In 1912, ten years after Portier and Richet’s discovery of anaphylaxis, Schlecht and Schwenker demonstrated that sensitized guinea pigs 24 hours after surviving challenging shock developed massive peribronchial eosinophilia. Using the Prausnitz-Küstner technique that identified human skin sensitizing serum antibody, Berger and Lang in 1931 reported the rapid accumulation of eosinophils in urticarial wheals of actively or passively sensitized patients after intracutaneous injection of corresponding specific antigen. In both instances, the nonspecific effect of a hypothetical chemotactic agent was postulated.

One or a combination of factors might explain the retarding of follow-up experimental study of eosinophil function. The issue of cell source was controversial. Did eosinophils originate in the bone marrow, or did circulating eosinophils result from overflow or discard from other developmental sites? Suitable experimental models were yet to be developed. Misleading uncertainties in hematologic identification in the rabbit and in some instances the guinea pig included the variable “heterophilic” capability of polymorphonuclear leukocytes taking up either eosin or methylene blue in conventional Romanowsky stains.


The painstaking pathologic study of bronchial asthma published by Huber (1883-1970) and Koessler (1879-1928) at the University of Chicago was one of the first attempts to substitute accurate measurements and physical changes for questionable assumptions of bronchospasm.

Their findings provided evidence of increased thickness of the walls of bronchi and bronchioles with outside diameters of more than 0.2 mm compared with similar structures in persons without asthma; all layers from epithelium to the outer fibrocartilaginous were affected. Hyperemia and cellular infiltration of the walls and increased activity of the glands leading to swelling and thickening could thus produce mechanical as well as chemical irritation of peripheral nerve endings and indirectly cause bronchospasm.

They noted that in only 1 disease, bronchial asthma, did blood, sputum, and tissue eosinophilia occur simultaneously. Eosinophilic infiltration of the bronchial wall was a characteristic histologic criterion of bronchial asthma, but its absence did not exclude asthma. Because eosinophilia was regarded as one of the chief manifestations of allergy, its absence in certain forms of bacterial asthma was regarded as evidence that there were types of asthma not of allergic origin. With the description of eosinophil granule major basic protein in 1973, Huber and Koessler’s observation can be viewed as an early suspicion of eosinophil pathogenicity in current day appreciation of asthma as an inflammatory disorder.

The role of the eosinophil generated in response to tissue invasive parasitic helminths was investigated by Butterworth (1945- ) in 1975 at the Nairobi Wellcome Research Laboratories in Kenya. Butterworth demonstrated that schistosomula can be damaged by a combination of normal human peripheral blood leukocytes and heat-inactivated sera from patients infected with Schistosoma mansoni; that the eosinophil is substantially the most active mediator of damage in normal peripheral blood; and that the mechanism of eosinophil damage of S mansoni was mediated by direct deposit of eosinophils on the helminth’s surface. Cells from patients with eosinophilia associated with other diseases were relatively inactive, and those from 3 patients with marked eosinophilia induced by schistosomiasis or other helminth infections did not show the increase in cytotoxic activity that would be predicted if all eosinophils were equally active. These findings indicated that the major, and possibly the only, cell type in normal human peripheral blood capable of inducing antibody-dependent, complement-independent damage to schistosomula was the eosinophil.1

The role of the eosinophil generated in response to tissue invasive parasitic helminths was explored by Mahmoud (1941-) in 1975 at Case-Western Reserve. Developing antileukocyte sera, Mahmoud studied their effects on partial immunity to schistosomiasis *in vivo* by quantitative assays for schistosomula in the lungs and adult worms in the portal venous system.

Mice infected with *Schistosoma mansoni* cercariae 16 and 32 weeks before rechallenge with cercariae showed reductions in the recovery of schistosomula of approximately 40%; adult recovery at 4 and 6 days was reduced by 60%. Treatment with antilymphocyte, antimacrophage, or antineutrophil sera had no effect on numbers of schistosomula recovered from the lungs of immune animals. In infected mice treated with antieosinophil serum, the numbers of schistosomula and adult worms recovered increased to levels seen in normal nonimmune animals. Sera from partially immune mice and passively transferred to noninfected mice conferred marked resistance to infection as measured by comparative recovery of schistosomula treated with antieosinophil serum. Antibody-dependent cell-mediated immunity to schistosomiasis *in vivo* was suggested and a role for the eosinophil in immune systems thus established.¹

In 1968, Parillo (1947- ), Fauci (1940 - ), and Wolff (1930-1994) at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, began the long-term study of patients with idiopathic blood, tissue, and bone marrow eosinophilia unrelated to helminth infection, allergic disease, malignancies, or autoimmune phenomena. The nebulous nature of the symptom complex was reflected in its varied conceptual nomenclature of eosinophilic leukemia, disseminated eosinophilic collagen vascular disease, Löffler's fibroblastic endocarditis with eosinophilia, and idiopathic eosinophilia.

In a 10-year follow-up of 26 individuals with the commonality of relatively mature cell hypereosinophilia and multiorgan dysfunction, they found involvement of almost any organ system, but characteristically cardiac, pulmonary, nervous system, or skin. Other than bone marrow, the most common was heart, demonstrating subendocardial fibrosis and restrictive cardiomyopathy.

Characteristics found useful in predicting responses to corticosteroid therapy were angioedema, elevated serum IgE, or prolonged eosinopenic response to single-dose challenge with prednisone. Hydroxyurea was judged the drug of choice in treating corticosteroid unresponsiveness, and in patients with progressive organ-system involvement with the intent to reduce the total leukocyte counts to the normal range (5000-10,000 cells/mm). Because none of their 26 patients developed myeloblast crisis as seen in chronic myelogenous leukemia, the goal was not to eliminate eosinophils but to reduce counts to the normal range, an approach that resulted in favorable clinical responses.1

That eosinophils may have a modulating effect as well as a damaging action through their major basic protein content was demonstrated by Austen and associates at Harvard and Robert B. Brigham Hospital in 1975. When triggered by phagocytosis and eosinophil chemotactic factor of anaphylaxis, eosinophils were found to release arylsulfatase, which inactivated the chemical mediator slow reactive substance of anaphylaxis (SRS-A). Austen and colleagues conceptualized that eosinophils arriving at sites of immediate hypersensitivity reactions might inactivate SRS-A and manifest other regulatory functions limiting or possibly terminating the allergic reaction.1