THE EFFECT OF ADRENOCORTICOTROPIC HORMONE ON THE DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS

A. B. Vinogradskii

The Hospital Therapeutic Clinic of the I Moscow Order of Lenin
I. M. Sechenov Medical Institute (Director – Active Member AMN SSSR A. L. Miasnikov)

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Atherosclerosis is one of the most important problems of modern medicine, and is at present regarded as an independent disease of the vessels, not connected with the changes caused in them by age. The leading role in the complex pathogenesis of this disease is ascribed to primary disturbances of lipoid metabolism [1, 2, 3, 4, 5, 9, 10, 14, 19]. The modern infiltration theory of atherosclerosis proposed by N. N. Anichkov is shared by many American investigators of this problem [25, 29, 30, 32].

Thanks to the classic experiments of N. N. Anichkov and S. S. Khalatov, research workers have received a convenient biologic model with whose help many questions of morphogenesis, pathogenesis, therapy and prophylaxis of atherosclerosis have been clarified. The essence and the cause of the disturbances of lipoid-cholesterol metabolism which lead to atherosclerosis have not yet been finally elucidated. In recent years a number of Soviet and foreign scientists have established the effect of some vitamins, neurogenic medicinal preparations, and hormones on this process [4, 13, 15, 16, 17, 24, 27, 30, 31]. Evidently the main significance in the development of atherosclerosis belongs to disturbances of neuroendocrine regulation, chiefly of lipoid metabolism. The data on the effect of adrenocorticotropic hormone of the pituitary (ACTH) and adrenal cortical hormones (cortisone, hydrocortisone, desoxycorticosterone) on cholesterolemia and atherosclerosis are conflicting. Some authors [22, 23, 28] note an inhibitory effect of these hormones on the development of experimental atherosclerosis, others either find no definite effect [24, 25, 30] or find exacerbation of atherosclerosis [21, 26, 32]. Dury (USA) reported at the IV Congress of Gerontologists that experimental atherosclerosis was ameliorated under the influence of cortisone; he associated this with a decreased permeability of blood vessel walls to cholesterol.

Taking into account the recent widespread use of adrenal cortical hormones and their stimulator ACTH for the treatment of various diseases and the important part played by these hormones in the regulation of lipoid metabolism, as well as the conflicting nature of literature data on this question, we undertook to study the effect of the Soviet ACTH preparation on experimental and clinical atherosclerosis [7].

EXPERIMENTAL METHOD

Two series of experiments on 40 rabbits weighing about 3 kg were staged during 1956-7 in order to study the effect of ACTH on atherosclerosis. The work was carried out at the S. I. Chechulin Central Scientific-Research Laboratory at the I Moscow Order of Lenin Medical Institute. All the animals were divided into control and experimental groups. In the first series of experiments the control animals were given cholesterol 0.1 g per 1 kg body weight for a period of 65 days, in the second series the dose was 0.2 g per 1 kg body weight, continued for an average of 105 days. The experimental group received, in addition to 10% solution of cholesterol in sunflower seed oil, subcutaneous injection of ACTH in doses of 5-10 units (up to 380 units over the experimental period) in the first series and 10-15 units starting from the 30th day of cholesterol feeding in the second series (total 600-900 units per rabbit).

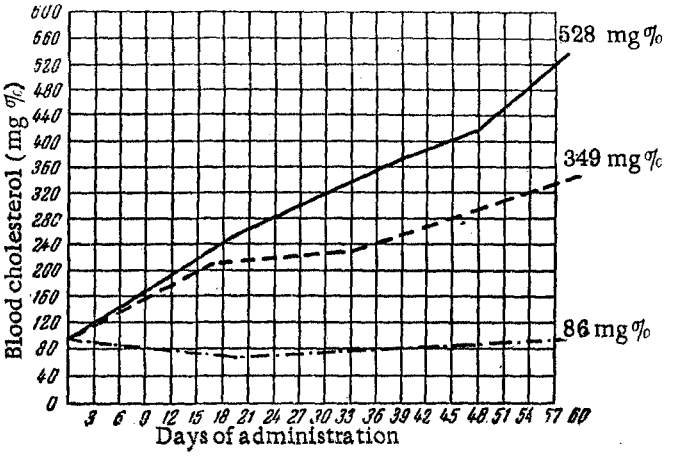

Fig. 1. Effect of ACTH on experimental hypercholesterolemia (first series of experiments).
Records: —— blood cholesterol level in rabbits given cholesterol; ---the same on administration of cholesterol + ACTH; -·-the same on administration of ACTH alone.

