REVIEW ARTICLE

THE HUMAN EOSINOPHIL: ROLES IN HOST DEFENSE AND TISSUE INJURY

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The Human Eosinophil

Roles in Host Defense and Tissue Injury

Peter F. Weller, MD, and Edward J. Goetzl, MD

THE EXTENSIVE DOCUMENTATION over the past 100 years of the disease states that are characterized by increased numbers of eosinophils in the blood and affected tissues has provided a foundation for understanding the normal functions and pathologic activities of eosinophils.[1,2] The results of modern cellular and biochemical investigations have suggested that eosinophils regulate immediate-type hypersensitivity reactions and control helminthic infections. Several unique constituents and functional adaptations appear to be critical to these special capacities of eosinophils to defend the host. In contrast, little is known of the factors that evoke and perpetuate in some circumstances the potential of eosinophils to damage host tissues and to elicit tissue fibrosis. This review will address predominantly the recent additions to the rapidly evolving understanding of the beneficial contributions and deleterious effects of eosinophils in a wide variety of human diseases.

I. Eosinophil Production and Distribution

Eosinophilopoiesis

Although some eosinophils are produced in extramedullary sites in fetal and neonatal animals,[3,4] by adulthood eosinophils are produced exclusively in the bone marrow, where the total number exceeds the number of eosinophils in the circulation by a factor of 200 in the rat [5] and 400 in the guinea pig.[6] A distinct bone marrow progenitor for the eosinophil has not been identified definitively, but several findings suggest that eosinophilic and neutrophilic leukocytes may be derived from different colony-forming units. Eosinophil colonies developed more slowly than neutrophil or macrophage colonies in *in vitro* cultures of human bone marrow.[7] Moreover, culturing of human bone marrow cells with cluster transplantation techniques permitted the demonstration of colonies composed solely of eosinophils, which developed independently of neutrophil and macrophage colonies.[8] Eosinophil colony-forming cells derived from mouse

From the Howard Hughes Medical Institute Laboratory at Harvard Medical School and the Department of Medicine, Harvard Medical School, and the Robert B. Brigham Hospital Division of the Affiliated Hospitals Center, Inc., Boston, Massachusetts.

Address correspondence to Edward J. Goetzl, MD, Seeley Mudd Building, Harvard Medical School, 250 Longwood Ave., Boston, MA 02115.

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bone marrow were separated by velocity sedimentation from the precursors of neutrophil and macrophage colonies.[9] The existence of distinct pathways of production or differentiation of eosinophils and neutrophils also is supported by the finding of normal or elevated levels of circulating eosinophils in patients with either congenital [10] or drug-induced [11] neutropenia and by the results of analyses of the development of certain unique enzymatic constituents of eosinophils. Eosinophil peroxidase, which is biochemically different from neutrophil myeloperoxidase,[12,13] remains at normal levels in the face of genetic deficiencies in neutrophil and monocyte peroxidase [14]; and, conversely, neutrophil myeloperoxidase is preserved when eosinophil peroxidase is genetically deficient.[15]

Immunologic Control of Eosinophil Production

Substantial evidence from *in vitro* and *in vivo* studies suggests that eosinophil production may be subject to immunologic control. Mouse lymphoid cells stimulated by pokeweed mitogen produced a factor with a molecular weight of 50,000 that elicited the formation of colonies of eosinophils in cultures of mouse bone marrow, spleen, and fetal liver cells.[9] The activity of the eosinophil colony-stimulating factor (CSF) was separated electrophoretically from that of the neutrophil and macrophage CSFs that were elaborated by the same cultures. In addition, factors that stimulated the production of eosinophils in cultures of mouse bone marrow cells were released from lymphocytes of mice sensitized to *Trichinella spiralis* after the addition of *Trichinella* antigen, but not heterologous antigens.[16] The secretion of soluble eosinophilopoietic factors by lymphocytes has been demonstrated *in vivo* as well. Peripheral blood eosinophilia was evoked in normal rats by the intraperitoneal implantation of cell-tight diffusion chambers containing lymphocytes from *Trichinella*-infected rats and *Trichinella* antigen.[17] Further, cell-free medium from cultures of splenic lymphocytes stimulated with specific antigen evoked peripheral blood eosinophilia in mice rendered eosinopenic by corticosteroid treatment.[18]

The sequestration in tissues of particulate antigens, as exemplified by the pulmonary or peripheral embolization of *Trichinella* larvae [19] or the pulmonary embolization of dextran beads [20] or γ-globulin-coated latex beads,[21] resulted in an eosinophilic response in rats and other experimental animals. The prolonged eosinophilia that was produced by an intravascular injection of *Trichinella spiralis* larvae was increased markedly by a second challenge with larvae.[19] The augmented eosinophil response to the second dose of larvae was prevented by neonatal thymectomy, administration of antilymphocyte serum, or chronic thoracic duct drainage,[17]

which suggested a dependence on T lymphocytes. The capacity for expression of the augmented eosinophil response was transferred adoptively to unprimed rats by thoracic duct or peripheral blood lymphocytes in suspensions or in cell-tight chambers, but not by cell-free lymph or plasma. Irradiation of rats eliminated the augmented eosinophilic response to injected larvae, which was restored only by reconstitution of the rats with both bone marrow cells and *Trichinella* antigen-primed lymphocytes. T-lymphocyte–deficient mice, which exhibited normal levels of neutrophilia in response to bacterial infections, required thymic reconstitution in order to manifest a peripheral blood eosinophilic response to *Trichinella* larvae.[22] Congenitally athymic mice similarly did not develop an eosinophilic response of the usual magnitude when infected with helminthic parasites such as *Schistosoma mansoni*,[23–25] *Ascaris suum*,[26] or *T spiralis*.[27]

That eosinophils are not totally absent in T-lymphocyte–deficient animals [23,24,28] suggests the existence of T-lymphocyte–independent pathways for eosinophilopoiesis. The serum of mice rendered eosinopenic with specific antieosinophil serum contains elevated concentrations of a low-molecular weight eosinophilopoietin, distinct from lymphokines, which stimulated intramedullary eosinophilopoiesis and produced peripheral blood eosinophilia.[29] A factor with similar activities has been identified in the serum of eosinophilic patients with schistosomiasis, but not in serum of patients with idiopathic hypereosinophilia.[30] In addition, it has been suggested that mast cells and IgE-producing B-cells are sources of eosinophilopoietins.[31]

Release and Distribution of Eosinophils

In three normal human subjects given a pulse of tritiated thymidine in order to analyze eosinophil kinetics,[32] the mean eosinophil generation time was 34 hours, and eosinophils were eliminated from the circulation randomly with a half-life of 2 hours. More complex patterns of eosinophil release and distribution were found in patients with hypereosinophilia, including the return of some tissue eosinophils to the circulation.[33,34] The eosinophilia of rats infected with *Trichinella* was associated with a shortening of the duration of each cycle.[35] The eosinophil generation time was reduced from 30 hours to 9 hours, and the emergence time from marrow to blood was shortened from 41 hours to 18 hours. The emergence time of neutrophils in the same rats was not reduced, which indicated that independent mechanisms govern the maturation and release of the two types of granulocytes.

Quantitative studies have indicated that the eosinophil is principally a tissue-dwelling cell. The number of eosinophils resident in tissues exceeds

that in the blood by approximately 100-fold in man,[36] 200-fold in the rat,[5] and 300-fold in the guinea pig.[6] In the tissues, eosinophils are distributed principally below epithelial surfaces exposed to the external environment. Thus, outside of the bone marrow, most eosinophils are found in the skin, lungs, gastrointestinal tract, lower urinary tract, and uterus.[5] It is not clear what factors govern the tissue distribution of eosinophils or what mechanisms underlie the eosinopenia induced by corticosteroids,[1] prostaglandins,[37] and β-adrenergic agents.[38,39] The eosinopenia that accompanies infections and other inflammatory states can be reproduced in animals by the intravenous injection of a partially characterized "eosinopenic factor" isolated from inflammatory exudates [40,41] and of defined chemotactic factors.

II. Cellular Properties of Eosinophils

The mature human eosinophil shares with the neutrophil and basophil an overall polymorphic shape, but the nucleus of the eosinophil is distinctly bilobed and lacks a nucleolus.[42] The most characteristic microscopic feature of the eosinophil is a class of large ellipsoidal cytoplasmic granules, which contain an electron-dense crystalloid core that is enclosed in a less dense matrix.[43] Large spherical primary lysosomal granules proliferate during the early development of eosinophils and mature into the crystalloid granules after the myelocyte stage.[44,45] Small and homogeneously dense cytoplasmic granules of eosinophils appear initially during the metamyelocyte stage, increase progressively in numbers with cellular maturation, and become more abundant in tissue-localized eosinophils as an apparently adaptive process.[46]

Eosinophil granules contain an array of enzymes generally comparable to those in neutrophil lysosomes, but the human eosinophil lacks lysozyme, and the content of peroxidase, β-glucuronidase, and acid phosphatase exceeds that of neutrophils by two to three times.[47] Physicochemical and functional polymorphism of acid phosphatase and other lysosomal enzymes is as common in eosinophils as in other leukocytes.[2] The peroxidase-hydrogen peroxide (H_2O_2)-halide microbicidal system of eosinophils is biochemically different from that of the neutrophils, which may be the basis for its distinctive functional roles in intact eosinophils. Although the peroxidases of both human eosinophils and neutrophils catalyzed the iodination of microbial and other proteins in the presence of H_2O_2,[48] only the neutrophil peroxidase utilized chloride for this reaction and catalyzed the efficient generation of bactericidal products from amino acids.[49] Inhibition of peroxidase activity by sodium azide significantly suppressed the microbicidal activity of neutrophils for *Staphylococci*, but increased the

staphylococcidal activity of eosinophils.[50] The utilization of lysostaphin to kill uningested *Staphylococci* demonstrated that sodium azide suppressed the intracellular killing of the organisms to a similar extent in both types of leukocytes. Thus the apparent stimulation of the eosinophil microbicidal process by sodium azide might reflect an enhancement of ingestion of the organisms. Nonetheless, the results suggest a greater contribution of peroxidase-independent microbicidal systems in eosinophils than in neutrophils. Peroxidase isolated from neutrophils or eosinophils is cytotoxic for lymphoma cells and other tumor cells *in vitro* in the presence of iodide and H_2O_2.[51] The tumor cell cytotoxicity of both intact neutrophils and eosinophils that were activated by phagocytosis or phorbol myristate acetate was inhibited completely by the peroxidase inhibitors sodium azide and aminotriazole, respectively, supporting a central role for myeloperoxidase and eosinophil peroxidase in this system. While myeloperoxidase and eosinophil peroxidase can utilize H_2O_2 and iodide to kill the schistosomula of *Schistosoma mansoni in vitro*,[51] a role for this pathway in the preferential schistosomulocidal activity of intact eosinophils has not been confirmed.

Enzymes that are preferentially contained in human eosinophils, as compared with other leukocytes, are localized either in the granules or in membrane structures. Arylsulfatase is found predominantly in the small granules of eosinophils from several species with lesser amounts in the crystalloid granules,[46] is present at levels 15 times higher than in neutrophils, and exhibits type B characteristics.[52] The content of phospholipase D in human eosinophils is nearly ten times higher than in neutrophils and more than two times higher than in mononuclear leukocytes.[53] Eosinophil phospholipase D has a molecular weight of 60,000 and an isoelectric point of 5.8–6.2 and cleaves choline from L-α-phosphatidylcholine with a optimum pH of 4.5–6.0. The lysophospholipase activity, which is present at concentrations eight times higher in eosinophils than in neutrophils, has a molecular weight of approximately 32,000 by gel filtration and appears to be localized predominantly in the plasma membranes.[54] Some granule-associated proteins without apparent enzymatic activity have been found exclusively or predominantly in eosinophils. A major basic protein of the core of crystalloid granules contains approximately 13% arginyl residues and has a molecular weight of 9200–11,000, depending on the species examined.[55,56] The abilities of major basic protein to precipitate with DNA, neutralize heparin, activate papain, and exhibit cytotoxicity for a broad range of cells appear to be based largely on its strong positive charge.[57] Other specific cationic proteins [58] and the Charcot-Leyden crystal protein [56] that have been extracted from eosinophil granules are chemically

distinct from the major basic protein. Some of the cationic proteins enhance coagulation by an effect on Hageman factor [59] and accelerate the conversion of plasminogen to plasmin by kinases.[60] Consistent alterations in the serum levels of such eosinophil-derived proteins have been noted in some human diseases,[61] but these observations have not clarified their biologic role.

III. General Functions of the Eosinophil

Modulation of Eosinophil Migration

Although eosinophils are positioned predominantly in the tissues, their unique effector capabilities can be manifested fully only after directional influx and local accumulation at sites of specific reactions. Eosinophil chemotaxis, initiated by the presentation of a concentration gradient of a stimulus, and chemokinesis, evoked as a function of stimulus concentration irrespective of a gradient, are regulated by several pathways.[62] Factors that are preferentially chemotactic and chemokinetic for eosinophils, as compared with other types of leukocytes, are elaborated by diverse immunologic reactions. The eosinophil stimulation promoter (ESP) is analogous to other lymphokines as it is generated and secreted in fully active form after challenge of sensitized lymphocytes with homologous antigen.[63] Specific antigen challenge of lymphocytes from sensitized guinea pigs results in the carrier-specific elaboration of an antigen-containing precursor macromolecule (ECF_p) that becomes chemotactic for eosinophils when mixed with homologous IgG-containing immune complexes.[64] Activation by immune complexes of the classical complement pathway and by microbial polysaccharides of the alternative complement pathway leads to the elaboration of fragments such as C5a and complexes such as $\overline{C567}$, which attract eosinophils, as well as other leukocytes, with no apparent preference.[65] In contrast, C3bBb of the alternative pathway is predominantly chemotactic for neutrophils.[66]

Although subacute and delayed immunologic pathways can contribute some principles capable of enhancing eosinophil migration, immediate-type hypersensitivity reactions produce the broadest spectrum of factors which selectively influence the traffic of tissue eosinophils.[2] IgE-dependent activation of fragments of guinea pig and human lung tissue releases from performed stores an array of eosinophil chemotactic stimuli including histamine,[67] low-molecular-weight acidic peptides termed the eosinophil chemotactic factor of anaphylaxis (ECF-A),[68,69] and a family of 1500–3000-dalton polypeptides.[70] Human lung ECF-A is comprised in part of two acidic tetrapeptides,[71] while the 1500–3000-dalton poly-

peptides exhibit varying acidity and hydrophobicity.[70] The immunologic challenge of mast cells also leads to the production and release of the lipoxygenase metabolites of arachidonic acid, 11-hydroxy-5,8,10,14-eicosatetraenoic acid (11-HETE), 12-HETE, and 15-HETE, as well as diverse cyclooxygenase metabolites of arachidonic acid, of which prostaglandin D_2 (PGD_2) is the quantitatively predominant product.[72] The HETEs are chemotactic for PMN leukocytes, with a preference for eosinophils, and exhibit chemokinetic activity at concentrations below the peak for chemotaxis.[73,74] PGD_2 is a highly potent chemokinetic factor for eosinophils and, to a lesser extent, neutrophils.[75] IgGa- and IgE-directed stimulation of the mast-cell–rich rat peritoneal cavity results in the elaboration of other lipid chemotactic and chemokinetic factors which act on eosinophils and neutrophils, of which the predominant principle is a cyclooxygenase-dependent chemotactic factor.[75]

The principles that regulate eosinophil chemotaxis by altering the activity of the stimuli or the responsiveness of the eosinophils have been reviewed.[62] The chemotactic factors are distinguished by differences in their capacity to induce a state of unresponsiveness to subsequent chemotactic stimulation, termed chemotactic deactivation.[76] The ratio of the concentrations of each chemotactic stimulus required for maximal deactivating and chemotactic effects varies from 10^{-3} for the ECF-A tetrapeptides to approximately 1 for 12-HETE and related lipid factors.[77] The ability of both the ECF-A tetrapeptides and histamine to elicit the selective accumulation of eosinophils *in vivo* [78] may be attributable both to chemotactic attraction and to local trapping of the eosinophils by a mechanism analogous to deactivation. ECF-A induces predominantly chemotactic deactivation, rather than activation, *in vitro* [79]; and histamine also exerts a major inhibitory effect on eosinophil migration *in vitro*, which may be mediated in part by an eosinophil-immobilizing factor that is released from mononuclear leukocytes by histamine.[80] It is likely that numerous functions of the eosinophil other than migration are altered by chemotactic factors, since it has been shown that C5a and formyl-methionyl peptides alter the adherence, oxidative metabolism, and lysosomal degranulation of neutrophils *in vitro* and neutrophil intravascular sequestration *in vivo*.[81]

Endocytosis and Associated Events

As for other leukocytes of the PMN series, eosinophils engulf particles, form phagolysosomes, and undergo lysosomal degranulation [82,83]; but both phagocytosis and bactericidal reactions are less efficient for eosinophils than for neutrophils *in vitro*.[50] The continued development of several constituents in maturing tissue eosinophils and the flexibility of expression of

some eosinophil receptors, to be discussed subsequently, suggest that, in contrast to the neutrophil, the eosinophil is capable of considerable functional adaptability. The vesiculotubular and other membranous structures in tissue eosinophils are analogous to those that appear within rat peritoneal eosinophils after an *in vitro* exposure to colloidal gold or fetal calf serum and thus may reflect sustained microendocytic activity.[84,85] The number of acid phosphatase- and arylsulfatase-positive small granules increases progressively during the development and maturation of tissue eosinophils.[46] Specific receptors have not been enumerated on tissue eosinophils, as compared with eosinophils in the circulation. The degranulation reactions of eosinophils also exhibit characteristics that differ from those of neutrophils. The phagocytosis of opsonized zymosan by eosinophils results in the release of histaminase, arylsulfatase B, and β-glucuronidase, while the calcium ionophore A23187 induces the selective release of histaminase alone.[83] Cytochalasin B inhibits the release of histaminase from eosinophils, but not from neutrophils. Of the immune complexes that elicit the release of granule-associated enzymes and the secretion of PGE_1 and PGE_2 from eosinophils, those containing IgE have the highest potency, while IgG-containing complexes are the most effective for neutrophils.[86,87]

IV. Involvement of Eosinophils in Immunologic Responses

The striking local eosinophilia observed in lymph nodes draining sites of immunization and in other tissues after the immunologic stimulation of mast cells and lymphocytes initially focused attention on the possible roles of eosinophils in the development of humoral and cellular hypersensitivity. However, the accumulation of evidence to the present suggests rather that immunologically derived mediators specifically attract eosinophils and direct eosinophil functions so that the responding eosinophils serve to contain and terminate the hypersensitivity reactions, especially those of the immediate type.

Eosinophil Surface Receptors

Eosinophils, like other leukocytes, have surface membrane receptors for immunoglobulins and complement components. Specific receptors for C3b, C3d, and C4 and for homologous and heterologous IgG have been demonstrated on eosinophils obtained from normal and hypereosinophilic subjects but, with the exception of the C3d receptor, were generally expressed at lower levels than on neutrophils.[88–92] As for mononuclear leukocytes, the C3d receptor on eosinophils is separate from the receptor that accommodates both C4 and C3b.[88] Although IgE receptors have not been identified by direct rosetting or binding techniques, the existence of such

receptors is suggested by the ability of complexes of human IgE and anti-human IgE to stimulate both the release of lysosomal enzymes and the production of prostaglandin E by human eosinophils.[87,93] Both complement and IgG receptors were increased in density on eosinophils of some patients with hypereosinophilia.[90,92] Histamine and the ECF-A tetrapeptides, but not serotonin or bradykinin, have been shown *in vitro* to increase the number of C3b receptors on eosinophils,[94] but a relationship of these effects to the increased expression of C3b receptors in hypereosinophilic syndromes has not been established.

Eosinophil Involvement in Antigen–Antibody Reactions and Delayed Hypersensitivity Responses

Prominent eosinophilia developed in the cortical areas of regional lymph nodes draining the sites of immunization of animals with protein or carbohydrate antigens.[95–97] The lymph node eosinophilia achieved peak levels within 1 day of the injection of antigen, persisted for 5–7 days after a single injection, and was augmented by repeated injections of antigen. The eosinophils in the lymph nodes were involved in the endocytosis of antigen–antibody complexes and have not been attributed a specific role in antibody production.[98,99]

While eosinophils may accumulate at sites of delayed hypersensitivity reactions,[100] the local production of antibody rather than a specific cellular phenomenon represents the underlying mechanism.[101] Several lymphocyte-dependent pathways of eosinophil accumulation have been described,[63,64,102] but only the chemokinetic and chemotactic lymphokine termed the eosinophil stimulation promoter (ESP) has been demonstrated to attract eosinophils in the absence of specific antigen or antibody.[103,104]

Modulation of Immediate Hypersensitivity Reactions

Peripheral blood and tissue eosinophilia are typical characteristics of mast-cell–mediated diseases.[105,106] Principles possessing specific eosinophil chemotactic activity have been isolated from tissue extracts of patients with allergic rhinitis and nasal polyposis [107] and from venous blood draining an area affected by a physical allergy, such as cold urticaria.[108] While eosinophilic infiltration usually develops rapidly after the initiation of a mast-cell–mediated reaction and subsides shortly thereafter, a recurrence of the manifestations of immediate hypersensitivity sometimes develops several hours after the initiating event and may be accompanied by a second wave of infiltrating eosinophils.[109,110]

The infiltrating eosinophils, attracted by a variety of mast-cell–derived mediators, manifest diverse capabilities for the modulation of the immediate hypersensitivity reaction (Table 1). Major basic protein, a principal

Table 1—Specialized Roles of Human Eosinophils in Host Defense

Role	Special function	Eosinophil activity or constituent
Modulation of immediate hypersensitivity reactions	Inhibition of mediator release	PGE_1/PGE_2
	Removal of extruded mast cell granules	Phagocytosis
	Nonenzymatic inactivation of heparin	Major basic protein
	Enzymic degradation of:	
	Histamine	Histaminase
	SRS-A	Arylsulfatase B
	PLF	Phospholipase D
	Lysophospholipids	Lysophospholipase
Control of helminthic infections	Cytotoxicity for opsonized larval and adult forms	C3b and IgG receptors
		Major basic protein
		Superoxide anion
	Damage to eggs	ESP
		Superoxide anion

constituent of the large granule of the eosinophil, binds and inactivates heparin in the fluid phase [57] and also facilitates the uptake and subsequent desulfation of heparin by macrophages.[111] Mast cell granules containing heparin and a chymotrypsinlike protease [112] are ingested by eosinophils,[113] as observed in bullous pemphigoid.[114] Eosinophils stimulated with anti-human IgE have been shown to release quantities of PGE_1 and PGE_2, which inhibit the release of histamine from basophils, and possibly mast cells, probably by elevating intracellular levels of cyclic AMP.[87]

Eosinophils also are endowed with a variety of enzymes capable of inactivating mast cell-derived mediators. Eosinophil histaminase, like that of the neutrophil, deaminates and inactivates histamine.[115] Arylsulfatase B, an enzyme present in the eosinophil in quantities exceeding those in neutrophils, is implicated in the inactivation of the slow-reacting substance of anaphylaxis (SRS-A) because of the ability of eosinophil arylsulfatase B to neutralize the biologic activity of SRS-A in a time- and dose-dependent manner.[116] Eosinophil-derived phospholipase D as well as phospholipase D of cabbage origin inactivates a platelet lytic factor (PLF) that is generated by IgGa-dependent challenge of mast-cell–rich rat peritoneal exudate cells but does not inactivate a concomitantly generated platelet-activating factor.[53,117] Eosinophil lysolecithinase activity [54] may detoxify the lysolecithins released from mast cells.[118] In addition, the eosinophil may facilitate the restoration of tissue mast cells after immediate hypersensitivity type reactions, because the depletion of eosinophils by prior treatment with specific antieosinophil serum markedly diminished the reaccumulation of histamine at cutaneous sites of IgG_1-mediated passive cutaneous anaphylaxis reactions in guinea pigs.[119]

V. Eosinophil Involvement in the Host Response to Helminths

Helminthic (nematode, trematode, and cestode), but not protozoan, parasites characteristically elicit a blood and tissue eosinophilia in animal and human hosts. The blood eosinophilia is most prominent during the stages of parasite migration through tissues,[120] although antihelminthic chemotherapy also may induce a transient elevation in the level of circulating eosinophils.[121] The augmented peripheral blood eosinophilia that is induced by helminths in sensitized animals is T-lymphocyte–dependent.[17] While helminths release some endogenous substances that are directly chemotactic for eosinophils,[122–124] the tissue accumulation of eosinophils may be attributable predominantly to the selective eosinophil chemotactic activities generated by the immediate and delayed immunologic responses of the host to the invading helminths.

Experimental evidence suggesting a special protective role for the eosinophil has been obtained in diverse helminthic infections,[125,126] but much of the detailed studies have dealt with *Schistosoma mansoni* or *Trichinella spiralis* [127] (Table 1). The *in vivo* protective effect of acquired immunity to *S mansoni* was abolished by administering monospecific antieosinophil serums to immune mice prior to reinfection with *S mansoni*.[128] Analogously, the protective passive immunity provided to mice by the administration of immune antischistosomal serum was abolished by the administration of antieosinophil serum prior to an initial infection.[129] Antineutrophil, antimacrophage, and antilymphocyte serums did not affect the resistance of the mice to *S mansoni*, thus implicating the eosinophil as a unique effector cell in host resistance to helminths.

The cytotoxic activity of human and baboon leukocytes for schistosomula prelabeled with chromium-51 has been investigated *in vitro*.[130,131] Cytotoxicity for the schistosomula was manifested by eosinophils of up to 90% purity, was not dependent on the presence of mononuclear leukocytes, and was ablated by antieosinophil serum but not by antineutrophil serum. The release of chromium-51 from the schistosomula was complement-independent but required specific antibody and was mediated by Fc receptors on the eosinophils.[131,132] Neutrophils have been found to release as much chromium-51 from schistosomula in the same system in recent studies, but the eosinophils induced more damage to the schistosomula than did neutrophils, as assessed by electron microscopy.[133] The eosinophil-mediated cytotoxicity was impaired by inhibitors of microfilament function, glycolysis, or esterase activity.[134] Intimate contact was observed between eosinophils and opsonized schistosomula and was followed by eosinophil degranulation and deposition of peroxidase-positive

material and the major basic protein on the surface of the schistosomula.[135,136] Purified eosinophil major basic protein, like other polycations, was capable of damaging the schistosomula.[137] Others have implicated the activity of eosinophil peroxidase in the killing of schistosomula.[138,139]

While the antibody-dependent mechanism of eosinophil schistosomulocidal activity predominates in mice, the infection of rats with *S mansoni* results in the activation of the alternative complement pathway, the fixation of C3b, and the binding of cytotoxic eosinophils to schistosomula through specific C3 receptors.[140] Human eosinophils also have been reported to bind to schistosomula by C3b receptors and the affinity of the binding as well as the efficiency of the subsequent cytotoxic reaction are augmented by histamine and the ECF-A tetrapeptides.[141] The expression of the IgG Fc receptors, which mediate the cytotoxic action of rat eosinophils on schistosomula, was enhanced similarly by extracts of mast cells and by the ECF-A tetrapeptides, while histamine was less effective.[142,143] The interpretation of the results of studies demonstrating specific eosinophil-mediated cytotoxicity against schistosomula must be tempered by observations that neutrophils [144,145] and macrophages [146,147] also exhibit cytotoxicity for schistosomula and *Trichinella* larvae. Thus, the relative contributions of these cell types to the immunologically mediated defenses of the host against various stages of helminthic parasites have not been established definitively.

VI. Human Diseases Associated With Eosinophilia

The Spectrum of Eosinophilic Syndromes

Peripheral blood and tissue eosinophilia are observed in a wide variety of allergic, parasitic, collagen-vascular and neoplastic diseases, some immune deficiency states, and a range of idiopathic conditions characterized by functionally significant tissue inflammation and fibrosis.[1,148,149] The absence of specific information regarding the etiology and role of the eosinophilia in such disorders has fostered several arbitrary schemes of classification. The eosinophilias may be subdivided either in broad terms derived from the concurrence or lack of association of the eosinophilia with an identifiable disease or according to the predominantly affected organ system. The first approach is illustrated by the consideration of the several types of reactive or secondary eosinophilias as distinct from the primary or idiopathic eosinophilias. In the second approach, the eosinophilias of each organ system are considered as a distinct group, irrespective of apparent etiology, as exemplified by the pulmonary eosinophilias and the cutaneous eosinophilias. While the current classifications provide some

framework for the organization of clinically complex information, any meaningful analysis of these disorders must be based on an understanding of the contributions of the specific pathways that recruit eosinophils and modulate special eosinophil functions.

The causes, cellular abnormalities, and immunologic features of the reactive and idiopathic eosinophilias have been presented in numerous recent reviews.[1,148–150] In contrast, the specific characteristics of the eosinophilic disorders have not been described systematically in relation to the predominantly involved organs. The pulmonary eosinophilic syndromes together constitute the most frequently recognized forms of tissue eosinophilia (Tables 2 and 3). Most of the pulmonary eosinophilias are characterized by focal atelectasis and infiltrates and by obstructive abnormalities of the airways.[150] In one such group (Table 2), elevated serum concentrations of IgE and increased numbers of mast cells in the walls of the airways suggest an involvement of immediate hypersensitivity pathways. The persistent eosinophilic pneumonitis exemplified by pulmonary hypersensitivity reactions to some drugs or to inhaled foreign proteins is associated with the development of specific IgG antibodies and, in some instances, IgE antibodies to the inciting agent.[151] Patients with the nodular eosinophilic pneumonitis of allergic bronchopulmonary aspergillosis have antiaspergillus antibodies of the IgE class and may have increased numbers of mast cells in the bronchial walls.[151,152] The serum concentration of IgE is markedly elevated in association with the pneumonitis of tropical eosinophilia; but as for other metazoan infections, only a portion of the IgE is specific for the filarial antigens.[153,154] Patients with the pneumonitis of idiopathic disseminated eosinophilic syndromes may have strikingly high serum levels of IgE without defined antigenic specificity and may manifest urticaria and angioedema, but the two abnormalities apparently are not related.[149,155] The transient pulmonary eosinophilia of Löffler's syndrome and the pulmonary eosinophilic infiltration associated with some forms of granulomatous angiitis and with rare anaplastic large cell lung tumors have no apparent relationship to the level of IgE or to manifestations of immediate hypersensitivity reactions.[150]

A comparably wide spectrum of cutaneous disorders with blood and tissue eosinophilia is characterized by tissue damage and, in some cases, chronic cutaneous fibrosis. Some patients with cutaneous eosinophilia have constitutional manifestations of disease or involvement of other organs (Table 4). Eosinophilic lymphofolliculosis is a disease of men consisting of facial, axillary, and inguinal eosinophilic furunculosis with granulomatous hyperplasia of the draining lymph nodes.[156] