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DYNAMICS OF THE CARDIOVASCULAR DISTURBANCES DEVELOPMENT AND THE CHANGE OF THE BLOOD LIPIDS IN DOGS WITH EXPERIMENTALLY INDUCED ATHEROSCLEROSIS

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-USSR-

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DYNAMICS OF THE CARDIOVASCULAR DISTURBANCES DEVELOPMENT AND THE CHANGE OF THE BLOOD LIPIDS IN DOGS WITH EXPERIMENTALLY INDUCED ATHEROSCLEROSIS

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[Following is the translation of an article entitled "Dinamika Razvitia Serdechno-Sosudistikh Narushenii i Izmenenii Lipidov Krovi Pri Vosproizvedenii Eksperimental'nogo Ateroskleroza u Sobak" (English version above) by V.N. Mentova and Z.T. Samoylova in Patologicheskaya Fiziologia i Eksperimental'naya Terapiya (Pathological Physiology and Experimental Therapy), Vol IV, No 4, Moscow, 1960, pages 32-38.]

The most recent type of coronary deficiency is cholesterol atherosclerosis, which is induced in dogs. In a series of works (6, 12, 13, 15) the impairment preeminently of coronary and cerebral vessels in dogs was established; that is, there was the same localization characteristic of the human illness. Also, because of the degree of development of their central nervous system and their metabolic processes, dogs are closer to humans than are rabbits, in which a more generalized type of atherosclerosis has been induced.

Not enough is known about the functional changes of both the heart and the coronary vessels in experimentally induced atherosclerosis.

The aim of the present work was the induction of atherosclerosis in dogs in order to observe the dynamics of the development of functional disorders of the heart and of the coronary vessels, and the comparison of these changes with certain indicators of lipoid metabolism.

The method of inducing atherosclerosis in dogs has not yet been perfected. It has been established that the suppression of thyroid function is necessary to the devel-

opment of atherosclerosis in dogs. However, the dosage and the method of administering cholesterol as well as other depressants varies according to the different authors.

The experiments were conducted with twelve adult dogs of different ages and sexes, with a weight variation of from eight to twenty-two kilograms. Four of them had high arterial blood pressure. Of these, three had an experimentally induced hypertonic renal condition which had existed from the age of one month to three years, and one dog had a spontaneously heightened pressure. All of these experimental dogs were receiving a daily dose of from 0.75 - 1.25 grams/kilogram of cholesterol, and 0.75 - 1.5 gm of methylthiourea. The two controls received only 1.0 - 1.5 gm of methylthiourea. As a control, changes in the body weight were observed. In some of the animals the state of thyroid function also was watched by means of radioindication. In all the dogs the cholesterol level in the blood was determined by the Grigg method. Before experimentation was commenced, this was effected not less than twice. Subsequently it was effected every 15 to 25 days. In some of the dogs, the phospholipid (lecithin) level in the blood was studied by means of the quinine hydrosulphate method, and the ratio of phospholipids to cholesterol was calculated.

An electrocardiogram [ECG] was taken with three standard and one pectoral lead while the dogs were quiet. ECG changes were then studied following physical exertion (a ten minute run on a treadmill), under conditions of a low oxygen tension test (the inhalation of a mixture containing 7% to 8% oxygen), and after the intravenous administration of adrenalin (20 - 30).

The exposed carotid artery was used to measure systematically the arterial blood pressure. Changes in the pressure were noted as hypotension-producing substances were introduced -- hexone, pentamine, nitrates, papaverine, chlorocystine -- in doses of one to two mg/kg.

Variations in the coronary circulation under the influence of the above-mentioned pharmaceuticals were also investigated in a chronic experiment using both healthy dogs and dogs with atherosclerosis. For this a thermoelectrode was imposed under sterile conditions upon the left coronary artery (using Noyence's modification). When the experiment was terminated after six to fifteen months, the animals were killed, and both a macro- and microscopic pathomorphological study was made of the organs.

