magnesium ammonium phosphate crystals in the form of coffin lids; 7—ammonium urate in the form of the stramonium fruit, only in alkaline urine; 8—calcium oxalate; 9—xanthine; 10 and 11—tyrosine and leucine, 12—cholesterol.

colloids may explain the disparity between the quantity of protein in the urine and the presence of casts. Casts more commonly occur in urine containing bile and bile acids precisely because bile acids are substances which precipitate colloids. Lastly, the character of the inner surface of the tubules, whose alteration affects the process of coagulation, is also of no small importance in the process of intratubular protein coagulation.

Granular casts arise as a result of granular degeneration of the epithelium of the renal tubules, in which case large amounts of protein granules appear in the protoplasm of the cells. Accumulating in the part of the epithelium which faces the tubular lumens these granules finally completely fill the lumens and are separated out as granular casts. The remaining healthy part of protoplasm of the epithelium with the nucleus retains its ability to regenerate.

Sometimes granular casts are covered with degenerated epithelial cells, thereby giving rise to epithelial casts. The existence of a tubule not infrequently ceases after abrupton of cell elements and their egress as casts; often a tubule is obliterated as a result of proliferation of surrounding connective tissue. Granular degeneration may be accompanied by phenomena of fatty degeneration; this explains the appearance of droplets of fat in the composition of such casts. Granular casts often have hyaline shafts. The ap-

pearance of hyaline casts in the urine cannot serve as proof of deep degenerative processes in the renal epithelium, whereas granular and especially epithelial casts denote more significant damage to the tubular apparatus of the kidneys.

Waxy casts have a greater diameter than all the other casts, which is attested by their appearance in enlarged tubules. Moreover, the shiny surface of these casts, the more clearly outlined contours and transverse fissures most probably indicate that they were formed long before from indurated hyaline casts. They are more common in chronic nephritis which run a severe course.

Along with casts the urine may contain cylindroids. Cylindroids are transparent, ramified and longer than casts. They appear in the urine in subsiding acute inflammatory processes, most probably when the character of coagulation of the substance excreted by the renal tubules has already altered and the process thus fails to reach the stage of forming real casts.

Impaired excretion of salts in the urine is the result either of disturbances in mineral metabolism or of primary renal dysfunction. For example, the content of chlorides, phosphates and sulfates in the urine decreases in fever, the concentration of phosphates and sulfates diminishes in uremia, excretion of phosphates and calcium noticeably increases in nephroses. Various salts—oxalates, phosphates, urates, etc.—settle out in cases of cholelithiasis (Fig. 141).

Renal Hypertension

Renal affections involving the vascular system, particularly glomerulonephritis and nephrosclerosis, are characterised by a rather *stable elevation of arterial pressure*, whereas in nephroses, when the tubular epithelium is attacked by degenerative processes, the arterial pressure is usually unaffected. In cases of diffuse nephritis the arterial pressure ordinarily rises to 180/100-200/120 mm Hg and higher, and is the most characteristic sign of the disease.

The role of renal dysfunction in the pathogenesis of renal hypertension is evident from the following experiments:

Special clamps were applied to the dog's renal arteries for the purpose of occluding the vessels and thus producing renal ischemia (Goldblatt). This gave rise to elevated blood pressure. Denervation of the ischemic kidneys did not eliminate hypertension. It follows that the cause of elevated blood pressure in ischemia was constriction of the peripheral vessels due to passage of a pressor substance from the kidneys into the blood.

It was subsequently found that the *pathogenesis of renal hypertension* consists in prolonged general or very extensive extrarenal increase in arterial tone due to formation of a special pressor substance—*angiotonin or hypertensin*. Its production requires the presence of *renin* (a substance of nitrogenous nature) which possesses

fermentative action and appears in the kidneys in cases of impaired renal blood supply, and experimentally—on compression of the renal arteries and development of ischemia. Renin in itself is not active, but on contact with *hypertensinogen* (a globulin in the blood plasma) it forms hypertensin which increases the tone of the peripheral vessels and causes a rise in blood pressure.

But the content of renin in the blood of animals with experimental renal hypertension increases only for a short time after constriction of the renal vessels. In the chronic stage of renal hypertension the amount of renin returns to normal despite the fact that the blood pressure remains elevated. Development of hypertension in animals is possible even after removal of the ischemic kidney. These data have led to a new conception according to which it is the depressor function of the kidneys, i.e., their ability to neutralise the effect of pressor substances formed in the organism outside the kidneys, that is impaired in renal hypertension, with the blood pressure rising as a result.

Renal Dropsy

Renal diseases are often accompanied by dropsy which is usually localised in regions of loosest connective tissue—eyelids, skin on the abdomen and back, scrotum, pelvic region and retroperitoneal space. Some cases are accompanied by ascites and hydrothorax.

There are three principal factors in the mechanism of renal dropsy: 1) a drop in the colloid-osmotic pressure of the plasma, 2) increased permeability of the capillaries, and 3) elevated capillary pressure.

The development of the foregoing phenomena is considered to be due to both renal and extrarenal causes.

The *renal causes* consist in dysfunction of the renal glomeruli and tubules. Albuminuria (especially in nephroses) is responsible for the decrease in plasma proteins, which results in a fall of the colloid-osmotic pressure of the plasma (to 15 mm Hg and lower instead of the normal 25-30 mm). This favours increased passage of fluid from the blood into the tissue and development of dropsy.

Renal dysfunction may also be responsible for retention of sodium and water in the blood, which in its turn causes disturbances in intermediate water and mineral metabolism, and development of dropsy due to a change in osmotic pressure.

However, the retention of sodium is not always due to renal dysfunction. A certain part may be played by *extrarenal factors*. In nephroses, for instance, despite considerable dropsy, its extent does not correspond to the sodium content in the blood. Moreover, there is no parallelism between the degree of hydremia observed in renal disease and the development of dropsy. This suggests that sodium is also retained in the tissues as a result of general disturb-

ances in water and mineral metabolism. This is likewise attested by data concerning the role of aldosterone—adrenocortical hormone and one of the important regulators of water and mineral metabolism—in the development of renal dropsy.

The advocates of the view that dropsy is of extrarenal origin hold that renal, as well as vascular and tissue affections, develop simultaneously under the influence of the same factors (infection, intoxication). Their argument is that capillaries are injured not only in the kidneys, but also in distal parts of the organism, and dropsy sometimes appears before the other signs of renal insufficiency.

But the concept of dropsy as of extrarenal origin is one-sided. The view that both renal and extrarenal factors come into play in the pathogenesis of renal dropsy is more justified, certain factors predominating in each concrete case and determining the characteristics of the given case of dropsy.

PATHOLOGY OF ENDOCRINE REGULATION

Endocrine regulation is effected by endocrine glands whose functions are closely coordinated. It was the only system of regulation of functions at the stages of evolutionary development of the animal world, at which there was as yet no nervous system. The development of nervous regulation did not terminate hormonal regulation, the two aspects of regulation combining to form the neuroendocrine system. Dysfunction of any of the endocrine glands is therefore never isolated, i.e., it is always associated with changes in the functions of the other endocrine glands and the nervous system.

INTERRELATIONS OF ENDOCRINE GLANDS IN THE PATHOGENESIS OF ENDOCRINE DISORDERS

The endocrine glands regulate the various functions of the organism by acting either antagonistically or synergistically. For example, disturbances in carbohydrate metabolism are not only due to primary hypofunction of the islets of the pancreas, but are also dependent on the functions of the anterior lobe of the hypophysis and the adrenal cortex. Adrenalin, the hormone produced by the adrenal cortex, increases the sugar concentration in the blood, whereas insulin acts contrariwise and reduces the blood sugar. With respect to the vascular reaction adrenalin and thyroxin are synergists. The synergism and antagonism of the hormones are also manifested in heat regulation and hematopoiesis, and in the processes of growth and development.

However, there is no direct or true antagonism or synergism. In the overwhelming majority of cases they are relative and manifest themselves at different points of application of the hormones. For example, by acting on glycogen and intensifying its transformation into glucose adrenalin causes hyperglycemia, whereas insulin produces the opposite effect by increasing the tissue consumption of glucose and transforming it into glycogen or fat.

Owing to the interrelation existing between the endocrine glands, dysfunction of any one gland leads to changes in the entire endocrine system. Affection of one endocrine gland therefore finally develops into a complex pluriglandular disease. This applies to many well-known endocrine diseases—exophthalmic goitre, diabetes, hypophyseal dystrophy, dwarfism, etc.

RELATIONS BETWEEN THE NERVOUS SYSTEM AND ENDOCRINE GLANDS IN THE PATHOGENESIS OF ENDOCRINE DISORDERS

The role played by the interrelations of endocrine glands in the pathogenesis of endocrine disorders can be established only if the entire complexity of these phenomena largely determined by the activity of the nervous system is taken into account (Fig. 142).

There is a good deal of proof that hormonopoiesis is regulated by the nervous system. The influence of sympathetic innervation on secretion of adrenalin by the adrenal cortex has long been demonstrated. Particularly convincing in this respect are experiments with cross circulation, i.e., artificial production of a vascular

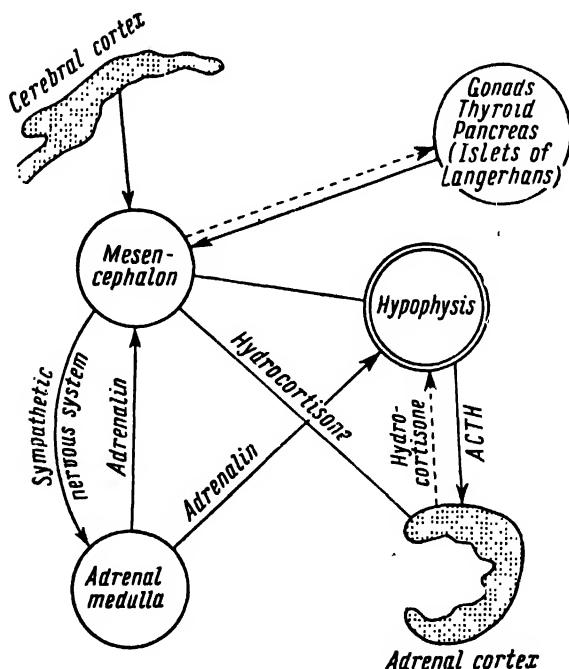


Fig. 142. Diagram showing relations between the nervous and endocrine systems. Dotted lines indicate hypothetic connections.

anastomosis in two animals (rabbits or dogs) with the arterial blood of one animal directed into the veins of the other. By stimulating the splanchnic nerve of one animal it is possible to observe an elevation of blood pressure also in the other animal due to increased secretion of adrenalin by the adrenal gland of the former and its passage into the blood stream of the latter. Transection of the splanchnic nerve gives rise to atrophy of the adrenal cortex on the corresponding side.

The influence of certain nuclei of the diencephalon on the function of the posterior lobe of the hypophysis has also been demonstrated. Many investigators now hold that the diencephalon has connections not only with the posterior, but also with the anterior lobe of the hypophysis. These connections are possibly also determined by the hormones that form in the nuclei of the tuber cinereum. Dysfunction of the diencephalohypophyseal system underlies the pathogenesis of such conditions as hypophyseal adiposis, diabetes insipidus, and a number of endocrine growth disturbances.

Proof is also available concerning nervous regulation of other processes of hormonopoiesis. For example, stimulation of branches of the vagus nerve running to the pancreas may cause increased secretion of insulin with a resultant decrease in the blood sugar. Electric stimulation of sympathetic branches which innervate the thyroid causes an increased amount of iodine—constituent of the hormone produced by the thyroid—to pass into the blood.

A number of experimental data attest that endocrine glands are an intermediate link in the transmission of influences of the cerebral cortex to the organs. For example, conditioned reflex output of urine is possible not only by an intact kidney, but also by a completely denervated kidney. However, in the latter case the elaboration of the conditioned reflex is impaired by preliminary severance of the connections between the hypophysis and the diencephalic region. In these experiments the cortical influence on the secretion of urine is exerted through the antidiuretic hormone.

Thus the *central nervous system can exert its regulating influence on the internal organs not only through the underlying parts of the nervous system, but also through the endocrine glands*. With the participation of endocrine glands nervous regulation evokes a longer reaction of the effector organ than it does through neural pathways alone.

The clinic has also furnished many facts demonstrating the role of the central nervous system in the appearance of endocrine diseases. Emotional experiences and overstrain are sometimes accompanied by endocrine dysfunction. For example, the acute form of exophthalmic goitre has been observed to follow psychic trauma, while psychogenic factors play an important part in the onset and development of diabetes mellitus and hypophyseal polyuria.

Tumours in the region of the diencephalon not infrequently cause hypophyseal dysfunction manifested in disturbances in metabolism and processes of growth and development.

The hormones secreted by endocrine glands may in their turn affect various functions of the nervous system. For example, folliculin—hormone produced by the ovaries—affects the function of the hypothalamus. Administration of folliculin to animals does not stimulate estrus after preliminary injury to the hypothalamus. Some hypophyseal hormones affect the organism through various cerebral structures.

For example, pituitrin which contains the hormone of the posterior lobe of the hypophysis alters the excretion of urine also through the central nervous system. Administered suboccipitally it inhibits urinary excretion to a greater extent than it does when administered intravenously or subcutaneously. The effect of thyrotropin, a thyroid-stimulating hormone produced by the adenohypophysis, is weakened by injury to the diencephalon.

Numerous experimental studies have shown that endocrine disturbances, as well as administration of hormones, are accompanied by changes in higher nervous activity. The character of changes due to hypo or hyperfunction of the endocrine glands may vary with the type of nervous system which determines its reaction to any stimulus.

The activity of the cerebral cortex altered by endocrine disturbances affects the functions of the lower parts of the nervous system. For example, hyperfunction of the thyroid increases the excitability of the vegetative nervous system. Hypofunction of the thyroid (myxedema) disturbs the functions of the higher parts of the brain and inhibits both divisions of the vegetative nervous system. Other endocrine disorders, for example, in diabetes, acromegaly and Addison's disease are also responsible for marked changes in the functions of the central nervous system often manifested in altered states of the vegetative nervous system.

SIGNIFICANCE OF CHANGES IN TISSUE ENVIRONMENT TO THE PATHOGENESIS OF NEUROENDOCRINE DISORDERS

Disorders of neuroendocrine regulation may be based on primary disturbances in organs and tissues which, owing to changes in their biochemical and physicochemical properties, begin to react to hormones in an unusual manner even when the latter are produced under physiologic conditions.

As regards the whole organism, in the presence of complex processes of interaction it is difficult to establish the significance of tissue, physicochemical and chemical disturbances in the neuroendocrine regulation of functions. However, in special experiments with isolated organs it is possible to observe that changes in the com-

position of the nutrient medium affect the action of adrenalin, insulin, thyroxin and other hormones.

For example, the effect of adrenalin on blood pressure increases on accumulation of amino acids in the blood. A very small dose of adrenalin, which produces no effect by itself, perceptibly elevates blood pressure when administered into the blood together with amino acids, for example, tyrosine and phenylalanine.

The vasoconstrictor effect of adrenalin also increases if the acidity of the nutrient fluid which washes the vessels of the isolated organ is increased to a certain limit; an increase in acidity above this limit weakens the vasoconstrictor effect of adrenalin and produces an opposite effect. This apparently explains the paradoxical effect of adrenalin in an inflamed focus in which acidosis develops. The glycogenolytic function of adrenalin diminishes in an alkaline medium and increases in an acid medium.

The specific thyroxin effect of intensifying the metamorphosis of tadpoles can be considerably weakened by increasing the concentration of calcium chloride in the fluid in which they live and develop. The same thing has been demonstrated with respect to other hormones.

Thus, as regards their functional manifestations the endocrine glands are in certain dependence on the metabolism and functional states of the organs and tissues on which they act. The state of the tissue environment is also significant for the functions of the nervous system which is closely connected with the endocrine system.

Changes in the ionic balance of the tissues affect the activity of the vegetative nervous system. Experiments have shown that potassium cations have to do with the parasympathetic, and calcium cations with the sympathetic nervous system. By changing the content of salts in the washing fluid which nourishes the isolated heart, for example, by creating a preponderance in calcium, it is possible, on stimulating the vagus nerve, to accelerate the activity of the heart; a preponderance of potassium increases the effect produced by the vagus nerve and inhibits or perverts the effect produced by stimulation of the sympathetic nerve. Thus cations (and possibly anions) take part in influencing both divisions of the vegetative nervous system on the tissues. This is also evident from the fact that stimulation of parasympathetic nerves usually causes mobilisation of potassium cations, and stimulation of sympathetic nerves—mobilisation of calcium cations which act on a number of functions like sympathetic nerves.

PATHOGENESIS OF ENDOCRINE DISORDERS

Endocrine disorders are manifested in *hyper-* or *hypofunction of endocrine glands*.

Hyper- or hypofunctional states of endocrine glands are characterised not only by functional, but also by morphological changes—

proliferation of specific glandular elements, accumulation of the products of secretion either in the form of colloidal substance or grains, or in atrophy, necrobiosis and concurrent multiplication of nonspecific elements of connective tissue which gradually replace the secretory cells. But the morphological picture of the gland structure does not always make it possible to infer its functional state.

Clinical and pathoanatomical investigations, as well as experimental studies of the results of extirpation of glands and the effect of administration of hormones, make it possible to judge whether the endocrine disease is of a hypo- or hyperfunctional character.

However, the pathogenesis of endocrine disorders cannot be reduced to phenomena of hypo- and hyperfunction of the endocrine glands. Different manifestations of the same endocrine disorder whose onset is based on changes in the same endocrine glands are often observed in different people. At the same time there are cases when phenomena characteristic of hypofunction of an endocrine gland are observed in hyperfunction of the same gland (for example, exophthalmic goitre based on hypersfunction of the thyroid may sometimes show signs of its hypofunction characteristic of myxedema). It is therefore assumed that in endocrine disorders there are not only quantitative, but also qualitative changes in the functions of endocrine glands, i.e., an affected gland elaborates a hormone which is qualitatively different from the normal hormone. However, the studies of the qualitative changes in the secretions of glands and their interaction, and of the disturbances in the relations between the nervous system, on the one hand, and the endocrine glands and tissue environment, on the other, warrants operation with only the concepts of hypo- and hyperfunction.

DYSFUNCTION OF THE THYROID

The disturbances in the functions of the thyroid are manifested mainly in disorders of metabolism and the processes of growth and development. This has been demonstrated by the results of extirpation of the thyroid in animals and the effects of thyroid extracts and hormones on the processes of metabolism and metamorphosis in lower vertebrates.

