SOME INDICES OF LIPID METABOLISM AND CHANGES IN THE CIRCULATORY SYSTEM OF DOGS WITH EXPERIMENTALLY INDUCED ATHEROSCLEROSIS WITHOUT THE USE OF CHOLESTEROL

(UDC 616.13-004.6-092-07 : [616.153.915 + 616.12-008.331]-07 + 616.12-073.97]-092.9)

A. A. Sukhanov and S. I. Serov

Sverdlovsk Institute of Health Resort Therapy and Physiotherapy
(Director N. V. Orlov)

(Presented by Member of the Academy of Medical Sciences, USSR, S. E. Severin)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 60, No. 7, pp. 34-37, July, 1965
Original article submitted March 18, 1964

Great significance in the pathogenesis of atherosclerosis is attributed to the function of the neuroendocrine apparatus and the condition of the vascular wall [1, 4]. It has been shown that when substances that enhance the permeability of the vessels are used, atherosclerotic changes in the arteries of rabbits are intensified [3]. In view of these data, certain indirect-action anticoagulants, the administration of which also increases the vascular permeability, are attracting attention [7]. In spite of the wide use of these preparations, the nature of their effect on the lipid-cholesterol metabolism has not been sufficiently studied.

In this work we studied the influence of dicoumarin on certain indices of the lipid metabolism and the functional state of the cardiovascular system in dogs under conditions of prolonged inhibition of the thyroid function with 6-methylthiouracil (6-MTU).

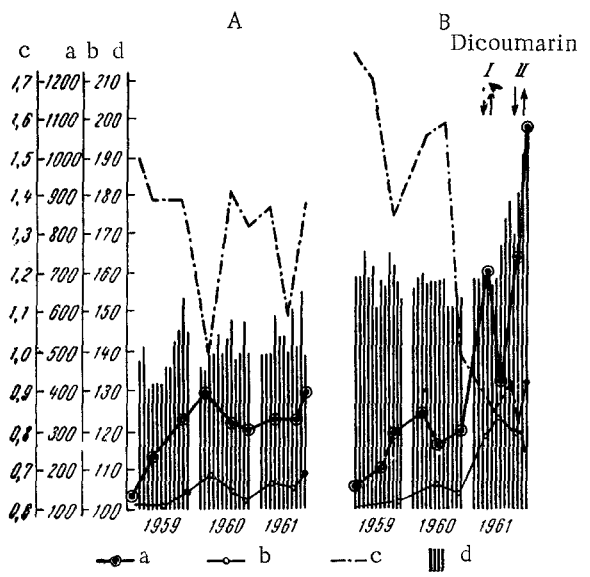

Fig. 1. Dynamics of changes in the functional indices of dogs during prolonged administration of 6-MTU (dog Roza—A) and under the influence of 6-MTU in conjunction with dicoumarin (dog Kukla—B). a) Cholesterol (in mg %); b) weight (in % of initial); c) lecithin-cholesterol coefficient; d) blood pressure (in mm Hg) (monthly average data).

EXPERIMENTAL PROCEDURE

The experiments were conducted en 10 dogs. Five animals were fed discoumarin while receiving daily injections of 6-MTU in a dose of 30 mg/kg (Raketa, Knopka, Dzhek, Druzhok, and Kukla). Five other dogs were controls. Three of them received dicoumarin without 6-MTU (Orlik, Damka, Kubik); two dogs received only 6-MTU (Roza and Kroshka). No toxic effect of 6-MTU was noted in any of the animals that received this preparation. Dicoumarin was administered daily for a period of 30-50 days, after six to seven months of administration of 6-MTU. The dog Kukla received dicoumarin in the form of two courses after 20 and 26 months. Dicoumarin was fed to the animals while monitoring the prothrombin index, which was basically maintained at a level of 30-50%, decreasing to 10-5% in individual animals (Knopka, Damka, Kubik, Kukla). *

The lecithin content in the blood (according to Blure) and the cholesterol level (by the Engel'gard-Smirnova method) were systematically determined in the dogs; the blood pressure and weight of the animals

*In the second course of dicoumarin.

