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ALTERATIONS IN LYMPHATIC VESSELS IN THE COURSE OF CHRONIC EXPERIMENTAL LYMPHEDEMA

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Morphological alterations in dog's extremital lymphatic vessels occurring in lymphatic edema were studied. Besides, alterations in chemical composition of the lymph, as well as alterations of lymph pressure and its flow were investigated.

In our previous report on the pathogenesis of lymph stasis, the method was described for inducing chronic experimental lymphedema of the leg in dog (2). The purpose of the present paper is to demonstrate the alterations observed in the course of such edema, namely a) radiological and morphological abnormalities of lymphatics, b) biochemical composition of lymph, and c) pressures and lymph flow in the hind leg of dog with lymphedema of 2 years' duration.

PROCEDURE

Determinations were performed in 12 dogs with experimental lymphedema of the leg, every 6 months in the period from the 6th to 26th month after the appearance of edema. Radiological lymphography with lipiodol UF and phlebography were carried out, the specimens of skin and lymphatics were taken for histological examination. Lymph protein level and composition, as well as coagulation and fibrinolysis were determined.

The following pressures were measured: a) tissue pressure in the skin, b) the pressure of intercellular fluid in Guyton's capsule situated subcutaneously (1), c) the pressure of lymph. The measurements were done at rest and during standard passive movements of the leg. The speed of the outflow of ^{131}I-labeled albumin, administered in a dose of 100 C to the lymphatic of the dorsal aspect of the leg was also determined.

RESULTS

Radiological investigations. Dilation of lymph vessels with valvular insufficiency was found in the legs of all animals (Fig. 1). Locally, the lymphatics were up to 5 mm broad. The contrast administered into the dorsal vessel of the leg filled the vessels below injection reciprocally. At least 50 ml of lipio-

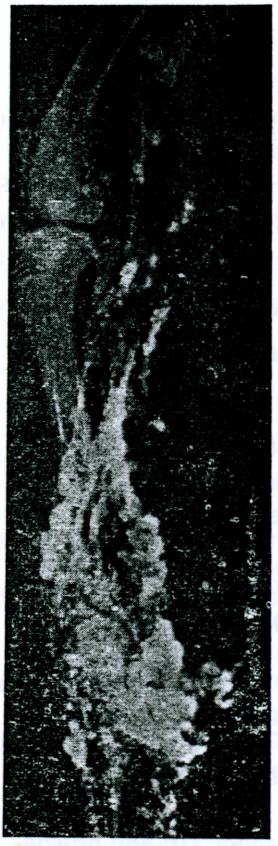

Fig. 1

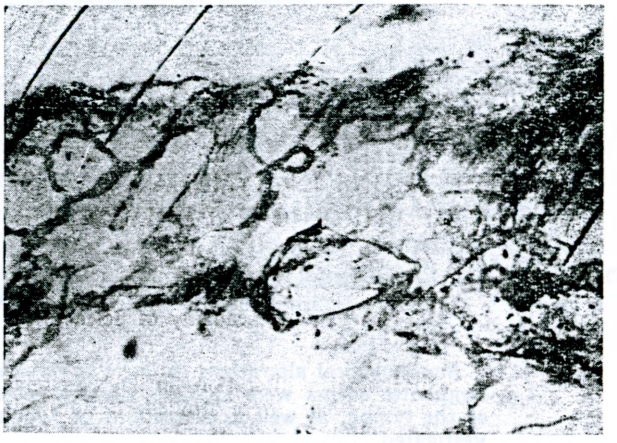

Fig. 2A

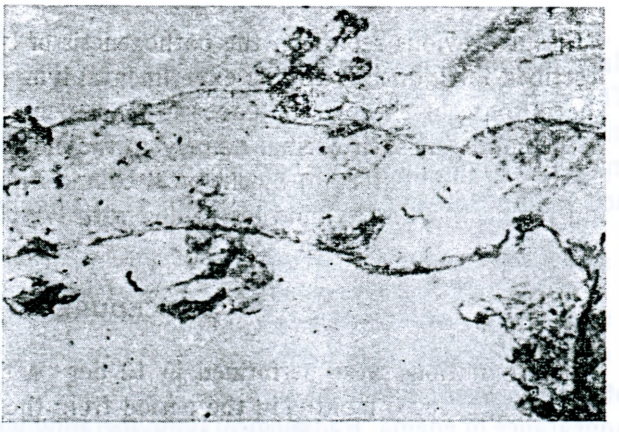

Fig. 2B

Fig. 1. Lymphogram of dog leg with 2-year lymphedema.
Fig. 2. Skin preparation as seen under stereomicroscope. A — numerous dilated lymph capillaries, and newly formed capillary loops, B — varicoid dilatation of lymphatic trunks.

