The effect of heparin on the development of experimental atherosclerosis

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The reports in the literature on the effect of heparin on the serum cholesterol and phospholipid contents are contradictory. Herzstein (1954) et al. [11], and Raynaud and his co-workers [16] consider that heparin does not affect the level of cholesterol and phospholipids in the blood, whereas other workers [7, 4] have found that heparin raises the serum cholesterol level of patients with xanthomatosis and atherosclerosis.

Graham et al. [10] showed that heparin causes conversion of higher classes of lipoproteins with a flotation rate Sf 10-30 into lower (Sf 5-10) and so on, as a result of which, in the author's opinion, there is inhibition of the development of experimental atherosclerosis in rabbits fed on cholesterol.

No less contradictory are the experimental results [9, 12, 13, 14, 15] on the effect of heparin on the development of atherosclerosis, although the majority of authors conclude that heparin inhibits the development of atherosclerosis in experimental animals.

It is possible that the difference in the experimental results of the various workers is due to the use of different doses of heparin. For this reason we set out to investigate the effect of large and small doses of heparin on the level of the blood cholesterol and phospholipids and on the development of atherosclerosis in rabbits during prolonged feeding with cholesterol.

Experimental method

Experiments were performed on 53 chinchilla rabbits weighing 2100-2600 g. All the rabbits were kept under identical conditions and on the same diet. Atherosclerosis was produced by N.N. Anichkov's method of feeding the animals for 100 days with a solution of cholesterol in sunflower oil (at the rate of 0.2 g of cholesterol per 1 kg body weight).

Heparin was injected intravenously every day in different doses into the experimental animals (28 rabbits): 15 rabbits received heparin in a dose of 30 mg, seven rabbits received 60 mg and six rabbits 3 mg. The controls (23 rabbits) received cholesterol only.

In order to ascertain the effect of heparin on the content of endogenous cholesterol and lecithin, two rabbits were injected every day with 30 mg of heparin intravenously.

Every 25 days the serum cholesterol content was estimated by the Engel'gardt-Smirnova method [6] and the phospholipids by the sulfite-hydroquinone method [2] with extraction by Bloor's method [8].

When 100 days had elapsed the animals were killed by air embolus of the lungs. At postmortem examination the aorta and heart were extracted. The aorta was fixed in 10% formalin solution and then stained with Sudan III in toto.
The degree of the atherosclerotic changes in the aorta was designated by ± signs (0 - no changes; ± - slight changes; ++ - moderate changes; +++ - severe changes, and ++++ - very severe changes).

A study of the effect of a single injection of heparin on the blood lipids of rabbits was carried out at various periods of cholesterol feeding. From 5-6 ml of blood was taken from the marginal vein of the rabbit's ear before and 30 minutes, 1-2 and 3 hours after the intravenous injection of heparin.

**EXPERIMENTAL RESULTS**

After a single injection of heparin, in not one of the 22 cases was any increase in the cholesterol level observed.

In four cases there was a reduction in the cholesterol content by about 10%, which we regard as within the normal limits of variation of the cholesterol level. In 18 cases, the reduction in the cholesterol varied between 12.5 and 32% of the original value.

The fall in the blood cholesterol content was observed 30 minutes after the injection of heparin and lasted for three hours. In some cases, after an initial fall in the cholesterol level it was observed to rise at the end of the second hour of the experiment, to fall again at the end of the third hour. The effect of a single injection of heparin on the level of the blood cholesterol is shown in the form of curves in Figure 1.

![Fig. 1. Change in the blood cholesterol of rabbits after a single intravenous injection of heparin. The curves represent the changes in the cholesterol content in percentages of the initial level; the dotted lines show the normal limits of variation of the blood cholesterol.](image)

Mention must be made of the relation between the degree of the reduction in the cholesterolemia and its initial level: the higher the initial blood cholesterol level the greater the degree of its fall. The magnitude of the fall in the blood cholesterol level did not depend on the dose of heparin used.

The lecithin content fell after injection of heparin (Figure 2) to approximately the same extent as the cholesterol content, so that the value of the coefficient lecithin/cholesterol was practically unchanged.

Thus, a single injection of heparin into rabbits with alimentary hypercholesterolemia led to a reduction in