PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

THE IMPORTANCE OF THE FUNCTIONAL STATE OF THE HIGHER DIVISIONS OF THE CENTRAL NERVOUS SYSTEM IN DISORDERS OF CHOLESTEROL METABOLISM

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For a long time clinicians have pointed out the important role of the nervous system in the etiology, pathogenesis and clinical course of atherosclerosis [2, 6, 7, 9, 11, 12], but the experimental approach to this problem is still inadequate.

Research carried out mainly by N. N. Anichkov (1912 – 1956) and his school has shown the importance of disorders of lipid metabolism in the etiology and pathogenesis of atherosclerosis and developed an experimental reproduction of this disease; the importance of an increased concentration of cholesterol in the blood and of changes in its physicochemical state in the development of atherosclerosis has also been demonstrated.

S. S. Khalatov [15, 16] and his co-workers, especially P. D. Gorizontov [5], have directed attention to the role of the brain in the production of hypercholesteremia, and moreover they regard the brain as a depot from which cholesterol enters the peripheral blood in increased amounts in certain pathological conditions.

P. I. Shchegolev [18] produced hypercholesteremia in animals by interference with the cerebral circulation (ligation and embolism of vessels). N. T. Shutova [17] observed that whereas during extirpation of a portion of the cerebral hemispheres in dogs hypercholesteremia appears, it does not do so after total extirpation of the cerebral hemispheres. P. D. Gorizontov [5], observing hypercholesteremia in dogs with experimental aseptic meningoencephalitis, first pointed out the important role of the neuroglia in the synthesis of cholesterol. The importance of the emotional factor in raising the blood cholesterol level has been discussed by Lyons [21] and by M. A. Chalisov, N. M. Vol'fson and D. N. Arutyunov [16].

Nevertheless, in all the investigations cited, no account has been taken whatsoever of the functional state of the higher divisions of the central nervous system when considering cholesterol metabolism. Papers showing the role of the functional state of the higher divisions of the central nervous system in the production of disorders of cholesterol metabolism and in the development of experimental atherosclerosis began to appear only very recently. Yu. T. Pushkar' [10], for instance, raised the excitation of the cerebral cortex in rabbits receiving cholesterol with their diet by the administration of phenamine to them, and observed a more severe atherosclerosis than in animals receiving cholesterol without phenamine. On the other hand, the blood cholesterol level can be lowered in rabbits and the severity of experimental atherosclerosis reduced by administration of chloral hydrate, according to the same author's findings. Analagous results were obtained by I. K. Shkhvatsabaya [19].

A. L. Myasnikov [6] observed an increase in the blood cholesterol in patients after administration of phenamine of caffeine, but sodium amytal and chloral hydrate lowered this level. F. K. Yarovoi, by repeated acupuncture in the region of the higher vegetative centers in rabbits receiving cholesterol with their diet, produced a more severe experimental atherosclerosis than in control animals in which no puncture was carried out.