dol UF were necessary to fill the entire lymphatic bed of the extremity. Only a negligable proportion of the contrast passed within 24 hours into the vessels of the true pelvis the rest being visible on the radiograms for a few weeks.

Microscopical investigations. Stereomicroscopical examination of the skin and subcutaneous tissue after previous staining with Berliner blue and fixation with methyl salicylate revealed a net of newly formed lymphatic

capillaries and varicous dilations of main lymphatics in all the animals (Fig. 2A, B).

Histological sections of the skin exhibited almost complete fibrosis with formation of numerous tiny lymphatic endothelium-lined spaces (Fig. 3). The wall of the main lymphatics was entirely fibrotic the muscle fibers being atrophied (Fig. 4).

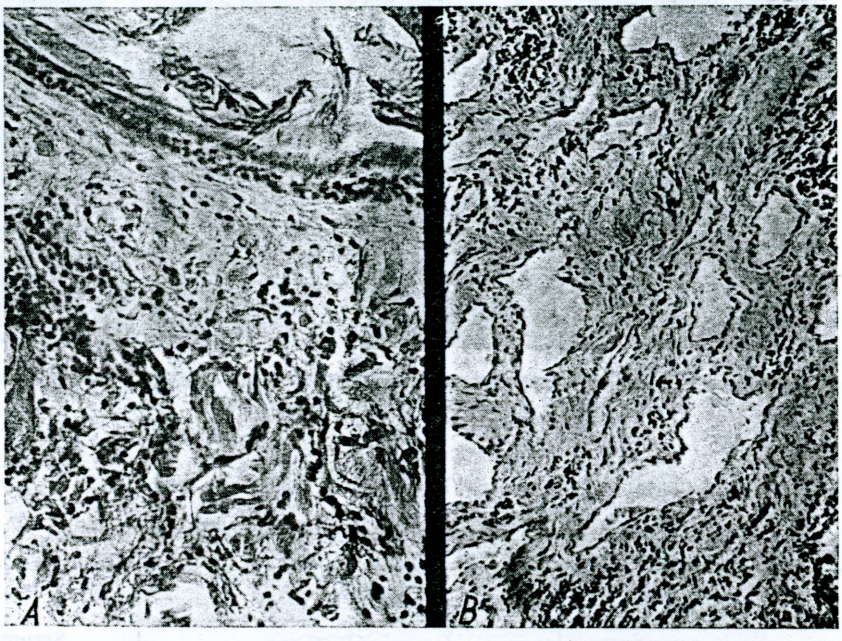

Fig. 3. Histological sections of skin in lymphedema. A — 6 months. Particular fibers separated with edema fluid. Abundant lymphocytic infiltrations, B — 24 months. Fibrosis, numerous lymphatic spaces lined by endothelium.

Biochemical investigation of the lymph. The mean protein level in lymph of the lymphedematous extremity was 1·55 g% (1·13—2·5) and did not differ from that in the lymph of healthy leg (Table I). The lymph protein fraction composition was the same in both extremities and corresponded in percent to that of blood serum. The water content in the skin of the lymphedematous leg was 0·79/1 g of skin on the average, as compared with 0·69 in normal skin. The time of lymph coagulation was dependent upon the content of coagulation factors, thus indirectly upon the lymph protein level. The mean time of recalcination was 124 min, and the prothrombin time — 25 min (Table II). Fibrinogen level reached up to 50 mg%. Fibrinolysis was absent.