The discovery of thyroxin which is a parahydroxydiiodophenyl ether of diiodotyrosine has greatly helped to study the problems connected with the pathology of this gland. Some authors are inclined to ascribe the changes in the functions of the thyroid wholly to variations in the content of thyroxin in the gland.

Although the iodine-containing thyroxin and the extracts from the entire thyroid produce a very similar effect on the main functions of the organism (basal metabolism, growth, heart action, etc.) the hormonal activity of the thyroid is not limited to production of

thyroxin alone. The dissimilar effects of thyroxin in different cases of thyroid insufficiency show that the etiology of thyroid diseases cannot be explained only by increased or decreased production of thyroxin. Thyroxin binds only part (20-25 per cent) of the total iodine of the thyroid. The latter apparently also contains other iodine compounds which are likewise very active physiologically. By hydrolysing iodothyroglobulin it is possible to obtain thyroxin and its antagonist—diiodotyrosine; *diiodothyronine*, another organic iodine compound and second thyroid hormone, has been discovered in the blood by means of chromatography.

Afunction and Hypofunction of the Thyroid

Ablation of the thyroid in animals causes within a few weeks *cachexia thyreopriva* which is characterised by diminished basal metabolism (an average of 12-35 per cent), decreased excretion of nitrogen in the urine and increased resistance of the organism to sugar. The temperature drops to the lowest normal level, there are trophic disorders of the skin and mucous membranes, the hair falls out, and the animals become apathetic, i.e., they keep lying about, can hardly move, become awkward and lose the formerly acquired conditioned reflexes.

Removal of the thyroid in young growing animals *arrests their growth and development* (Fig. 143). This condition is characterised by disturbances in ossification of cartilages, failure of bones to grow in length, and persistence of epiphyseal sutures. Sexual development is clearly retarded. The anterior lobe of the hypophysis and the adrenal cortex are enlarged.

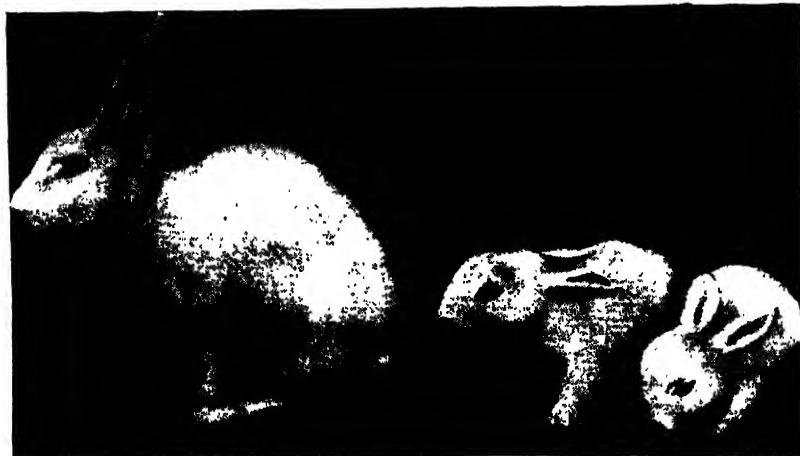


Fig. 143. Normal rabbit (left) and thyroidectomised rabbits (right).

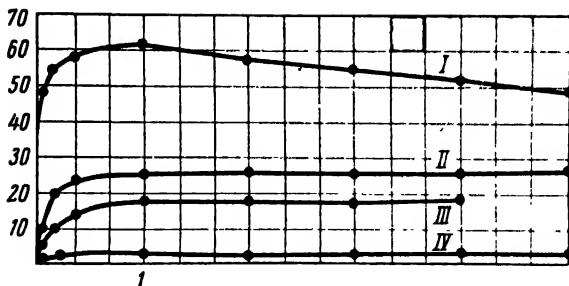


Fig. 144. Accumulation of radioactive iodine (I^{131}) in the thyroid in different disorders of its secretory function. Axis of abscissas—days of iodine administration; axis of ordinates—iodine retained in the organism (in %). Curves: I—hyperthyroidism; II—euthyroid goitre*; III—normal; IV—hypothyroidism (Hamilton).

In cases of hypofunction or afunction of the thyroid human adults develop myxedema; the phenomena observed in man differ from those developing in experimental animals after removal of the gland.

In this condition the skin is yellowish and has a waxy tint; it is pale, dry, rough and cold to touch. The condition is characterised by swelling of the mucosa and noticeable deposition of a mucin-like fluid in the subcutaneous cellular tissue of the face and certain other parts of the body (in the region of the supraclavicular fossae, arms and legs). The swelling is not a result of mucin formation, but is due to accumulation of protein-rich fluid in the tissues.

Because of the swollen mucosa the face becomes dull and inexpressive; it is puffy and its features are altered. A change in the voice (due to laryngeal deformity) and respiratory difficulties are observed. Respiration becomes shallow and slow. Trophic disorders appear—the skin grows dry, the hair falls out, and the nails become brittle. The heart rate slows down, the sexual function fails, and hypoplasia of the gonads is observed. Basal metabolism is noticeably diminished (20-50 per cent). The specific dynamic effect of protein, nitrogen metabolism and the heat exchange are decreased. Mild hypothyroidism may cause adiposis. Myxedema is marked by generally diminished cerebration and obtusion of the reactive ability of the organism. These phenomena are based on weakened functions of the nervous system, especially the cerebral cortex.

The presence of hypothyroidism is also attested by the thyroid's lowered tolerance of the iodine isotope (I^{131}) administered into the organism (Fig. 144).

Childhood myxedema (Fig. 145) closely resembles the myxedema of adults, although it has certain specific characteristics manifested in growth disorders (dwarfism) and disturbances in the development

* Euthyroid goitre is the form in which basal metabolism remains normal.

of the genitalia. The processes of cartilage ossification are impaired, and the zones of ossification between the diaphyses and epiphyses of tubular bones remain open. Enchondral and periosteal ossification is disturbed.

All these phenomena perceptibly diminish and some of them even disappear altogether as a result of ingestion of thyroid or injection of thyroid extract (Fig. 146). These facts and the temporary successful results produced by transplantation of the thyroid show that myxedema and all closely related forms of thyroid disease are actually hypothyroidism and athyroidism.

Thyroid disease of a hypofunctional character is not infrequently accompanied by a pathological enlargement of the thyroid, so-called *goitre*. However, enlargement of the gland alone is not indicative of the character of affection which may be both hyper- and hypofunctional, depending on the changes in the gland itself.

Of the hypofunctional or afunctional states of the thyroid often accompanied by its enlargement (*goitre*) mention must be made of so-called *sporadic cretinism* observed mainly in children with congenital hypo- or athyroidism.

In addition to sporadic, there is also *endemic goitre*. It is observed among inhabitants of certain areas, especially in the mountains (Alps, Carpathians, Pamirs and Caucasus) and highlands. Endemic goitre is sometimes accompanied by somatic underdevelopment and rather marked mental retardation. The mucosa is either slightly swollen or not. The growth of bones in length is



Fig. 145. Childhood myxedema before and after treatment with thyroid preparations.



Fig. 146. Myxedema caused by hypofunction of the thyroid at different age periods before and after treatment.
a—at 25 years age; b—at 32 years of age; c—at 32 years of age after treatment with thyroid preparations.

delayed, ossification is retarded, the epiphyseal sutures close late. The structure of the skeleton is impaired. Owing to the retarded development of the base of the skull the nose remains sunken-in and flattened, the face is asymmetrical and puffy, the development of the jaws and entire masticatory apparatus is defective. The skin is pale, dry and wrinkled. The genitalia are underdeveloped. Basal metabolism is often normal. The amount of iodine in the thyroid is diminished.

The favourable results of prevention and treatment of endemic goitre with iodine and experimental production of changes in the thyroid analogous to endemic goitre attest that the origin of this disease is connected with chronic deficiency of iodine in the water and food or its improper utilisation by the gland. It is possible to produce goitre in animals by depriving them of iodine during fetal development or in the first months of life. In these cases the thyroid is considerably enlarged. For example, in dogs given food deficient in iodine the weight of the thyroid reaches 100 g within 18 months, whereas in the control animals given normal food the gland weighs only 1 g.

The possibility of producing goitre and reducing the function of the thyroid by means of cyanides (for example, methyl cyanide, potassium thiocyanate) and thiocompounds (for example thiourea, thiouracil) has been established experimentally. The former depress utilisation of iodine by the thyroid, the latter—formation of hormones in the gland.

Hyperfunction of the Thyroid

Exophthalmic goitre (Basedow's disease) and closely related thyrotoxicoses are hyperfunctional diseases of the thyroid.



Fig. 147. Severe form of exophthalmic goitre (exophthalmos and characteristic facial expression).

of part of the thyroid produces a favourable effect.

Another proof is that a number of phenomena characteristic of this disease can be produced in animals by injection of thyroid extract and even thyroxin alone.

The appearance of most of the aforementioned signs of exophthalmic goitre is due to increased excitability of both the central and peripheral nervous systems, that of the sympathetic division of the nervous system in particular. Every now and then, however, a form of exophthalmic goitre with manifestations of increased activity of the parasympathetic division of the nervous system is observed. Sometimes exophthalmic goitre develops suddenly, following a psychic trauma, which denotes dysfunction of the cerebral cortex in its pathogenesis. In these cases the cerebral cortex exerts its influence on the function of the thyroid through the subcortical region which is associated with the function of the anterior lobe of the hypophysis.

Some part in the mechanism of exophthalmic goitre may be played by *increased secretion of a thyrotropic hormone by the hypophysis*, a hormone which stimulates the function of thyroid. The possibility that exophthalmic goitre may be directly stimulated by the central nervous system is not excluded.

The development of exophthalmic goitre also involves other endo-

Exophthalmic goitre is characterised by an enlargement of the thyroid which is usually caused by proliferation of the epithelium and its congestion, exophthalmos (Fig. 147) due to increased tone of the smooth muscle situated behind the eyeball and having sympathetic innervation, tachycardia produced by stimulation of the sympathetic nervous system of the heart, increased metabolism (50 per cent and higher), excessive heat production and heat loss, and heightened irritability. This disease is caused by hyperfunction of the thyroid, which is evident from a comparison of the symptoms of this disease with those of myxedema; the symptoms of the two diseases are in many respects opposite to each other (Fig. 148).

That hyperthyroidism underlies exophthalmic goitre is also attested by the fact that the thyroid retains radioactive iodine and that removal

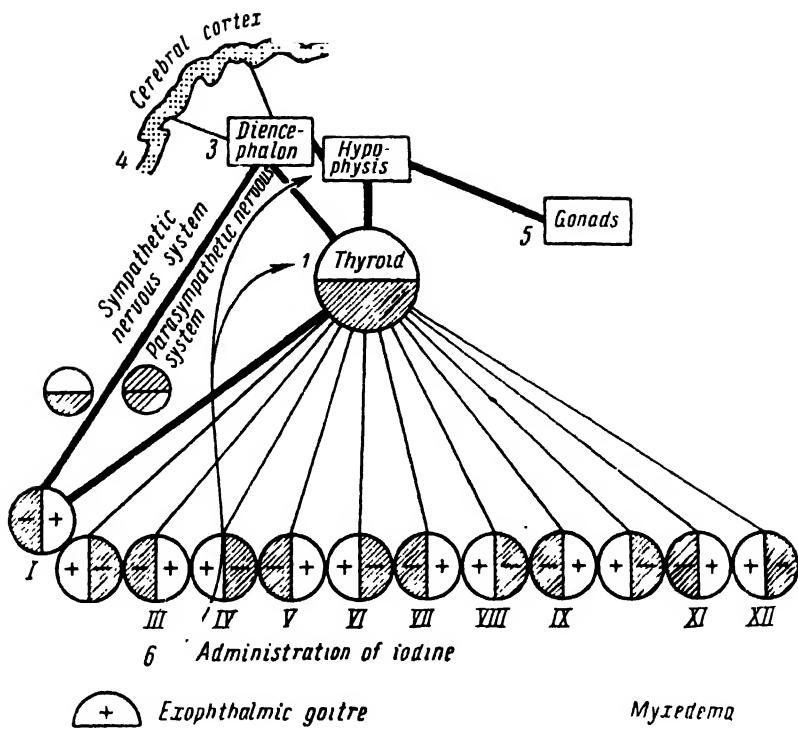


Fig. 148. Diagram showing disorders of the thyroid function (Hoff).

Various thyroid disorders caused by affections of:

1—the thyroid itself; 2—thyrotropic function of the hypophysis; 3—diencephalon; 4—cerebral cortex; 5—gonads; 6—effect of exogenously administered iodine
 Figures from left to right indicate: I—intensified function of the nervous system; II—Cations; III—acidosis; IV—increased iodine in the blood; V—intensified metabolism; VI—intensified heat exchange; VII—increased respiration; VIII—increased minute volume of the heart; IX—increased mass of circulating blood; X—increased blood sugar; XI—intensified glycogenolysis; XII—diminished cholesterol in the blood

crine glands; for example, the functions of the pancreas and gonads are diminished. Involvement of other endocrine glands in the pathologic process in exophthalmic goitre perhaps explains why a thyroidectomy sometimes proves ineffective.

DYSFUNCTION OF THE PARATHYROIDS

Parathyroid insufficiency, especially total afunction of the parathyroids, leads to development of *tetany*.

Sluggishness, anorexia and thirst are observed in the animal (dog or monkey) already on the second day after complete removal of the parathyroid glands. 48-72 hours after the operation in cases of acute development of the symptoms the animal exhibits signs of increased



Fig. 149. Characteristic position of monkey's hand during attack of tetany developing after removal of the parathyroids (Noel Paton).

neuromuscular excitability—motor disorders manifested in quiverings of the muscles and unsteady gait; the limbs seem to become stiff and unable to bend; the disorder is characterised by tonic spasms of the limbs (Fig. 149). Intermittent clonic spasms are observed soon afterwards.

The foregoing phenomena are followed by an acute *attack of tetany* with manifestations of excitation of the central nervous system in the form of tonic spasms, laryngospasm, vomiting and severe diarrhea. The intensity of these phenomena differs in different animals. In cases of severe dyspnea and tachycardia the very first attack may lead to death, but more often the animal

survives; then comes the second attack, sometimes the third, etc. During one of the attacks the animal dies as a result of spasm of the respiratory muscles, the diaphragm and the rima glottidis.

In cases of chronic tetany these symptoms are mild and trophic disorders come to the fore—emaciation, loss of hair, purulent affection of the eyes, development of cataracts, irregular ossification and calcification of the teeth and destruction of the enamel which lead to dental fractures with ulcers forming on the mucosa near the sites of the fractures.

A meat diet hastens the onset of attacks since in this case various protein metabolites accumulate in the organism more rapidly, guanidine bases particularly hastening the onset of attacks of tetany.

In man tetany is most commonly observed in childhood. The symptoms of this disease are not so clearly pronounced as in experimental tetany. Tetany may also occur in adults as a result of surgical intervention on the thyroid and injury to the parathyroid glands, hemorrhages into these glands, tumours and inflammatory processes. Spasmophilia observed mainly in children is apparently also connected with hypofunction of the parathyroid glands.

Tetany is marked by a tendency to convulsions, increased tone of the facial and occipital muscles and the diaphragm, and a characteristic position of the hand during attacks (Fig. 150). Laryngospasm is characterised by respiratory disturbances manifested in expiratory difficulties and signs of oxygen deficiency.

Man most commonly has *latent tetany* which may manifest itself in psychic disorders, trauma and infections.

Increased electric and mechanical excitability of the nerves and muscles is the common sign of all forms of tetany.

Acute forms of tetany often lead to death. Chronic forms are most frequently characterised by trophic tissue disturbances. Sometimes tetany begins with pathologic phenomena in the gastrointestinal tract (excessive intestinal peristalsis, diarrhea and hyperchlorhydria).

The vegetative division of the nervous system is noticeably impaired; this is manifested in laryngospasm, spasm of the esophagus and cardia, tachycardia, and sharp reaction to adrenalin and pilocarpine.

The carbohydrate, protein and especially mineral metabolism is altered. Many phenomena, for example, hyperglycemia, accumulation of ammonia and certain nitrogenous bases in the blood are most likely due to convulsions which are so characteristic of tetany. Accumulation of guanidine bases in the organism and their excretion in the urine are considered more specific of tetany.

The mechanism of tetany is connected with disturbances in mineral metabolism.

The content of calcium salts in the blood decreases to 7 and even 5-4 mg%, that of ionised calcium being particularly decreased; the content of the antagonistic potassium and sodium is usually increased. The connection between the disturbances in calcium metabolism and the content of calcium in the blood, on the one hand, and parathyroid insufficiency, on the other, is also attested by the fact that the active extract from these glands (parathormone) causes in animals, especially after removal of the parathyroids, phenomena which are the reverse of the ones just described, namely, an increase in calcium cations and decrease in potassium and sodium cations.

The Ca/P in the blood decreases as a result of a diminution in the calcium and a certain increase in phosphorus (up to 5-7mg% instead of the normal 2-4 mg%). The parathyroid hormone blocks the



Fig. 150. Characteristic position of the hand (obstetrician's hand) during attack of parathyroid tetany.

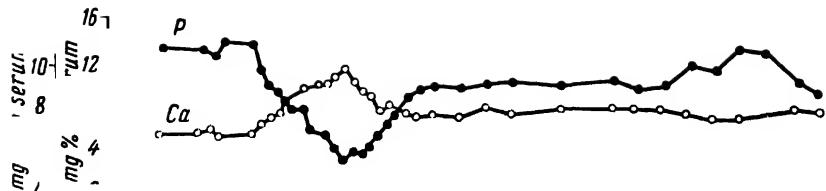


Fig. 151. Effect of the parathyroid hormone on the calcium (*Ca*) and phosphorus (*P*) level in the blood serum (Albright and Ellsworth).

reabsorption of phosphorus and increases that of calcium in the renal tubules (Fig. 151). The diminution in active calcium in the blood and tissues taking place in tetany is also considered to be connected with tissue alkalosis developing after extirpation of the parathyroids.

Alkalosis is conducive to more intense attacks of tetany. Increased alkalosis caused by excessive pulmonary ventilation and loss of carbon dioxide is also accompanied by phenomena of tetany—*hyperventilation tetany*. The same thing occurs in *gastric tetany* which develops as a result of frequent vomiting and loss of hydrochloric acid with the gastric juice. Ionisation of calcium in the blood is diminished in both cases.

The diminution in active calcium partly explains the heightened excitability of the neuromuscular system in tetany. Administration of calcium salts produces a favourable effect by arresting the attacks. But this favourable effect of calcium salts is brief and the subsequent injections of calcium do not so appreciably influence the course of tetany. Thus, disturbances in calcium metabolism cannot fully explain the development of tetany.

Systematic administration of active parathyroid preparations raises the level of calcium in the blood in parathyroprival animals and makes it possible to keep them alive for many months after the operation.

Endocrine pathology in man also includes phenomena of *parathyroid hyperfunction*, as in the so-called *generalised fibrous osteodystrophy* which is characterised by resorption of the osseous substance and subsequent replacement of osseous tissue by fibrous tissue with frequent deformations and fractures of bones. These cases are marked by increased calcium, diminished phosphorus and increased excretion of calcium and phosphorus in the urine.

This disease often exhibits adenomatous proliferation of the parathyroid glands. By repeated injections of active parathyroid preparations it has been possible to produce bony changes in dogs similar to those found in patients with *generalised fibrous osteodystrophy*.

DYSFUNCTION OF THE HYPOPHYSIS

The studies of the dysfunction of the *hypophysis cerebri* and its effects on the organism go considerably beyond this gland because the nuclei of the diencephalon (*nucleus supraopticus* and *nucleus paraventricularis*) are connected by nerve fibres with the posterior lobe of the hypophysis and form with it a single diencephalo-hypophyseal system. Impairment of this system underlies a number of diseases. The same pathologic phenomena may be experimentally produced by stimulating the posterior lobe of the hypophysis and the diencephalon.

Information is now available concerning neurosecretion by the nuclei of the anterior portion of the hypothalamus and the influence of the hormones they secrete on the function of the adenohypophysis (Bergmann).

The connections between the cerebral cortex and the internal organs are maintained not only through the inferior parts of the nervous system, but also through the hypophysis. Dysfunction of the cerebral cortex may therefore cause disturbances in a number of visceral functions also neurohypophyseally.

The hypophysis secretes about 25 hormones some of which regulate the basic functions of the organism (Fig. 152). All of these hormones are apparently of an albuminous nature.

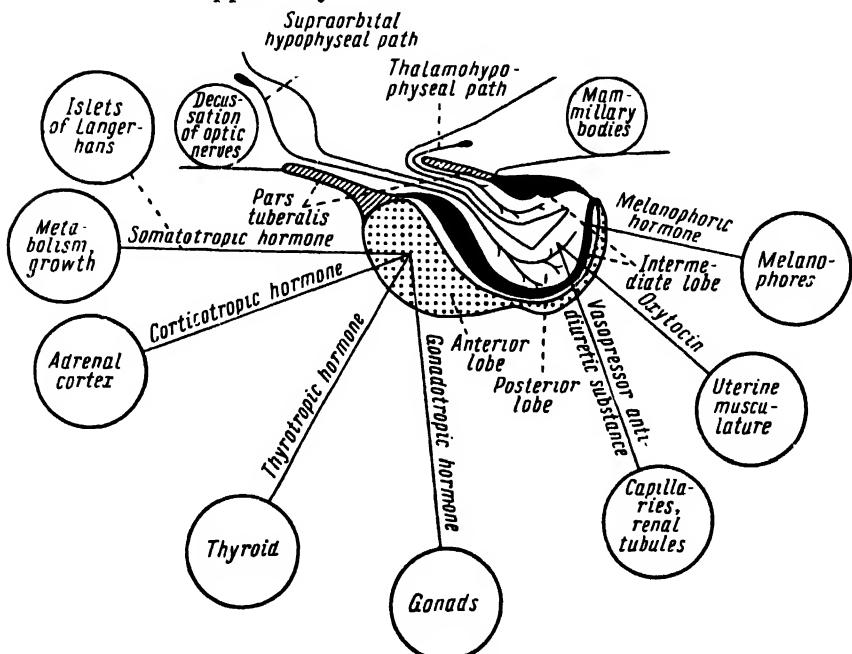


Fig. 152. Diagram showing connections of the hypophysis with the other endocrine glands and functions. Dotted lines indicate hypothetic connections.

Experimental Dysfunction of the Hypophysis

Ablation of the anterior lobe of the hypophysis in young animals causes mainly an *arrest of growth and sexual development*. On the other hand, administration of extracts from the anterior lobe of the hypophysis results in increased growth of animals (Fig. 153 A and B).

The delayed growth of the tubular bones in cases of hypofunction of the anterior lobe of the hypophysis is manifested in retarded closure of the epiphyseal suture. It is also marked by long persistence of the milk teeth, metabolic disturbances (increased limit of sugar assimilation, and phenomena of adiposis), drop in body temperature and impaired heat regulation. Atrophic changes are also observed in other endocrine glands, mainly in the adrenal cortex, the pancreas and thyroid. The animals remain infantile; the development of the gonads is retarded and the glands are smaller in size; the external genitalia are also poorly developed.

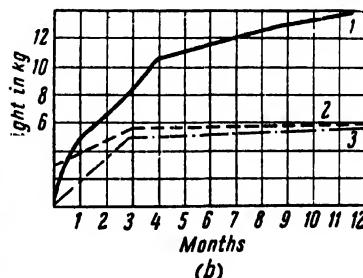
The participation of the anterior lobe of the hypophysis in the *processes of growth and development* is expressed in its secretion of a somatotropic hormone which stimulates the growth of young animals (Fig. 154).

Of the other phenomena observed after removal of the anterior lobe of the hypophysis mention must be made of *adiposis and hypofunction of the gonads* (Fig. 155).

A function of the crinogenic hormones of the anterior lobe of the hypophysis causes dysfunction of the corresponding endocrine glands. A function of the thyrotropic hormone leads to hypofunction of the animal's thyroid, while a function of the adrenocorticotropic hormone (ACTH) results in hypofunction of the adrenal cortex which leads to diminished basal metabolism, adynamia and extinction of the function of the gonds.



(a)



(b)

Fig. 153. a—effect of removal of the hypophysis on the growth of pups; left—normal animal, right—hypophysectomised animal of the same litter, b—curves showing increase in body weight during the period of growth in normal (1) and two hypophysectomised (2 and 3) pups of the same litter (L. N. Karlik).

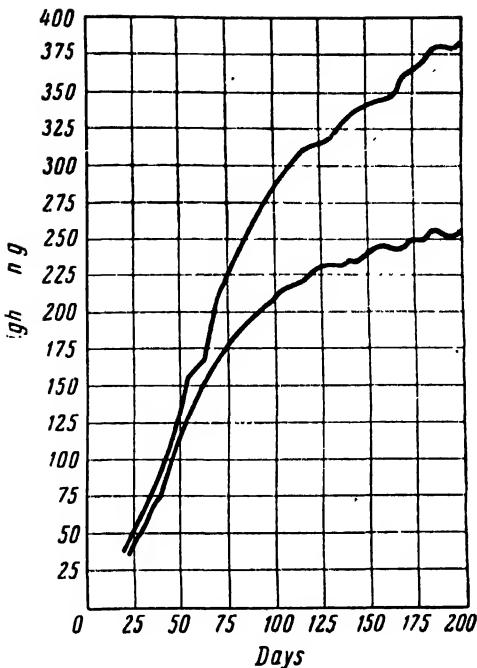


Fig. 154. Weight increase in 38 young rats given daily injections of extract from the anterior lobe of the hypophysis (upper curve) compared with the weight increase in the same number of animals not given the extract (lower curve) (Evans).

Particularly noticeable is the effect of a function of the anterior lobe of the hypophysis or its extract on the function of the gonads and through them on the entire system of reproductive organs and secondary sex characters. This effect is conditioned by the *gonadotropic hormones* of the anterior lobe of the hypophysis.

Removal of the posterior lobe of the hypophysis usually causes *polyuria* which soon passes, although in some cases it persists for a long time. The antidiuretic hormone produced by the posterior lobe of the hypophysis perceptibly reduces the excretion of urine, especially in cases of polyuria, by stimulating reabsorption of water in the renal tubules. Very brief polyuria is observed in cases of total removal of the hypophysis. For the onset of prolonged polyuria it is necessary to preserve the anterior lobe of the gland. It is therefore believed that polyuria developing after removal of the posterior lobe of the hypophysis is due to an increase in the diuretic function of the anterior lobe of the gland. An extract from the posterior lobe of the hypophysis, which inhibits the

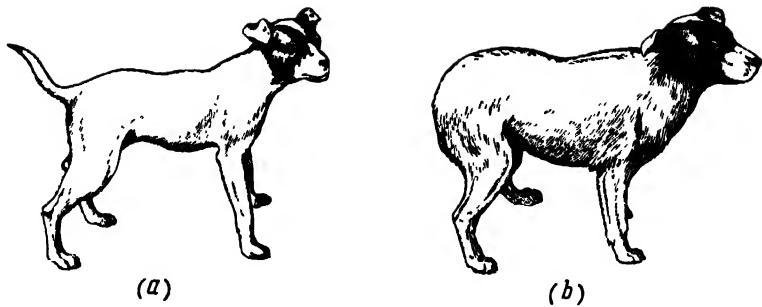


Fig. 155. a—young dog before operation on the hypophysis and b—the same dog with marked adiposis 51 days after the operation.

excretion of urine, constricts the arterioles and capillaries, thereby elevating the arterial pressure, and causes a slowing of the heart rate. The antidiuretic and vasoconstrictor effect is due to the action of *vasopressin*, the hormone of the posterior lobe of the hypophysis. This hormone is a peptide containing nine residues of amino acids and twelve-member cycle formed by disulfide bridges.

Oxytocin, another hormone, which very closely resembles vasopressin in chemical structure, has also been isolated from the posterior lobe of the hypophysis. Both these hormones have now been produced synthetically.

Oxytocin raises the tone of the uterus, the smooth muscles of the intestines, the bladder and gallbladder. Extracts from the posterior lobe have long been used to stimulate labour. The uterus of a sexually immature guinea pig is particularly sensitive to extracts from the posterior lobe of the hypophysis.

According to latest information the hormones of the posterior lobe of the hypophysis are formed in the neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus whence they pass into the posterior lobe of the gland. They are secreted under the regulatory influence of the nervous system.

Intermedin, a melanocyte-stimulating hormone which alters, in particular, the size of the melanophores (pigment cells) in the skin of frogs, has been isolated from the intermediate lobe of the hypophysis.

Hypofunction of the Anterior Lobe of the Hypophysis in Man

Hypophyseal infantilism in man is the result of hypofunction of the anterior lobe of the hypophysis, insufficient secretion of the somatotropic hormone.

Early destruction (for example, by a tumour) of the anterior lobe of the hypophysis may lead to *dwarfism* with normal bodily proportions and mental development generally corresponding to age, with underdeveloped genitalia and senile appearance.

Hypofunction of the hypophysis often causes *adiposogenital dystrophy*. This disease is characterised by deposition of fatty substances in the subcutaneous adipose layer, especially of the chest, abdomen and pelvis, and is accompanied by underdevelopment of the gonads and the secondary sex characters. The skin is thick, dry, cold and somewhat edematous. In young, growing individuals the disease is manifested not only in adiposis, but also in arrested growth, persistence of the epiphyseal suture of the tubular bones, and underdevelopment of the gonads and the secondary sex characters.

But such adiposis may also develop with a seemingly intact hypophysis in cases of hydrocephaly or a tumour growing at some distance from the gland. These cases apparently involve dysfunction of the central vegetative zones of the diencephalon (the infundibulum and floor of the third ventricle) and impairment of their connections with the hypophysis.

Acute hypophyseal hypofunction in man leads to development of a severe disease—*hypophyseal cachexia* or Simmond's disease (Fig. 156). This disease is characterised by extreme emaciation, diminished metabolism, atrophy of the bones, loss of hair and teeth, atrophy of the sexual apparatus, the thyroid and adrenal cortex. Many of these phenomena are the opposite of those observed in acromegaly which is caused by hyperfunction of the anterior lobe of the hypophysis. A function of the hypophysis, which is responsible for hypophyseal cachexia, is due to embolism of the hypophysial vessels or destruction of the hypophysis by tuberculosis, syphilis or tumours.

Phenomena resembling those of hypophysial cachexia in man may be observed in experiment (in rats) after removal of the hypophysis.

Lastly, *diabetes insipidus* is also caused by dysfunction of the posterior lobe of the hypophysis. It also develops in cases of tumours and infectious processes on the base of the brain as a result of impairment of the diencephalon and its connection with the posterior lobe of the hypophysis.



Fig. 156. Hypophyseal cachexia patient (Thannhauser).

Hyperfunction of the Anterior Lobe of the Hypophysis in Man

Acromegaly is due to hyperfunction of the anterior lobe of the hypophysis, and excessive secretion of the growth hormone. It most commonly occurs in cases of neoplastic proliferation of the anterior lobe (adenoma). This disease (Fig. 157) manifests itself in a full-grown organism in excessive growth of the fingers and toes, supra-orbital ridges, nose, chin and cheekbones; the hands and feet are considerably enlarged. The growth affects mainly the bones and soft tissues.

Owing to secondary lesions in the *sella turcica* acromegaly is accompanied by impairment of vision, dizziness, vomiting and headache. Moreover, the onset of the disease is characterised by increased sexual desire which subsequently decreases. Disturbances are observed in protein, carbohydrate and salt metabolism (for example, glycosuria).

If hyperfunction of the anterior lobe of the hypophysis occurs in a growing organism, its result is *hypophyseal gigantism* (Fig. 158) which is characterised by excessive bodily growth with normal proportions. The epiphyses of the tubular bones long remain open. Proliferation of the basophilic cells of the anterior lobe of the



Fig. 157. Acromegaly.

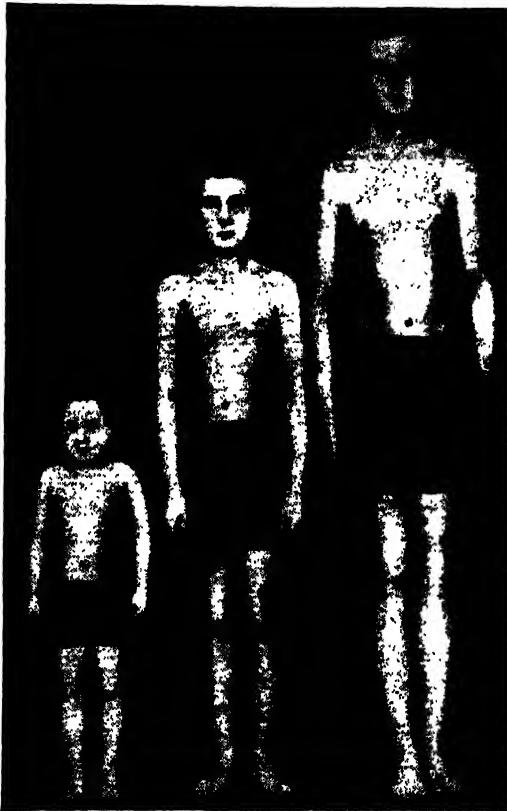


Fig. 158. Growth disorders of hypophyseal origin.

Left—14-year-old patient measuring 100 cm in height (hypophyseal dwarfism). In the middle—normal boy; right—boy 13 years 10 months old, measuring 186,8 cm (hypophyseal gigantism) (N. A. Shereshevsky).

hypophysis (*basophilic adenoma*) underlies *Cushing's disease* (*pituitary basophilism*) which is characterised by adiposis of the face, neck and trunk (but not the limbs), elevated blood pressure and an increased erythrocyte count, hypogenitalism (phenomena of masculinisation in women), hyperglycemia and glycosuria. In this disease the adrenal cortex is usually also hypertrophied.

Connections of the Hypophysis with the Other Glands

Studies of the disorders of the hypophyseal function have made it possible to establish connections of the *anterior lobe of the hypophysis with the thyroid, adrenal cortex, gonads and pancreas*.

Extracts of the anterior lobe of the hypophysis contain a *thyrotropic hormone* which causes hyperplasia and stimulates the function of the thyroid. Hyperfunction of the anterior lobe of the hypophysis not infrequently leads to enlargement of the thyroid, whereas its dysfunction may be accompanied by atrophy of the thyroid.

The *adrenocorticotrophic hormone* (ACTH) of the anterior lobe of the hypophysis stimulates the function of the adrenal cortex and secretion of glucocorticoids (hydrocortisone, etc.) by the cortical substance. The desensitising and anti-inflammatory effect of the adrenocorticotrophic hormone in many respects coincides with the analogous effect of hydrocortisone and is apparently due to stimulation of the production of the latter hormone. Administration of extracts from the anterior lobe of the hypophysis causes proliferation of the cortical substance of the adrenals. The same thing is observed in acromegaly. Removal of the hypophysis is followed by atrophy of the adrenals, in young animals--by arrested development of these glands.

According to Selye, the relations between the ACTH and the hormone of the adrenal cortex underlie the general adaptation syndrome which manifests itself as a response to severe or prolonged physiological stress (see Chapter Four).

The anterior lobe of the hypophysis is also connected with the gonads. This connection is due to its secretion of *gonadotropic hormones*. One of them --a *follicle-stimulating hormone* (FSH)— hastens maturation of follicles and increases spermatogenesis; another—a *luteinising hormone* (LH)—determines the onset of ovulation in the ovaries and stimulates the interstitial cells in the testes. A comparatively small amount of these hormones is excreted in the urine.

The secretion of these gonadotropic hormones by the adenohypophysis is regulated by the function of the hypothalamus where there are inhibitory and stimulatory centres sensitive to the hormones produced by the gonads. This ensures autoregulation in the hormonal activity of the gonads.

The substance which has been obtained from the placenta and is similar to but not identical with the follicle-stimulating hormone also possesses high gonadotropic activity. During pregnancy it is excreted in the urine in much greater amounts than the follicle-stimulating hormone. The biological test for early pregnancy (Aschheim-Zondek test) is based on discovering this hormone in the urine by its effect on the ovarian follicles of sexually immature mice. If the woman whose urine is injected is pregnant the ovaries of the mice will be enlarged, hyperemic and hemorrhagic and will show maturation of the ovarian follicles.

The anterior lobe of the hypophysis contains prolactin, another gonadotropic—*luteotropic*—hormone (LTH) which stimulates hor-

monopoiesis in the corpus luteum and regulates the function of the mammary glands. Its effect is observed only after cessation of labour and of the inhibitory influence of the follicle-stimulating hormone on the mammary glands.

Antagonistic relations exist between the *anterior lobe of the hypophysis and the islet apparatus of the pancreas*; this is evident from the fact that insulin hypoglycemia can be eliminated by administration of a large dose of extract from the anterior lobe of the hypophysis and that after extirpation of the anterior lobe of the hypophysis animals become more sensitive to insulin and tolerate pancreatic diabetes more easily. This influence of the hypophysis on carbohydrate metabolism is explained by an antagonism between the somatotropic hormone and insulin. The effect of the somatotropic hormone consists in inhibiting the function of hexokinase and stimulating gluconeogenesis. Some cases of diabetes mellitus and diabetic phenomena observed in acromegaly are due to hyperfunction of the anterior lobe of the hypophysis and increased secretion of the somatotropic hormone.

DYSFUNCTION OF THE GONADS

The internal secretion of the gonads plays an enormous part in the processes of growth, development and sexual maturation.

The ovaries contain hormones of the follicular apparatus and the corpus luteum. The hormones secreted in the follicles are *estrogens*—estradiol and the products of its transformation—estrone and estriol. Estrogens cause the proliferative phase of the menstrual cycle in women and estrus in animals. A biological method of discovering estrogens by their ability to stimulate estrus in castrated mice has been elaborated on this basis.

Progesterone is a hormone formed in the corpus luteum. It causes the secretory phase of the menstrual cycle, the preparation of the uterine mucosa for the implantation of the fertilised ovum and formation of the decidua, i.e., it regulates the development of the fertilised ovum. The hormone of the corpus luteum also regulates the development of the mammary glands during pregnancy. As long as corpora lutea function in the ovaries no menstruation or ovulation takes place.

In the testes the internal secretory role is played by specific spermatogenic cells and apparently interstitial elements (so-called Leydig cells). Male sex hormones have been isolated from the urine (*androsterone*) and from the seminal glands (*testosterone*); a number of derivatives (methyltestosterone and testosterone propionate) has also been obtained. All sex hormones—male and female—resemble cholesterol in structure.

Experimental removal of testes or ovaries in young animals before the beginning of sexual development causes disturbances in

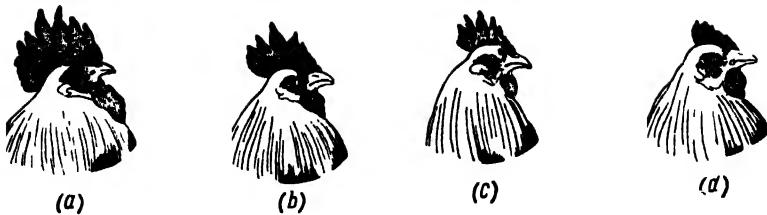


Fig. 159. Rooster's head after castration.

a—on the day of the operation; *b*—25 days later; *c*—35 days later; *d*—40 days later.

growth and development. The distinctive properties of males and females are somewhat obliterated and a kind of intermediate (intersexual type) develops. The skeleton becomes elongated and the ossification and closure of epiphyseal sutures is retarded. Also retarded is the sexual maturation and development of secondary sex characters, for example, the comb and spurs in cocks (Fig. 159). The development of the larynx is impeded and the voice changes, losing its sonorousness and strength.

Castration of adult animals causes less clearly marked phenomena and affects mainly the metabolism; the oxidative processes diminish and deposition of fat is observed. The sexual instinct perceptibly weakens. In females the uterus and mammary glands undergo retrograde development. Higher nervous activity is impaired, the inhibitory reactions are weakened and the processes of excitation are intensified.

All these phenomena apparently develop not only because of the absence of the gonads, but also because of the resultant hypofunction of the thyroid and hypophysis.

The foregoing phenomena can be for a certain time eliminated by transplantation of gonads. Transplantation of gonads to castrated individuals of the opposite sex masculinises females and feminises males (Figs. 160 and 161). However, the transplant cannot function long and is gradually resorbed.

Attempts have been made to transplant to man, in cases of sexual insufficiency, testes from monkeys or other animals (heterotransplantation) and from man (homotransplantation). However, the inferences drawn on the basis of these transplantations are in many respects exaggerated; these transplantations, especially heterotransplantations, have not been observed to produce any long-term effects.

Gonadal insufficiency (hypogenitalism) in man may be congenital (*eunochoidism*) and acquired, as in cases of intoxication or infection (typhus, gonorrhea, syphilitic orchitis), or castration.

Hypofunction of the gonads before sexual maturity (early castration) also causes disturbances in growth manifested in late



Fig. 160. Feminisation of guinea pigs of one litter.
a—castrated male, b—normal female, c—feminised male, d—normal male

closure of the epiphyseal sutures; the skeleton becomes elongated, the legs growing in length more than the body. A marked under-development of the genitalia, almost complete absence of hair on the face, pubis and in the axillae, as well as absence of menstruation and of the *libido*, are observed; the voice remains childish.

A function of the gonads after the onset of sexual maturity (late castration) has somewhat different manifestations, depending on sex.

In women a function of the ovaries results from their surgical removal or prolonged exposure to roentgen rays. These cases are marked by frequent rushes of blood to the head, dizziness and a number of phenomena characteristic of the climacteric.

In men the somatic phenomena in cases of gonadal afunction are more strongly pronounced. The secondary sex characters become atrophied, the memory weakens, considerable fatigability develops, appreciable adiposis is observed, and the processes of active inhibition in the cortex are diminished.



Fig. 161. Masculinisation of guinea pigs of one litter.
a—masculinised female; b—castrated female; c—normal female; d—normal male.

The hypofunctional state of the gonads is not infrequently combined with the impaired functions of the anterior lobe of the hypophysis, the thyroid and the adrenals.

A hyperfunctional state of the gonads (*hypergenitalism*) may be constitutional; it manifests itself in premature sexual development and phenomena which are the opposite of those observed in castration, namely, the muscles and genitalia are well developed, metabolism is increased and all sex characters are more clearly marked. The phenomena of hypergenitalism are often due not to primary hyperfunction of the gonads, but to the increased function of the adrenal cortex or tumours in the pineal body (*epiphysis cerebri*).

DYSFUNCTION OF THE ADRENALS

The adrenals consist of two parts—the medullary layer and the cortex—which differ morphologically as well as functionally.

Adrenalin, the hormone of the medullary layer, is also elaborated by the chromaffin tissue in the spinal ganglia of the sympathetic chain. Noradrenalin, or arterenol, which resembles adrenalin and is also found in the medullary layer of the adrenals, possesses high physiologic activity and is a mediator of the sympathetic nervous system. Corticoid hormones, or *corticosteroids*, have been obtained from the cortical substance of the adrenals (Fig. 162). Some of them, as glucocorticoids, mainly hydrocortisone (17-hydroxycorticosterone) and cortisone which is only one-third or one-fourth as active, influence predominantly carbohydrate metabolism, facilitating formation of glucose from proteins. Others—mineralocorticoids, (desoxycorticosterone (DOC) and aldosterone)—regulate the relations between potassium and sodium ions in the blood and tissues (aldosterone is 20-30 times as active as desoxycorticosterone). *Androsteroids*, which by their action belong to sex hormones, constitute the third group.

Hydrocortisone and cortisone have found application as anti-inflammatory and antiallergic agents. Desoxycorticosterone and aldosterone, on the contrary, intensify the inflammatory reaction.

Elaboration of glucocorticoids is stimulated by the adrenocorticotrophic hormone, whereas secretion of mineralocorticoids is stimulated partly by the somatotropic hormone of the hypophysis.

Total removal of the adrenals quite soon results in the animal's death (in dogs death ensues in about 5-8 days), the animal manifesting the following symptoms: strongly pronounced adynamia, diminished basal metabolism, low body temperature, apathy, sharp depression of reflex activity, weakness, vomiting, reduced arterial pressure and excessive excretion of water. Such animals exhibit hemoconcentration, the volume of the plasma drops from 55 to 40 per cent and lower, and the erythrocyte count increases to 10 million per 1 mm³ of blood. Mineral metabolism is impaired—

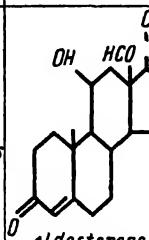
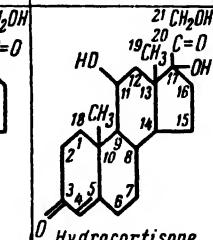
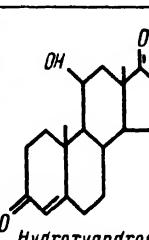
Steroid hormones of the adrenal cortex	Mineralocorticoids	ACTH ↓ Glucocorticoids	Androcorticoids
Main properties	<i>Na and H₂O retention</i> <i>K excretion</i> <i>Elevation of blood pressure</i>	<i>Glyconeogenesis,</i> <i>eosinopenia,</i> <i>lymphopenia,</i> <i>anti-inflammatory</i> <i>and anti-allergic action</i>	<i>Anabolic action,</i> <i>masculinisation</i>
Hormones found in the venous blood of the adrenals	 <p>Aldosterone</p>	 <p>Hydrocortisone</p> <p>C-21-steroid</p> <p>Corticoid</p>	 <p>Hydroxyandrostenedione</p> <p>17-ketosteroid</p>

Fig. 162. Corticosteroids, principal hormones of the adrenal cortex (A. Prader's modified diagram).

the content of sodium in the blood decreases, the alkali reserves diminish, and the content of potassium increases. All these disturbances are the result of renal dysfunction and impaired processes of filtration and reabsorption. The level of sugar in the blood also drops, and the content of glycogen in the liver and muscles decreases (Fig. 163).

The life of adrenalectomised animals can be prolonged by administration of an increased amount of sodium chloride and water with food deficient in potassium. This fact attests the important role played mainly by sodium and potassium salts in the pathogenesis of these disturbances in salt and water metabolism. Decreased sodium and increased potassium in the blood are due mainly to dysfunction of the renal tubules. Excessive excretion of sodium chloride by the kidneys also causes a loss of water, as well as concentration of and diminution in the plasma, which is one of the causes of reduced blood pressure. Weakened blood circulation in the kidneys leads to further disturbance in their functions and apparently to retention of nitrogenous products and their accumulation in the blood.

The muscular weakness characteristic of the operated animals and the favourable effects produced by corticosteroids, mineralo- and glucocorticoids, especially aldosterone and hydrocortisone, indicate that the phenomena developing after extirpation of the ad-

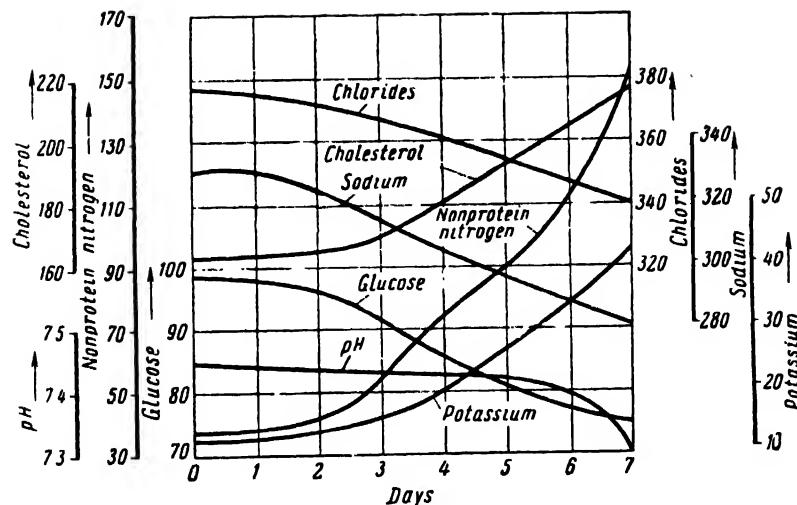


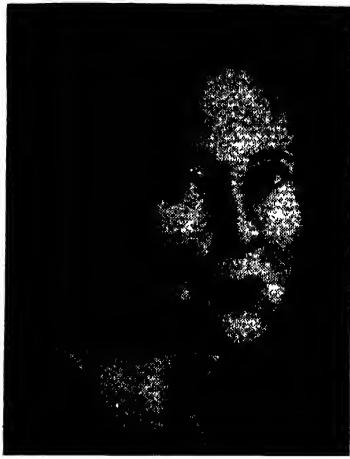
Fig. 163. Changes in the blood of dogs after removal of adrenals. Designations (except pH) in mg% (Grollman).

renals are based on a function mainly of the hormones of the adrenal cortex. Administration of adrenalin with glucose can prolong the life of the operated animals only for a short time (Perelman).

Hypofunction of the adrenals in man is observed in *Addison's disease*. The disease is characterised by general adynamia and apathy with depressed higher nervous activity, loss of weight, hypothermia and impaired carbohydrate metabolism; disturbances in the gastrointestinal tract are manifested in anorexia and frequent alternation of constipation and diarrhea; the sexual function is weakened, and a characteristic pigmentation (a deep bronzing) of the skin and mucous membranes gradually develops. Biochemical changes analogous to those developing in animals after removal of the adrenals are found in the blood of the patients. Cachexia develops and death ensues. Tuberculous affection of the adrenals is the most frequent cause of this disease.

The *pigmentation of the skin* is due to accumulation of amino acids (dioxyphenylalanine and possibly tyrosine) in it, the amino acids transforming into pigment under the action of enzymes. These amino acids accumulate in Addison's disease because of disturbances in the process of their transformation into adrenalin. It is known that in the normal organism tyrosine serves as the material for formation of adrenalin either directly or through preliminary conversion into dioxyphenylalanine.

However, administration of adrenalin in Addison's disease is not particularly effective, whereas administration of preparations of



Effect of adrenocortical tumour on woman's secondary sex characters.

Fig. 164. Before disease.



Fig. 165. One year after onset of the disease.

the cortical part of the adrenals, especially aldosterone, produces a favourable effect; adynamia disappears, the pathologic phenomena in the gastrointestinal tract cease, the blood pressure rises, the mineral metabolism is restored, and the pigmentation diminishes. These data confirm that *hypofunction of the cortical part of the adrenals* plays an important role in the pathogenesis of Addison's disease.

Glucocorticoids apparently also play some part in detoxifying the toxic substances forming as a result of impaired metabolism. The cortical layer of the adrenals perceptibly reacts to many forms of intoxication, including those of infectious origin (for example, in diphtheria); this fact is referred to as proof.

The function of the cortical part of the adrenals is connected with the function of the gonads. Phenomena of accelerated somatic and sexual development, most commonly of a male type, are observed in the organism in cases of tumours in the cortical part of the adrenals. Changes in gonadal function are also observed in mature organisms in cases of tumours of the adrenal cortex. In females tumours of the adrenal cortex produce phenomena of masculinisation (virilism, Figs. 164 and 165) which are manifested in cessation of menstruation, growth of hair in unusual places and in unusual amounts (hirsutism, Fig. 166), appearance of a masculine voice and other secondary sex characters. These phenomena are due to *hyperfunction of the cortical substance of the*



Fig. 166. Hirsutism. 17-year-old female patient. Adenoma of the right adrenal cortex.

adrenals. The data on the secretion by the adrenal cortex of substances which chemically and biologically resemble sex hormones are therefore particularly important.

Hyperfunction of the medullary layer of the adrenals is rarely observed in man, for example, in connection with a tumour developing in the adrenal medulla (pheochromocytoma). These cases are characterised by attacks of spasm of the cardiac vessels, acceleration of the pulse, elevation of blood pressure and dilatation of the pupils; these phenomena are easily explained by excessive secretion of adrenalin.

Attempts were made to ascribe the elevation of blood pressure, diminished sugar tolerance and development of arteriosclerosis in hypertensive vascular disease to hyperfunction of the adrenal medulla, but these assumptions have not as yet been proved.

Medullary insufficiency may underlie some forms of hypotension. For pathology of the pancreas see Chapter Six.

DYSFUNCTION OF THE PINEAL BODY

Dysfunction of the pineal body (epiphysis cerebri) occurs rarely and mainly in childhood. Tumours which destroy the pineal body are observed in children under 12 years of age and are accompanied by *untimely sexual maturity and precocious mental development*. *Rapid development of the primary and secondary sex characters* is one of the early symptoms of the so called epiphyseal syndrome. Little is as yet known concerning the pathogenesis of this disease since the physiological role of this gland has not been sufficiently studied. The experiments of extirpating the pineal body have been very few since this gland is extremely difficult of access. Extirpation of this gland in young cocks produces signs of early sexual maturation. Most scientists explain the characteristic phenomena in the epiphyseal syndrome by *hypopinealism*.

DYSFUNCTION OF THE THYMUS

Very little is as yet known about the function of the thymus. Experimental observations attest that the thymus has to do with processes of growth, development and sexual maturation.

Removal of the thymus in dogs, cats and rabbits several days or weeks after birth leads to disturbances in bony growth: the tubular bones remain short and become soft and brittle, their epiphyses thicken, the calcium content of the bones diminishes and the calcium balance becomes negative. Disturbances in sexual development manifested in accelerated development of the gonads have been observed in a number of cases. The antagonism between the thymus and gonads is also attested by the fact that castration often impedes the normal involution of the thymus. Experiments of feeding dogs with thymus or injecting its extracts show that this gland affects calcium metabolism and skeletal growth.

Impeded involution of the thymus is sometimes observed in man.

The foregoing observations cannot as yet serve as incontestable proof of the endocrine function of this gland, which requires deeper study.

PATHOLOGY OF THE NERVOUS SYSTEM

GENERAL ETIOLOGY OF NERVOUS DISORDERS

Disturbances in the function of the nervous system arise under the influence of various pathogenic factors which happen to affect it. These influences may manifest themselves as reflex disturbances and direct reactions of various neural structures.

The main causes affecting the nervous system may be conditionally divided into exogenous and endogenous.

The *exogenous causes* are extraordinary stimuli which act on the organism from the external environment; they include: 1) physical, mechanical and electric traumas, and radiant energy; 2) intoxications; 3) infections (especially rabies, tetanus, poliomyelitis, meningitides and encephalitides); 4) autointoxication (poisoning by faulty metabolic products formed within the body), and 5) conditioned pathogenic stimuli and influences through the second signal system (verbal stimuli).

The following *endogenous causes* are distinguished: 1) circulatory disorders—organic (sclerosis, hemorrhages, vascular thrombosis and embolism) and functional, due to disturbances in the blood flow (cerebral anemia and hyperemia, etc.); 2) tumours, scars, and exudates which may exert pressure on nervous tissue or its supplying vessels; 3) dysfunction of endocrine glands and impaired metabolism in the nervous tissue; 4) peculiarities of age and sex, which not infrequently determine the reaction of the nervous system to external pathogenic agents.

