AUTOIMMUNE REACTIONS IN EXPERIMENTAL NECROBIOTIC LESIONS OF THE MYOCARDIUM

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Changes resembling those of focal myocytolysis and contractures were found in the myocardium of rabbits with adrenalin myocarditis and of dogs with experimental myocardial infarction caused by ligation of the left coronary artery. These changes progressed into colliquative or coagulative necrosis, followed by the formation of granulomas and foci of sclerosis. Anticardial autoantibodies were found in the peripheral blood, reaching a maximum on the 3rd-5th day from the beginning of the experiment. A correlation was established between the dynamics of the morphological and immunological manifestations.

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The objects of the present investigation was to make a more detailed study of the dynamics of autoimmune manifestations previously described [3-5] in animals in association with necrobiotic changes in the myocardium, and to compare the immunological and morphological findings.

EXPERIMENTAL METHOD

Experimental myocarditis was produced in 90 rabbits weighing 2.8-3.2 kg by intravenous injection of caffeine and adrenalin. Experimental myocardial infarction was produced in dogs by ligation of the anterior descending branch of the left coronary artery at various levels. The animals were sacrificed and blood taken at intervals of between 10 min and 20 days after the operation. Serologic investigation by the passive hemagglutination method (with control by the inhibition reaction) was carried out as in previous studies [3-5]. The material was subjected to statistical analysis [9]. The methods of histological investigation (including polarization and phase-contrast methods) are described elsewhere [6-8].

EXPERIMENTAL RESULTS

Degenerative changes in the myocardium in adrenalin myocarditis were mainly localized in the wall of the left ventricle, were focal in character, and could be detected within the first 10-15 min of the experiment. Changes of two types were observed in the muscle cells: myocytolysis, detected in polarized light by disappearance of the anisotropic substance of the myofibrils and in phase contrast by the decrease in optical density of the cytoplasm, swelling and partial destruction of the sarcosomes (Fig. 1), and contracture of the myofibrils, characterized by an increase in anisotropy of the A-discs and subsequent formation of a continuous anisotropic conglomeration and by death of the nucleus, i.e., coagulation necrosis of the cell (Fig. 2).

The myocytolysis was usually partially reversible, but with more severe damage it changed into colliquative necrosis, absorption of the dying cell taking place within the first day without participation of cells of the infiltrating lesion. Coagulated muscle cells were destroyed only with the assistance of leukocytes and macrophages derived from the blood stream, and destruction was complete by the 3rd-4th day of the experiment. The granulomas which formed changed into scars. After ligation of the coronary artery in dogs extensive necrobiotic foci developed in the zone of ischemia, and these underwent resorption and organization with subsequent scar formation.

In most animals physiological anti-organ antibodies were detected before the experiment in titer not exceeding 3.8-4.2 $\log_2$ indices. In all experimental animals an increase in titers of anticardial autoantibodies

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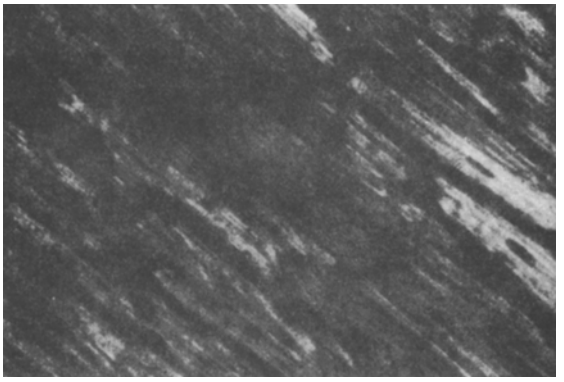

Fig. 1. Myocardium of rabbit dying 15 min after injection of adrenalin. Multiple foci of myocytolysis, photographed in polarized light. Objective 10, ocular 20.

