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MORPHOGENESIS OF PNEUMONIA DURING ALTERED IMMUNITY

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The great diversity of connections between immune and inflammatory reactions makes it difficult to draw a sharp line between them and to evaluate their interdependence [5]. The aim of this investigation was to study the effect of various changes in the immune response on the development of inflammation of the lungs.

EXPERIMENTAL METHOD

Pneumonia lasting 2 weeks was induced in 30 Wistar rats, divided into five groups (with six rats of the same weight and sex in each group) by introduction of a foreign body (Kapron thread 0.4 mm in diameter and 3 cm long) into the trachea by the method in [3]. Additionally, animals of group 1 received subcutaneous injections of 25 U of heparin twice a day every day for 3 weeks (1 week before and 2 weeks after introduction of the thread). Animals of groups 2 and 3 received intramuscular injections of cyclophosphamide in a dose of 0.6 mg on alternate days and phytohemagglutinin (PHA) in a dose of 5 mg once every 5 days respectively for 3 weeks (1 week before and 2 weeks after introduction of the thread). Animals of group 4 received a single subcutaneous injection of 1.5 ml of sterile mineral oil 5 days before introduction of the thread into the trachea. According to data in the literature [1] this inhibits complement-dependent reactions (heparin) and leads to various kinds of stimulation (PHA, mineral oil) and to inhibition of immunity (cyclophosphamide). Group 5 (control) consisted of six rats with pneumonia for 2 weeks. Sections of lung tissue were stained with hematoxylin and eosin, by Van Gieson's method, and for DNA by Feulgen's and RNA by Brachet's methods, for glycoproteins (GP) by the PAS reaction, and for glycosaminoglycans (GAG) by the method of Hale and Muller. The density of cellular infiltration was studied morphometrically by the dot counting method [2]. Titers of heterophilic agglutinins (by a modified Paul–Bunnell method) and of antistaphylococcal antibodies (passive hemagglutination test) were determined in blood sera. The cellular immune response was estimated from the difference between limb volumes before and 48 h after injection of 0.2 ml of standard *Neisseria catarrhalis* allergen into the footpads. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Inflammation of the lungs of 2 weeks' duration was characterized by the development of acute catarrhal bronchitis with moderate peribronchial exudation. In some cases acinar bronchopneumonia developed. There was a moderate microfocal interstitial reaction in the form of thickening of the alveolar septa by edema and concentrations of macrophages and lymphocytes around single vessels. Histochemically an increase in the content of DNA (nucleus), RNA, GAG, and GP (cytoplasm) was observed in the epithelium of most bronchi, the vascular endothelium, and septal cells, pointing to the development of an anabolic type of tissue reaction.

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TABLE 1. Density of Cellular Infiltration (in conventional units) around Bronchi during Inflammation of the Lungs and Treatment with Immunomodulators

Statistical index	Group of animals (pneumonia for 2 weeks)				
	control	1	2	3	4
M	0,237	0,367	0,335	0,304	0,268
$\pm m$	0,015	0,009	0,032	0,006	0,022
P	—	<0,001	<0,02	<0,01	>0,1

TABLE 2. Immune Response during Inflammation of the Lungs and Treatment with Immunomodulators (M ± m; n = 6)

Parameter studied	Group of animals (pneumonia for 2 weeks)				
	control	1	2	3	4
Log. of reciprocals of titers of heterophilic agglutinins	1,655±0,067	1,204±0,109	1,304±0,1	2,408±0,155	1,745±0,112
P		<0,01	<0,02	<0,01	>0,01
Log. of reciprocals of titers of antistaphylococcal antibodies	1,602±0,095	1,903±0,173	—	2,371±0,297	—
P		>0,1		<0,5	
Difference between volumes of hind limbs before and 48 h after injection of 0.2 ml of Neisseria catarrhalis allergen into footpads, ml	0,017±0,017	0,258±0,027	0,217±0,031	0,183±0,028	0,12±0,02
P		<0,001	<0,001	<0.001	<0,01