During the first months of feeding the animals cholesterol with methylthiourea, little change was noted in the general health except for a gradual increase in body weight

and a corresponding lowering of thyroid function. After the sixth to seventh months of experiment, the general health of the dogs deteriorated. In some dogs there was a sharp increase in fat. The animals became less active and experienced shortness of breath and rapid tiring from physical exertion, especially the hypertonic dogs.

The cholesterol blood level varied from 62 mg% to 128 mg% in the control period, with an average of 109 mg%. In the course of the experiment the cholesterol blood level gradually increased at different rates in the various dogs. In dogs with normal arterial blood pressure the increase of cholesterol blood level was more gradual and not as great (fig 1). The dog named Kutsego (fig 1) is an example. After ten months the cholesterol level in his blood increased from 105 mg% to 390 mg%. Only toward the last, after ten to fifteen months, did the blood cholesterol level in some dogs rise to 1,000 mg%. In the dogs with hypertension, the rise of the blood cholesterol level was more rapid and reached higher figures more quickly. The increase in the blood cholesterol level was for the most part uneven, with large fluctuations being registered (fig 1).

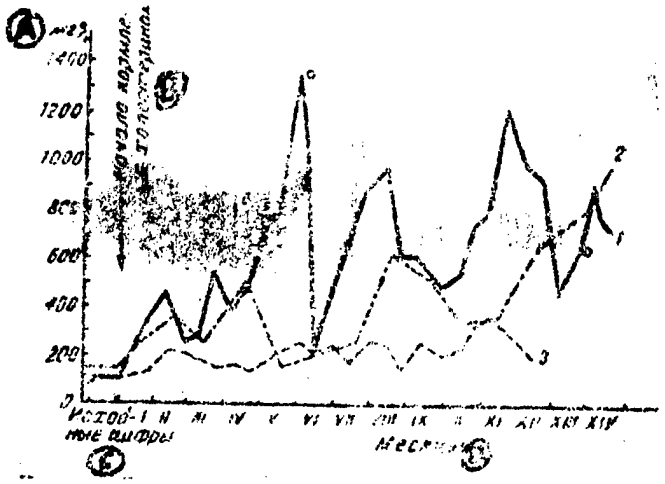

Fig 1. Cholesterol level in blood of dogs.

1- dog with hypertension; 2,3- dotted line: dogs with normal arterial pressure; x- introduction of methylthiourea begins o- methylthiourea treatment ends. A- mg%; B- commencement of cholesterol feeding; C- beginning figures; D- months.

During the course of the experiment the phospholipid level in the blood also increased. However, its increase was less than that of cholesterol. The phospholipid level reached 1422 mg% with an average of 405 mg%. The fluctuation of phospholipid concentration in most ani-

mals paralleled the fluctuation of cholesterol concentration. The ratio of phospholipids to cholesterol decreased. During the control period, the coefficient equalled 3.5 - 5.0; at the end of the experiment it dropped to 0.9 - 1.5.

Systematic electrocardiogram studies were made during two to two and a half months in the control period and throughout the duration of the experiment. The normal electrocardiogram of a dog sometimes changes from day to day. This variation diminishes as the animal becomes accustomed to experimental conditions. The second limiting factor of some dogs' electrocardiograms is that the negative T wave in any one of the leads can change its direction daily during the experimental period. Before starting the experiment, commencing with the third to the fifth months, we observed the voltage decrease of the electrocardiogram waves, especially of the QRS comples. In the initial phase we watched it in specific leads and later in all the leads. From the fourth to the fifth month of the experiment the T wave was negative in certain leads, but in the later stages (after the tenth month) in some of the dogs the T wave remained steadily negative in all leads. The S - T interval changed position in an isometric ratio (fig 2A).