Investigation of lymph pressures and flow. Tissue pressures of intercellular fluid and lymph in a healthy extremity at rest and after passive movements are

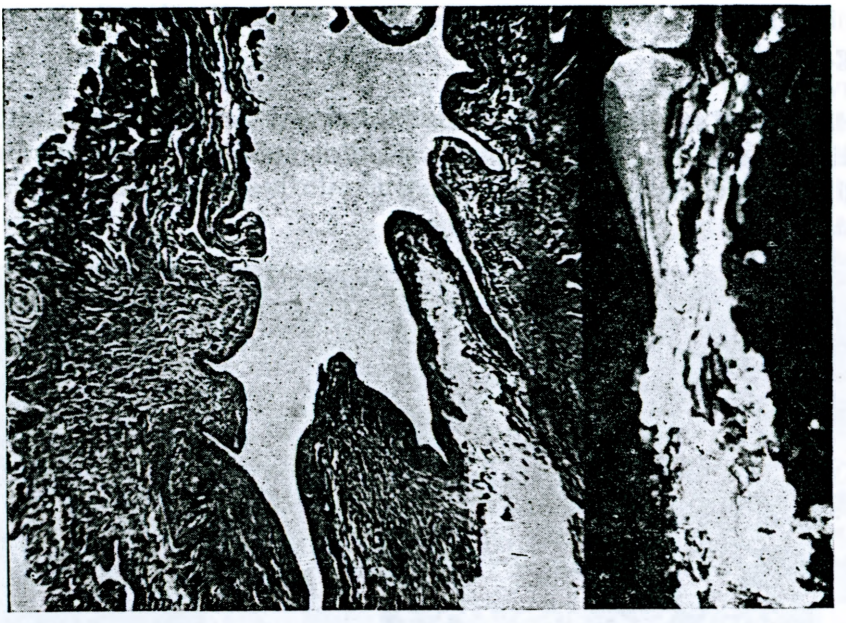

Fig. 4. Histological section of lymph vessel of extremity. Wall is thick, fibrotic, devoid of muscular fibers.

Table I

Mean lymph protein level in lymph from lymphadematous leg

	Lymph from		Serum
	lymphedematous leg	healthy leg	
Total protein (9%)	1·55 (1·13—2·5)	1·46 (0·7—2·6)	6·91 (6·43—7·9)
Albumin (9%)	0·62 (40%)	0·54 (37%)	2·69 (39%)

shown in Fig. 5A and B. Skin tissue pressure, both in a lymphedematous and healthy extremity, was about 1 mm Hg. It did not change during movements. The pressure of intercellular fluid, measured in a Guyton capsule inserted subcutaneously, was both in the lymphedematous and healthy leg 5—8 mm Hg below zero, at rest. During passive movements in normal skin this pressure dropped considerably, even to — 30 mm Hg, being, however, almost unchanged in lymphedematous skin; there it showed only a few fluctuations during each

