THE INFLUENCE OF NICOTINE ON EXPERIMENTAL ATHEROSCLEROSIS

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Although the question of the injurious effect of smoking on the body has been discussed for more than a century, it still cannot be considered fully settled. In particular, insufficient study has been given to the question of the action of nicotine on the heart and the blood vessels.

E. A. Zhebrovsky [3] and A. Z. Kozdoba [4] attempted to reproduce atherosclerosis experimentally by the intravenous injection of a solution of nicotine, but their work was not very convincing, since the changes produced in the blood vessels of rabbits were not identical with atherosclerosis in man. The changes in the rabbits' aortas which took place under of the influence of nicotine were focal necrotic lesions with subsequent deposit of lime; other toxic substances also evoke these same changes in the blood vessels.

Great credit in the study of atherosclerosis goes to N. N. Anichkov [1, 2] and his coworkers, who reproduced atherosclerosis in animals by prolonged feeding with pure cholesterol.

We used this model in the work described here, the object of which was to ascertain the effect of nicotine on the development of alimentary hypercholesterolemia and experimental atherosclerosis in rabbits. In connection with this the morphological changes were studied in the aorta and the coronary vessels of animals which had received nicotine and of animals in which experimental atherosclerosis was induced by nicotine and cholesterol simultaneously.

EXPERIMENTAL METHODS

Rabbits of the chinchilla breed 8 to 10 months old and averaging 2 kg in weight were used as experimental animals. All the animals were kept under identical conditions and received the same feed. The experiment lasted 115 days. The animals were given nicotine and cholesterol every day except holidays.

The rabbits were divided into three groups. The first group (10 animals) received 0.2 ml of a 1% solution of nicotine daily; later their dose was increased, as they were observed to become gradually accustomed to the nicotine(in those cases in which they did react to the introduction of the poison at the beginning of the experiment, the reaction ceased to appear after a few days).

The second group (14 rabbits) received the same amount of nicotine daily and, in addition, 0.2 g cholesterol per os, dissolved in 2 ml sunflower oil.

The 10 rabbits in the third group, the control group, were given 0.2 g cholesterol daily, dissolved in 2 ml sunflower oil, but received no nicotine.

We deliberately selected comparatively small doses of cholesterol for both the control and the experimental rabbits in order to be able to determine more precisely the difference in the degree of development of atherosclerosis in them.

Observations were made on the development of alimentary cholesterolemia under the influence of nicotine; every 7-10 days the cholesterol content in the blood of the animals of the first and second groups was determined by Grigault's method. At the end of the experiment all the rabbits were killed by introducing 10-15 ml of air into the aural vein. In the postmortem dissection the aorta in its whole length together with the heart was prepared.

Then a pathohistological examination was made of the aorta and the coronary vessels. On the freezing microtome sections were made for microscopy from the section of aorta previously taken in the thoracic section from each preparation. Sections were also prepared from the heart at its foundation in order to discover any microscopic changes which might have taken place in the coronary vessels of the heart.

The prepared specimens were stained with hematoxylin-eosin in order to show any possible hyalin degeneration in the muscle tissue, with Sudan III for fat, and with picrofuchsin in order to determine changes in the elastic fibers of the blood vessels.

In all, we prepared 348 specimens: 2 aorta and 2 heart specimens for each of the three stains.

EXPERIMENTAL RESULTS

In the animals of the first group, which had received only nicotine, the following changes were observed in the aorta and the coronary vessels. Macroscopic inspection revealed that the inner wall was quite smooth and shiny, without any deposits. There was a considerable swelling in the aorta wall in some places accompanied by homogenization of the muscle fibers. The elastic fibers were acutely swollen, focally fragmented, and partly disintegrated. There were no deposits of fat in the intima of the aorta and the coronary vessels.

