

Heparin and Heparinocytes in Elephantiasis Scroti.

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Through the brilliant researches of Jorpes¹ and Holmgren and Wilander² it has been well established that the mast cells or heparinocytes are cellular sources of heparin. However, heparin of the basophilic granules is not identical with circulating heparin or heparin extracted from tissues. The mast cell heparin is monosulfuric acid, and when released is transformed into di, tri, and tetra-sulfuric acids, circulating or tissue heparin being a mixture of all of these elements.^{3,4}

The distribution of heparinocytes in the tissues varies considerably in different species. In dogs, abundant heparinocytes are found in the lobules and veins of the liver, whereas in rabbits and rats they are scanty or absent here. In rats, abundant heparin is found in the skin. The intestines of the various animals all contain many heparinocytes; the lungs show a moderate number, and the spleen only a few. Rats contain fewer but larger heparinocytes than rabbits and dogs.^{2,5}

It has been shown that heparin and similar compounds if given intravenously are taken up by the macrophages, particularly of the liver, spleen and lymph nodes, and that some is excreted through the kidneys.⁶ That this is not the cause for the dissipation of heparin is apparent from studies involving splenectomy; complete hepatectomy; combined nephrectomy, splenectomy, and hepatectomy; injections into the bone marrow of the tibia;

ligation of the carotid and vertebral arteries; blockade of the reticulo-endothelial system with India ink; stimulation of the reticulo-endothelial system by histamine, and depression of it by antihistaminic drugs.^{7,8}

The pathology of the heparinocytes has hardly been studied. It is known only that the tissue mast cells are greatly increased in urticaria pigmentosa in man⁹ and in solitary "mastocytomas" in man⁹ and in dogs.¹⁰ Oliver, Bloom and Mangieri,¹¹ who recently analyzed two dog mastocytomas chemically, found 20.1 g of a crude heparin in 330 g of tissue from a well differentiated tumor; from this they extracted 2,460,000 A.C.U. or 492,000 I.U. of heparin per kilogram of tumor, *i.e.*, 50 times as much as found in the liver of normal dogs. Paff, Bloom and Reilly¹² succeeded in cultivating these mast cells; they made the interesting observation that only mast cells grew in the cultures, as though the product elaborated by these cells prevented growth of other cells.

The present report deals with mast cells and heparin in a human scrotum amputated because of elephantiasis. The study was prompted by the observation of absence of thrombosis in this disease. It was speculated that coagulation of lymph and blood in the obstructed tissue was possibly prevented by excess heparin produced locally.

The owner of the scrotum, a white pastry

¹ Jorpes, J. E., Heparin, Oxford University Press, 1946.

² Holmgren, H., and Wilander, O., *Z. mikr. anat. Forsch.*, 1937, **42**, 242.

³ Jorpes, J. E., and Gardell, S., *J. Biol. Chem.*, 1948, **176**, 267.

⁴ Jorpes, J. E., Werner, B., and Aberg, B., *J. Biol. Chem.*, 1948, **176**, 277.

⁵ Wilander, O., *Skand. Arch. Phys.*, 1938-9, **81**, Suppl. 15.

⁶ Asplund, J., Borell, U., and Holmgren, H., *Z. mikr. anat. Forsch.*, 1939, **46**, 15.

⁷ Begany, A. J., and Seifter, Joseph, *Fed. Proc.*, 1948, **7**, 206.

⁸ Seifter, J., and Begany, A. J., *Am. J. Med. Sci.*, 1948, **216**, 334.

⁹ Sutton, R. L., and Sutton, R. L., Jr., *Diseases of the Skin*, St. Louis, 1939.

¹⁰ Bloom, F., *Arch. Path.*, 1942, **33**, 661.

¹¹ Oliver, J., Bloom, F., and Mangieri, C., *J. Exp. Med.*, 1947, **86**, 107.

¹² Paff, G. H., Bloom, F. H., and Reilly, C., *J. Exp. Med.*, 1947, **86**, 117.