Effect of Dicoumarin on the Blood Cholesterol Level in Dogs that Received and did not Receive 6-MTU

Name of dog	Blood cholesterol level (in mg %)								
	Initial (M ± m)	against a background of the use of dicoumarin				after discontinuation of dicoumarin			
		Weeks							
		1	2	4	6	1	2	4	6
	Received 6-MTU								
Kukla*	322± 7,5	408	460	816	816	1410	770	496	376
Kukla†	375± 7,5	316	530	786	856	1060	668	937	1744
Raketa	387±28,0	436	—	596	854	720	808	904	440
Knopka	205±17,0	452	—	928	664	468	—	548	776
Dzhek	244±28,0	444	360	480	700	380	332	358	212
Druzhok	318±16,0	272	—	420	460	360	332	376	488
Total	308±17,5								
	Did not receive 6-MTU								
Orlik*	172±15,0	242	212	212	240	180	—	244	228
Orlik	185±17,0	224	242	256	212	180	—	268	188
Damka	202±26,0	152	356	292	204	212	—	242	312
Kubik	204±21,0	188	212	276	236	212	—	156	184
Total	190±19,0								

*During the first course.
† During the second course.

were measured, and the ECG was recorded, using a functional load in the form of intravenous injection of 0.01% adrenalin in a dose of 0.2-0.4 ml.

RESULTS OF THE EXPERIMENTS

As the investigations showed, the cholesterol level in the blood gradually increased against a background of prolonged administration of 6-MTU, beginning with the third to fourth month. This increase, while not reaching any significant magnitude, was statistically reliable ($P < 0.001$). The administration of dicoumarin in courses against this background led to a sharper increase in the blood cholesterol (see table). In this case the lecithin-cholesterol coefficient was sharply reduced (from 1.5-2 to 0.5-0.3). The blood cholesterol increased more substantially in the females than in the males. The greatest change in the level of this index was noted in the dog Kukla, which received 6-MTU before dicoumarin for a longer period than the other animals. The more the level of hemocoagulation was reduced, the more pronounced the hypercholesterinemia. However, this condition set in the females even after a negligible decrease in the prothrombin index, within limits of 40-50% (Raketa).

The blood cholesterol level was unchanged in the intact dogs under the influence of dicoumarin, although in individual animals hemorrhagic symptoms were noted in this case (Kubik, Damka), indicating a considerable disturbance of the vascular permeability. Thus, an increase in the vascular permeability is accompanied by hypercholesterinemia only in dogs with an impaired thyroid function, which indicates the importance of the endocrine factor in the disturbance of lipid-cholesterol metabolism in animals.

Functional investigations showed that in animals that did not receive 6-MTU or that received this preparation for short periods, dicoumarin did not cause any significant changes in the blood pressure and ECG. Sharper changes in the indicated indices were established in the dog Kukla, which received 6-MTU for 26 months. This dog exhibited not only a sharp rise in the blood cholesterol level, but also a sharp increase in the blood pressure and again in weight (Fig. 1). Negative shifts on the ECG were noted during the adrenalin test, along with a decrease in the voltage of the waves in the initial recordings (Fig. 2). In dogs that received only 6-MTU during the same period, these symptoms were less pronounced (see Fig. 1, dog Roza).

