plasm necrosis, fragmentation of granular and agranular cytoplasmic reticula is observed. Simultaneously they are fragmented and expanded, forming so-called small and large vesicles.

The proliferative activity of hepatocytes 7 and 10 days postoperation is virtually the same as that in intact controls but is reliably higher than in sham-operated animals in similar periods of follow-up.

Close contacts of lymphocytes with hepatocytes are extremely rare in sham-operated and intact animals.

Hence, lymphocyte flow into the liver is enhanced in the early periods of regeneration of this organ. Lymphocytes come in close contact with hepatocytes and reticuloendotheliocytes, forming microtunnels over the entire proliferative wave in the regenerating liver, starting from its genesis to the point where mitotic activity starts to wane (4-48 h postoperation). At the time of total decline of proliferative activity the number of contacts is no different from that in the control, that is, they are just solitary.

The number of close contacts between hepatocytes and lymphocytes in the course of the proliferation wave gives grounds for suggesting that both the mitogenetic function and mitostatic activity are realized similarly, the only difference being that different lymphocyte subpopulations may come in contact. It is, however, possible that the persistence of a high number of lymphocytes coming in contact forms a second proliferation wave which we failed to detect. The existence of substance exchange between contacting cells, and the trend of movement and nature of these substances are still to be elusidated.

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Lymph Circulation in the Febrile Reaction and Possible Antipyretic Correction

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UDC 616-092:612.55]-06:616.42-008.1]02:615.212.3

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol.117, № 2, pp. 180-181, February, 1994
Original article submitted November 16, 1993

The febrile reaction in dogs, as established experimentally, is accompanied by a significant intensification of the lymph flow. Metapyrin provides a strong boost to the lymph circulation, improving exchange processes between the blood and tissues.

Key Words: *febrile reaction; lymph circulation; Metapyrin*

The febrile reaction (FR) is known to be accompanied by marked changes in the function of organs and systems and, consequently, by disturbances in homeostasis. The nature of these disturbances varies widely depending on age. On the other hand, a key role is played by the lymphatic system in the maintenance of a constant internal environment due to its reliable resorptive and

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0007-4888/94/0002-0181$12.50

TABLE 1. Lymph Flow Rate (liter/kg/sec×10^{-6}) in the Thoracic Duct in the Febrile Reaction ($M \pm m$)

Animals	Control	Pyrogenal administration		
		single		5 times, 6th day
		after 2.5-3 h	after 5-5.5 h	
Dogs	0.61±0.07	1.59±0.22*	1.71±0.24*	0.95±0.29**
Puppies	0.84±0.13	1.89±0.17*	2.17±0.21*	1.38±0.20**

Note. Here and in Table 2: * – $p<0.001$, ** – $p<0.05$.

transport function, which is largely responsible for the qualitative and quantitative metabolic changes taking place in the microcirculatory bed.

In view of this and to further our previous investigations of lymphatic system pathophysiology in typical pathological reactions [10], we studied the dynamics of the lymph flow in FR effected by the widely used antipyretic Metapyrin in dogs and puppies.

MATERIALS AND METHODS

Experiments were carried out on 52 mongrel dogs weighing 4.6-25.5 kg and 44 puppies aged 1-2 months weighing 1.4-6.1 kg. FR was simulated by i.v. administration of pyrogenal at 10 μg/kg. The control animals received apyrogenic physiological solution. In certain experimental series 1.5 h after pyrogenal injection a 50% Metapyrin solution was administered i.v. in a dose of 25 mg/kg body weight. The rate of the lymph flow was determined by the quantity of lymph discharged when the thoracic duct (TD) was cannulated. The animals were sacrificed by a lethal dose of a narcotic.

RESULTS

The studies showed (Table 1) that the quantity of lymph discharged from the TD is greater in the control puppies, than in adult dogs. Just a single pyrogenal administration was accompanied by a marked intensification of the lymph flow, which manifested itself in an increase of the lymph flow rate that was most pronounced at the stage where the body temperature fell (2.8-fold in dogs and 2.6-fold in puppies). The lymph flow was also accelerated (1.6-fold) after a 5-day fever.

