The effect of Novocain and certain new anti-cholinergic drugs on the course of experimental atherosclerosis

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That regression of the atherosclerotic process is possible has been demonstrated both clinically and experimentally in studies of its pathogenesis and morphogenesis and of methods for its treatment and prevention [1, 4, 10]. This makes it very important to find new pharmacological substances which will prevent or arrest the development of atherosclerosis.

The substances which have been investigated in this connection include those inhibiting the central nervous system (Luminal, Barbamyl [sodium amytal], chloral hydrate, et al.), or inhibiting the development of lipoidosis in the arterial walls, drugs which stimulate the central nervous system (Phenamine [amphetamine sulfate], caffeine et al.), which act to intensify the alimentary hypercholesteremia of lipoidosis in the aorta, and substances affecting the autonomic nervous system [15 et al.].

The association of the atherosclerotic process with endocrine disturbances has prompted investigations of the effect of hormonal preparations on the course of atherosclerosis: Thyroidin [dessicated thyroid preparation] [14], synestrol and testosterone propionate [7], and adrenocorticotropic hormone [3].

This research has led to the discovery of several substances which arrest the development of atherosclerosis: B-sitosterol, certain vitamins, vanillone, phenexane, etc.

Works by Rumanian scientists [12] have shown the beneficial effect of Novocain on age changes in the blood vessels.

Moreover, N. E. Kavetskii [5] has shown that the administration of a combination of Novocain and ascorbic acid eliminates hypercholesteremia in patients with atherosclerosis.

A study of cholesterol metabolism during regression of experimental atherosclerosis in rabbits has demonstrated that Novocain helps reduce the cholesterol stably combined with proteins [8].

On the other hand, N. T. Kovaleva [6] concluded that the course of experimental atherosclerosis deteriorates under the influence of Novocain. This conclusion was based only on Novocain's effect on the blood cholesterol.

There are, therefore, contradictions in the literature data cited concerning Novocain's effect on the course of atherosclerosis. This led us to conduct an experimental study of Novocain's effect on the course of atherosclerosis compared with that of various anticholinergic agents.

METHOD

In the first series of experiments, cholesterol was administered perorally through a gastric probe by N. N. Anichkov's generally accepted method in a dose of 0.5 g per rabbit daily in the form of a 10% solution in oil for 120 days. The second series of experiments was performed on animals in which atherosclerosis was induced by a daily feeding of 3 g cholesterol combined with 50 g grated carrot for a period of 90 days [16]. The course of the atherosclerotic process was controlled by the blood cholesterol level, as determined by the Grigo method, and the lecithin content as determined by the Fiske-Subbarow method (for phosphorus). The animals were sacrificed at different intervals after the experiment began. We studied the morphological changes in the animals' aortas and determined the total content of lipids by extracting them from the wall, using the method employed by K. G. Volkova. All the experimental substances were administered to the animals subcutaneously.
RESULTS

The experiments were performed on 27 rabbits, which were divided into five groups.

The first, or control, group of five animals was given cholesterol and a physiological solution daily. Pronounced cholesteremia was observed in the rabbits of this group during the cholesterol feeding period, reaching an average level of 1477 mg% ± 187.33 toward the end of the fourth month (see figure).

![Cholesterol content (mg%)](image)

**Cholesteremia curves of control and experimental rabbits.** 1) Control; 2) cholesterol + Novocain; 3) aprophene; 4) diprophene.

After four months of observation, the animals of the control and experimental groups were sacrificed by air embolism. The heart and all of the aorta above its bifurcation were removed. Macroscopically, we found the walls of the aortas in the three control rabbits to be thickened by the development of large, connected atheromatous plaques which projected into the vascular lumen. Plaques were observed along the whole length of the aorta, but were particularly marked in the thoracic section. Four plus marks (++++) were used to denote the degree of atheromatosi found in these rabbits; the atheromatosis found in the aorta of the other two control rabbits was somewhat milder. Lipid deposits were also observed in the thick mass of the aortic valves.

Microscopic examination of sections from the aorta, stained with sudan III, showed an irregular thickening of the intima by lipid deposits and atherosclerotic plaques in all five of the control rabbits.

The lipids extracted from the aortas of the control animals constituted an average 118 mg±11.7 which, with an average aorta weight of 825.4 mg±123.5, comes out to 14.3 mg±4.7 of lipids per 100 mg of tissue (Table 1).

In the second group (seven rabbits), to which Novocain (10 mg/kg) was administered, we observed rapidly increasing cholesteremia during the first six weeks of the experiment. The blood cholesterol level went up to 800 mg%, but was somewhat lower (600-700 mg%) by the end of the fourth month. The atherosclerotic changes in the aorta were considerably less pronounced than in the control (++ in three rabbits and + in two).

The average amount of lipids found in the aortas of the animals of this group was 35.6 mg±2.9, with an average aorta weight of 611.3 mg±63.1, so that 5.6 mg ± 0.43 of lipids was found per 100 mg of aortic tissue (see Table 1).

Under the microscope, most of the preparations made from the rabbits' aortas showed small lipid deposits in the tunica interna; the tunica media of one rabbit also showed such deposits.

In the third group of rabbits (five animals), which was given cholesterol + aprophene [a,a-diphenylpropionic acid β-diethylaminooethyl ester hydrochloride] (5 mg/kg), we observed a gradual increase of blood cholesterol during the first nine weeks of the experiment (to 500-600 mg%) and a still greater increase in the cholesterol level toward the end of the experiment (see figure). In most of the animals, the morphological changes in the aorta approximated those in the control. A high degree of aortic atheromatosis (+++) was found in three rabbits, a somewhat milder degree (+++) in two.

Microscopically, the aorta showed considerable lipoid deposits in the tunica interna and an accumulation of foam cells. Diffuse lipoid infiltration was found in separate sections of the tunica media.

In the fourth group of rabbits (five animals) received diprophene [thiodiphenylacetic acid β-di-n-propylaminoethyl ester hydrochloride] (5 mg/kg). Throughout the experiment (120 days), the cholesterol level in all five rabbits was the lowest of all the experimental series, the maximum being 500-550 mg% (see figure).

The morphological changes in the aortas were negligible. The microscope preparations showed some thickening of the intima due to "pulverulent" lipid deposits in the tunica media, in the form of "dust" in the foam cells.