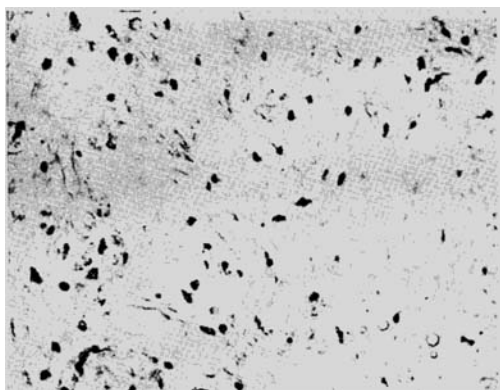


FIG. 1.
Abundant mast cells (heparinocytes) between distended lymph spaces.

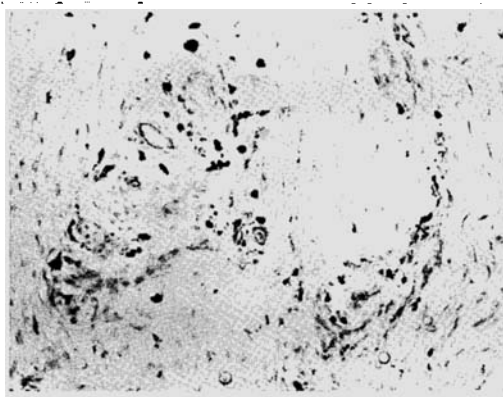


FIG. 2.
Abundant mast cells (heparinocytes) around blood and lymph vessels.

chef 55 years of age, came from Italy when he was 10. At 24, draft board examiners noted firm masses in both inguinal regions. When he was 43, the patient observed enlargement of the scrotum. He visited a physician only when the scrotum weighed over 50 lbs. and almost touched the floor. There was an invagination where the penis would normally be. The skin of the legs was congested and slightly cyanotic. There were superficial varicosities of all leg and thigh veins. The bleeding time was one minute, and the clotting time $5\frac{1}{2}$ minutes.

Microscopic examination of tissue from the scrotum revealed numerous heparinocytes in the neighborhood of lymph and blood vessels (Fig. 1 and 2).

From 10 kg of tumor tissue, 11.11 g of crude heparin were extracted, following de-

scribed methods.^{13,14} Preparation of both the barium and the sodium salt yielded four fractions totalling 1.4 g of purified material. Plasma clotting studies were performed on thawed citrate dog plasma, using the photoelectric method as described by Foster.¹⁵ One fraction of the heparin preparation in a concentration of 30 gamma per ml inhibited the clotting of plasma for 10 minutes, as opposed to $2\frac{1}{2}$ minutes for the normal. Thirty gamma of a second fraction per ml prolonged the clotting of rabbit whole blood for 385 minutes, as compared with a control clotting time of 4 minutes. Intravenous injection of 5 mg of tumor heparin per kg into rabbits produced marked anticoagulation which reached its maximum within 15 minutes. A blood sample taken 15 minutes after the injection clotted in 65 minutes. A sample taken an hour after injection clotted in the normal time of 3 minutes.

The most potent fraction both *in vitro* and by direct intravenous injection into rabbits was of the same potency as the best commercial heparin currently used in clinical practice. The remaining fractions showed activity to a lesser degree. The fact that these fractions were not capable of purification to higher potency probably resides in the fact that most of the material was obtained from the mast cells and corresponded to Jorpes' lower sulfur-containing sulfuric acids, as the mono- and the di-sulfuric acid.

Summary and conclusions. Microscopic examination of a human scrotum amputated because of elephantiasis showed numerous heparinocytes around lymph and blood vessels. One hundred and twenty-six mg of purified heparin per kg of wet tissue was obtained. Based on the purified material, the scrotum contained at least 16,380 I.U. of activity per kg of fresh tissue. These findings are further evidence that mast cells are sources of heparin. They also explain the absence of thrombosis in elephantiasis.

¹³ Charles, A. F., and Scott, D. A., *Tr. Roy. Soc. Canada*, sect. 5, 1934, **28**, 55.

¹⁴ Kuizenga, M. H., and Spaulding, L. B., *J. Biol. Chem.*, 1943, **148**, 641.

¹⁵ Foster, R. H. K., *Am. J. Physiol.*, 1948, **152**, 577.