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EFFECT OF HYDROCORTISONE ON THE DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS

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KEY WORDS: hydrocortisone; lymph nodes; experimental atherosclerosis.

In the study of the pathogenesis of atherosclerosis attention is increasingly being paid to the role of immunologic factors in the onset and development of the disease [1, 4, 8]. An autoimmune theory of the pathogenesis of atherosclerosis has recently been formulated [5].

An important place in these investigations is occupied by analysis of immunologic mechanisms in the development of experimental atherosclerosis in rabbits, for the role of specific sensitization in the formation of atherosclerotic lesions in the arteries can be studied in detail [1, 3, 9].

Additional information in this direction can be provided by experiments with hydrocortisone which, with its wide spectrum of action, also has a marked immunodepressive effect [7]. This property of the glucocorticoids in experimental atherosclerosis was the object of the present investigation.

EXPERIMENTAL METHOD

Experiments were carried out on 51 rabbits. The results of a study of the immunocompetent system in 22 healthy rabbits also were used. Experimental atherosclerosis was induced by Anichkov's method (dose of cholesterol 0.2 g/kg body weight). To depress the immune response in the rabbits' lymphoid organs hydrocortisone was injected intramuscularly in a dose of 3.75 mg five times a week for 4 weeks (total dose 75 mg per course) and for 12 weeks (225 mg per course).

During the experiment the serum levels of atherogenic lipoproteins (combined fraction of β- and pre-β-lipoproteins) and cholesterol were determined. The atherosclerotic index in the aorta was calculated by Avtandilov's method after staining the blood vessels with Sudan III *in toto*.

The quantitative morphological study of the immunocompetent system was conducted on preparations from the mesenteric and para-aortic lymph nodes after staining by Brachet's method in the manner described by Pigarevskii et al. [6]. Cells that are the most characteristic indicators of the immune response, namely small lymphocytes, lymphoblasts, plasmablasts, and immature and mature plasma cells, were subjected to quantitative analysis in the T- and B-zones of the lymph nodes. The level of circulating antibodies against collagen and elastin was determined by Chudomel's reaction using guinea pig complement and, as antigens, collagen and elastin isolated by the method of Ivanovskii et al. [2].

EXPERIMENTAL RESULTS

Analysis of the blood serum showed that the level of the combined fraction of β- and pre-β-lipoproteins and of cholesterol in the blood of the rabbits receiving hydrocortisone in addition to an atherogenic diet was indistinguishable from the corresponding values in animals receiving the atherogenic diet alone, and by the end of the experiment it was 15-20 times higher than initially.

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A different picture was observed in the morphological study of the severity of atherosclerosis in the aorta. On macroscopic examination of the aortas at the end of the experiment the atherosclerotic index in animals receiving hydrocortisone together with the atherogenic diet was 7.7 ± 3%, compared with 74.5 ± 12.1% in rabbits not receiving hydrocortisone. Comparison of the area of the atherosclerotic lesions in the aortas with biochemical changes in the blood serum showed that despite the identical blood levels of lipoproteins and cholesterol toward the end of the experiment, the severity of the atherosclerosis in rabbits receiving hydrocortisone at the same time was 9.6 times less ($P < 0.05$) than in the animals of the control group receiving the high cholesterol diet only. These results confirm the view expressed previously, that hyperlipidemia alone is insufficient to cause the development of atherosclerosis, and that additional factors are necessary [1, 9]. One such factor could be immunologic damage to the vessel wall [5]. It is this which makes the morphological study of the immunocompetent system of the rabbits particularly interesting. Previous investigations showed that in experimental atherosclerosis a definite and well-marked pattern of changes is observed in the lymph nodes and spleen, which follow the B-type of development [6].

The results of the present investigation showed that considerable degenerative changes are observed in the T- and B-zones of the lymph nodes as early as after 4 weeks in animals receiving hydrocortisone, with or without an atherogenic diet. The paracortical or T-zone of the lymph nodes became atrophied. The small- and medium-sized lymphocytes, normally its predominant constituent cells, disappeared. This process continued to develop and after 12 weeks of the experiment the paracortical zone was completely cell-free and had disappeared throughout its previous extent (Fig. 1a).

Similar changes also were found in the B-zone. After four weeks of the experiment the cortex of the lymph nodes became thinner, and after 12 weeks of administration of hydrocortisone it was completely without secondary lymphoid follicles with developed germinal centers (Fig. 1a). Among cells of the plasmacyte series in the sinuses of the medullary layer the number of mature plasma cells was reduced by three-quarters ($P < 0.05$) compared with normal (Fig. 1b). The medullary cords also were extremely thin and poor in cells.

