STRUCTURAL CHANGES IN THE BLOOD VESSELS AND PARENCHYMA OF THE LUNGS IN EXPERIMENTAL HYPERCHOLESTEROLEMIA AND ATHEROSCLEROSIS

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The study of structural changes in the cardiovascular system in experimental models of atherosclerosis has led to enunciation of the hypothesis of the initial role of injury to the microcirculatory bed (MCB) and of microcirculatory distrubances in the mechanisms of atherosclerosis and, in particular, in the development of coronary atherosclerosis [3, 4, 8].

Close functional interaction is known to exist beween the respiratory and circulatory systems. Evidence has been obtained to show the important role of the lungs in metabolism of lipids and biologically active substances and in general and local immune reactions. In recent years investigators have had their attention drawn to the combination of atherosclerosis with chronic nonspecific lung diseases (CNLD) [1, 9, 10]. Meanwhile the genesis of the vascular changes in the lungs in hypercholesterolemia (HCh) and hyperlipoproteinemia has received little study.

In the investigation described below structural changes in the intramural vessels, MCB, and other components of the lung during the formation and stabilization of HCh were analyzed.

EXPERIMENTAL METHOD

Experiments were carried out on 42 rabbits. To produce HCh, animals of group 1 received a single dose of 0.5 g/kg body weight of cholesterol (ChS) with the food. Material was analyzed after 1, 3, 6, 15, 24, and 48 h and after the 12th day. Animals of group 2 were kept on an atherogenic diet (AGD). Material for investigation was taken on the 4th, 7th, 11th, 12th, 30th, 60th, 90th, 120th, and 240th days. Intact animals (group 3) served as the control. Method of light (staining with hematoxylin and eosin by Van Gieson's and Goldman's methods) and electron microsocopy (fixation in 1% buffered OsO_4 solution, embedding in Araldite, sections stained with uranyl acetate and lead citrate by Reynolds' method) were used.

EXPERIMENTAL RESULTS

During the first hours (1, 3, and 6 h) after administration of ChS changes were observed in MCB, mainly in the capacitive component (Fig. 1a). The lumen of the postcapillaries and of the terminal, lobular, and postlobular channels of the pulmonary vein was sharply dilated and filled with lipemic plasma and erythrocytic aggregates. Spastic changes and plasmarrhagia were observed in the small intramural branches of the pulmonary artery and in the arterioles. The changes were more marked after 15 h, when the blood ChS level was high (1 g/liter, compared with normal 0.2 g/liter). Meanwhile some thickening of the interalveolar septa, the appearance of small local areas of dystelectasis, and a marked perivascular and peribronchial lymphoid-plasma cell and macrophagal reaction were observed. During the electron-microscopic investigation attention was drawn to marked dilatation of the capillary lumen in the interalveolar septa, swelling of the entothelium of the microvessels, and narrowing of the alveolar cavities (Fig. 2a). The number of type II alveolocytes was increased and disorganization of the lamellar bodies and edema and loosening of the fibers of the basement mem-

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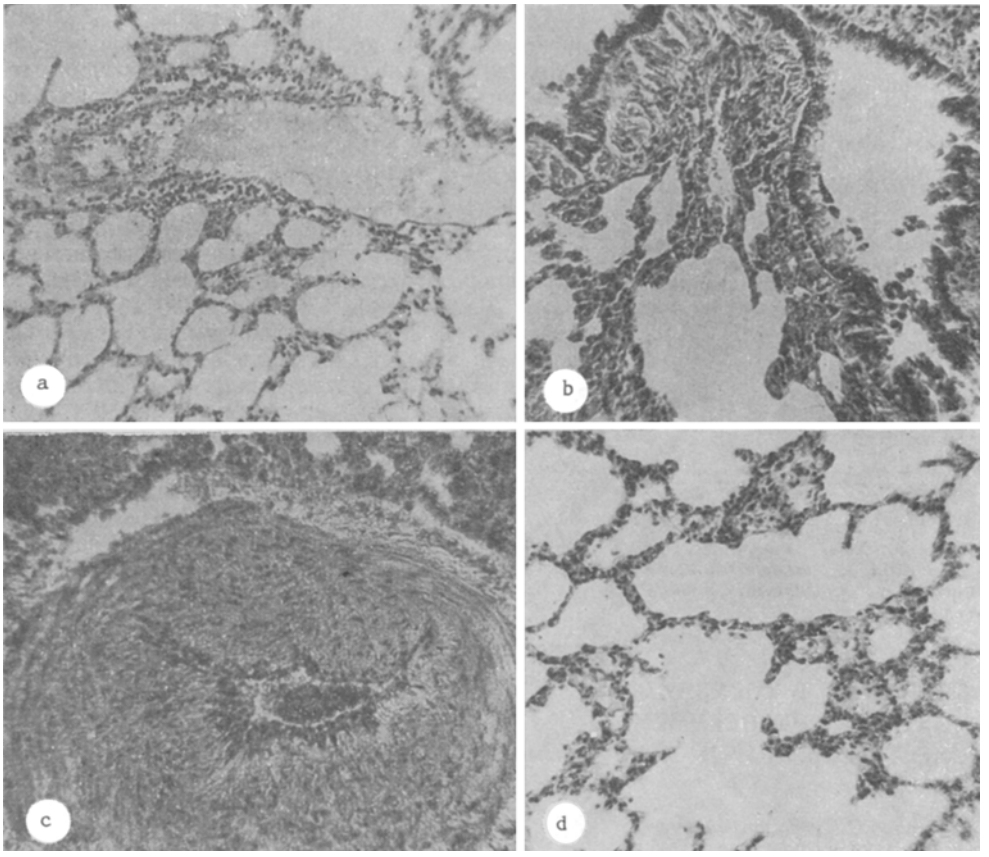