A 1.5-fold acceleration of the lymph discharge from the TD was noted in the intact animals 30 min after i. v. administration of Metapyrin and it was preserved for 1 h (Table 2). There was a marked (3.3-fold and 1.3-fold) rise of the lymph flow rate in animals with FR as compared to the control dogs and the animals not treated with Metapyrin, respectively. A daily i. v. administration of the antipyretic against the background of prolonged FR (for 5 days) was accompanied by a nearly 2.5-fold increase of the lymph flow rate, whereas in untreated animals the same increase was only 1.6-fold. The intensification of the lymph flow in 5-day FR against the background of Metapyrin administration was more marked as compared to a single injection.

Analyzing the data obtained, we postulate, that the higher values of the lymph flow rate in the TD in healthy puppies are probably related to age-dependent peculiarities of the phase rhythmic activity of lymph vessels (LV), this activity being higher in young animals than in mature ones [9]. In addition, the lymph flow rate depends on the number of valves in LV and on the degree of development of the lymphatic pathways, characteristics which are more pronounced in young animals [4]. The latter exhibit more intensive lymph production as well [2].

TABLE 2. Effect of Metapyrin on the Lymph Flow (liter/kg/sec×10^{-6}) in the Thoracic Duct in Dogs in FR ($M \pm m$)

Animals	Before Metapyrin administration	Minutes after Metapyrin administration						
		0-30	30-60	60-90	90-120	120-150	150-180	180-210
Intact	0.53±0.08	0.60±0.07	0.81±0.12**	0.80±0.11**	0.66±0.09	0.54±0.08	0.53±0.08	0.52±0.07
Treated with pyrogenal: one time	1.13±0.15	1.50±0.15	2.03±0.17*	2.14±0.18*	1.63±0.21**	1.54±0.15**	1.22±0.12	1.24±0.11
5 times 6th day	not treated with Metapyrin 0.95±0.29					treated with Metapyrin 2.38±0.19*		

As is evident from the findings, the characteristic reaction of the lymph flow in FR is an increase of the lymph flow rate regardless of the animal's age. The rise of the vascular permeability and the change of the sympathetic nervous system tonicity, resulting in a dilatation of LV, an increase of the number of anastomoses, and the opening of collateral lymphatic pathways, are probably the important factors in lymph flow variation. Humoral shifts are also significant factors in the increase of the lymph flow rate in FR. The activity of the sympathicoadrenal system and the processes of catecholamine biosynthesis and release are intensified in FR [1]. And it is known that the latter intensify the lymph flow and stimulate the contractile capacity of LV [8]. In addition, histamine as well as the kallikrein-kinin system play a certain role in the increase of the lymph flow rate in FR. The initial rise of the lymph flow is primarily due to their effect on LV motility, and later to the increase of lymph production resulting from the increased microvessel permeability. Intensification of lymph production stems from an increase of the area of functioning blood and lymph capillaries, from a rise of the colloid-osmotic pressure in terminal parts of the lymphatic system, from the increased permeability of lymph capillaries, and from intensification of their filtrative and resorptive capacity [3]. On the other hand, we found a rise of the histamine level and changes in the content of the kallikrein-kinin system components in the lymph and blood in FR [5,6].

The lymph flow rate in FR increases due to the stepped-up lymph production as well as to the considerable increase in the number of contracting LV and their valves and their enhanced contractility, as was established in our previous studies [7].

Discussing the possible mechanisms of the increase of the lymph flow rate due to Metapyrin, we proposed that it is related to the activation of LV contractility and to the decrease of their tonicity, which is markedly increased in febrile animals due to the intensive sympathicoadrenal stimulation. As a consequence, the LV capacity increases and the lymph flow from dilated vessels is facilitated. Stimulation of the contractility of smooth-muscle structures of the LV wall and dilation of their lumen result in a marked acceleration of the lymph flow. Thus, it may be assumed that the antipyretic effect of Metapyrin, along with the known mechanisms, is probably related to changes of lymph production and transport. The lymph flow is therewith multiply intensified, which improves the resorption and transport of cell metabolites from the interstitial space via the lymph pathways and thereby enhances the exchange processes between the blood and tissues.

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