A parallel analysis of the level of circulating antibodies against structural antigens of the vessel wall showed that the antibody level in the serum of animals receiving hydrocortisone plus an atherogenic diet was lower than in the group of animals receiving the atherogenic diet alone. A fall in antibodies against collagen was observed in the 8th ($P < 0.01$) and 12th ($P < 0.001$) weeks of the experiment, and against elastin in the 4th and 8th weeks ($P < 0.05$) of the experiment. It can therefore be concluded that the glucocorticoid hydro-

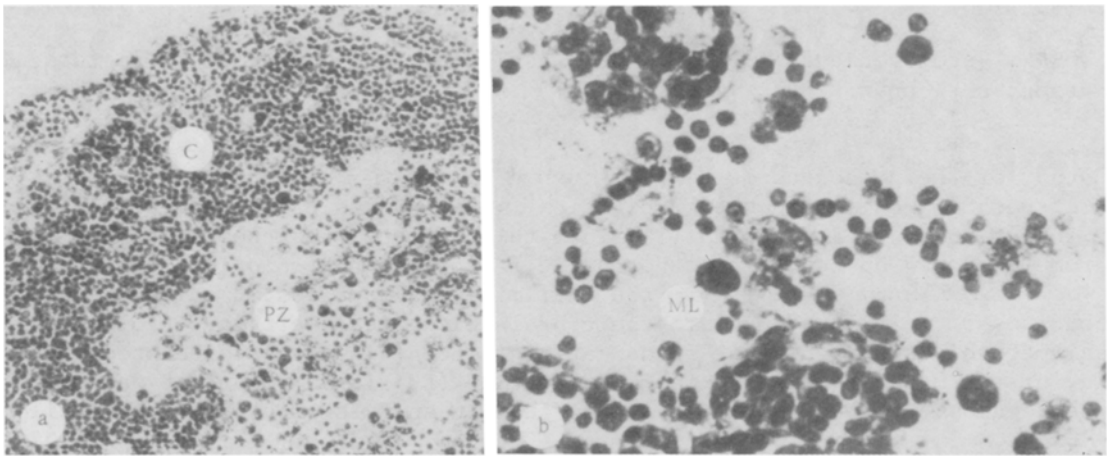

Fig. 1. Morphological changes in lymph nodes in experimental atherosclerosis in animals additionally receiving hydrocortisone. a) Reduction in thickness of cortex (C), which contains no secondary lymphoid follicles with germinal centers. Atrophy of paracortical zone (PZ). Period of experiment, 12 weeks, 200×; b) sinuses of medullary layer (ML) contain solitary lymphoid cells. Particles of pigment in littoral cells. Period of experiment, 4 weeks, 600×. Staining by Brachet's method.

cortisone has a marked immunodepressive action and lowers the circulating antibody level through its action on peripheral organs of the immune response, in which it produces severe degenerative changes.

In the experiments with hydrocortisone, just as in those with an immunodepressant [1], a connection was again found between the state of the peripheral lymphoid organs and the development of atherosclerotic lesions of the blood vessels. Whereas in animals kept on an atherogenic diet only the B-system of peripheral lymphoid organs was activated and, parallel with this, progressive development of experiment atherosclerosis was observed [6], when the atherogenic diet was accompanied by administration of hydrocortisone the opposite picture was observed and, despite the high blood lipid level, accompanied by inhibition and atrophy of the B-system of lymph nodes and spleen, the severity of atherosclerotic lesions of the arteries was sharply reduced.

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ANTICONVULSANT EFFECT OF STIMULATION OF THE MESENCEPHALIC RETICULAR FORMATION IN ANIMALS WITH EXPERIMENTAL PHOTOGENIC EPILEPSY

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KEY WORDS: photogenic epilepsy; lateral geniculate body; mesencephalic reticular formation; anticonvulsant stimulation.

The study of the pathogenesis of experimental photogenic epilepsy [3], arising when a generator of pathologically enhanced excitation is formed [5] in the lateral geniculate body (LGB), by injection of tetanus toxin (TT) into this nucleus, has shown that the formation of this syndrome is based on two main pathogenetic factors: 1) pathological enhancement of specific sensory excitation passing through the thalamic relay nucleus; 2) disturbance of nonspecific mechanisms of stabilization of rhythmic brain electrical activity. Following analysis of neuronal mechanisms of generator organization in LGB [4] it was postulated that inhibition of activity of the mesencephalic reticular formation (EP) is an important pathogenetic component of the development of epileptic seizures (ES) in animals with photogenic epilepsy [2].

The investigation described below was devoted to the testing of this hypothesis: to study whether generalized ES can be depressed by increasing MRF activity as a result of electrical stimulation.

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