Fig. 1. Structural changes in lungs at different stages of experimental atherosclerosis. a) 15 h after a single dose of ChS: lumen of venule is dilated and filled with lipemic plasma, marked perivascular cellular reaction. Hematoxylin and eosin, 80×; b) after 2 months on AGD: destructive changes in epithelium of terminal bronchioles, deformation of their lumen. Goldman's stain, 80×; c) 1 month on AGD: constriction of a small artery and hypertrophy of its muscular coat. Van Gieson's stain, 200×; d) 3 months on AGD: focal emphysematous changes. Van Gieson's stain, 80×.

brane were observed (Fig. 2c). The number of lysosomes and of residual bodies in the alveolar macrophages increased and lipid granules were seen. The intensity of the changes listed above diminished toward 24-48 h of the experiment (parallel with the fall in the ChS level to 0.5 and 0.3 g/liter respectively).

Transferring the animals to an AGD (2nd, 4th, 7th, 9th, and 12th days) aggravated changes in MCB in the intramural branches of the pulmonary artery, and other structural elements of the lungs. Blood capillaries in the alveolar septa were sharply dilated and congested, their endothelium was edematous, and extravasation of erythrocytes was visible along the course of the capillaries and in the lumen of several alveoli. In some small arteries, which were in a state of constriction, hypertrophy of the muscular coat and some thickening of the intima were present (Fig. 1c). Foci of atelectasis and emphysematous areas appeared in the lung tissue, and the macrophagal reaction in the alveolar septa was fairly intensive. In some groups of muscle fibers in the wall of bronchii of varied caliber, lipid inclusions were visible. Sclerotic changes developed in the perivascular and peribronchial tissue and in the alveolar septa.

After 1-2 months changes in the microvessels continued to progress (Fig. 2b) and marked edema was present in the endotheliocytes, in which large lipid drops could sometimes be seen. A characteristic feature of this period is an increase in the number of small arteries with intimal thickenings and with hypertrophy of the muscular coat, containing large accumulations of lipids, and also the formation of atherosclerotic plaques in these vessels, and arteriovenous shunts were found. Against the background of progression of the sclerotic changes, the foci of dys- and atelectasis and of emphysema grew larger (Fig. 1d).