In the tenth month of the experiment, the hypertonic dog, Malysh, suddenly developed a sharp arhythmia. There were centricular extrasystole, a partical auriculoventricular block, and a paroxysmal taxicardia which apparently was related to the acute nutritive damage of the coronary circulation (fig 2B). There was a simultaneous degeneration in the general well-being, and the arterial pressure fell to normal and even to hypotonic figures (90 - 110/70 mm). The arhythmia disappeared after three days. The general health gradually improved, and a higher blood pressure was re-established.

The earliest changes in cardiac activity became apparent under the load of physical activity. During the control period the cardiac rhythm increased in the first one to two minutes of physical exertion. After fifteen to twenty minutes it slowed down or returned to the original rhythm (fig 3). With this an increase in the amplitude of waves P and T was noted. During the experiment the increase in cardiac rhythm was more pronounced and more prolonged. The subsequent abatement was frequently absent (see fig 3). The amplitude of the T wave decreased.

The electrocardiogram changes observed during the control period with the low oxygen tension test -- the increase in cardiac rhythm, the decreased amplitude of the T wave or its change to the negative -- all these indices were less pronounced in the experimental period.

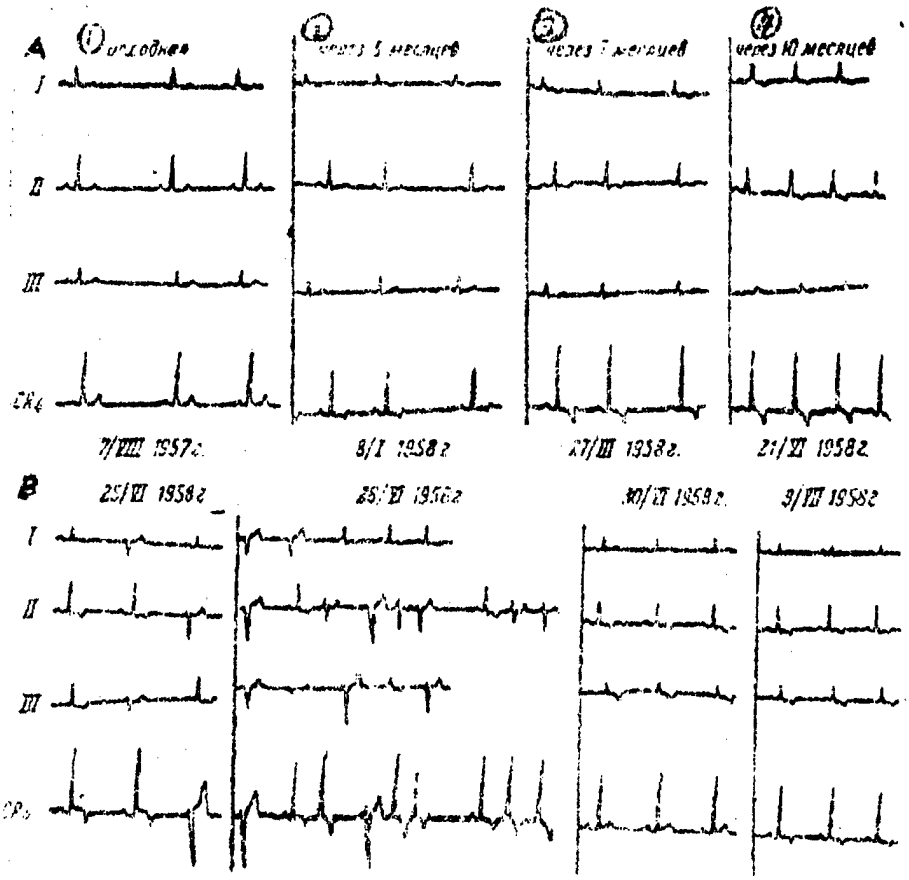

Fig. 2. Electrocardiogram changes at different phases of the experiment.

A. - dog named Sharik; B. - dog named Malysh
1 - initial; 2 - after five months; 3 - after seven months; 4 - after ten months

The injection of adrenalin into atherosclerotic dogs often produced varying arhythmias -- ventricular extrasystoles, a partial auriculoventricular block, and absence of the bradycardial phase. The reaction of the coronary system to adrenalin also varied. During the first to the second months the pressure reaction increased. Later it diminished, was absent, or became depressed.

In some of the dogs a gradual increase in the cardiac rhythm was observed, especially seven to ten months after the beginning of the experiment. Dogs who received only methylthiourea experienced a slowing down of the heart beat.

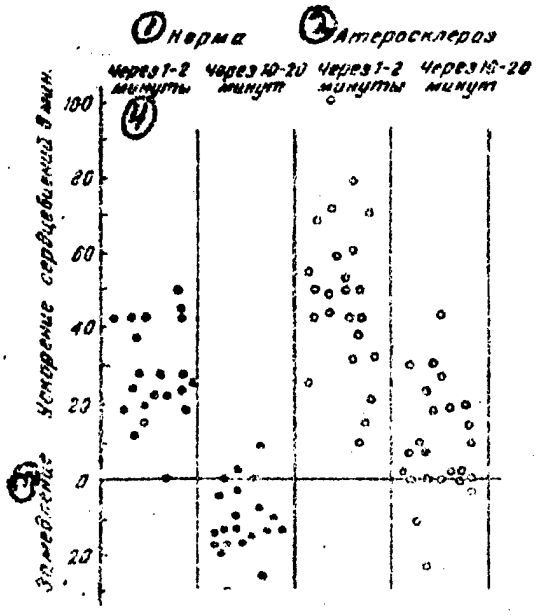

Fig. 3 Changes in cardiac rhythm after physical load.

1 - normal; 2 - atherosclerosis; 3 - decrease increase in heart-beat (in min.); 4 - after 1-2 min.

During the experimental period the fluctuation in the dogs' arterial pressure was greater than in the control phase. It sometimes went down to 10 - 15 mm, or, conversely, was somewhat raised. In dogs with long-standing hypertension, after nine to ten months of experiment, the deterioration of the general health and the cardiac weakness was accompanied by lowered arterial pressure. Atherosclerotic dogs had a characteristically longer period of depressed reactions when subjected to hypotonic substances -- hexone, pentamine, nitrates -- without any increase or even a lowering in the rate of decrease of arterial pressure. Also noted was a smaller increment in the quickening of the heart-beat under the influence of hexone and pentamine.

The excellent vessel-enlarging properties of pentamine and chlorocystine were brought to light during the study of the speed of coronary circulation. In atherosclerotic dogs the coronary vessels enlarged more gradually under the influence of hypotonic substances. The enlargement was greater and more prolonged than in healthy dogs. This was especially evident in dogs with acute atherosclerotic degeneration of vessels.

A macroscopic study of the animals' organs showed that the coronary vessels are the first to be affected and are affected more strongly than the aorta or the blood vessels of other organs. Atherosclerotic plaques were discovered in the brain vessels, especially at the base.

In hypertonic dogs the atherosclerotic changes were more marked than in dogs with normal blood pressure. The coronary vessels in some parts were hard, yellowish-white tubes which did not collapse after an incision (fig. 4).

Fig 4. Atherosclerotic impairments in the coronary vessels of the dog Malysh (hypertonic) after eleven months of experiment. A-front view; B-side view. Under the left auricle are seen the wires of the ingrown thermoelectrode.

Fig 4. cont'd

Fig 4. cont'd

C - rear view

In dogs with normal pressure, only separate atherosclerotic plaques were found on the wells of the coronary vessels. This gave the vessels the appearance of a chaplet. The blood vessels of the thyroid gland were affected in most dogs, with an enlargement of the thyroid itself.

Microscopic studies sometimes showed such a marked thickening of the internal coat that the vessel opening could scarcely be distinguished. The atherosclerotic plaques contained a large measure of double-rupturing lipids and cellular material. In areas of greatest lipid accretion a degeneration of atheromatose masses was observed. In some cases this process continued into the middle coat of the vessels. Fibrosis was discovered in most of the animals. There were also areas of degeneration of varying sizes in the myocardium, and in some areas destruction of muscle fibers as well as calcium deposits were found.