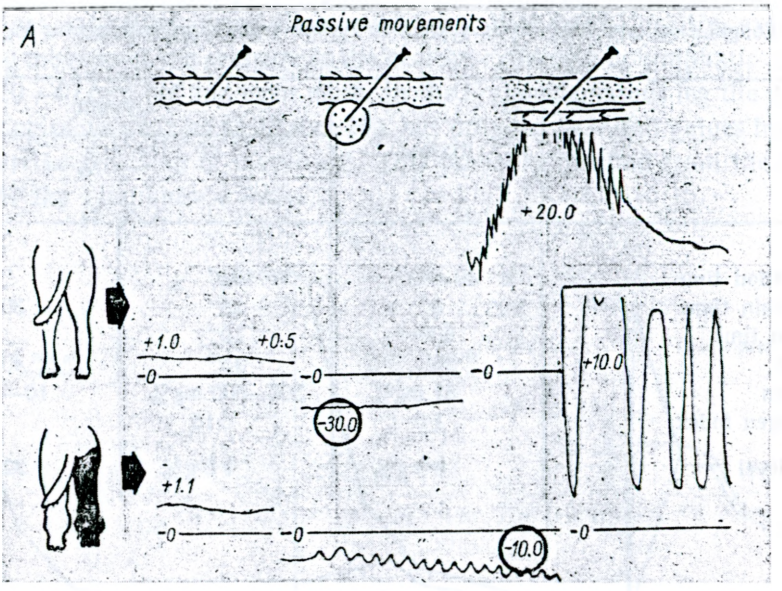

Fig. 5A

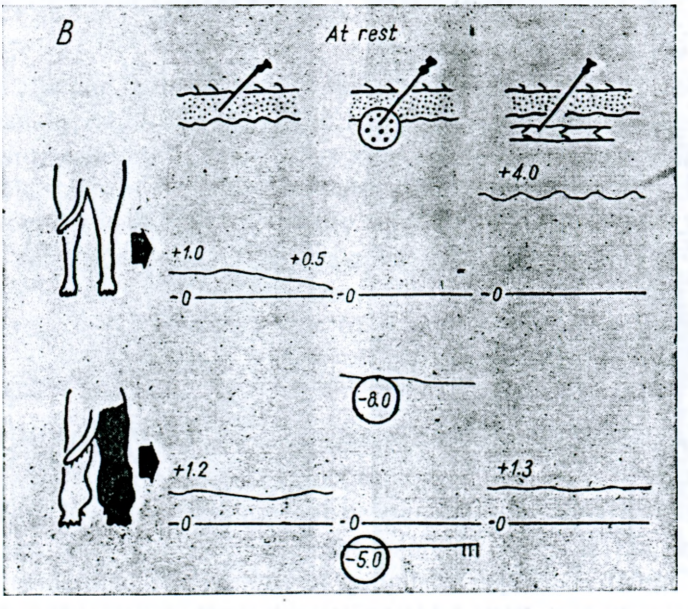

Fig. 5B

Fig. 5. Tissue pressure of skin, intercellular fluid and lymph. A — at rest, B — during passive movements.

Table II

Coagulation and fibrinolysis system in lymph from lymphadematous leg

	Plasma	Lymph	
			% as related to plasma
Recalcination time	40—60″	124″	
Prothrombin time	8″	25″	30
Thrombin time	50″	10″	
Factor V	36″	15″	40
Fibrinogen	51 mg%	300—500 mg%	10—16
Plasminogen index	1·0	0·15	
Protein level	6·9 g%	1·5 g%	22

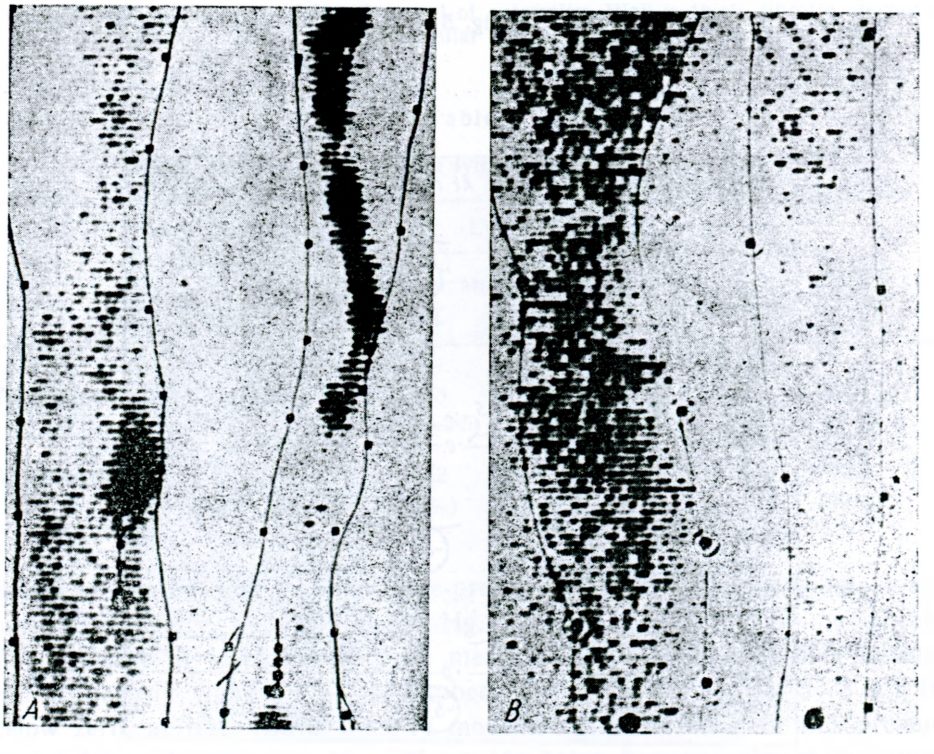

Fig. 6. Scintigram performed after administration of ^{131}I-labeled albumin into the lymphatic vessel of lymphedematous and healthy extremity A — after 1 hour, B — after 8 days.

movement of the extremity. The pressure of the lymphedematous leg in lymphatics was not raised, many times even lower than in the healthy extremity.

