Heparin, Histamine and Mast Cells

IT IS APPROPRIATE that in this the centenary year of the birth of Paul Ehrlich we should review briefly his first discovery, made while he was still a medical student. This is the granular basophil cell of the tissues for which he proposed the name “mast cell” (“mast” = food) in the belief that its metachromatic granules contain a reserve foodstuff derived from the products of lymph stasis and that numerically the cells reflect the nutritional state of the connective tissues. Later Ehrlich and his pupils observed somewhat similar cells with basophilic metachromatic granules in the blood—first in chronic myeloid leukemia, later in normal blood—and thus came to recognize a second type of mast cell, the blood mast cell, basophil or mast leucocyte. Whereas in certain lower organisms the two types of mast cell are freely interchangeable (not unexpectedly perhaps since extramedullary hemopoiesis is common at this level of evolution), it appears that in higher vertebrates partition occurs between the tissue mast cell and the blood mast cell; the first remains throughout a cell of the connective tissues; the second behaves as a normal member of the marrow granulocytes. Indeed, in 1938 when Michels compiled his unsurpassed review of the mast cell, the evidence suggested that “aside from an identical basophilic metachromatic staining reaction of the granules, the two cell types have nothing in common”. Even as Michels was writing, the position had changed.

THE MAST CELL AND HEPARIN

Scandinavian workers had for long been investigating a powerful anticoagulant first isolated from dog liver and hence called “heparin”; Jorpes, finding that heparin stained metachromatically with toluidine blue, requested his histological colleagues to search the tissues for a metachromatic component which might indicate the site of formation of heparin. Once the essential clue, metachromatism, was forthcoming, the problem was quickly solved; Holmgren and Wilander re-discovered the metachromatic granules in the mast cells and Jorpes was able to show that there is good correspondence between the mast cell contents of various tissues and their heparin yields. Cartilage, the only other important tissue which stains metachromatically, is almost devoid of anticoagulant activity. For a time then it seemed that the mystery of Ehrlich’s mast cells had been solved leaving it merely for later workers to consolidate the position by showing that as the mast cell content of a particular tissue increases, so does its heparin content rise until, in a mast cell tumor, the heparin value becomes extreme.
A curious anomaly of heparin release in the dog is that it is accompanied by a simultaneous release of histamine, both the heparin and the histamine in this particular species being derived mainly from the liver. This, and the clinical evidence of histamine release in urticaria pigmentosa (skin lesions composed of mast cells) in children led the writer to enquire whether histamine as well as heparin might be located in the tissue mast cells. An investigation into the origin, distribution, and fate of the tissue mast cells in the normal rat was followed by an experiment in which a lethal dose of a fluorescent histamine liberator was traced to its site of action in the mast cells of the loose tissues of the peritoneum. However, if the same dose is given so slowly that signs of histamine release appear, the mast cells are not found in course of disruption. Recently we have repeated and extended this work using a more specific and a less toxic histamine liberator, 'compound 48/80'. This relationship between mast cells and histamine in the peritoneum of the rat has been neatly illustrated by Fawcett who showed that once the mast cells have been discharged by an intraperitoneal injection of distilled water, compound 48/80 is no longer able to release histamine from the peritoneum; its target has already been destroyed. Mota has studied the disruptive effects of peptone on the tissue mast cells of the dog, and it is noteworthy that it is only in the dog that anticoagulant heparin and histamine are released together in vivo. As with heparin, there is a striking positive correlation between the histamine values and the mast cell contents of a wide variety of normal and pathological tissues. Likewise the histamine values in mast cell tumors are exceptionally high. Thus the evidence for histamine in tissue mast cells is at least as good as it is for heparin and in some cases is even better. Perhaps, therefore, we should reorientate our thinking and regard the release of anticoagulant heparin into the dog's blood as the abnormal event which accompanies the disruption of its tissue 'histaminocytes'. Yet the heparin is believed to be there in the mast cells of other species even though it fails to manifest itself as an anticoagulant in the peripheral blood. The solution of one problem merely poses another.

Blood and Tissue Mast Cells

Thus far we have spoken only of the pharmacological activities of the tissue mast cells. However, at the time that my colleagues and I in Scotland were investigating the properties of the tissue mast cells, Helen T. Graham and her associates in Washington were tracing much of the histamine of the peripheral blood to the basophil cells, the mast leucocytes—a finding which has subsequently been endorsed by Ehrich and by Code and Mitchell. Moreover, it now appears that the blood mast cell is also rich in heparin. Thus, while we agree with the histologists that the mast cells of blood and tissues in higher organisms differ both in parentage and in habitat, nevertheless the trends of modern research do suggest, as Ehrich himself believed, that their similarities outweigh their differences and that functionally the two cell types may have much in common. The pace of research on the mast cells has again quickened since Michels wrote his review. On the one hand the mast cell has now displaced the
eosinophil\textsuperscript{28, 29} from its central rôle in histamine release; indeed, it has recently been suggested that the eosinophil is endowed with antihistaminic properties.\textsuperscript{30} On the other hand, we are faced with a cell which in at least one species, the dog, liberates a powerful anticoagulant into the blood stream and in other species can be made to yield heparin by vigorous chemical extraction. But is the fact that the dog's blood becomes incoagulable in shock states sufficient reason for regarding anticoagulant heparin as the natural secretory product of all mast cells? Ehrlich's riddle is by no means solved, and for its final answer we may yet have to turn to his original view and seek our information in the connective tissues.\textsuperscript{31}

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