Our experiments reaffirm that the pattern of atherosclerosis in dogs is characterized chiefly by impaired coronary and cerebral arteries. The earliest symptoms of change in heart function become apparent under physical stress (during the second month of the experiment). During the third and fourth months electocardiogram abnormalities develop. The QRS complex voltage falls off, at first in some and then in all the leads. The S - T interval is displaced, and the T wave becomes constantly negative. Transitory changes are possible against this background of progressive increase in electrocardiogram abnormalities. This gives reason to suppose that foci of impairment develop

and that these are related to the prolonged vessel contraction or even to myocardial infarction. As a consequence of stenosing atherosclerosis of the coronary vessels, the dogs develop cardiosclerosis. The electrocardiogram changes are characteristic of chronic coronary deficiency. The degree of electrocardiogram deviations in the dogs at the end of the experiment corresponded to the degree of morphological degeneration of the coronary system.

There are indications in the literature on the subject that agree with our observations regarding the T wave and the S - T interval in experimental atherosclerosis in dogs (8, 10, 11). However, these studies were not accompanied by observations of the dynamics of electrocardiogram changes. Indications on the important, from our point of view, electrocardiogram deviation are absent. This deviation, a decrease in R wave voltage, can testify to the damage done to heart muscle depolarization associated with metabolic changes in the myocardium. In experimental cardiosclerosis in rabbits there is also a marked decrease in the QRS voltage (7).

During the development of atherosclerosis in dogs, there is a break-down in the nerve regulation of the coronary circulation in the early phases of the disease. Thus, as a reaction to physical stress, there is a stronger than normal and more prolonged initial quickening of the cardiac rhythm. Ganglion-blocking substances produce a less marked tachycardia. There is no bradycardial phase when adrenalin is introduced. Hypotonic substances produce a longer period of depression in cardiac rhythm and an enlargement of coronary vessels. These functional changes agree with the known facts of morphological changes in extra-cardial vagal ganglia, and in the central nervous system in coronary atherosclerosis (9).

A direct relationship was not established between the indices of the functional condition of the cardiovascular system and the indices of lipoid metabolism. By the indices of the latter we mean cholesterol, phospholipid level in the blood, and the $\frac{\text{phospholipid}}{\text{cholesterol}}$ coefficient. While hypercholesterolemia and hyperlecithinemia fluctuated sharply, there was, at the same time, little significant change in the arterial blood pressure. We regard the periods of increased lipoid level in the blood as a decompensation of the mechanisms regulating lipoid metabolism. This undulation can in some measure be compared to N.N. Anichkov's (1,2) description of the cyclical nature of the atherosclerotic developmental process.

In our experiments hypertension emerges as a factor which furthers the development of atherosclerosis. This

was observed earlier in rabbits (4, 5, 14). However, it must be emphasized that this fact can hardly be related to the hemodynamic, mechanical influence of hypertension. The earlier and more acute development of hypercholeserolemia in hypertonic dogs than in normal ones allows the supposition that hypertension destroys the regulation of lipoid metabolism.

The study of atherosclerosis in dogs takes on a greater significance because of the resemblance of its cardiovascular changes to those in humans. The fact that in order to produce atherosclerosis in dogs we must not only introduce excess amounts of cholesterol, but thyroid malfunction must also be present, brings this atherosclerotic pattern closer in a pathological sense to the human ailment. This is true in so far as clinical data (3 et al) point to the significance of thyroid malfunction in the development of atherosclerosis.

The atherosclerotic pattern in dogs opens greater possibilities for the study of this ailment's characteristic progress and its related phenomena: changes in the coronary vessels, myocardium, and in cardiac conductivity. It would also be useful in experimental therapy studies.