Some part in the etiology of a number of nervous diseases is also played by heredity which forms in the process of interaction between the organism and the external environment.

PATHOLOGIC PHYSIOLOGY OF HIGHER NERVOUS ACTIVITY

The teaching on higher nervous activity originated by Pavlov has opened extensive prospects for investigating the pathologic phenomena arising in the cerebral cortex. The diseases of the brain have been given new elucidation from the point of view of the

analysing function of the cerebral cortex and the complex relations existing in it between the two basic processes—excitation and inhibition.

The first studies of partly or completely decorticated animals were inadequate since any surgical influence on the cerebral cortex, in addition to causing the loss of certain functions, produced phenomena which must be attributed to the surgical trauma and concomitant compensatory processes. Such animals were subsequently studied by the more objective, conditioned reflex method.

Effects of Complete Removal of the Cerebral Cortex

After complete bilateral removal of the cerebral cortex (decortication) dogs lapse into long sleep which is interrupted only for micturition and defecation. Subsequently sleep is often alternated with waking.

With good care decorticated animals may live for an indefinitely long time. They are incapable of differentiating external stimuli and can barely orient themselves in the surroundings. The dogs appear to be blind and deaf, although they react to light and sound. They do not respond when called by name, do not recognise their master, do not go up to food and do not discriminate odours, but eat the food introduced into the oral cavity.

The dogs retain their motoricity, posture and the forms of locomotion conditioned by the function of the diencephalon and the striopallidal system. However, the agility and smoothness of movements are noticeably impaired. The unconditioned skeletal-motor reflexes become crude and imperfect. Rapid fatigability is observed.

Owing to the loss of the inhibitory function of the cortex, decorticated animals become more aggressive, their skin grows more sensitive, all formerly elaborated conditioned reflexes disappear and elaboration of new ones is impossible. Only unconditioned reflex activity is retained, but it, too, is considerably weakened.

In monkeys extirpation of the cerebral cortex causes still greater disturbances which are manifested in a loss of skills, marked motor disorders and loss of mimicry and gestures.

Decortication also causes disturbances in vegetative functions. The salivary glands cannot properly adjust their secretory activity to the quantity and quality of the food introduced into the oral cavity. The same thing occurs in the secretory function of the gastric glands. Disturbances in the regulation of the cardiovascular and respiratory systems are observed. The heart rate is accelerated, the animals develop dyspnea, heat regulation is altered, the immune reactions diminish, the oxidation and reduction processes are impaired, and young animals fail to grow normally.

Removal of the cerebral cortex, which results in the loss of the conditioned reflexes, also affects the function of the analysors,

i.e., the neural structures which unite the peripheral receptors, afferent nerves and corresponding portions of the cerebral cortex in a single functional unit. The ability of fine analysis and synthesis is lost. The retained subcortical unconditioned reflex activity and its highest manifestations—instincts—are incapable of ensuring a normal existence of animals under the constantly changing conditions of the external environment.

Effects of Partial Removal of and Injury to the Cerebral Cortex

The disturbances in nervous activity were also studied after removal of the cortex of one hemisphere, the anterior or posterior parts of both hemispheres, and the central part of one of the cortical analysors, for example, the auditory, visual, cutaneous or motor analysors. All these forms of surgical intervention provoke pathologic phenomena connected with the site and extent of injury, as well as general disturbances in the functions of the cerebral cortex.

Removal of the cortex of one hemisphere results in the following pathologic phenomena.

1. *Asymmetry of movement*, i.e., absence of coordinated movements on both sides. This asymmetry is the result of a function of the motor centres of one hemisphere. Owing to the decussation of the motor pathways the movements of limbs are inhibited on the side opposite to that of the removed cortex. The side on which the cortex was removed is also affected by the absence of the normal coordination in the work of similar centres in both hemispheres, which gives rise to disturbances in the coordination of movements.

2. *Higher threshold of stimulation* on the affected side, lower cutaneous and pain sensitivity, and higher general excitability due to the impaired normal relations between the cortex and the subcortical region.

3. *Slight atrophy of the skeletomotor apparatus* due to a certain disturbance in the trophic processes on the side opposite to the site of affection. Partial injuries to the cortex also result in impaired perception of stimuli and their impaired coupling in the cortex.

Extirpation of various portions of the cerebral cortex causes a function of analysors (auditory, visual, cutaneous, etc.). The results of this afunction are weakening or disappearance of conditioned reflex reactions and a certain disturbance in the function of the afferent part of the reflex arcs, i.e., a function of some particular part of the cortex. For example, if the dog is deprived of the occipital and temporal lobes of both hemispheres, it largely loses its ability normally to react to various visual and auditory stimuli. It cannot distinguish objects and complex sounds. During the initial period

following the operation the dog retains only a general reaction to light and sound. Later light and sound may even become conditioned reflex stimuli, but differentiated inhibition, analysis and synthesis of visual and auditory stimuli almost completely disappear.

Experiments with elaboration of conditioned reflexes have shown that the limits of the central nuclei of analysors are not strictly defined. After removal of some analysing portion of the cerebral cortex the functions may in some measure be restored by peripheral parts or scattered regions of the analysor, which suffice to effect the same reaction, although in an imperfect, elementary form. For example, after removal of the central part of the visual analysor it is possible to elaborate a conditioned reflex only to the intensity of light, but not to individual objects. After extirpation of the auditory analysor the dog ceases to hear the differences in the details of sound and reacts only to the strength of the sound, i.e., it loses the power of higher analysis and synthesis of sound perception.

Phenomena of loss of higher analysis and synthesis are also observed after removal of other analysors, for example, the cutaneous and motor analysors in cases of ablation of the anterior part of the cortex of both hemispheres.

The *restorative abilities* of the cerebral cortex depend on its plastic properties underlying adaption to new conditions of activity. Such plasticity determines the relative resistance of the nervous system to any injury.

Experimental *impairment of the circulation* in the cerebral cortex (by ligation or compression of the cerebral vessels) leads to disappearance of conditioned reflexes with subsequent incomplete restoration in cases of development of collateral circulation. Impaired circulation is also accompanied by a weakening of the processes of internal inhibition, and disturbance in the motor, sensory and vegetative functions. Phenomena of diffuse inhibition and a pathologic inertness of cortical processes were observed in other experiments.

Effects of Trauma to the Cerebral Cortex. Surgical influences on and trauma to the brain involve certain functional changes which develop in a certain sequence.

1. Diffuse inhibitory effect of trauma on the entire mass of the hemispheres. It develops because of irradiation of inhibition which takes in not only the cortex, but also subcortical structures, and results in temporary partial or complete disappearance of conditioned and certain unconditioned connections. The trauma may lead, depending on its character and extent, to unconsciousness and even coma; several vegetative functions are impaired with resultant vomiting, respiratory and cardiovascular disorders, and cerebral edema.

2. Weakening of the processes of active internal inhibition, impaired lability of inhibition and, in addition, impairment of the

process of excitation at first manifested in an excessive reaction to the stimulation. The end result is general motor inhibition which is sometimes accompanied by impairment of hearing and speech disturbances.

3. Abatement of the effects of the trauma and extensive manifestations of dysfunction of the injured analyzer with simultaneous development of a process of restoration beginning with restoration of functions of regions farthest removed from the site of injury. The last to be restored (under favourable conditions) is the function of the injured part.

4. Pathologic phenomena in cases of scar formation, the scar pressing on and stimulating the surrounding parts of the cerebral cortex. The result is weakened cortical activity alternating with convulsive seizures.

Functional Disturbances in Higher Nervous Activity

The studies of stable functional disorders of higher nervous activity are fundamentally new and most productive.

In experiment it has been possible by special procedures to produce in the cerebral cortex stable functional disturbances in the normal relations between the processes of excitation and inhibition, their strength, lability and mutual balance. The resultant disturbances in higher nervous activity are called experimental neuroses and are biological models of the neurotic states observed in the clinic.

These disturbances also include the pathologic states of higher nervous activity produced in experiments involving impaired vegetative and metabolic functions, for example, in connection with injury to the subcortex, removal of endocrine glands, intoxication and infection.

Experimental Neuroses

Mechanisms of Experimental Neuroses. Experimental neuroses arise as a result of *overstrain of the basic nervous processes*—excitation and inhibition, their strength and lability—in the cerebral cortex. They also result from a clash of the nervous processes.

The most important pathogenic agents capable of causing a disturbance in the relations between the basic nervous processes are: 1) stimuli (conditioned and unconditioned) excessively strong or unusual for the nervous system of the given animal; 2) excessively difficult, very fine marginal differentiations or protracted influence of conditioned inhibitory reflexes; 3) continuous and rapid alternation of positive and negative stimuli; 4) change in the habitual order in the system of positive and negative conditioned reflexes, i.e., change in the dynamic pattern which implies a fixed sequence of the processes in the cerebral cortex.

The following experiments may serve as examples of experimental neurosis produced by overstrain of the inhibitory process.

A conditioned reflex to a light circle flashed on a screen was elaborated in a dog. Subsequently the dog was supposed to differentiate the circle from an ellipse with a plane of the same size and with the same lighting, the ellipse having a 1:2, 2:3 or even 4:5 semi-axis ratio. Whereas the flashing of the circle was reinforced by an unconditioned stimulus—food, the flashing of the ellipse was not so reinforced. The differentiation was gradually achieved, i.e., the circle became a conditioned stimulus, whereas the ellipse produced no effect due to extintive inhibition. The ellipse thus became a conditioned inhibitory agent.

Attempts were subsequently made to elaborate a finer differentiation by gradually reducing the difference between the ellipse and the circle. The animal was given the task of making increasingly finer distinction between the positively reinforced stimulus (circle) and the inhibitory, unreinforced, differentiated stimulus (ellipse).

When an ellipse closely resembling a circle in form, with a 7:8 or 8:9 semi-axis ratio, was introduced into the experiment, it was no longer possible to obtain a complete differentiation. Some time later all the previously elaborated differentiations in the dog were brought to naught, and the dog's behaviour sharply changed. The dog was continuously excited and restless, tore off the instruments attached to him, bit through the rubber tubes, refused food, etc. Thus the dog suffered a nervous breakdown. Subsequently, when all these phenomena disappeared, all differentiations had to be elaborated anew. But this time it required a much longer period, and at the marginal differentiation (an ellipse with an 8:9 semi-axis ratio) the ability to discriminate disappeared again, the dog became greatly excited and lapsed into a very intense neurotic state.

It was also possible to produce an experimental neurosis in dogs by extraordinary and unusual influences, for example, by a strong noise (made by a rattle) or sudden explosion of powder.

Of special interest in this respect is the development of neurosis in the dog in connection with a natural calamity—a flood. Unusual motor excitement, almost total disappearance of all previously elaborated conditioned bonds and phenomena of inhibition of the cortex were observed in one of the experimental dogs after a flood; the dog refused food. Normal relations in the cerebral cortex were re-established only two months after the flood. Then the following experiment was performed: while the dog was in the stand water was allowed to trickle into the room (through a hubber tube installed beforehand) and form a puddle on the floor. Reproduction of a situation resembling the flood provoked a repeated nervous breakdown in the dog, manifested in intense motor excitement,

dyspnea, disappearance of all natural and artificial conditioned food reflexes, total refusal of food, etc.

The animals' reactions to experimentally produced neurosis *vary with the type of nervous system*. It is easier to produce a neurosis in the weak, inhibitable type (melancholic) and the strong, unbalanced type (choleric) than in the strong, balanced and active type (sanguine), and, especially, in the strong, balanced and inert type (phlegmatic). The strong, unbalanced type often lapses into a neurotic state in cases of overstrain of the inhibitory process, whereas extraordinarily strong stimuli fail to affect it. The weak, inhibitable type usually reacts with a breakdown under overstrain of both the inhibitory and stimulatory processes. The inhibitory reaction of the cortex is characterised by sluggishness, sleepiness and total disappearance of the previously elaborated conditioned reflexes. Disinhibition of previously consolidated inhibitory reactions and general motor excitement are observed in excitable animals.

In addition to the type of nervous system, all factors which affect the efficiency of cortical cells—age, nutrition, intoxication, infection—also play some part in the development of experimental neuroses.

Phenomena of excitation, disinhibition or inhibition with a diminution in positive conditioned reflexes may predominate in experimental neurosis. Not infrequently, however, neuroses are mixed and show a very complex and variable picture with stimulatory and inhibitory processes alternating in the entire cortex.

The activity of the cerebral cortex may be restored after some rest, moderation of the experimental conditions, decreased overstrain of higher nervous activity, and by a number of drugs which affect excitation or inhibition, for example, bromides, caffeine, a combination of both, and hypnotics.

Characteristics of Experimental Neuroses. Experimental neuroses are characterised by disturbances in the basic properties of the nervous system, which normally determine the relations of the stimulatory and inhibitory processes. The following phenomena are observed:

1. *Diminished efficiency of the nerve cells*, decreased strength of the nervous processes, particularly weaker internal inhibition which may be accompanied by increased excitability and may end in intense inhibition.

2. *Disturbed balance between excitation and inhibition*. Different periods are characterised by predominance either of excitation or inhibition.

3. *Pathologic mobility* of the basic cortical processes. The disturbances in mobility are manifested in both pathologic inertness and pathologic lability. *Pathologic inertness* consists in an excessively inert state of the stimulatory process when, according to

Pavlov, "the stimulatory process becomes more stubborn and persistent and does not so readily yield to the legitimately arising inhibitory influences". The mobility of the stimulatory process diminishes particularly in dogs of the phlegmatic type, which are even normally noted for a certain inertness of the stimulatory process.

Excessive mobility of the stimulatory process, rapid alternation of excitation and inhibition is called *pathologic lability*. The action of a conditioned stimulus gives rise to a very quick and strong reaction which rapidly exhausts itself. This disturbance in the stimulatory process is called stimulatory weakness or explosiveness.

In experimental neuroses pathologic mobility may occur not only in the stimulatory, but also in the inhibitory process. For example, in the dog an overstrain of the inhibitory process, mainly by prolonging the differentiation, may lead to instability of this process. In these cases periods of normal higher nervous activity alternate with periods of its depression and extinction of conditioned reflexes. Complex defence reflexes sometimes manifest themselves against the background of the weakened inhibitory process; these reflexes arise in a situation which in some way resembles the one in which the animal was subjected to an influence that threatened its intactness. It is in this manner that various phobias arise, for example, bathophobia (as fear of staircases), pyrophobia, fear of the experimenter, etc. The effects and fine mechanism of the disturbances in lability of cortical processes in experimental neuroses are not well known as yet.

4. *Phasic states* which are peculiar disturbances in the normal relations between the stimulatory and inhibitory processes, which manifest themselves in a disturbed relationship between the action of the stimulus and the response reaction.

Phasic phenomena may arise not only in pathology, but also (for a very short time, usually a few minutes) during transition from waking to sleep.

The following phases are distinguished in experimental neuroses: 1) *equalising phase* in which all conditioned stimuli, regardless of their strength, produce an equal effect; 2) *paradoxical phase* in which weak stimuli produce a strong effect and strong stimuli—the weakest effect; 3) *ultraparadoxical phase* in which positive stimuli begin to act as negative ones and vice versa, i.e., the reaction of the cerebral cortex to the stimuli is perverted; 4) *inhibitory phase* which is characterised by a weakening or total disappearance of all conditioned reflex reactions.

It is not always possible to observe a strict sequence in the development of phasic phenomena.

The phasic phenomena in experimental neuroses in many respects coincide with the phase discovered earlier by Wedensky on the nerve fibre during its transition to the parabiotic state.

In cases of repeated overstrain of higher nervous activity experimental neuroses may be not only acute, but also chronic, i.e., they may last for months and even years. At the same time it should be noted that the nervous system is highly adaptable to repeated applications of the same difficult task.

5. Chronic nervous traumas leading to development of a severe neurotic condition result in *vegetative disorders* manifested in trophic ulcers, inflammatory and hypertrophic processes, dysfunction of the internal organs, for example, of the cardiovascular system, hematopoiesis, respiration, digestion, bile secretion, output of urine, etc.

The decisive role in the origin of these phenomena is apparently played by the functionally impaired, pathologically weakened cerebral cortex, by its weakened inhibitory influence on the subcortical ganglions and the vegetative-endocrine system which is connected with them.

Focal Functional Disturbances in the Cerebral Cortex in Experimental Neuroses. Experimental neuroses may sometimes involve certain areas of the cerebral cortex and lead to development of foci of functional disturbances, more or less "isolated points" in the cerebral cortex. Under the action of conditioned stimuli these "affected points" of the cortex manifest their pathologic inertness and irregular reaction to stimuli; the activity of the cortex is for a time disturbed. The other stimuli, being applied where they cannot act on an affected point evoke the usual reactions of the cerebral cortex.

Focal impairment was found, for example, in the following experiment.

An inhibitory-type dog was subjected to a process of modifying a negative conditioned reflex to a positive conditioned reflex. The modification was achieved by a continuous combination of a negative conditioned stimulus with an unconditioned stimulus. When the attempts at such modification were long unsuccessful, signs of limited disturbances appeared. The differentiating stimulus (metronome) began to evoke phasic phenomena. In the presence of definite stimulation (for example, by a metronome) all the other conditioned stimuli produced no effect; at the same time the cortex exhibited signs of a pathologic state, i.e., it ceased to react by excitation to strong stimuli and entered various phases of inhibition to the point of total inhibition. Until then all conditioned auditory stimuli had produced the usual effects. It follows that in this case it was a matter of some disturbance in the cortical auditory analyzer, of overstrained mobility of its nervous processes.

A rather stable overstrain of the nervous processes, a disturbance in the relations between excitation and inhibition developed in the affected, isolated point of the cortex. In this pathologic point the stimulus either intensifies the process of inhibition, which sub-

sequently irradiates and involves other cortical cells, or acts on the pathologic focus as a destructive agent and produces considerable deviations in conditioned reflex activity. Such focal dynamic disturbances have been repeatedly observed in experimental neuroses.

However, functional disturbances in certain foci of the cortex must not be regarded as strictly isolated and anatomically localised. They maintain constantly changing connections with other areas of the cortex, influence the state of the entire cortex and, under certain conditions, provoke disturbances in its activity as a whole.

Experimental neuroses and discovery of the laws governing their development have served as a model for studying the pathogenesis of the disorders of higher nervous activity in man.

On the basis of experimental and clinical observations Pavlov developed a very original and fruitful conception of the mechanism of development of such neuroses as neurasthenia, psychasthenia and hysteria, indicated the ways of investigating the pathogenesis of disturbances in higher nervous activity in schizophrenia and certain other diseases, and explained the phenomena of hypnosis, delirium and hallucinations.

Disturbances in Higher Nervous Activity in Vegetative and Endocrine Disorders, Intoxications and Starvation.

Vegetative and endocrine disorders affect higher nervous activity.

Removal of the upper cervical sympathetic ganglia and transection of the cervical sympathetic nerve intensify inhibitory processes and cause development of inertness with a general diminution in conditioned reflex activity which are not completely restored for a period of up to one year after infliction of the injury. Transection of the splanchnic nerves and bilateral removal of the abdominal sympathetic chains may lead to intensification of the stimulatory and weakening of the inhibitory process. These changes in the function of the cerebral cortex produced by action exerted on the sympathetic nervous system are apparently due to influences of the sympathetic nervous system on the activity of the brain. Some role in this may also be played by changes in the activity of the adrenal glands which have sympathetic innervation.

Artificial injury to the optic thalamus and hypothalamus is accompanied by a sharp weakening of the stimulatory and inhibitory processes with a predominance of the latter. Normally the anterior part of the hypothalamus apparently exerts a tonic influence on the cerebral cortex and increases its adaptability, whereas the posterior part inhibits the cortex.

In time the artificially produced disturbances in the vegetative functions may disappear in virtue of the plastic compensatory capacities of the cerebral cortex.

An important part in the cortex-subcortex relations is played by the *brain stem reticular formation*. It has been experimentally shown that influences of the cortex are transmitted to the lower

parts of the nervous system through the reticular formation. On the other hand, the reticular formation exerts an influence on the activity of the cortex. The descending influence is manifested in the fact that one zone of the reticular formation inhibits the motor function of the spinal cord, while its other zone facilitates the influence of the cortex on the same motor elements. Moreover, stimulation of the reticular formation leads to inhibition of afferent excitations which are produced, for example, by stimulation of one of the posterior roots of the spinal cord. The ascending influence of the reticular formation manifests itself in increased tone of all areas of the cerebral cortex. Injury to the reticular formation eliminates this influence with the result that the animal lapses into a sleepy state. The influences of a number of humoral substances on the cortex, for example, the effects of adrenalin, certain anesthetics and hypnotics are apparently also exerted through the reticular formation. Lastly, the reticular formation is closely connected with the functions of the subcortical structures which regulate the vegetative functions of the organism.

Dysfunction of the endocrine glands is often accompanied by clearly marked, but usually reversible changes in the reactivity of the cortex.

A diminution in conditioned reflexes and difficulty of elaborating differentiations, as well as phenomena of diffuse inhibition and drowsiness are observed in dogs during estrus, pregnancy and lactation. These phenomena are apparently due to changes in the functions of the gonads; the phasic states observed during sexual excitement are probably caused by negative induction which affects the entire cortex.

Distinct changes in higher nervous activity occur in endocrine disorders artificially produced by extirpation of endocrine glands or injection of their extracts.

In dogs *castration* causes perceptible weakening of internal inhibition, then increased external inhibition and general diminution in conditioned reflex activity. Circularity—periodic changes in higher nervous activity—manifests itself several months later. For some time it is disorderly, then it improves, but periodically becomes disorderly again. However, the periods of disorderly higher nervous activity grow increasingly fewer and the disturbances weaker. Gradually higher nervous activity becomes relatively normal, which indicates the existence of adaptive mechanisms in the organism. At the same time, castration results in excessive fragility and vulnerability of the nervous system, especially the cerebral cortex. Such animals readily suffer nervous breakdowns, and it is not difficult to stimulate development of experimental neuroses in them.

The character of changes in higher nervous activity following castration largely depends on the type of nervous system. For example, in dogs of the strong type these changes are particularly

clearly marked in the first months after castration, following which they gradually disappear. Owing to the loss of sexual stimuli representatives of the weak type display greater efficiency for some time after castration, but then succumb to the same disturbances in higher nervous activity as do those of the strong type. These disturbances sometimes persist for many months.

Analogous disturbances in higher nervous activity are observed in old dogs mainly as a result of the loss of hormonal influences of the gonads. Here, too, the processes of internal inhibition are the first to be affected; this is followed by phenomena of external inhibition and diminution in conditioned reflex activity. Ligation of a seminal duct or transplantation of a young seminal gland into the scrotum causes a temporary, but clearly marked increase in the excitability of the cortex and improves its efficiency.

Changes in higher nervous activity are also caused by *ablation of the thyroid*. Thyroidectomised dogs exhibit weakening of the stimulatory and inhibitory processes, sharply decreased excitability of the cerebral cortex and diminished ability to elaborate conditioned reflexes. Contrariwise, injections of thyroidine increase the excitability of the cortex and produce phenomena of general motor excitement. Prolonged administration of thyroidine leads to nervous exhaustion with phasic phenomena and development of diffuse protective inhibition.

Removal of the parathyroids sharply reduces conditioned reflex activity and disturbs the relations between excitation and inhibition, weakening the stimulatory and relatively increasing the inhibitory process. The parathyroid hormone causes the inhibitory process to predominate over the stimulatory process. In such cases a correspondence between the changes in the blood calcium and the character of cortical function has been established.

Stimulation of the hypophysis in connection with dysfunction of the hypothalamus disturbs the normal relations between the stimulatory and inhibitory processes and produces phenomena of sleep inhibition. Predominance of inhibition and increased unconditioned reflex activity have also been observed after injections of large doses of pituitrin, a hypophysial preparation, which noticeably affects the work of both the cerebral cortex and the subcortex.

Removal of the adrenals results in diminished conditioned reflex activity and development of phasic states in the cortex, whereas injections of large doses of adrenalin cause phenomena of diffuse inhibition following a temporary increase in excitability.

The *action of toxic substances*, for example, bacterial toxins, alcohol, acetone, benzene, carbon monoxide, cyanides, bulbocapnine, amphetamine sulfate, etc., is also accompanied by early signs of disturbances in higher nervous activity.

Usually the first and most to be affected in animals are processes of internal inhibition; not infrequently there is a rather long

period of increased cortical excitability with disinhibition of inhibitory conditioned reflexes. Diffuse inhibition in the cortex with depression or disappearance of the conditioned and sometimes of certain unconditioned reflexes occurs at the height of intoxication. Phasic phenomena may arise against the background of developing diffuse inhibition; in some forms of intoxication these phenomena are observed during the period of increasing pathologic symptoms and in other forms—during the period of their retrograde development.

Diffuse irradiating inhibition is of a protective nature and is directed against exhaustive toxic influences. Inhibition spreads from the evolutionary youngest forms of nervous activity to the oldest, i.e., unconditioned reflex forms.

Clearly marked disorders of vegetative functions develop as a result of irradiation of inhibition to the subcortex. Intoxications run a very severe course in weak and unbalanced dogs, while representatives of strong and balanced types of nervous system offer the greatest resistance to intoxications.

It is also possible to produce symptom complexes of various intoxications through conditioned stimuli after establishing connections between the stimuli and the intoxications. After being repeatedly combined with an injection of small doses of apomorphine which stimulates the vomiting centre the sound of an organ pipe alone served as a conditioned stimulus that provoked nausea and vomiting.

In this manner it is possible to produce a number of conditioned pathologic phenomena, namely, morphine intoxication, poisoning with camphor, bulbocapnine, carbachol, eserine, etc.

Starvation causes nervous phenomena resembling those observed in infectious and toxic processes. It is also characterised by disturbances in internal inhibition, onset of phasic phenomena, and weakening or disappearance of conditioned reflexes. In starvation the development of inhibition is apparently due to exhaustion of the nerve cells.

At the same time it is important to note that nervous breakdowns (derangement of higher nervous activity) and overstrain of the nervous processes caused by the difficult tasks given the animals in experiment prolong and complicate the process of starvation suffered by them.

Factors affecting the general condition of the organism, for example age characteristics and metabolic disorders, may alter the reaction of the organism to conditioned pathologic stimuli.

Experimental Therapy of Disturbances in Higher Nervous Activity. Experimental reproduction of functional disturbances in higher nervous activity has not only made it possible to investigate a number of most important pathogenic regularities in the activity of the higher parts of the brain, but has also helped to establish prin-

ples of experimental therapy of disturbances in higher nervous activity in various pathologic states. The impending danger of exhaustion of the cortical cells can be prevented by agents which increase protective inhibition.

It has been possible noticeably to increase the phenomena of protective inhibition by long rest. Administration of bromides whose physiologic effect consists in strengthening the inhibitory process has proved very helpful. In other neurotic cases a favourable effect has been produced by combined action of bromides and caffeine. Long drug-induced and especially natural and conditioned reflex sleep has often produced a positive effect on the activity of higher parts of the central nervous system.

It has also been possible to suppress the effect of toxic substances by conditioned reflexes. For example, the effect of toxic doses of morphine has been weakened by means of conditioned inhibition. Clearly marked phenomena of protective inhibition observed at the height of intoxication or during its retrograde development justify the attempts to evoke and deepen such inhibition by means of long physiologic or drug-induced sleep for the purpose of favourably influencing the affected organism.

DISORDERS OF SENSITIVITY

Sensitivity disorders arise as a result of impaired transmission of excitation along sensory nerves from the peripheral receptors and along afferent nerves to the cerebral cortex. Changes in sensitivity are closely connected with motor reactions which are essentially reflex reactions. The motorium itself has a large number of receptors—proprioceptors. Disturbances may also occur on various levels of the central nervous system, i.e., lesions are possible in the grey matter of the posterior column, conduction paths in the spinal cord and the medulla oblongata, the optic thalamus, the ascending parietal gyrus and upper temporal region of the cerebral cortex.

Forms of Sensitivity Disorders

Sensitivity may be diminished—*hypesthesia*, lost—*anesthesia*, and increased—*hyperesthesia*.

Diminished sensitivity is due to weakened impulse conduction, loss of sensitivity—to complete absence of impulse conduction. Sensitivity may be increased artificially by stimulation of various parts of the sensory nervous system. Combinations of both are possible, i.e., diminution in or loss of one form of sensitivity (tactile) may be combined with increase in another form of sensitivity (pain).

Paresthesia is manifested by abnormal sensation of pain, temperature, etc. (numbness, prickling, etc.).

There are also *simple* and *complex* forms of sensitivity.

Simple sensitivity is in turn divided into *exteroceptive* or superficial (of the skin and mucosa), *proprioceptive* or deep (of the muscles, joints and bones) and *interoceptive* (of the internal organs).

Exteroceptive sensitivity is sensitivity to pain, touch and temperature; proprioceptive sensitivity is the sense of active and passive movements, pressure and vibration; interoceptive sensitivity reflects the state of the internal organs.

Complex sensitivity includes the sense of localisation (determination of the site of application of the stimulus), sense of discrimination (ability to distinguish between two simultaneously applied stimuli), sense of space, sense of body position and sense of recognising objects by touch (*stereognosis*).

Sensitivity may be *cortical*, *epicritic*, which makes it possible to appreciate fine distinctions of stimuli (it underlies the ability to establish fine relations between stimuli and motor reactions), and *thalamic*, *protopathic*, phylogenetically older, characterised by coarse, elementary perception and underlying the automatic motor reflexes.

Anesthesia and Hypesthesia. The following forms of anesthesia are distinguished according to the character of lost or diminished sensitivity: *anesthesia proper* or tactile anesthesia, *analgesia* or pain anesthesia, *thermoanesthesia*—loss of the perception of thermal impressions, and loss of *deep* or *proprioceptive* sensitivity, i.e., disturbance in the appreciation of the position of organs in space.

Transection of or *injury to a peripheral sensory nerve* causes the loss of all forms of sensitivity in the region covered by the function of this nerve. In such cases the animal ceases to react or reacts weakly to cold and heat, pain stimuli, contact and change in the position of the body.

Transection of several adjacent *posterior roots* causes loss of sensitivity on the surface of the zone in which the sensory fibres of these roots are distributed. Injury to the grey matter of posterior cornua causes dissociative disorders of sensitivity. Pain and temperature anesthesia develops, while the tactile and proprioceptive forms of sensitivity are retained since the conductors are severed not in the grey matter of the posterior cornua, but higher—in the medulla oblongata.

Dissociative disorders of sensitivity may arise only in cases of *injury to the spinal cord and the medulla oblongata* since in them the pathways of pain and temperature sensitivity run apart.

The peculiar distribution of the disturbances in sensitivity and motor functions can be observed after transection of one lateral half of the spinal cord (Brown-Séquard experiment). A disturbance in pain and temperature sensitivity is observed on the side opposite to the site of injury, whereas loss of tactile sensitivity and of the

motor function occurs on the side of the injury. This cross damage is due to the fact that the conductors of pain and temperature sensitivity cross over as they enter the spinal cord. A decussated loss of sensitivity is also observed in unilateral injury upward of the medulla oblongata.

Injury to the optic thalamus causes decussated impairment of all forms of sensitivity.

Lastly, *injury to the sensory regions of the cerebral cortex* causes decussated diminution in or loss of sensitivity on the periphery. In this case the sense of localisation of organs and the appreciation of the shape of objects are impaired; pain and temperature sensitivity is disturbed somewhat less.

Loss of sensitivity may also arise on a functional basis, for example, in *hysteria* or excessive stimulation of receptors due to intense trauma when pain impulses from the periphery are blocked.

Hyperesthesia and Paresthesia. *Hyperesthesia* can be provoked in animals by removal of the cerebral cortex. For example, a decorticated dog displays a violent defence reaction when its back is stroked. The reason is that loss of cortical sensitivity disinhibits thalamic sensitivity.

Intense hyperesthesia often arises reflexly as a result of injury to the nerves or formation of a neuroma which stimulates the proximal end of the transected nerve, as in trauma of the sciatic nerve. In this case sensitivity is greatly intensified and is characterised by burning pain (*causalgia*).

Paresthesia, i.e., perverted sensitivity arises in cases of unusual stimulation of peripheral nerves or central sensory structures, for example, the nuclei of the optic thalamus or the ascending parietal gyrus (in circulatory disorders, intoxications and inflammatory processes). These cases are marked by peculiar sensations of crawling, burning or numbness.

Pain Sensation. Pain is one of the main signs of a pathologic process reflecting structural and functional disturbances. The character and intensity of pain vary very widely, and depend on both the cause of the pain and the properties of the affected organism. Pain may be caused by various exogenous (mechanical, chemical, physical, etc.) and endogenous (circulatory disturbances, tumours, inflammation and accumulation of metabolites) factors.

Pain arises as a result of stimulation of the body surface and disturbances in the sensitivity of internal organs, for example, in lesions in serous membranes, spastic contractions of hollow organs or their distention.

Pain may be of cortical and thalamic origin. Thalamic pain differs from cortical pain by its high stimulation threshold, great intensity, prolonged after-effect and absence of precise localisation.

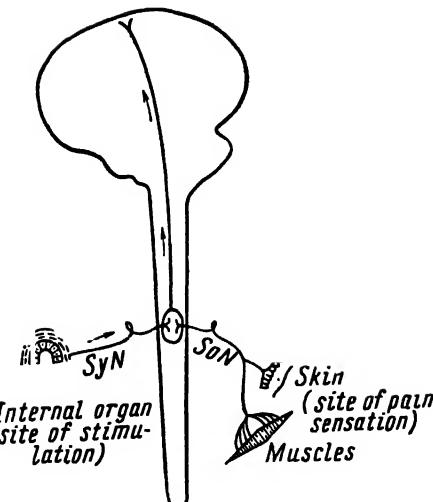


Fig. 167. Diagram of the mechanism of visceral pains (viscerosensory reflex). SyN—sympathetic nerve; SoN—somatic nerve. Impulse from stimulated internal organ travels through the grey matter of the spinal cord along the spinothalamic tract to the cerebral cortex. This results in pain referred to the region of the somatic nerve which is on the same segmental level in the spinal cord as the sympathetic nerve which innervates the given internal organ.

Cortical sensitivity inhibits thalamic sensitivity, for which reason loss of cortical sensitivity causes a strong thalamic pain reaction of the animal to the stimulus.

Algetic disturbances in the sensitivity of internal organs arise as a result of reflexes effected by the viscerosensory system, by means of which impulses from the internal organs are transmitted through afferent fibres to the spinal cord and higher and thence to the spinal endings of cutaneous receptors (Fig. 167).

Owing to these viscerosensory reflexes in some internal diseases (for example, angina pectoris, appendicitis and cholelithiasis) certain portions of the skin are characterised by increased pain sensitivity (Zakharyin-Head zones).

The sensation of pain is accompanied by changes in the activity of the vegetative division of the nervous system. This is manifested in dilation of the pupils, elevation of blood pressure, hyposecretion of the digestive glands, anuria, hyperglycemia, tachycardia and adrenalinaemia. Pain is also accompanied by reflex hypersecretion of hormones (adrenocorticotropic hormone, vasopressin and adrenalin) which participate in the defensive physiologic reactions of the organism that ensure restoration of functions, for example, elevate the blood pressure, increase blood clotting (in hemorrhages), intensify immune reactions, etc.

MOTOR DISORDERS

Motor disorders are caused by dysfunction of various parts of the motor nervous system. They are based on disturbances in the conduction of impulses to muscles along motor nerves.

The causes of motor disorders may be inflammatory changes (mainly of an infectious origin), traumas, hemorrhages, thrombosis, embolism, or functional changes produced by hysteria or psychic trauma.

The disturbances in the motor nervous system manifest themselves as paralyses, pareses, hyperkinesias and impaired synkinesis and neuromuscular coordinations.

Loss of Motor Functions

The total loss of motor functions due to complete interruption of the spread of motor impulses is known as *paralysis*; it is manifested in total inability to perform voluntary movements. Incomplete loss of motor functions, i.e., weakening of voluntary movements is called *paresis*. All paralyses and pareses may be divided into *peripheral* and *central*.

Peripheral paralyses and pareses arise as a result of complete or incomplete destruction of a peripheral motor neuron, which may be due to affection of cells of the anterior cornua of the spinal cord, the anterior roots of the spinal cord or peripheral motor nerves. Polyneuritides due to avitaminoses, inflammation of nerves or nervous plexus may serve as an example of peripheral paralyses. In the last case polyneuritides are also accompanied by disturbances in sensitivity in corresponding regions.

Experimentally a peripheral paralysis can be easily produced by transection of any peripheral nerve which contains motor fibres. For example, in the dog transection of the sciatic nerve in the region of the middle third of the thigh is followed by paralysis of the shin flexors and the muscles of the paws. When the animal moves it drags the lower part of the affected limb. The anterior cornua of the spinal cord, where the cells of peripheral motor neurons are localised, may be affected in traumas or injuries to the cord.

These phenomena are reproduced in experiment by transection of the spinal cord.

The transection is followed by *spinal shock* which is marked by sharply decreased excitability and depression of reflex activity of the regions located below the site of transection. The function of the part of the spinal cord above the transection is almost unaffected. In spinal shock all motor reflexes disappear, the blood pressure drops, the urinary and defecation reflexes are absent. In dogs the reflex contractions of skeletal muscles begin to be restored within several hours. In spinal shock the complete disconnection between the parts of

the spinal cord eliminates the impulses arising in the higher parts of the central nervous system and influencing the excitability of the segmental apparatus of the spinal cord (Trendelenburg).

Peripheral paralyses are characterised by the loss of both voluntary and reflex movements. Owing to complete absence of efferent impulses the muscles lose their tone, and *hypotonia* develops. In passive movements the muscles offer no resistance.

Another feature of peripheral paralyses is *muscular atrophy* (Fig. 168).

The atrophy develops gradually as a result of muscular inactivity and disturbances in the metabolism and natural tone of the muscles.

In peripheral paralyses the *tendon reflexes* disappear because the impulses from the muscles cannot evoke reflex contractions of these muscles.

The *electroexcitability* is also *impaired* with the result that the "reaction of degeneration" sets in. Stimulation of a nerve with electric current evokes no contraction of the muscle it innervates. In cases of direct stimulation of the muscle the latter does not respond when acted upon by alternating current, but does react when acted upon by direct current; in these cases the stimulation threshold is elevated, and the contractions become *sluggish* and *vermicular*. In contrast to what takes place normally the anodal closure produces stronger contractions than does cathodal closure.



Fig. 168. Muscular atrophy and deformity of the monkey's right lower limb in chronic poliomyelitis (Levaditi).

Central Paralyses and Pareses. The loss or weakening of conduction of a central motor neuron causes paralyses and pareses.

The following forms of central paralyses and pareses are distinguished: *hemiplegia* or *hemiparesis*—affection of half of the body opposite to the site of affection in the central nervous system; *monoplegia*—affection of one limb; *paraplegia*—simultaneous affection of either the upper or lower limbs; *tetraplegia*—paralysis of the muscles of both sides of the body.

Impairment of a central motor neuron is caused by hemorrhages into the internal capsule, thrombosis and

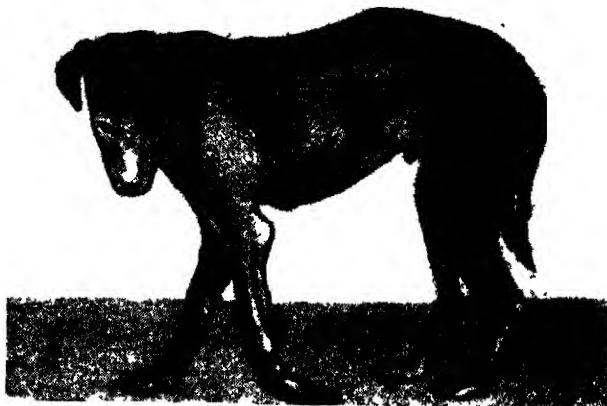


Fig. 169. Position of the dog after injury to the right side of the motor zone of the cortex (removal of the sigmoid gyrus), paralysis on the left side

embolism of cerebral vessels and cerebral tumours. Mainly the cells of the motor area of the cortex or their axons in the pyramidal tracts are affected, the peripheral motor neuron remaining intact.

A brief total loss of the motor function is followed by *hypertonia*—excessive muscle tone—which manifests itself on attempts to perform passive movements, for example to flex an arm or leg, in which case the investigator feels a characteristic springy resistance. Voluntary movements are lost, the reflex reactions are retained and even intensified because the inhibitory influences on the reflexes coupling in the spinal cord are weakened as a result of affection of the central apparatus. Atrophy is negligible or does not develop at all. The tendon reflexes are intensified and their reflexogenic zones are extended. For example, in cases of central paralysis the patellar reflex can be evoked by a tap not only against the patellar tendon, but also against the thigh or lower leg.

Disinhibition manifests itself in intensification of the extension reflex (Babinski's sign—extension of the great toe with fanning of the other toes on exciting the sole) or the flexion reflex (Bekhterev-Mendel reflex—dorsal flexion of the second to fifth toes in normal individuals when the dorsum of the foot is tapped).

Reflex stimulation may give rise to *muscular spasm* and even *contracture*; for example, the upper limb is brought closer to the body and is flexed in the elbow joint, the limb is pronated and the fingers are flexed; the lower limb is extended in the hip and knee joints, the foot performing a grasping movement.

The degree of a central motor affection and its extension to particular muscle groups depend not only on the focus of affection but also on dissociation of functions and compensation, for exam-

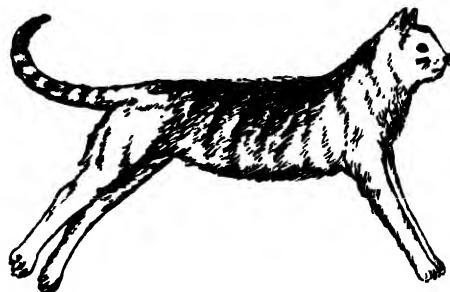


Fig. 170. Decerebrate rigidity in the cat.

ple, the substitution of one affected hemisphere for the other. The more differentiated the functions of the central motor apparatus, the more difficult the substitution for and restoration of the motor functions.

The unilateral affection of a central motor neuron in the cerebral cortex causes paralysis of the limbs on the opposite side since, owing to decussation of most pyramidal fibres on the borderline between the brain and spinal cord, the left hemisphere innervates the right side of the body, and vice versa (Fig. 169).

The character of the paralyses depends on the degree of affection not only of the brain, but also of the brain stem. Transection of the brain stem affects, in addition to the pyramidal tracts, also the extrapyramidal tracts; tetraplegia develops, the paralysed limbs are extended, and the tone of the muscles of the neck and back increases (decerebrate rigidity) and results in opisthotonus—the head is bent backward, the jaws are locked and the trunk is arched forward (Fig. 170).

Extrapyramidal motor disorders are characterised not so much by loss of motor functions as by phenomena of *dissociation*. Disturbances in the relations between the cerebral cortex, subcortical ganglions, the cerebellum and spinal cord arise. These conditions are marked by *loss of synkinetic movements*. The automatism inherent in movements diminishes, the voluntary movements become difficult and slow. The movements are generally insufficiently co-ordinated. The patient appears fixed in his posture and moves like an automaton. In extrapyramidal disorders the plastic muscle tone increases and *rigidity* develops owing to affection of the pallidal and thalamic regions (for example, in carbon monoxide poisoning). General rigidity is observed.

Muscular hypertonia which arises in cases of extrapyramidal lesions is not spastic, as in pyramidal paralyses, but displays *excessive static tone* with difficult transition to dynamic tone, i.e., in attempts to change the position of a limb the resistance is equal in

the agonists and antagonists in all phases of the movement. Inhibition arises at the very outset. The limb remains in the position artificially imparted to it.

There is also a group of central paralyses which arise on a functional basis, as in *hysteria*. These paralyses may simulate various forms of coarse organic lesions, but unlike the latter they do not exhibit the phenomena which are considered especially characteristic of true paralyses.

Hyperkinesias

Hyperkinesias are involuntary, excessive movements; they may be spinal, pyramidal and extrapyramidal, and may result from stimulation of motor regions of the central nervous system.

The causes of hyperkinesias are not yet completely clear. In addition to reflex and direct stimuli (metabolic disturbances, inflammation, etc.), an important part is played by a function of the higher inhibitory apparatus (*putamen* and *caudate nucleus*), which leads to disinhibition of corresponding motor zones. Combinations of stimulation of one portion of the brain with disinhibition of another are also possible.

Hyperkinesias of spinal origin are characterised by fibrillary contractions, i.e., isolated contractions of various muscle fibres, for example, in spinal muscular atrophy. Fibrillary contractions are observed in any stimulation of a peripheral motor neuron.

Hyperkinesias of pyramidal origin are most commonly manifested in *convulsive states*. The convulsions may be tonic and clonic.

Tonic convulsions are characterised by periodic protracted involuntary muscular contractions.

Clonic convulsions are intermittent rhythmic involuntary muscular contractions alternating with relaxations. Tonic convulsions result from stimulation of subcortical ganglia, clonic convulsions —from excitation of the cerebral cortex.

Experimentally convulsive seizures can be produced by passing electric current through the animal's brain.

Clonic convulsions are followed by tonic convulsions in guinea pigs during *anaphylactic shock*. Alternation of clonic and tonic convulsions is observed in *epilepsy*. Convulsions may also be the result of *traumatic injury*, *poisoning with bacterial toxins* (*in tetanus, rabies*) or *metabolites* (for example, in diabetic and hepatic coma).

Convulsions may be of a *reflex* character, due to strong pain stimulation, as in stimulation of the sciatic nerve or posterior roots (by scars or neuroma), or as in inflammation of the meninges. Such stimulation in the central nervous system gives rise to foci of stable excitation.

The affected focus in the central nervous system, which causes convulsions, probably reacts to stimulation according to the prin-

ple of the dominant, thereby renewing or intensifying the convulsive seizure.

Convulsive seizures grow more frequent under the influence of emotions and various external stimuli.

Lastly, convulsions may be produced by *conditioned reflexes*; for example, a convulsive seizure may occur under the influence of a situation in which it had occurred previously.

The *hyperkinesias of extrapyramidal origin* include *chorea* and *athetosis*. *Chorea** is characterised by involuntary, fast and irregular action of some group of muscles, mainly those of the face and proximal parts of the extremities. *Athetosis*** is also characterised by convulsive, but slower movements primarily in the distal parts of the extremities, the movements involving simultaneously the agonists and antagonists; sometimes the convulsions involve the entire muscular apparatus.

Hyperkinesias include the involuntary, extremely rapid contractions of a certain group of muscles, which do not produce any change in the position of the body or limbs, and the involuntary movements which reproduce various motor acts of mimicry and gesticulation, for example, winking, shoulder-shrugging, knitting of the brow, etc.

Hyperkinesias of extrapyramidal origin not infrequently manifest themselves in the form of tremor. There are various forms of tremor of toxic origin, for example, in chronic alcohol poisoning and mercury poisoning; some forms are due to organic lesions (Parkinson's disease and multiple sclerosis).

Disturbances in neuromuscular coordinations occur in cases of lesions in certain parts of the central nervous system, as the motor zones of the cerebellar cortex, optic thalamus, brain stem, labyrinth and posterior columns of the spinal cord which receive the signals from the proprioceptors of the skeletomuscular system and the receptors of the visual and vestibular apparatus on the position of the various parts of the body, the speed of movements and resistance to these movements. Inadequacy or absence of these signals affects the coordination of movements.

Affection of the cerebellum and the temporal and frontal lobes associated with it leads to disturbances in the coordination of movements without paralyses; these disturbances are known as *ataxia*.***

Ataxia is manifested in lack of muscular coordination in standing still (static ataxia) or in movement (dynamic ataxia). In the latter case the movements lack smoothness, precision and balance.

Animals deprived of the cerebellum move with difficulty; they

* From the Greek word *choreia*—dance.

** From the Greek word *athetos*—without position.

*** From the Greek word *ataxia*—disorder.

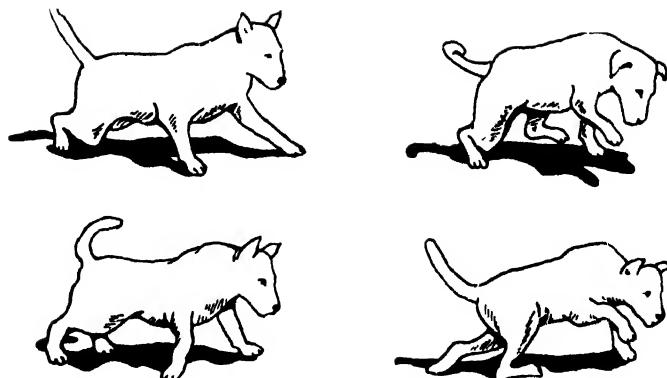


Fig. 171. Incoordination of movements in the dog after removal of the cerebellum (Dusser de Barrene).

throw out their legs, which are struck against the floor, and stagger, as the result of impaired tone of the abductors and adductors of the limbs (Fig. 171).

Ataxia is distinguished according to localisation as cerebral, cerebellar, labyrinthine and spinal.

DYSFUNCTION OF THE VEGETATIVE NERVOUS SYSTEM

Disturbances in the functions of the vegetative nervous system may arise as a result of lesions in its different parts or may accompany different disorders of the reflex activity of the central nervous system. The vegetative neural structures form part of the reflex arcs which connect the higher parts of the central nervous system with peripheral organs (Fig. 172).

Functional disturbances may be observed in different parts of the vegetative nervous system and may be manifested as afunction, stimulation or mixed phenomena. They are caused by infection, intoxication, trauma, etc. In experiment they are produced by transection or stimulation of various neural structures.

The *affections of peripheral vegetative nerves and ganglions* vary very widely. In animals afunction of the sympathetic trunk causes rapid emaciation, dilation of vessels, excessive heat loss, drop in body temperature and in blood pressure, and a noticeable diminution in adaptability. Opposite phenomena develop in cases of stimulation of sympathetic nerves, namely, constriction of vessels, elevation of blood pressure, tachycardia and increased metabolism.

Vegetative disturbances in the internal organs may be caused by lesions in corresponding vegetative nerves since any organ usually has both sympathetic and parasympathetic innervation. In these cases efferent impulses spread over sympathetic nerves diffusely

because their preganglionic fibres run to several ganglia which in turn send fibres to various organs, whereas parasympathetic ganglia are located near the corresponding organs or even within them.

Moreover, in cases of lesions in the vegetative nervous system exclusion of vegetative nerves is soon manifested in increased sensitivity of the denervated structures, for example, sympathectomy makes the denervated vessels excessively sensitive to adrenalin, whereas transection of the parasympathetic nerves which innervate the iris renders the latter excessively sensitive to parasympathomimetic substances. In the mechanism of these phenomena a certain part is apparently played by the increased permeability of the capillaries of the denervated organ and the fact that this organ is more easily penetrated by physiologically active substances.

Impairment of the functions of the *spinal vegetative centres and tracts* (for example, in injuries and infections) is manifested in dysfunction of the vasomotorium, pilomotorium and perspiration of the corresponding sections of the skin.

Lesions in the vegetative zones of the lumbar and sacral parts of the spinal cord cause dysfunction of the bladder and genitalia.

Brain stem vegetative disorders arise as a result of lesions in the medulla oblongata, the pons varolii, and cerebral peduncles with the corpora quadrigemina. They are manifested in dysfunction of the vagus nerves, as well as respiratory and circulatory disturbances, and are due to hemorrhage, thrombosis, embolism, tumours or infections (for example, in poliomyelitis).

Lesions in the hypothalamus vary the most widely because the hypothalamus is connected by nervous pathways with the higher and lower neural structures and has neural connections with the hypophysis. Experimental destruction of the tuber cinereum proves fatal. Electric or mechanical stimulation of various portions of the tuber cinereum is accompanied by *disturbances in vegetative functions*, namely, vasomotor disorders (Karplus and Kreidl), elevated blood pressure, dilated pupils, excessive perspiration, and changes in thermoregulation, respiration, heart action and metabolism.

Disturbances arising in the hypothalamus cause various *vegetative disorders*, for example, impaired metabolism, diabetes insipidus, fever, circulatory disturbances and dysfunction of the smooth muscles.

There are experimental and clinical data on the role of the hypothalamus in inducing sleep. Prolonged sleep is sometimes observed in cases of tumours, encephalitis and other diseases of the hypothalamus. This can evidently be explained by disturbances in the functional relations between the hypothalamus with its vegetative functions and the activity of the cerebral cortex, namely, the intensification of the process of inhibition in the cortex.

All the aforementioned pathologic symptoms come particularly

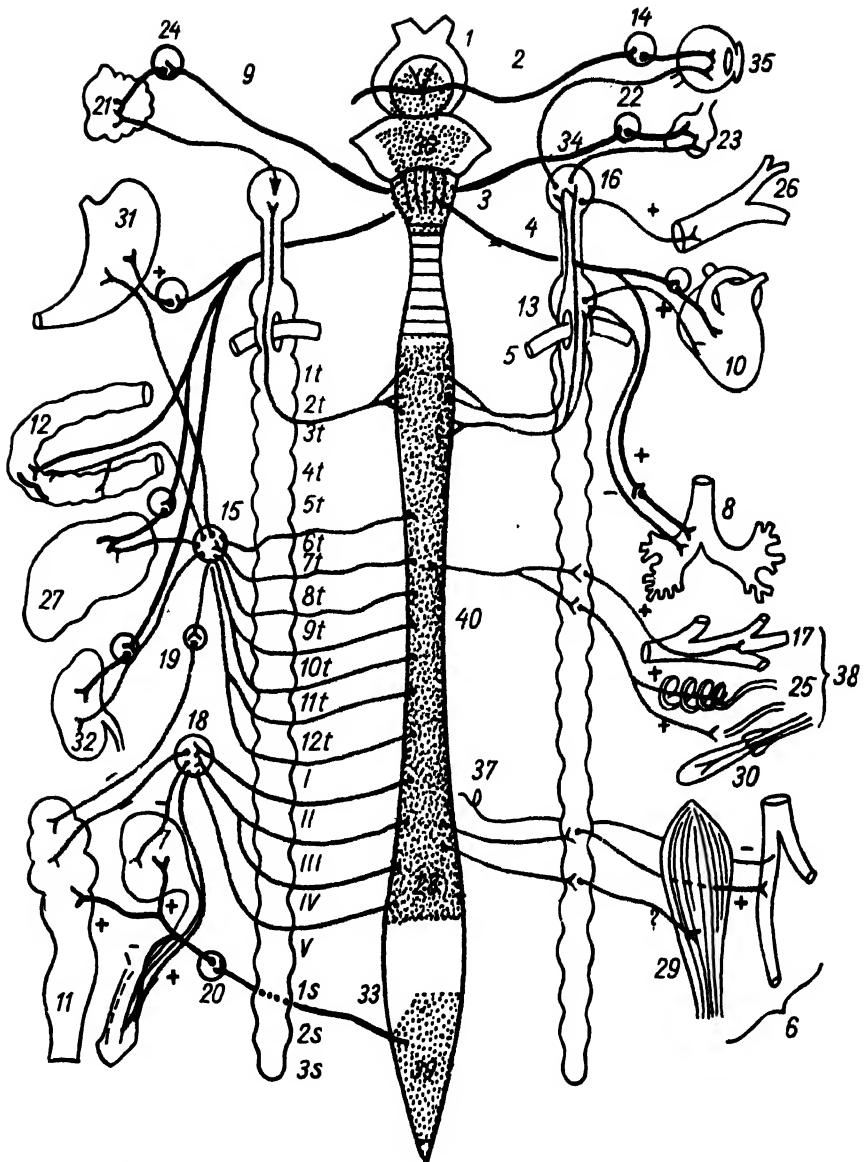


Fig. 172. Diagram showing innervation of man's internal organs by the sympathetic (red) and parasympathetic (blue) divisions of the vegetative nervous system
 11-12t - thoracic ganglia; I-V-lumbar ganglia; 1s-3s - sacral ganglia; 1-optic nerve
 2-oculomotor nerve; 3-facial nerve; 4-vagus nerve; 5-subclavian artery; 6-limbs; 7-bladder;
 8-bronchi; 9-chorda tympani; 10-heart; 11-descending colon; 12-small intestine; 13-
 inferior cervical ganglion; 14-ciliary ganglion; 15-ceeliac ganglion; 16-superior cervical
 ganglion; 17-vessels; 18-inferior mesenteric ganglion; 19-superior mesenteric ganglion; 20-
 pelvic ganglion; 21-submaxillary gland; 22-sphenopalatine ganglion; 23-lacrimal glands;
 24-submaxillary ganglion; 25-sweat glands; 26-cerebral vessels; 27-liver; 28-lumbar part
 of spinal cord; 29-muscles; 30-arrectores pylorum; 31-stomach; 32-kidneys; 33-erigens;
 34-greater superficial petrosal nerve; 35-pupils; 36-pons; 37-posterior root; 38-body; 39-
 sacral part of spinal cord; 40-thoracic part of spinal cord

to the fore during rapid development of pathologic phenomena in the hypothalamus, whereas in cases of their slow development processes of compensation involving the lower neural structures come into play.

Disorders of the vegetative functions may also arise as a result of affection of the cerebral cortex. For example, stimulation of various areas of the cortex alters the diameter of the pupils and the secretion of the salivary and lacrimal glands, causes changes in bile secretion, increases intestinal peristalsis, contracts the bladder and impairs respiration and cardiovascular activity. Vegetative nervous disorders often arise in cases of emotional stress, hypnotic suggestion, and many disturbances in the functions of internal organs, in whose pathogenesis an important part is played by dysfunction of the cerebral cortex, as is the case in ulcers, hypertensive vascular disease, angina pectoris, bronchial asthma and diseases of metabolism.

Cortical regulation of vegetative functions is effected through subcortical structures where the efferent vegetative pathway of the reflex arc begins. On the other hand, the hypothalamus in its turn affects the function of the cerebral cortex.

A very important role in performing vegetative nervous functions and maintaining the relations between the cerebral cortex and the vegetative nervous system is ascribed to the brain stem reticular formation which has close connections with the functions of the cortex, thalamus, hypothalamus and medulla oblongata (Magoun, Moruzzi).

For example, the reticular formation of the medulla oblongata takes part in regulation of respiration and blood circulation. An analogous formation in the hypothalamus apparently participates in the regulation of heat and metabolism.

General Dysfunction of the Vegetative Nervous System

The effects produced by sympathetic and parasympathetic innervation are usually antagonistic, i.e., where one system stimulates, the other inhibits (Langley). For example, sympathetic stimulation of the heart accelerates its action, whereas parasympathetic stimulation slows it. Stimulation of the parasympathetic nerve increases salivation, while stimulation of the sympathetic nerve decreases it. The same applies to the visceral innervation of vessels and smooth muscles.

The recognition of antagonism between the two divisions of the vegetative nervous system was also based on data concerning the effects produced by specific vegetative substances—sympathomimetic (mainly adrenalin) and parasympathomimetic (acetylcholine and pilocarpine)—which at first sight exert contrary influences on a number of vegetative functions.

The antagonism between the two divisions of the vegetative nervous system began to be interpreted so that stimulation of one necessarily led to depression of the other and vice versa. It was assumed that there was an absolute antagonism between the two divisions of the vegetative nervous system and a high "tone" of one absolutely excluded or weakened the "tone" of the other. This gave rise to a mechanistic comparison of the relations between the sympathetic and parasympathetic nervous systems with scales, and the concept of possible results in the form of unbalance between them.

The discovery of a certain antagonism between the sympathetic and parasympathetic nervous systems in its time motivated a suggestion that a disturbance in their normal balance, i.e., predominance of one division of the vegetative nervous system over the other (depression of the tone of one by the high tone of the other) was possible in pathology.

This gave rise to wrong concepts of *parasympathicotonia*, or *vagotonia*, and *sympathicotonia*; it was suggested that there are people with an excess of either parasympathetic or sympathetic tone, the former being vagotonics and the latter sympathicotonics.

Vagotonia was characterised by excessive perspiration, constriction of the pupils, excessive salivation and lacrimation, bradycardia, hyperchlorhydria, intensified peristalsis, etc., whereas sympathicotonia was characterised by deficient perspiration, dryness in the mouth, tachycardia, dilatation of the pupils, and intestinal atonia.

Attempts were even made to establish the character of the tone of the vegetative nervous system in different people by means of pharmacological and physiological tests.

Subsequently, however, the hypothesis of vago- and sympathicotonias failed to win recognition.

Studies in anatomy have shown that in a number of organs there is no double vegetative innervation and that there can be no question of antagonism of the two divisions of the nervous system in these organs. For example, the sweat glands and pilomotor muscles have only sympathetic innervation. Some internal organs, as the esophagus, apparently have only parasympathetic innervation. Moreover, *antagonism is not discovered in all cases of double innervation*. For example, in the gastrointestinal tract the relations between the sympathetic and parasympathetic fibres are very intricate and do not always fit into the pattern of functional antagonism between these systems. The same applies to a number of other organs.

The effects of the pharmacological agents which served as another substantiation of the concept of sympathico- and vagotonias are likewise not always definite enough. The same effects are not infrequently produced by pilocarpine, adrenalin and other

antagonistic substances simultaneously on the sympathetic and parasympathetic divisions of the nervous system, for example, on perspiration or the sugar level in the blood.

Thus it has turned out that there are no absolute sympathicotonias or vagotonias because along with excessive excitability of the vagus nerve in the heart, diminished excitability of the vagus nerve in the gastrointestinal tract can be observed in the same organism. Neither physiologic, nor pharmacologic, nor yet clinical methods of research indicate the existence of isolated changes in either division of the vegetative nervous system. On the contrary, there are data which indicate that *stimulation of one part of the vegetative division of the nervous system often leads not to inhibition, but to excitation of the function of the other part.*

The extensive material accumulated on the question of participation of the vegetative division of the nervous system in physiologic and pathologic processes demonstrates not so much antagonism, as functional *synergism of these two divisions.*

The data on central regulation of vegetative functions and the ability of the higher parts of the nervous system to compensate for vegetative disorders indicate that changes in the general excitability of the vegetative division of the nervous system must be regarded as the result of a loss of or increase in the inhibitory influence of the central regulatory mechanisms on the vegetative nervous system. In cases of impaired synergism of both divisions of the vegetative nervous system states of predominant excitability of the sympathetic or of the parasympathetic division may temporarily develop (Fig. 173).

Thus the modern concepts of the functions of the sympathetic and parasympathetic divisions of the nervous system very greatly differ from the former dogmatic assertions of their antagonism.

Today there are reasons to believe that diseases of the vegetative nervous system are *plurivegetative disorders*. They are characterised by simultaneous dysfunction of both the sympathetic and



Fig. 173. Diagram showing correlation between the vagus and sympathetic nerves. Increased or diminished function of one of the divisions of the vegetative nervous system involves marked increase or diminution in the function of the other division.

parasympathetic divisions of the nervous system (for example, subthalamic syndromes in encephalitis, Wilson's disease, etc.) and are manifested in altered functioning of various organs.

The mechanism of total and partial excitability or depression of the vegetative functions is actually still more complicated. The vegetative division of the nervous system is dependent on the functioning of the cerebral cortex and subcortex and is an intermediate link in the transmission of impulses from cerebral centres. At the same time the vegetative nervous system regulates the secretory activities of the glands. In pathology, in cases of dysfunction of the vegetative nervous system the hormones produced by endocrine glands may in their turn exert an influence on both its divisions.

Moreover, the activity of the vegetative nervous system is also affected by disturbances in the functional state of the reacting organs, changes in their physicochemical properties and metabolism.

It is well known that vegetative nerves perform their functions with the aid of mediators—sympathin (noradrenalin) and acetylcholine. In accordance with chemical mediation the vegetative fibres are divided into adrenergic and cholinergic (Dale and Feldberg). The cholinergic fibres include all parasympathetic, individual sympathetic (for example, those innervating the sweat glands), preganglionic sympathetic and motor fibres; the adrenergic fibres include the overwhelming majority of postganglionic sympathetic fibres. In pathology an important part is played by accumulation of chemical factors of nervous excitation, i.e., adren- and cholinergic substances which form in the processes of metabolism, in the nervous tissue in particular. These substances and the enzymes and ions, which counteract them (for example, cholinesterase, ions of potassium and calcium), play an important part in the realisation of vegetative impulses and in the mechanisms of vegetative dysfunction, for example, in anaphylaxis, ulcers, hypertensive vascular disease, general vegetative nervous insufficiency and neuroses.

Disturbances in the Trophic Function of the Nervous System

Dysfunction of the nervous system underlies many trophic disorders. The phenomena observed in muscles in cases of impairment of a peripheral motor neuron or of disturbances in the growth and calcification of bones after transection of the sympathetic nerve may serve as examples of such disorders. Lesions in the nervous system often accompanied by trophic disorders in the skin are manifested as changes in keratinisation, hair growth and epidermis regeneration, as well as in depigmentations, hypertrophies, necrosis, trophic edemas, and disturbances in fat deposition (so-called asymmetric lipomatosis).



Fig. 174. Hemiatrophy of the face—atrophy of the bones and tissues on the left side (Hoff).

Trophic disorders of nervous origin are observed in such diseases as scleroderma, syringomyelia, and facial hemiatrophy (Fig. 174).

Trophism* usually implies the aggregate of the processes which regulate tissue nutrition. Some authors held that a nervous dystrophy must involve structural disorders based on lesions in the nervous system. That was a clinical and morphological concept of trophism. Many proofs of the participation of the nervous system in structural trophism have been adduced; these include perforating ulcers of the feet developing in tabes dorsalis, trophic ulcers of the lower extremities in injuries to nerves, and ulcers experimentally produced in animals by various influences on different parts of the nervous system. Functional, biochemical disturbances in the tissues without visible structural changes were not considered trophic disorders. Thus the concept of nervous trophism was limited and essentially only morphologic.

Thanks to Pavlov's investigations a new concept of nervous trophism has been elaborated. Nervous trophism is understood as

* From the Greek word *trofeo*—I nourish.

regulation by the nervous system of the level of chemical processes operating in the tissues and ensuring *function* as well as *structure*.

In the process of evolution of the animal world, as the animal species developed and improved, the nervous system increasingly determined the level of breakdown and restoration of chemical substances in the tissues and the metabolism of the whole organism according to its requirements. In the organism of the higher animals and man trophic disorders are therefore often based on disturbances in the functions of the nervous system.

Trophic disorders may arise in cases of dysfunction of various neural structures. *Lesions in peripheral nerves* may be accompanied by trophic disturbances in the tissues. For example, injury to the tibial nerve often causes chronic ulcer of the foot. The loss of conductivity of the sciatic nerve causes trophic disorders in the muscles it innervates. In cases of chronic stimulation of the peripheral and sensory nerves by hemorrhages and compression trophic disorders in the form of skin ulcers are observed.

Lesions in the spinal cord may also cause trophic disorders—decubitus ulcers in paralyses due to diffuse transverse lesions in the spinal cord, chronic perforating ulcers of the feet in connection with tabes dorsalis, and diseases of the joints (arthropathies). Trophic disturbances in the skin and joints are also clearly marked in syringomyelia characterised by formation of cavities and proliferations of neuroglia in the grey matter of the spinal cord.

Lesions in the brain may cause trophic disorders manifested in disorderly deposition of fat in the organism, vascular disturbances accompanied by tissue changes, affection of joints, decubitus ulcers (in hemiplegias, etc.). Numerous available data indicate that *lesions in the diencephalon* cause trophic disorders manifested in metabolic disturbances, adiposis, etc. (Fig. 175).

It has also been possible to produce trophic disorders experimentally by injuring various neural structures, especially in the diencephalon.

In his first studies of the efferent nerves of the heart Pavlov (1883) convincingly proved the trophic nature of the two antagonistic nerves—one intensifying and the other weakening the cardiac contractions. In his opinion these nerves regulate the nutrition and metabolism of the heart muscle. Later, in chronic experiments following operation on the gastrointestinal tract of dogs he observed development of trophic disorders in the form of skin ulcers, inflammation, loss of hair, and ascending paralyses. He regarded these trophic disorders as reflex disturbances due to a stretching of the tissues and the nerves they contained, following surgical intervention.

The question of trophic disorders of a reflex origin, i.e., pathologic trophic reflexes, was thus raised for the first time.

The reflex origin of trophic disorders is attested by the results of



Fig. 175. Adiposis in monkey developing after injury in the region of the hypothalamus Weight before operation—3.1 kg. 14 months after operation 12.9 kg (Fulton).

many studies. For example, suturing a thread soaked in turpentine to the proximal end of a transected sciatic nerve causes development of an ulcer on the opposite extremity. In this case, as experiments with transection of nerves have shown, the efferent part of the reflex arc is the sympathetic part of the nervous system.

Orbeli's investigations have demonstrated the adaptational trophic role of the sympathetic division of the nervous system in the activity of striated muscles. In experiments the trophic function of the sympathetic nerve was discovered with respect to tissue respiration, heat exchange, and the chemical and physicochemical properties of muscular tissue. The sympathetic nervous system also exerts a trophic influence on cerebral tissue.

In pathology it is also possible to discover the role of sympathetic nerves in the regulation of tissue nutrition and metabolism, for example, in inflammation and vegetative asymmetries of a central origin (Alpern). These data are also confirmed in the clinic where various trophic disorders (ulcer of the foot, scleroderma, arthropathies, etc.) developing as a result of lesions in sympathetic ganglia, the sympathetic trunk or the afferent part of the reflex arc are observed. Experimental data on the trophic function of parasympathetic nerves, the parasympathetic fibres of the posterior roots in particular, are available.

As a result of numerous studies Speransky suggested a theory of the neurotrophic nature of all pathologic processes, basing the pathogenesis of trophic disorders on disturbances in the reflex activity of the nervous system. From this point of view all parts

of the nervous system participate in the development of trophic disturbances. By stimulating any part of the nervous system it is possible to produce disturbances not only in the corresponding part of tissue, but also in remote tissues and throughout the organism. This phenomenon is due to development of the process in the nervous system from the very outset and rearrangement of intraneuronal relations.

Changes in intraneuronal relations and in the functional state of the entire nervous system may completely alter the reaction of the organism to the same stimulus. To prove this, the data that are adduced show that the same stimuli (for example, infections) exert different influences on trophic processes, depending on the functional state of the receptor apparatus and the entire nervous system.

From these positions attempts were made to explain by neurotrophic disturbances the development of inflammation, allergy, disorders of tissue growth, and resistance of the organism to infections. Extremely strongly pronounced and similar trophic disorders were produced in experiment by application of pathogenic stimuli to various parts of the central nervous system.

Other studies, for example, experiments with extirpation of the cerebral cortex or impairment of its functions, established the significance of cortical disorders in the pathogenesis of trophic disturbances. The removal of both hemispheres is followed by a number of trophic disorders manifested in retarded growth and metabolic disturbances. Trophic disturbances were also observed in experimental neuroses. Chronic experimental neurosis is often accompanied by marked trophic disturbances on the skin and in internal organs, such as inflammation, eczema, tissue irritations and even tumours.

All the aforementioned studies disclose many new and important facts of neutrotrophic disorders and at the same time indicate the necessity of studying the intermediate stages of the complex reflex processes underlying the development of trophic disturbances.

Trophic disorders are often caused by secondary factors engendered by dysfunction of the nervous system. For example, injuries to peripheral afferent nerves are followed by loss of sensitivity in the corresponding portions of tissue, which in its turn renders it easily susceptible to trauma and infection.

However, in these cases, too, trophic disorders may also arise in the absence of harmful external factors. For example, intracranial transection of the trigeminal nerve causes trophic disorders in the eye, not only because of its loss of the protective mechanism, but also as a result of impaired tissue permeability and metabolism (Zaiko).

Ligation of motor nerves may cause muscular atrophy also indirectly, i.e., by dint of their inactivity. Such atrophy most commonly develops as a result of affection of peripheral motor nerves

and anterior cornua of the spinal cord. But in this case, too, the loss of purely trophic impulses plays an important part. This is evident from the fact that despite the absence of movements muscular atrophy is much less frequently observed in central, cortical paralyses because in such cases spinal innervation and muscular excitability are retained, whereas in peripheral paralyses the muscles are deprived of all inflow of nervous impulses.

There are various views concerning the *mechanism of action of the nervous system on tissue trophism*. According to some conceptions, the most important part in the development of tissue disorders is played by dysfunction of vasomotor nerves. Disturbances in circulation caused by stimulation of the nervous system lead to development of pathologic processes. However, this explanation is inadequate for a concept of the pathogenesis of trophic disorders because it is impossible to reduce the great variety of neurogenic disturbances in the tissues to changes in the vasomotor reactions alone. There is every reason to believe that the nervous system also exerts a direct influence on tissue metabolism because in many tissue disturbances of nervous origin it is impossible to find any vascular disorders of an intensity corresponding to the intensity of these disturbances.

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