It can thus be concluded from the results of this investigation that irreversible disturbances of growth of hippocampal neurons and of their metabolic maturation due to hypothyroidism in the early postnatal period may be one stage in the pathogenesis of functional disorders of the CNS.

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SYSTEMIC RELATIONS OF KINETICS OF BLOOD LEUKOCYTES AND INFLAMMATORY INFILTRATION CELLS IN A ZONE OF INFARCTION OF THE RAT HEART

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The fundamental ideas of the character of the inflammatory infiltrate in a zone of myocardial infarction during its healing have been described in many publications [3, 8, 10, 12, 14, 15]. However, no special study has yet been undertaken with the aim of establishing systemic relations between the kinetics of the blood leukocytes and the kinetics of inflammatory infiltrate cells in a zone of myocardial infarction. Since the view has become established that cells of a focus of aseptic inflammation are hematogenous in origin [9, 16], the study of these problems may be not only of theoretical, but also of practical importance.

In connection with the facts described above, the aim of the present investigation was to determine correlation between the kinetics of blood leukocytes and the kinetics of inflammatory infiltrate cells in a zone of myocardial infarction in rats during healing.

EXPERIMENTAL METHOD

Experiments were carried out on 266 male rats weighing 183 ± 17 g. Myocardial infarction was produced by ligation of the lateral artery of the left ventricle under sterile conditions and under general anesthesia with controlled respiration. The animals were killed between 5 min and 30 days after the operation, in accordance with prevailing instructions. In sections cut through the zone of myocardial infarction and stained with hematoxylin and eosin, by Van Gieson's, Weigert's, and Brachet's methods, and using the "fields" method of Glagolev [2] with modifications, the packing density of polymorphonuclear leukocytes (polymorphs), macrophages, lymphocytes, fibroblasts, eosinophils, plasma cells, and mast cells was determined. The relative number of granulocytes and agranulocytes was determined at various times of the experiment during the life of the animals, on blood films stained by the Romanovsky–Giemsa method, and the ratio between them was calculated and called the blood leukocyte shift index (BLSI).

To estimate the effect of operative trauma on the kinetics of the blood leukocytes in myocardial infarction, similar investigations were carried out on 29 rats undergoing a mock operation, which was limited to pericardiotomy.

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TABLE 1. Changes in BLSI of Rats after Production of Experimental Myocardial Infarction and after Control Thoracotomy (M ± σ)

Group of animals	Time of investigation, days									
	initial value	1	3	5	7	10	15	20	25	30
Experimental	0,34±0,14	0,95±0,57	0,76±0,54	0,61±0,30	0,61±0,30	0,52±0,23	0,78±0,27	0,43±0,17	0,35±0,10	0,30±0,08
Control	0,43±0,21	0,87±0,43	0,89±0,38	0,63±0,24	0,50±0,16	0,75±0,34	0,54±0,20	0,41±0,21	0,39±0,11	0,47±0,09

TABLE 2. Packing Density of Inflammatory Infiltrate Cells in Zone of Myocardial Infarction in Rats at Different Times of Experiment (M ± σ)

Form of cells	Time of investigation, days			
	1	3	5	7
Polymorphs	$28\cdot10^{-2}\pm45\cdot10^{-2}$	$29\cdot10^{-3}\pm17\cdot10^{-2}$	$12\cdot10^{-5}\pm97\cdot10^{-4}$	
Macrophages	$40\cdot10^{-3}\pm23\cdot10^{-2}$	$56\cdot10^{-3}\pm23\cdot10^{-2}$	$50\cdot10^{-3}\pm22\cdot10^{-2}$	$26\cdot10^{-3}\pm15\cdot10^{-2}$
Lymphocytes	$14\cdot10^{-3}\pm10\cdot10^{-2}$	$29\cdot10^{-3}\pm17\cdot10^{-2}$	$67\cdot10^{-3}\pm25\cdot10^{-2}$	$26\cdot10^{-3}\pm16\cdot10^{-2}$
Plasma cells	—	—	—	$25\cdot10^{-4}\pm90\cdot10^{-3}$
Fibroblasts	—	$25\cdot10^{-2}\pm43\cdot10^{-2}$	$30\cdot10^{-2}\pm46\cdot10^{-2}$	$23\cdot10^{-2}\pm43\cdot10^{-2}$
Eosinophils	—	—	$50\cdot10^{-4}\pm69\cdot10^{-3}$	$86\cdot10^{-4}\pm92\cdot10^{-3}$
Mast cells	—	—	$19\cdot10^{-2}\pm14\cdot10^{-2}$	$10\cdot10^{-3}\pm10\cdot10^{-2}$

Form of cells	Time of investigation, days				
	12	15	17	20	25
Polymorphs		—	—	—	—
Macrophages	$58\cdot10^{-4}\pm75\cdot10^{-3}$	—	—	—	—
Lymphocytes	$58\cdot10^{-4}\pm74\cdot10^{-2}$	$11\cdot10^{-3}\pm84\cdot10^{-3}$	$11\cdot10^{-4}\pm32\cdot10^{-3}$	$31\cdot10^{-5}\pm17\cdot10^{-3}$	$17\cdot10^{-5}\pm13\cdot10^{-3}$
Plasma cells	$18\cdot10^{-3}\pm13\cdot10^{-2}$	$27\cdot10^{-3}\pm16\cdot10^{-2}$	$94\cdot10^{-4}\pm91\cdot10^{-3}$	$84\cdot10^{-5}\pm29\cdot10^{-3}$	$25\cdot10^{-4}\pm43\cdot10^{-3}$
Fibroblasts	$11\cdot10^{-2}\pm29\cdot10^{-2}$	$88\cdot10^{-3}\pm28\cdot10^{-2}$	$78\cdot10^{-3}\pm26\cdot10^{-2}$	$56\cdot10^{-3}\pm23\cdot10^{-2}$	$89\cdot10^{-3}\pm26\cdot10^{-2}$
Eosinophils	$19\cdot10^{-3}\pm13\cdot10^{-2}$	$51\cdot10^{-4}\pm61\cdot10^{-3}$	$29\cdot10^{-4}\pm44\cdot10^{-3}$	—	—
Mast cells	$93\cdot10^{-4}\pm87\cdot10^{-2}$	$27\cdot10^{-4}\pm49\cdot10^{-3}$	$28\cdot10^{-4}\pm42\cdot10^{-3}$	—	—