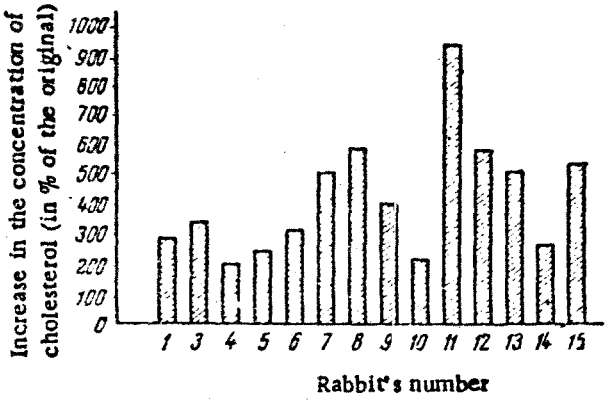

Fig. 1. Maximum increase in the concentration of cholesterol in the blood in relation to the original amount in rabbits receiving cholesterol and nicotine.

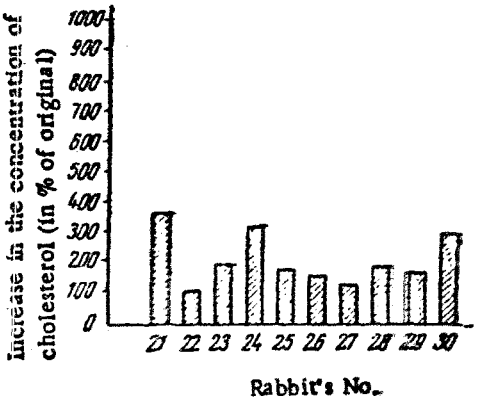

Fig. 2. Maximum increase in the concentration of cholesterol in the blood in relation to the original concentration in rabbits of the third (control) group.

In the coronary vessels of the heart there was a pronounced thickening of the walls of individual medium and small vessels with expansion of the intima. The elastic membrane of the coronary vessels was swollen, and in some places discomplexed. Pronounced plethora of the interstitial tissues was observed, with stases in some places. There were no fat deposits in the walls of the changed and unchanged coronary vessels.

Thus, nicotine evokes considerable dystrophic changes in the walls of the aorta and the coronary vessels.

In the animals of the second group, which had received nicotine and cholesterol, the amount of the latter in the blood gradually increased, especially rapidly after the 40th day. As will be seen from Fig. 1, the cholesterol content in the blood of these rabbits increased 217-945% (5 to 10 times in half of them). The lipodosis of the aorta in this group of animals was considerable.

The deposit of lipoids in the form of platelets and spots was very characteristic; they not only occupied the thoracic aorta but also covered a considerable surface of the abdominal aorta, extending over almost the whole inner surface of the aorta, with greatest accumulations in its beginning part, in the area of the ascending section, the arch, and the descending aorta. Histological examination revealed massive deposits of fat (cholesterol ester) in the intima of the aorta for almost its whole length. Deposits of fat were also observed in the vasa vasorum, filling almost the whole lumen of the vessel. The wall of the aorta was loosened; elastic fibers were easily seen which in places were elongated and swollen to varying degrees.

In the large coronary vessels the fat deposits were not extensive. In the small and medium-caliber vessels considerable deposits of fat were visible. In the small vessels the elastic tissue was swollen and of a poor color.