CONCLUSIONS

1. The atherosclerotic pattern in dogs is characterized first by impairment of the coronary and cerebral arteries.

2. During the electrocardiogram experiments there is, from the third to the fifth month, a falling off of the waves' voltage (especially the R wave). The T wave becomes negative in all leads, and the S - T interval is displaced in relation to the base line. These electrocardiogram changes correspond in degree to the morphological affection of the cardiovascular system.

3. The impairment of nervous control of the vascular system is evidenced in that after physical stress, a more prolonged and powerful initial cardiac rhythm is present as compared with the normal rhythm at the beginning of the experiment, there is a decrease in taxicardia produced by ganglion-blocking substances, there is produced an absence of taxicardia with the injection of adrenalin, and there are depressive reactions and the reactions of the coronary vessels prolonged by hypotonic substances.

4. The development of hypercholesterolemia and hyper lecithinemia during the experiment is uneven, with the presence of fluctuations.

5. Direct correlation is lacking between the indices of the functional condition of the cardiovascular system and the indices of lecithin metabolism.

BIBLIOGRAPHY

1) Anichkov, N.N. Ateroskleroz (Atherosclerosis), Moscow, 1953, page 7. 2) ———. Trudy 14-go Vsesoyuzn. S"ezda Terapevtov (Proceedings of the 14th All-Soviet Symposium ofTherapists, Moscow, 1958, page 19. 3) Vaynbaum, Ya.S. Tezisy Dokl. k Sessii Po Probleme "Ateroskleroz i Infarkt Miokarda" (Report at the Symposium on the Problem "Atherosclerosis and Myocardial Infarction"), Moscow, 1958, page 6. 4) Volkova K.G. Ateroskleroz (Atherosclerosis), Moscow, 1953, page 53. 5) ———. Trudy 14-go Vsesoyuzn. S"ezda Terapevtov (Proceedings of the 14th All-Soviet Symposium of Therapists), Moscow, 1958, page 45. 6) Gromov, L.I., Gersamia, G.K., Soldatov V.V. Tezisy Dokl. Mezhinstitutskoi Nauchnoi Konferentsii Po Voprosam Eksperimental'noi Kurortologii (Report at the Interinstitute Scientific Conference on the Problems of Experimental Treatment Methods), Moscow, 1958, page 52. 7) Kipshidze, N.N. Pat. Fiziol. i Eksper. Ter. (Pathological Physiology and Experimental Therapy), 1957, No 6, page 34. 8) Reshchikov, V.P., Vasilenko F.D. Tezisy Dokl. Mezhinstitutskoi Nauchnoi Konferentsii Po Voprosam Eksperimental'noi Kurortologii (Report at the Interinstitute Scientific Conference on the Problems of Experimental Treatment Methods). 9) Seranova, A.L. Tezisy Dokl. K Sessii Po Probleme "Ateroskleroz i Infarkt Miokarda" (Report at the Session on the Problem "Atherosclerosis and Myocardial Infarction"), Moscow, 1958, page 29. 10) Serov, S.I. Dokl. i Tezisy 2-y Ural'skoi Konferentsii Fiziologov, Biokhimikov, i Farmakologov (Report at the 2nd Ural Conference of Physiologists, Biochemists, and Pharmacologists), Perm, 1957, page 58. 11) ———. Tezisy Dokl. Mezhinstitutskoi Nauchnoi Konferentsii Po Voprosam Eksperimental'noi Kurortologii (Report at the Interinstitute Scientific Conference on the Problems of Experimental Treatment Methods), Moscow, 1958, page 41. 12) Sinitsyna, T.A. Ateroskleroz (Atherosclerosis), Moscow, 1953, page 68. 13) ———. Tezisy Dokl. k Konferentsii Po Probleme "Ateroskleroz i Koronarnaya Nedostatochnost'" (Report at the Symposiumon the Problem "Atherosclerosis and Coronary Deficiency"), Moscow, 1956, page 5. 14) Smolenskii, V.S. Ateroskleroz (Atherosclerosis), Moscow, 1953, page 63.

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