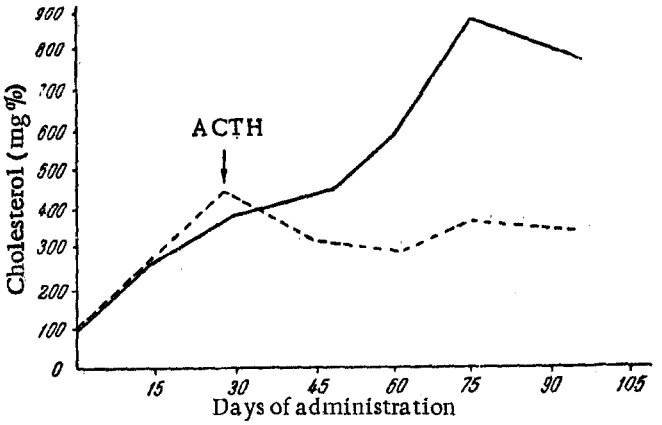

Fig. 2. Effect of ACTH on experimental hypercholesterolemia (second series of experiments).
Records: —— cholesterolemia in control animals (cholesterol); ---the same in experimental rabbits (cholesterol + ACTH).

In the first series of experiments 7 animals received only injections of ACTH without cholesterol feeding. All the animals were subjected to blood cholesterol determinations by Grigaut's method prior to beginning the experiment.

Analysis of the data obtained shows that hypercholesterolemia in the experimental animals was considerably lower and developed more slowly than in the case of the control animals (Figs. 1, 2). The control animals had a hypercholesterolemia of 500-800 mg% by the end of the experiment, whereas in the experimental animals it was 350-360 mg%. Hypercholesterolemia in the second series of experiments began to fall from the moment of ACTH administration (Fig. 2). The blood cholesterol level was checked in 5 rabbits 18-20 hours after the first injection of 15 units ACTH, and in all cases there was marked decrease of hypercholesterolemia (by 50-250 mg%).

In the case of rabbits which received ACTH alone the cholesterolemia remained practically unchanged and was within normal limits. At the end of the experiment the rabbits were sacrificed by the air embolus

method; the heart and aorta were excised in toto and examined for lipoidosis by means of Sudan III staining, also in toto.

EXPERIMENTAL RESULTS

The aortas of the control group showed marked atherosclerotic changes, mostly along the whole length of the aorta, often with involvement of the area at the mouth of the coronary vessels. In some preparations from the second series of experiments lipoidosis spread within the coronary arteries. Considerable lipoidosis was also observed in the pulmonary artery.

The degree and spread of aortic lipoidosis in the experimental group of rabbits (cholesterol + ACTH) were less pronounced than in the control group (Fig. 3, a, b). Less marked lipoidosis was found in the experimental group in the pulmonary artery and in the region of the mouth of the main coronary vessels.

There were no aortic changes in the rabbits who had received ACTH alone.

The data obtained point to an inhibitory weakening action of ACTH on experimental atherosclerosis which is evidently associated with its inhibitory effect on the development of hypercholesterolemia and lowering of blood vessel wall permeability observed on administration of ACTH.

It is possible that in our experiments the inhibitory effect of ACTH on the development of alimentary hypercholesterolemia is connected with increased breakdown of excess cholesterol, which in some measure compensates for the metabolic disturbance. Such a supposition agrees with the data of S. M. Leites [11, 12] concerning the regulatory effect of ACTH in the process of compensation for some deviations in metabolism (adaptational action of ACTH). The constantly administered large doses of excess cholesterol in our experiments naturally prevented complete normalization or compensation of cholesterol metabolism.

It should be added that in some of the rabbits in the experimental group in the second series of experiments determinations of arterial blood pressure were made on the carotid artery exteriorized in a skin flap; the cuff method was used. The arterial pressure was increased against the background of ACTH administration and varied from 110 to 170 mm Hg. Despite this there was no exacerbation of atherosclerosis in the experimental animals. This is apparently connected with the influence of ACTH on factors which inhibit atherosclerosis, being more pronounced than the unfavorable effect of hypertension on atherosclerosis.