Stereometric data were processed by the ES 1022 computer in accordance with special programs. The programs were based on methods of morphometry and stereology [1, 4, 5, 11, 17].

EXPERIMENTAL RESULTS

The data in Tables 1 and 2 demonstrate close correlation between the kinetics of the blood leukocytes and the kinetics of inflammatory infiltrate cells in the zone of myocardial infarction during healing. At the beginning of the acute period of myocardial infarction, when signs of necrobiosis were developing in the zone of the infarct, the number of leukocytes rose sharply, mainly because of granulocytes. This was reflected in a sharp rise in the values of the BLSI index during the first few hours and days of development of myocardial infarction. The inflow of polymorphs into the zone of the infarct increased in intensity. After 2 days, the density of their distribution in the zone of infarction was uniform. Toward the 3rd-5th days, signs of necrobiosis were mainly complete, and the pool of polymorphs necessary for this purpose was formed as early as by the end of the first day. After 1 day, the density of polymorphs in the zone of infarction and the value of BLSI began to decrease. These results can be explained by data [7] showing that redistribution of the blood leukocyte pool toward the focus of injury takes place before destructive changes have developed in it.

Meanwhile, along with polymorphs, macrophages and lymphocytes appeared in the zone of myocardial infarction. However, their number here increased more slowly. Not until the 5th day was the peak value of the number of macrophages and lymphocytes observed in the zone of infarction. The impression was created that proliferation of inflammatory infiltrate cells in the zone of infarction and immigration of precursors of inflammatory infiltrate cells into it, together with other systems, are controlled by mechanisms of necrobiosis and, in particular, by the unique kinetics of the polymorphs.

The results suggest that control of the kinetics of the different subpopulations of inflammatory infiltrate cells in the zone of infarction is effected through feedback mechanisms.

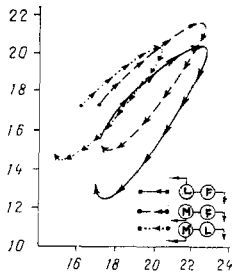

Fig. 1. Diagram showing systemic relations between kinetics of macrophages (M), lymphocytes (L), and fibroblasts (F) of zone of myocardial infarction during healing. Natural logarithms of cell populations in zone of infarction plotted along axes. Arrows indicate axis on which values of features are plotted.

In other words, not only are the phenomena of granulation tissue development controlled by the mechanisms of necrobiosis, but necrobiosis also is controlled by the phenomena of granulation tissue development.

Two critical periods were observed in the changes in size and packing density of the lymphocytes: after intervals of 4 and 7 days, respectively. At this time the number of, first, fibroblasts (after 2 days) and, later, plasma cells (after 4-5 days) in the zone of infarction increased. The hematopoietic stem cell, as we know, can differentiate in different directions, and this evidently includes transformation into a fibroblast [6, 9]. This factor is evidently of great importance in the cooperative relations determined between fibroblasts, macrophages, and lymphocytes in a zone of myocardial infarction. As will be clear from Fig. 1, changes in the number of these forms of cells are synchronized with each other in time and space.

The proliferative pool of granulation tissue cells in the zone of myocardial infarction is formed on the 5th-7th day. Later changes in the number and packing density of the different forms of cells in the zone of myocardial infarction are less important. On the 12th-15th day, the packing density of the different forms of granulation tissue cells in the zone of infarction is stabilized. Simultaneously with this, a second wave of neutrophilic leukocytosis is observed in the blood. Changes in the number of blood leukocytes in this period of myocardial infarction are difficult to correlate with changes in the direction of differentiation of stem cells. On the one hand, in this case any such jump is impossible in the changes in values of BLSI, and on the other hand, the blood granulocytes may be deposited in sinuses of the bone marrow [6, 13]. In this connection, it must be assumed that this change in the kinetics of the blood leukocytes is one mechanism of stabilization of the proliferative pool of cells of the granulation tissue developing at the site of the infarct. The dynamics of BLSI in the control animals must also be taken into account, for they also had a second peak of BLSI after an interval of 10 days. If the time taken for necrobiosis of the zone of infarction is taken to be about 5 days, and that the tissues destroyed during simple thoracotomy with pericardiotomy are eliminated in the course of 24 h, these differences in the time course of BLSI in animals of the control and experimental groups are readily explained, more especially because the mechanism of healing of the infarct and of the operation wound is the same — granulation tissue formation followed by organization and scar formation.

After 15 days of synchronous stabilization of the proliferative pool of the granulation tissue cells in the zone of infarction, normal values of BLSI were gradually restored. The results are evidence that after 15 days structural organization of the postinfarct scar takes place without any significant changes in cell kinetics. Renewal of the proliferative pool of cells of the organizing granulation tissue under these conditions ought to lead to synchronization of the numbers of cells emigrating from it and immigrating into it. It can be tentatively suggested that limitations due to its size are imposed on the number of granulation tissue cells in the zone of myocardial infarction.

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