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Special Review Article

THE RESPONSES OF THE BASOPHIL LEUCOCYTE*

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The basophil leucocytes were first observed in the blood of a patient with myeloid leukaemia by Ehrlich in 1891 (1) and because of their resemblance to tissue mast cells which he had previously described and differentiated from the plasma cells of Waldeyer (2), he called these "blood mast cells". Considerable controversy arose over the relationship between those two types of cells. Ehrlich's conviction that the "blood mast cell" was of myeloid origin and that the tissue mast cell arose in the mesenchyme from undifferentiate precursors has been amply substantiated by later workers. It is, however, of considerable interest that in various species there is a reciprocal relationship in numbers between these cells. Among mammals, "blood mast cells" are more numerous in the rabbit, whereas in rats and mice tissue mast cells preponderate (3). Apart from its motility the chief morphological features which distinguish the basophil leucocyte from the mast cell are its smaller size, more rounded shape, its relatively scanty cytoplasm and its polymorphous, usually bilobed, nucleus (4).

There is, however, a danger of drawing too close an analogy between the two types of cells. For example, it is well known that exposure both *in vitro* and *in vivo* of rat mast cells to Compound 48/80 causes them to degranulate and to release histamine (5, 6, 7). It has been claimed that basophil leucocytes are also degranulated by Compound 48/80 (8, 9) but Levi and Meneghini (10) were unable to confirm this. In a recent study, Haye and Schneider (11) have confirmed that Compound 48/80 will release histamine from rat mast cells but will not release histamine from human and rabbit basophils.

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There is ample evidence based on studies carried out on humans, horses and guinea pigs, to shown that the metachromasia of the granules of the basophil leucocytes (13, 14, 15) like that of tissue mast cells (12) is due to the presence of sulphated mucopolysaccharides—and heparin in particular. The function of these mucopolysaccharides is not entirely understood. It is usually accepted that one of their functions may be to bind and inactivate histamine within the cell but there seems to reason why, after release, heparin should not exercise further intrinsic pharmacological effects which include an antimitotic activity (16, 17), the precipitation of collagen from procollagen (18), inhibition of hyaluronidase (19, 20), an antiprothrombin activity associated with the prevention of agglutination of platelets (21), the stimulation of hair growth in rabbits (22), the production of hair loss in man (23, 24, 25) and a clearing factor in hyperlipaemia (26, 27). However, in the discussion at a symposium on mast cells and basophils Lagunoff (28) suggested that "heparin is not a physiologically or pharmacologically reactive agent but rather a structural component of the granule that holds the granule together and serves to bind the two more active agents, the histamine and the protease." Both Coupland (29) and Higginbotham (30) believe that the polysaccharide is available for binding purposes and that the structure of the granule resembles an ion exchange resin. The granule could thus act as a detoxifying agent.

Almost all the histamine in human blood is present within the leucocytes of the buffy coat of blood, and is mainly confined to the granulocytes; a great increase of the histamine per unit of blood (up to more than 200 times the upper limits of normal) is found in chronic granulocytic leukaemia; less marked elevations occur in polycythemia vera, but no increase is found in polymorphonuclear leucocytosis of non-leukaemic origin. Valentine (31) investi-

gated the relationship of blood histamine to the absolute basophil count in human blood. His observations made in patients with granulocytic leukaemia indicated that the histamine when expressed on the basis of the amount present in 10^8 granulocytes gave a positive correlation with the basophil percentage and a negative correlation with the percentage of other myeloid elements, i.e. high histamine values were related to high percentage of basophils, conversely, values of histamine were highest when the percentage of myeloid cells was relatively low. On the basis of these findings Valentine claimed that basophil cells were the principal carriers of histamine in non-leukaemic blood. Later workers have confirmed that there is a close correlation between the number of circulating basophil leucocytes and the histamine content of the blood (32, 33).

The formation of histamine in human basophil leucocytes was studied by Lindell, *et al.* (34) and Hartman, *et al.* (35). Blood samples were incubated with radioactive histidine and the histamine formed from radioactive histidine was extracted and measured. It was thus possible to demonstrate that basophil leucocytes were able to form histamine as well as storing it.