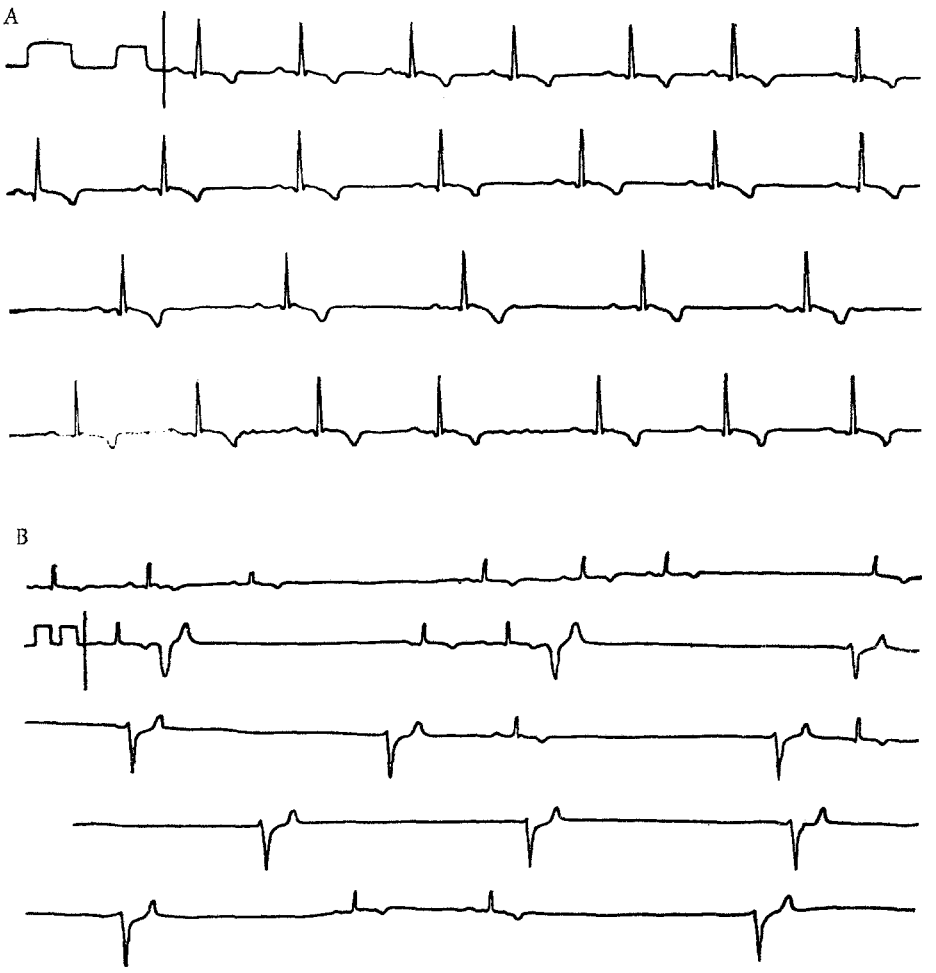

Fig. 2. ECG of dog Kukla. A) At the beginning of the experiment. Intravenous injection of 0.4 ml adrenalin solution (1 :10,000). No pathological changes detected on the ECG; B) at the end of the experiment (after two years, five months). Decrease in the voltage and disturbance of the heart rhythm after the injection of 0.2 ml of adrenalin solution (1 :10,000). In both cases the recording was made over a period of 90 sec. First ECG—initial, subsequent—after injection of adrenalin.

The dogs Kukla and Roza were killed after two years and nine months. Morphological investigations of the cardiovascular systems of these animals showed the presence of atherosclerotic changes, most pronounced in the dog that received dicoumarin [6].

An explanation of the results obtained, which agree with certain literature data [2, 5, 8], should be sought in a disturbance of the thyroid function. Dicoumarin only intensified these disorders. It may be that the enzymatic processes in the liver, which regulate the decomposition and excretion of cholesterol, are more impaired under the influence of this preparation. Disturbance of a number of enzymatic processes in the liver during prolonged therapy with dicoumarin derivatives has been noted [9]. Evidently another promoting factor in the development of the pathological process is a disturbance of the vascular permeability.

The data obtained indicate the possibility of developing and experimental model of atherosclerosis in dogs wiuthout the use of cholesterol.

LITERATURE CITED

1. I. V. Davydovskii, L. A. Gulina, and A. I. Ozarai, Arch. Pat., No. 7, (1962), p. 10.
2. A. P. Zysko, In the book: Atherosclerosis and Myocardial Infarct [in Russian], Moscow, (1959), p. 161.
3. L. V. Kasatkina, Kardiologiya, No. 4, (1961), p. 30.
4. A. L. Myasnikov, Ibid., No. 1, (1963), p. 3.
5. N. A. Ratner, et al. In the book: Atherosclerosis and Coronary Insufficiency [in Russian], Moscow, (1956), p. 155.
6. S. I. Serov, M. P. Goryunova, E. V. Evstyukhina, et al. Summaries of Reports at the First All-Russian Congress of Health Resort Therapists and Physiotherapists [in Russian], Moscow, (1963), p. 11.
7. A. A. Sukhanov and E. K. Bogomolova, Kardiologiya, No. 3, (1962), p. 58.
8. Z. Reinis, et al., Cas. Lek. ces., 91, (1952), p. 58.
9. H. E. Renschler, et al., Dtsch. Arch. klin. Med., Bd. 208, S. 524. (1963).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. ***Some or all of this periodical literature may well be available in English translation.*** **A complete list of the cover-to-cover English translations appears at the back of this issue.**