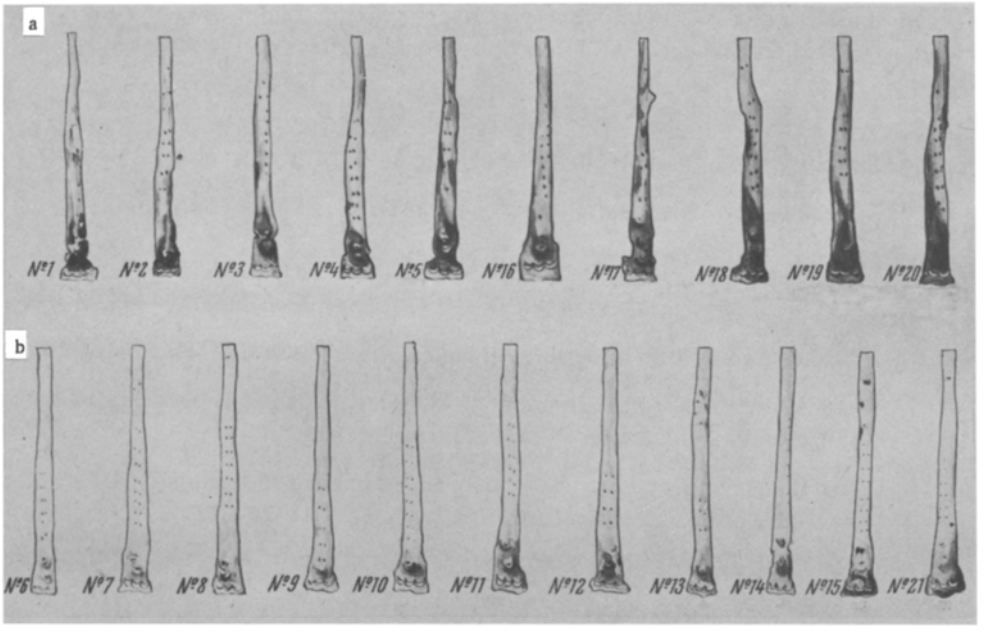

Fig. 3. Rabbit aortas (second series of experiments).
a) Control group, given cholesterol; b) experimental group given ACTH + cholesterol.

Since these experiments made use of a hormone which stimulated the adrenal cortex, we were interested to see what changes took place in this gland. The adrenals of the rabbits which had received cholesterol were considerably enlarged in size and their weight (1.38-1.45 g) was several times that of normal adrenals. Such enlargement is explained by lipoid infiltration of the adrenal cortex.

The adrenals of rabbits which had received cholesterol and ACTH showed less fatty infiltration but were also markedly enlarged due to hyperplasia of the secretory zone of the adrenal cortex, associated with its increased function.

The following changes were found in the adrenals of rabbits which had received ACTH alone: increase in size, weight (up to 0.88 g), hyperplasia of the fascicular and glomerular zones of the cortex, unequal distribution of lipoids and their reduced amount compared with normal adrenals. All these changes are characteristic for a state of increased function of adrenal cortex [6].

According to literature data [18, 20] prolonged administration of ACTH to rabbits is accompanied by secretion into the blood not only of large amounts of corticosterone but also of hydrocortisone.

It must be noted that despite the sufficiently clear and convincing nature of the results obtained concerning the effect of ACTH on the development of experimental atherosclerosis and hypercholesterolemia in man, we are far from suggesting that this preparation be used as a therapeutic agent for atherosclerosis in man, since ACTH has a number of other undesirable side effects on the organism. However, the present work can have definite meaning in defining indications and contraindications for the therapeutic use of ACTH. It is possible that disturbances in cholesterol metabolism are not in themselves contraindications for the use of ACTH since the experimental data obtained point to a regulatory effect of ACTH in disturbances of cholesterol metabolism.

SUMMARY

Two series of experiments were carried out on 40 rabbits. The author studied the effect of ACTH on the development of experimental atherosclerosis (according to N. N. Anichkov's method). The data obtained make it possible to draw a conclusion on the inhibiting effect of ACTH in the development of hypercholesterolemia and experimental atherosclerosis.

Prolonged administration of ACTH increases the functional activity of the adrenal gland, while the arterial pressure shows a certain rise.

Single administration of ACTH in presence of hypercholesterolemia decreases the blood cholesterol level in 18-20 hours. It is probable that ACTH has a controlling effect on the disturbed cholesterol metabolism.

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