It would seem that the human basophil—unlike that of the rat—contains no 5-hydroxytryptamine (36, 37).

It has been claimed that basopenia may occur in infectious diseases, in acute rheumatism, in anaphylactoid purpura and in thyrotoxicosis (38, 39, 40, 41, 42, 43, 44, 45). Basopenia was considered by Mitchel (45) to be a result of stress in these diseases. Code, Mitchell and Kennedy (46), Osada (47), Boseila, *et al.* (48) and Camerada, *et al.* (49) noted that experimentally, cortisone, ACTH and thyroxin could cause a decrease of circulating basophil leucocytes, but with the ACTH and cortisone the corresponding eosinopenia was much more pronounced. It has already been mentioned that basophilia is a common accompaniment of granulocytic leukaemia (14).

Physiological variations in the number of basophil leucocytes in man were studied by Rorsman (50) who noted that food intake, moderate exercise and mechanical lesions of the small blood vessels did not influence the number of circulating basophils. Males and females had the same numbers of basophils. The mean basophil count he found to be 45 per mm^3 blood with a tendency to be higher in subjects between 40 and 59 years of age.

There is no doubt that the scantiness of knowledge of the function of the basophil is in part due to the lack of a satisfactory method for their direct enumeration in capillary and venous blood. Indirect methods, based on a total white blood cell count and differential count are slow and aggregation of platelets obscures the basophils which become entrapped. In previous direct methods (51, 52) the staining of the basophils is often diffuse because of the water solubility of the mucopolysaccharides.

A more recent method appears to offer promise. This is based on the addition of cetylpyridinium chloride to the toluidine blue solution. This lyses the red cells, at the same time rendering the mucopolysaccharides insoluble (53). Aluminum sulphate is added to mordant the dye (54). Using 0.02 ml of blood from a thumb prick in a 1/10 dilution, counts may be made in a Fuchs-Rosenthal chamber in 5 to 10 mins. As staining is fast, counts may be done up to a week after taking the sample. Using this method Cruickshank and Cooper (53) gave the mean basophil count of humans as 40 per mm. which is close to the figure given by Rorsman (50).

Some early observations of Canon (55), Franca (56) and Amaniera (57) indicated that the basophil leucocytes had a close association with human allergic reactions—basophilia was noted in patients with asthma and after serum treatment. Also, studies on rabbits and guinea pigs (58, 59, 60, 61, 62, 63) demonstrated that following an injection of antigen the number of basophil leucocytes increased in the blood, bone marrow and at the site where antigen was injected.

Because of the reports of a decrease in the level of blood histamine in patients with urticaria (64, 65) and because of the known high histamine content of the basophil leucocyte, Rorsman and others (33, 66, 67, 68) investigated the role of this cell in the circulating blood of patients with urticaria of different types. They demonstrated a decrease in the number of circulating basophils (below 10 cells/mm) in patients with acute allergic urticaria. This basopenia was correlated with a decrease

in the patients blood histamine. No evidence of such changes was found in the circulating blood of patients with non-allergic urticaria (69, 70).

In parallel with the tissue mast cell, Rorsman (69) considered it likely that the histamine release and basopenia in urticaria was brought about by a degranulation mechanism. The bone marrow of patients with urticaria gave normal basophil counts. He failed to find any partially degranulated basophils in the circulation and pointed out that total degranulation would render these cells unrecognisable.

Shelley and Juhlin (71), Shelley (72) and Shelley & Juhlin (73) claimed that basophil leucocytes from allergic subjects degranulated when exposed to specific antigen *in vitro* and also that serum from allergic subjects when mixed with antigen and normal rabbit basophils caused these to degranulate. On this basis 'direct' and 'indirect' tests were proposed as diagnostic procedures for several allergic conditions such as drug allergy, insect bites, serum sickness, contact dermatitis, asthma, hayfever and ulcerative colitis.

A study has been recently completed on the direct allergic degranulation of basophils in 52 patients and 43 normal subjects (74). It was shown that of 21 atopic subjects (sensitive to various pollens), 13 gave positive direct degranulation of basophils *in vitro*. Nine of 11 patients sensitive to penicillin reacted similarly. It was of interest that in the former group there was direct correlation between the size of the prick test reaction and the severity of the degranulation. However, only two of the penicillin sensitive patients gave positive skin tests and thus the basophil test seemed to be a more reliable index. In all only threequarters of the subjects with Type I (75) sensitivity gave positive direct tests.