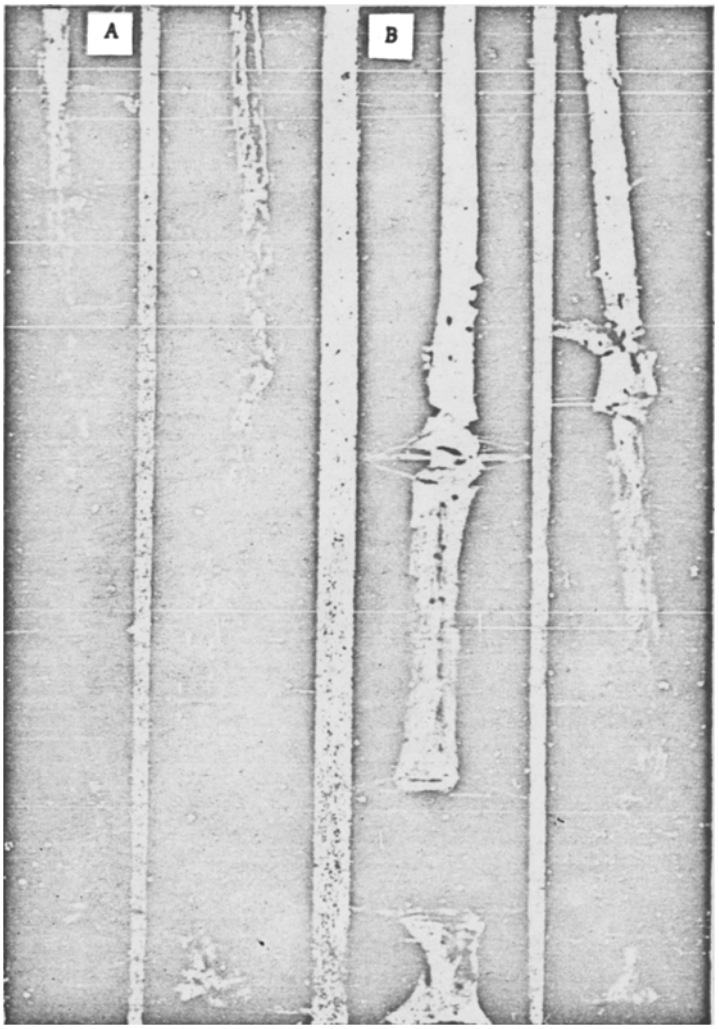

Fig. 3. Prepared specimens of aortas of rabbits which had received nicotine with cholesterol (A) and of rabbits which had received only cholesterol (B).

In the control animals, those of the third group, which had received only cholesterol, the amount of the latter in the blood increased steadily (Fig. 2), but considerably more slowly and to a lesser degree than in the rabbits of the second group.

As will be seen from Fig. 2, the cholesterol content was found to have increased 90-364%, but it reached four times the original amount in only 3 of the 14 animals.

The lipoid deposits in the aorta were also considerably less pronounced in this group of rabbits. On the inner surface of the aorta there were visible only isolated lipoid deposits in the form of platelets and spots, situated in the area of the arch and the descending portion of the aorta. Over all its remaining extent the aorta of these rabbits was smooth and shining.

In histological examination small focal deposits of cholesterol ester were detected in the intima of the aorta; in places the elastic fibers showed a slight straightening and an irregular swelling.

There were no deposits of fat in the walls of the small and large coronary vessels.

Thus, we established that in rabbits receiving nicotine with cholesterol the degree of increase of cholesterol in the blood and the degree of development of atherosclerosis was considerably higher than in rabbits which had received cholesterol alone.

The question of the mechanism of action of the nicotine arises: does it play a role in the development of atherosclerosis only through an increase of the cholesterol or are the dystrophic changes induced by it in the walls of the blood vessels of significance? In order to come nearer to a solution of this question we compared the degree of atherosclerosis of the aortas in the rabbits of the second and third groups with approximately the same level of cholesterol.

Thus, in rabbits Nos. 21 and 30 (Fig. 2) of the control group the cholesterol content of the blood increased 291-364%, but there was only a slight atherosclerosis of the aorta. In rabbits Nos. 1 and 3 of the experimental group the increase in cholesterol was approximately the same, 291-331%, but the atherosclerosis was rather pronounced.

This provides a basis for concluding that the degree of atherosclerosis is determined not only by the degree of cholesterolemia; the dystrophic changes induced by nicotine in the wall of the aorta and the coronary vessels contribute to the speedier deposit of lipoids in them.

LITERATURE CITED

[1] N. N. Anichkov, Klin. Med., Vol. 15, No. 3, pp. 347-356 (1937).

[2] N. N. Anichkov, Proceedings of the First All-Russian Congress of Pathologists* (Moscow, 1924), pp. 357-361.

[3] E. A. Zhebrovsky, Russ. Vrachebnoe, Vol. 7, No. 13, pp. 429-431 (1908).

[4] A. Z. Kozdoba, Novy. Khir. Arkh. 1929, No. 75 (10), pp. 340-351.

[5] M. P. Kravkov, Principles of Pharmacology* (Moscow-Leningrad, 1933). Parts 1 and 2.

*In Russian.