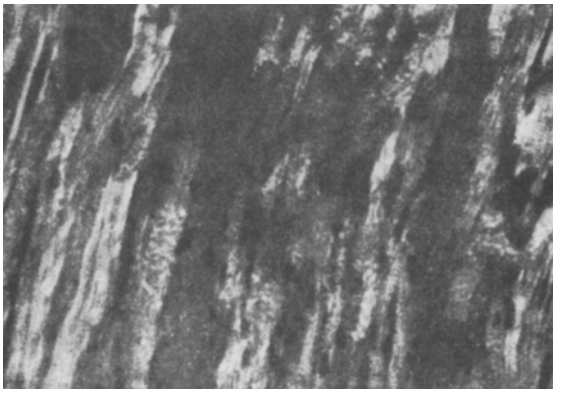

Fig. 2. Foci of granular degeneration of anisotropic material of myofibrils and contracture of myofibrils in myocardium of rabbit 24 h after injection of adrenalin. Photographed in polarized light. Objective 10, ocular 20.

to 7.8-8.3 was observed during the course of the investigation. The titers of antikidney autoantibodies were unchanged. A marked increase in titers of anticardial antibodies was found on the 1st-2nd day of the experiment, followed by a statistically significant decrease on the 5th-7th day, with a second rise after the 9th-11th day (Fig. 3). By the 40th-60th day of the experiment the autoantibody titers had fallen to the physiological level. In dogs with myocardial infarction a relationship was discovered between the size of the pathological focus and the autoantibody level. For instance, the mean autoantibody titer associated with a small infarct was 5 ± 0.4, rising to 6.3 ± 0.3 with a medium-sized focus and 8.7 ± 4 with a large focus. The coefficient of correlation between the size of the pathological focus was 0.691 and the degree of probability of the correlation 0.02.

The first increase in autoantibody titers coincided in time with the onset of necrosis of muscle cells in the myocardium and developed in the early period of the experiment (from the 1st to 3rd day), when resorption of necrotic material took place. A fresh rise in antibody titers was found in later periods against the background of scar formation, while secondary degenerative changes took place in neighboring muscle cells, accompanied in some cases by contracture of myofibrils, but leading not to necrosis, but to gradual atrophy of the damaged cells.

The increase in titers of anticardial autoantibodies during the first day after the beginning of the experiment cannot be regarded as a response of the animal body to a foreign or pathologically changed antigen, because reactions of this type do not develop sooner than after 2-3 days [10]. The parallel which exists between the early morphological changes and immunologic changes provides an explanation of this finding from the standpoint of the theory of primary immunologic reactivity of the organism [1, 2]. It may be

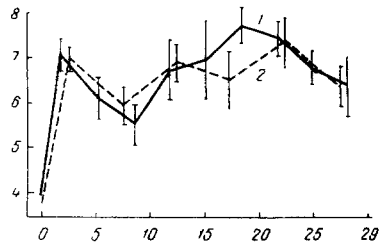

Fig. 3. Dynamics of titers of anticardial autoantibodies in experimental myocardial infarction and adrenalin myocarditis. Ordinate, logarithms of titers; abscissa, days from beginning of experiment. 1) Myocarditis; 2) infarction.

postulated that during death of myocardial cells, proteins which were formed previously during embryogenesis and are complementary to later structures are liberated and enter the blood stream, as is shown by an early increase in titers of anti-organ autoantibodies. However, Grabar's hypothesis concerning the physiological role of the normal serum globulins, adapted more or less specifically to the transfer of products of cell breakdown, and accordingly detected in immunologic reactions as normal or physiological autoantibodies [11, 12], is a possibility which cannot be ruled out.

Comparison of published data with our results as described above suggests that the entry of a large quantity of breakdown products of muscle cells into the blood stream in the early stages of development of the pathological process increases the production of normal globulins or causes structural modification of the other blood serum proteins so that they acquire complementary properties relative to the breakdown products. Both these mechanisms possibly play a part in the appearance of anti-organ autoantibodies in the early stages of development of the pathological process. The second increase in titers of anticardial autoantibodies at later periods against the background of the connective-tissue reaction shows that the system of secondary immunologic reactivity has become involved in the immunologic processes at this stage.

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