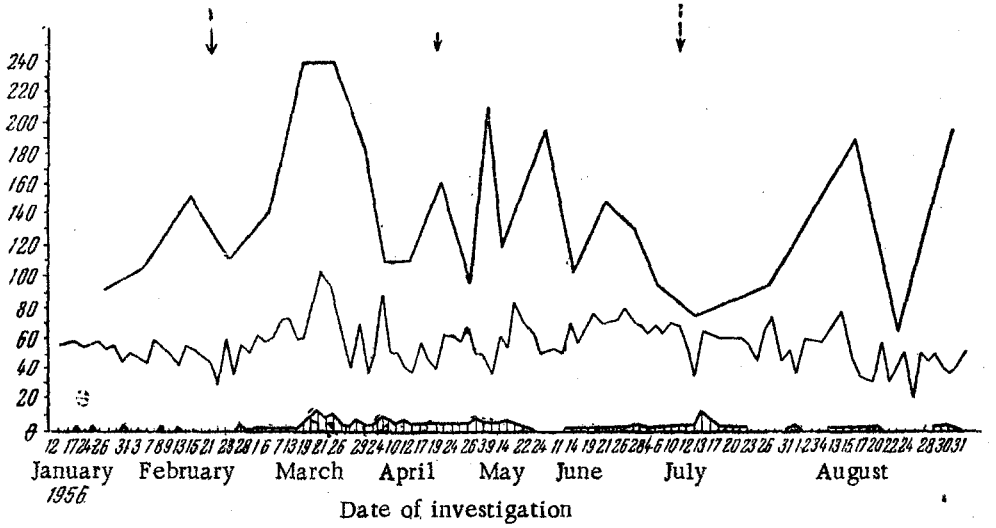

Fig. 1. Changes in the cholesterol level (upper curve), the sum of the positive conditioned reflexes in the experiment (middle curve) and the differentiation (lower curve) in the dog Lira under normal conditions and during disturbance of the higher nervous activity. In the period between the arrows ↓ – establishment of a delayed interoceptive reflex; the arrow ↓ corresponds to the moment of the "conflict". Cholesterol content in mg%; magnitude of conditioned reflexes and differentiation in divisions of the scale (1 drop = 2 divisions).

These findings are in full agreement with the large volume of work testifying to the role of the higher divisions of the central nervous system in disorders of metabolic processes and of the function of the internal organs [3, 13].

The aim of the present investigation was to study the influence of the functional state of the higher divisions of the central nervous system – especially the cerebral cortex – on cholesterol metabolism.

EXPERIMENTAL METHOD

The investigation consisted of chronic experiments on 4 dogs with fistulas of the stomach, the urinary bladder and the parotid salivary gland. As a rule we measured daily in each dog the serum cholesterol concentration by Sacchetti's method. In 2 dogs (Lira and Rika) conditioned food reflexes were established by the classical method of Pavlov. After consolidation of a system of positive and inhibitory conditioned reflexes, a disturbance of the functional state of the higher nervous activity was created: at first by over-exertion of the process of inhibition during the production of a delayed conditioned reflex, and later by over-exertion of the mobility of the basic nerve processes during a "conflict" of an associated pair of positive and inhibitory conditioned reflexes.

In the remaining two dogs no conditioned reflexes were established. Disturbance of the functional state of the central nervous system was produced by conflict of food and defensive unconditioned reflexes (at the same time as they received a food stimulus the experimental animals were subjected to the action of an electric current of 5 v).

EXPERIMENTAL RESULTS

In the dog Lira (weight 16 kg) positive conditioned food reflexes were established after the 7-10th combination and consolidated after the 15-20th combination. Differentiation was established equally quickly (10-12 applications); it was complete and rarely disinhibited. The stereotype of conditioned reflexes consisted of the following stimuli in order: bell, light (100 w), metronome with 120 beats per minute, differentiation – metronome with 60 beats per minute, positive interoceptive conditioned reflex to rhythmic stimulation of the stomach by means of a rubber balloon (pressure 20-30 mm of mercury). The time lag of the reflexes was 20 seconds. The interval between the conditioned reflexes was 5 minutes. After consolidation of the stereotype the magnitude of the positive conditioned reflexes was varied only negligibly on the days of the experiments. In all the experiments