None of 9 patients with allergic contact dermatitis, or of 43 normal subjects gave positive tests. The basophils of 11 patients with chronic non-allergic urticaria were also examined and did not degranulate when exposed to a wide range of common allergens. These negative findings in relation to contact sensitivity are consistent with current views that contact sensitivity is a form of 'delayed' type hypersensitivity in which antibody is bound to the cells of the reticulo-lymphoid-monocyte system (76). Moreover, there is evidence that the specificity of the carrier protein in haptene protein complexes is important (77). The role of the basophil in delayed type hypersensitivity cannot, however, be dismissed entirely since accumulation of these cells at skin test sites seems adequately documented. Marked local basophilia has been described in allergic contact dermatitis, as well as, in the delayed reaction following intradermal injection of metal in sensitive subjects (78, 79, 80). Likewise, accumulation of the basophils at the site is a feature of intracutaneous tuberculin test (81, 82). The migration of the basophil leucocytes to a positive skin test site (which was recorded in patients with active tuberculosis only) has been studied at intervals with "Roebuck's skin window" technique (82). Local basophilia in light induced inflammations, and in photoallergic contact reactions to 4-chloro-2-hydroxybenzoic acid-N-n-butylamide have been reported also (83, 84, 85). The part the basophils play in such reactions is not known.

In the indirect system, Haye, *et al.* (74) encountered difficulties because of the "toxicity" of many normal and allergic sera to rabbit basophils. Only 19 of 29 sera from allergic subjects caused less than 30% degranulation of rabbit basophils even in the absence of antigen. These sera were obtained from 12 pollen sensitive subjects and 7 sensitive to penicillin. Indirect degranulation was obtained from 7 of the atopics and 6 penicillin sensitive patients. It is, therefore, clear that some two-thirds of those patients with a type I ('immediate') hypersensitivity carry a serum factor which is probably an antibody and which can degranulate basophils in the presence of the appropriate antigen. These conclusions are in close agreement with similar studies (86, 87, 88) and imply that from the clinical viewpoint the response of basophil leucocytes 'in vitro' must be interpreted with caution. It is reasonable to assume the presence of hypersensitivity when a positive result occurs, but foolhardy to assume that a negative result indicates the absence of hypersensitivity.

The actual mechanism of degranulation and histamine release, however, is well worthy of closer study and the evidence suggests that they are not necessarily coincidental. For example, in the study just described, measurements were made of histamine before and after exposure of five allergic subjects' basophils to

antigen at 37°C using heparin as anticoagulant. Although antigen caused histamine release in all 5, degranulation occurred in only two. Moreover, it was shown that in the human at least degranulation could be obtained at 20°C and also in the presence of EDTA although it is well substantiated that histamine release only occurs at 37°C and requires the presence of Ca^{++} (89, 90). A further logical difficulty has already been raised (69)—if a basophil has degranulated, how does one recognise it?

Attempts have been made to clarify some of these problems by experiments on rabbits and guinea pigs (91). Basophil counts were made on the same preparations which were used for degranulation tests and experiments were made at 37°C and 20°C as well as in the presence of EDTA and heparin. Both species behaved similarly—a dramatic fall in the basophil count occurred only in the heparin preparation at 37°C. However, degranulation could be detected in all preparations—maximal in the heparin preparation at 37°C, and minimal in the EDTA preparation at 20°C. Thus the effect of antigen would seem to be a total disruption of a proportion of the basophils associated with partial degranulation of others. This implies that the granules still retain some physical contact with the cytoplasm of the cell.

In conclusion, it would seem that although we now know how basophils behave under a variety of circumstances, we are not much wiser as to actual functions performed in various physiological and pathological conditions. Because it is so much easier to deal with the mast cell, it has been the subject of more intensive investigation and there has been a tendency to translate basophil function in terms of mast cell behavior during the whole of this century. A new look at basophils in their own right is suggested.

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