During movement the pressure of the healthy extremity in lymphatics quickly rose to 20—40 mm Hg and even more. In the lymphedematous leg the pressure rose during movement up to 10 mm Hg, but dropped to initial values immediately after the cessation of movement. This probably resulted from the insufficiency of the lymphatic valves.

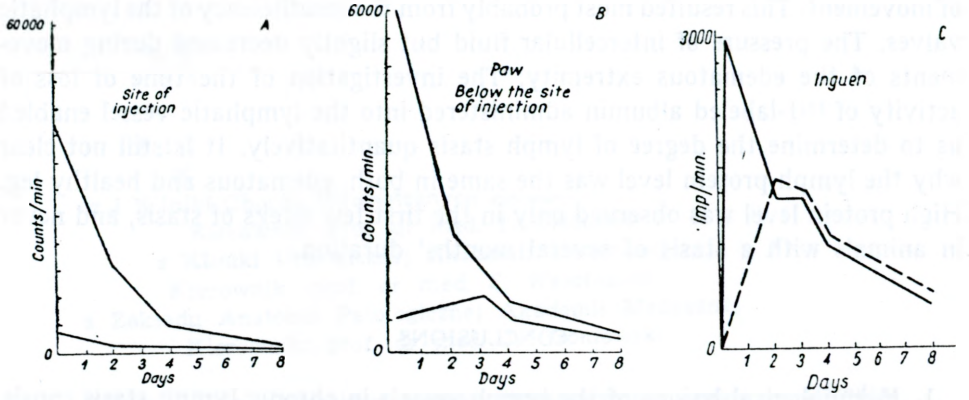

Fig. 7. Loss of activity of ^{131}I-labeled albumin within 8 days after administration into the lymphatic vessel of leg. A — area of administration, B — below area of administration, C — in inguinal area (continuous line — lymphedematous leg, interrupted line — healthy leg).

^{131}I-labeled albumin, administered to the vessel of the dorsal aspect of the leg quickly spread in its entire lymphatic system, even in retrograde direction (Fig. 6A). Scintigrams performed 8 days after albumin administration revealed its considerable stasis in the lymphedematous leg; at the same period it flowed out totally from the vessels of the healthy leg (Fig. 6B). Fig. 7 show the curves of loss of ^{131}I-albumin activity in the area of its administration, in the peripheral portion of the leg and the inguinal area.

DISCUSSION

In cases of long-lasting lymph stasis morphological lesions concern all portions of the lymph vessels, in other words both capillaries and main trunk of the leg. On the capillary level the formation of new capillaries is characteristic. They anastomose and form a dense net in the papillary layer of the skin almost reaching the epidermis. The number of lymphatic capillaries in the skin with long-lasting lymph stasis is thus many times higher than in the normal one. In all large lymphatic vessels the formation of oval varicoid dilatations is typical

the wall of which consists of one layer of endothelial cells. They are formed in areas where the vessel wall is the weakest. The stasis also causes the destruction of valves. Therefore the entire lymphatic system of the extremity is transformed into a system of tubes in which the one-direction centripetal lymph flow during muscular contractions of the leg is impossible.

Otherwise than expected lymph pressure in the vessels of lymphedematous leg was normal. Skin tissue pressure and intercellular fluid pressure were also normal. During movement of the lymphedematous leg the lymphatic pressure slightly rose but turned back to initial values immediately after the cessation of movement. This resulted most probably from the insufficiency of the lymphatic valves. The pressure of intercellular fluid but slightly decreased during movements of the edematous extremity. The investigation of the time of loss of activity of ^{131}I-labeled albumin administered into the lymphatic vessel enabled us to determine the degree of lymph stasis quantitatively. It is still not clear why the lymph protein level was the same in both, edematous and healthy leg. High protein level was observed only in the first few weeks of stasis, and never in animals with a stasis of several months' duration.

CONCLUSIONS

1. Morphological lesions of the lymph vessels in chronic lymph stasis consis in the formation of new lymphatic capillaries, as well as in the varicoid dilatation of the main vessels.
2. In spite of long-lasting lymph stasis lymph pressure is the same in the lymphedematous and healthy leg.
3. Protein level is the same in lymph derived from the lymphedematous and healthy leg.

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