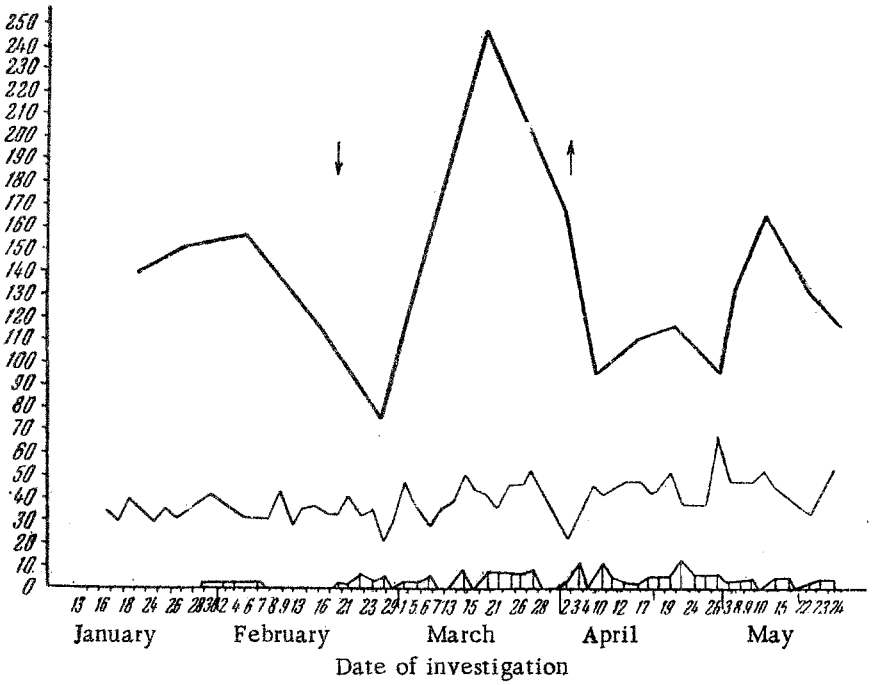

Fig. 2. Changes in the level of the cholesterol and the conditioned reflexes in the dog Rika. In the period between the arrows a delayed conditioned reflex was being established. Notation as in Fig. 1.

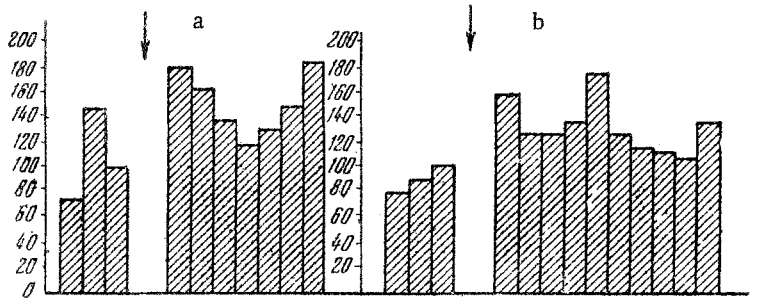

Fig. 3. Cholesterol concentration (in mg%) before and after conflict between food and defensive unconditioned reflexes. The arrows indicate the moment of conflict of the reflexes.
a) In the dog Buket; b) in the dog Churik.

there was a relationship between the magnitude of the conditioned reflex and the physical strength of the stimulus. The conditioned reflexes to the bell and metronome with 120 beats per minute were always greater than those to light and to interoceptive stimulation of the stomach. After the establishment of a background of normal higher nervous activity and the determination of the fluctuations in the level of the blood cholesterol of the dogs, the positive interoceptive conditioned reflex was converted into a delayed (by 3 minutes) conditioned reflex with the aim of causing over-strain of the inhibitory process.

The establishment of a delayed interoceptive reflex was a very difficult task for this dog and led to the disturbance of its higher nervous activity. The first changes in conditioned reflex activity were observed after 4 days and were shown by a decrease in the magnitude of the positive conditioned salivary reflexes; later on an increase of excitation gradually appeared, and differentiation was disinhibited; in addition equalizing and paradoxical phases were noted at a high conditioned reflex level.

The production of a delayed conditioned reflex continued for 40 days of the experiments, but was inconclusive and these delayed reflex experiments were discontinued.

The normal blood cholesterol in the dog Lira varied from 90 to 152 mg%. In the process of establishment of the delayed conditioned reflex there was a sharp rise in the cholesterol level (to 240 mg%); subsequently the cholesterol fluctuated considerably for a long period of time (Fig. 1).

After the conclusion of the delayed conditioned reflex experiments, taking 2 – 3 weeks, the state of the higher nervous activity was restored to normal. The cholesterol level fell to its original value. Later, one month after the conclusion of these experiments a "conflict" of the cortical processes was induced in the dog. Changes were then observed once again in the level of the conditioned reflexes and in the blood cholesterol level; this time, however, the hypercholesteremia was less marked, although for several months after the conclusion of the conditioned reflex experiments the cholesterol level was higher than normal (150, 194, 202 mg%).