Under the influence of heparin the principal form of inflammation of the same duration which developed was confluent lobular bronchopneumonia with solitary small abscesses. The use of cyclophosphamide and PHA led to similar changes in the character of inflammation of the lungs, namely the development of bronchiectasis with abscesses, the cavities filled with debris and residual macrophages, leukocytes, and lymphocytes. Large perifocal foci of pneumonia with lung abscess were observed. The more severe inflammatory changes under the influence of heparin, cyclophosphamide, and PHA compared with the control also was confirmed by morphometric data (Table 1). Meanwhile, under the influence of cyclophosphamide and PHA activation of proliferative processes was observed, leading to organization with the formation of thin and thicker connective-tissue bands, and also to metaplasia of the epithelium of the bronchiectases. Histologically, the concentrations of DNA (nucleus), RNA, GAG, and GP (cytoplasm) in the residual epithelium of the bronchi, endothelium of the blood vessels, and septal cells were reduced, indicating a catabolic type of tissue reaction, and resulting from the greater intensity of alterative than of anabolic changes [4].

Injection of mineral oil caused the development of typical granulomatous inflammation at the site of injection (subcutaneous layer of the limb). In the lungs in this case, as in the control animals, acute catarrhal bronchitis developed. The density of cellular infiltration under these circumstances was the same as in the control (Table 1). However, in this case the bronchitis was of a less marked and diffuse character. The severity and extent of spread of the interstitial reaction were significantly reduced. Histochemically, anabolic changes were observed in the principal cell structures of lung tissue.

The results show that compared with the control the most severe inflammation of the lungs was induced by cyclophosphamide and PHA (bronchiectasis with abscess formation), rather less severe by heparin (bronchopneumonia), whereas injection of mineral oil caused only some inhibition of the inflammatory process in the lungs.

The results of the immunologic investigations (Table 2) showed that the modification of inflammation which was used was not dependent on the immunoregulatory effect of the substances used or on the transformation of immunity which took place. The increased severity of inflammation compared with the control (bronchiectasis with abscess formation, bronchopneumonia) corresponded both to activation of the humoral immune response (PHA) and to its inhibition (cyclophosphamide, heparin), as reflected in the titer of heterophilic agglutinins in the blood sera. Along with the more severe inflammation after injection of heparin and

PHA than in the control, there was a correspondingly unchanged and increased titer of antistaphylococcal antibodies. Injection of mineral oil, leading to inhibition of inflammation, meanwhile, had no effect on the humoral immune response. Despite this difference in the severity of inflammation of the lungs, all the immunomodulators used led to activation of the cellular immune response, as shown by the results of the skin tests (compared with the control). The different intensities of the cellular response depending on the substances injected likewise did not correspond to differences in the course of the inflammatory process. No correlation was found between the character of the immune response and activation of proliferative processes leading to connective tissue formation, which can be regarded as an indicator of transition from acute to chronic inflammation [4]. As was noted, the most marked manifestations of organization with connective tissue formation were observed in animals receiving cyclophosphamide and PHA: The former responded to inhibition of the humoral response, the latter to its activation. Compared with the control, heparin caused maximal, and mineral oil caused minimal activation of the cellular immune response, whereas in this case there was no significant difference in the intensity of proliferation compared with the control.

Besides existing views on the importance of immunodeficiencies and immunopathological reactions in the development of inflammatory processes, the results of this investigation thus provide a basis for the view that the course of inflammation may be independent of the state of immunity.

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IMMUNOMORPHOLOGICAL INVESTIGATION OF INDUCTION OF CYTOCHROME P-450PB IN THE EMBRYONIC AND PREGNANT FEMALE RAT LIVER IN RESPONSE TO PHENOBARBITAL

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The microsomal monooxygenase system plays an important role in the detoxication of foreign lipophilic compounds entering the body. In the intermediate stages of metabolism, highly reactive compounds may be formed, capable of combining with biological macromolecules and, consequently, giving rise to mutagenic, carcinogenic, toxic, teratogenic, and other effects. Since embryonic tissues are sensitive to factors of this kind, the state of this enzyme system and, in particular, of its terminal component (cytochrome P-450) both in embryos and in pregnant females is interesting. A quite considerable number of investigations has already been conducted on the cytochrome P-450 content in the embryonic liver and its induction [4-6, 9]. It has been shown that the cytochrome P-450 content in the rat embryonic liver is low, and that there is no response to administration of cytochrome P-450 inducers.

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