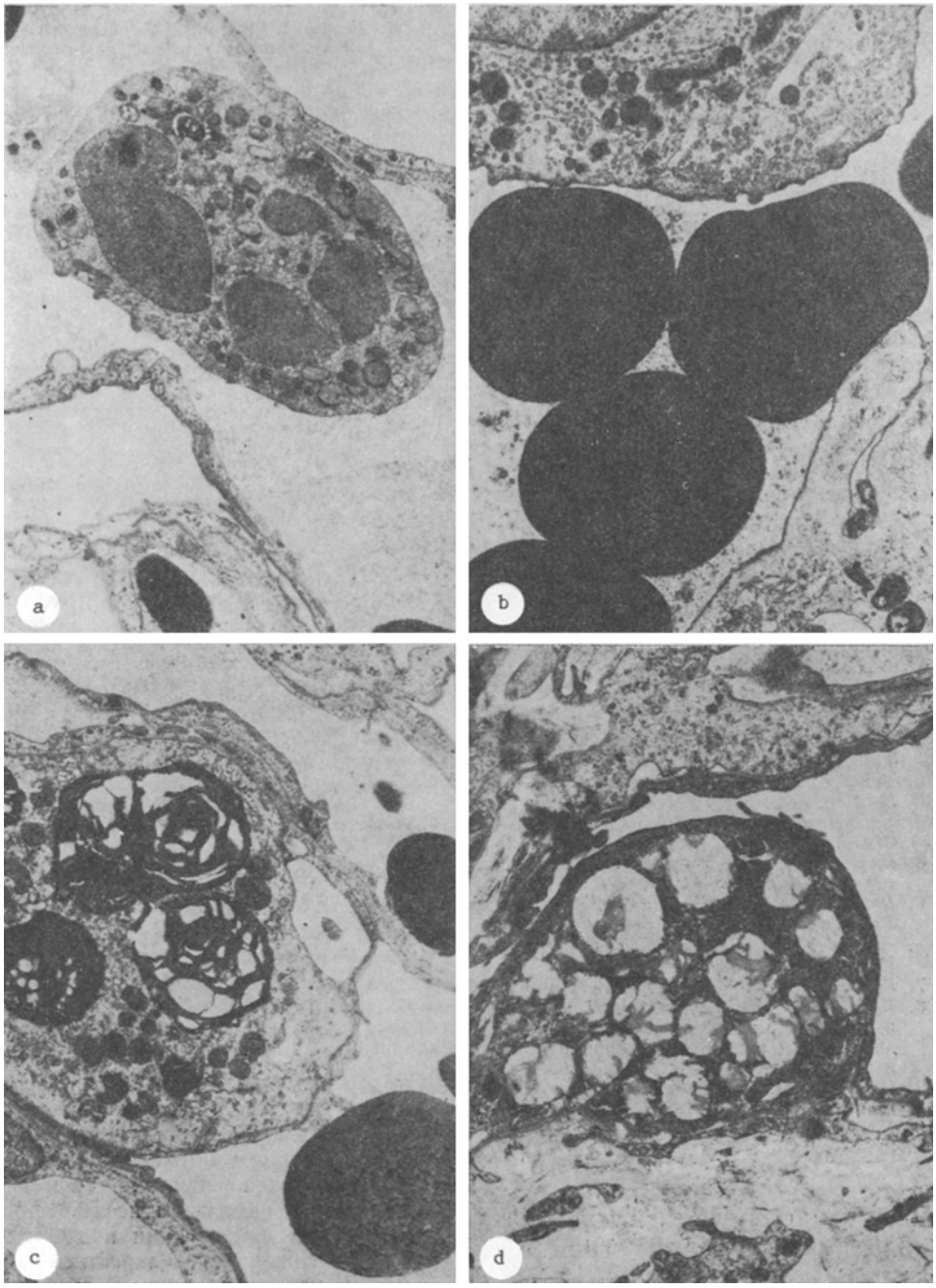

Fig. 2. Structural changes in air-blood barrier of lung in early stages of atherogenesis: a) 15 h after a single dose of ChS: capillary lumen is dilated, edema of microvascular endotheliocytes and type I alveolocyte; b) diet for 1 month: stasis of erythrocytes in microvessel; c) 15 h after single dose of DhS: disorganization of osmiophilic lammelar bodies in type II alveolocytes; d) diet for 1 month: disappearance of osmiophilic lamellar bodies from type II alveolocytes, increase in thickness of air-blood barrier. Magnification: a, c) 9000×; b) 15,000×, d) 11,000×.

After 3-8 months changes in the intermural arteries of varied caliber became dominant: Fibrous and atheromatous plaques formed. The area of the foci of atelectasis and emphysema in the lung tissue became larger. Destructive changes were found not only in the bronchioles and small bronchi (Fig. 1b), but also in the bronchi of large caliber. Focal atrophy of smooth-muscle cells, death of chondrocytes, and massive areas of cellular infiltration, both in the wall and peribronchially, were observed in the larger bronchi. Reduction of capillaries, an increase in the number of collagen microfibrils and elastic structures, and thickening of the basement membrane took place in the alveolar septa. The intensity of the vascular and tissue changes correlated with the HCh level [5].

The structural changes discovered in the lungs in the course of experimental atherosclerosis were found to be similar to the picture observed in diabetes mellitus [9] and in the so-called "senile emphysema."

In the lungs, just as in the internal organs [4, 5], the primary lesion in experimental HCh or hyperlipoproteinemia [5] is in the microcirculatory bed, evidence of the generalized character of the response of the terminal part of the vascular system to one of the leading risk factors in atherogenesis. The combination of changes found in the capillary endotheliocytes of the alveolar septa, the epitheliocytes (types I and II), and the alveolar macrophages at different stages of atherogenesis suggests that even in the early stages of pathological process the permeability of the air-blood barrier and synthesis of lung surfactant are disturbed [7]. Structural changes developing in the vascular system of the lungs in animals kept on an AGD, in the form of long-term constriction of arterioles and small arteries, structural changes of occulsive type in the small branches, and the subsequent formation of fibrous and atheromatous plaques, may be accompanied by increased peripheral resistance in the pulmonary circulation and development of pulmonary hypertension [2, 6].

Atherosclerotic changes in the small and larger branches of the pulmonary artery appear and progress parallel with the development of this process in the coronary arteries [4].

On the whole the results of this investigation indicate an important role for disturbances of lipid metabolism in the development of lung pathology and they may be relevant to the elucidation of the pathogenesis of CNLD, especially in old people.

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