In the dog Rika (weight 15.5 kg) the stereotype consisted of the same stimuli acting in the same order as in the case of Lira. In Rika the normal blood cholesterol level varied between 75 and 156 mg%.

In normal conditioned reflex activity in this dog a more pronounced fluctuation was observed in the magnitude of the positive conditioned reflexes; differentiation was not always complete and was easily disinhibited. Establishment of a delayed interoceptive conditioned reflex was also difficult in this dog. We were unable to produce such a reflex in the course of 40 experiments, and the process of establishing it itself caused a disturbance of higher nervous activity; it was expressed by the appearance of phasic changes in the positive conditioned reflexes and by the more marked disinhibition of differentiation.

In the course of the first 2 weeks of establishment of a delayed reflex the cholesterol level did not exceed normal, but at the end of the third week it rose to 246 mg% and stayed at this level for 10 days. After the conclusion of the experiments to establish a delayed conditioned reflex the higher nervous activity and the cholesterol level in the blood returned very rapidly to their original values (Fig. 2).

In the dog Buket the normal cholesterol level was 82 – 105 mg%, and in the dog Churik it varied between 75 – 150 mg%. In these dogs a conflict was induced between alimentary and defensive reflexes. As shown by research in I. T. Kurtsin's laboratory, this method causes a functional disorder of the central nervous system and of the activity of internal organs. After the conflict between the reflexes in these dogs the cholesterol level is raised for a long time. In Buket the maximum cholesterol concentration was 176 mg%, and in Churik – 187 mg% (Fig. 3).

It is clear from the experimental results given that the disturbance of the functional state of the higher divisions of the central nervous system caused a rise of the blood cholesterol level, followed by considerable fluctuations. This is shown by the fact that the increase in the blood cholesterol and the sharp fluctuations of its level coincided in time with the appearance of maximal changes of conditioned reflex activity in the experimental dogs. It must be remembered that our experimental animals were not subjected to excessively severe nor frequent trauma to the central nervous system; nevertheless the cholesterol concentration reached a higher level during disturbance of higher nervous activity than that which was produced by giving the dogs a diet rich in lipids. Under these circumstances the high cholesterol level was maintained (especially in the dog Lira) for a considerable length of time too after the conclusion of the conditioned reflex experiments. This is all the more interesting because we know that the blood cholesterol level in dogs cannot be raised for a long period of time by feeding the animals with cholesterol. I. E. Ganelina [4], for instance, by feeding dogs on cholesterol for several months, succeeded in raising the blood cholesterol from 90 – 118 to 160 – 170 mg%, but when the administration of cholesterol ceased, its concentration in the blood rapidly fell.

The results which we obtained, showing the sustained increase in the cholesterol level in dogs in response to action on the functional state of the higher divisions of the central nervous system only, appear to us to be of great interest; they show the important role of the higher nervous centers in the regulation of cholesterol metabolism and they bring us closer to an understanding of the mechanism of those disturbances of cholesterol metabolism which, in the modern view, lead to the development of atherosclerosis.

SUMMARY

Experiments were performed on 4 dogs in condition of chronic experiments. The blood serum cholesterol level was determined. Food conditioned reflexes were formed in 2 dogs by the classical Pavlov's method. After consolidation of the positive and inhibitory conditioned reflex a disturbance of the functional condition of the higher nervous activity was induced by overstraining of the inhibitory process in forming the delayed conditioned

reflex. The functional condition of the central nervous system was disturbed in 2 dogs by the clash of the food and defense reflexes. In disturbance of the functional condition of the central nervous system an increase of the blood cholesterol level was observed. The time of the rise of blood cholesterol level and of sharp variations in its level coincided with the appearance of maximal changes in the central nervous system. These experiments demonstrate the role of the functional condition of the higher portions of the central nervous system in disturbance of cholesterol metabolism.

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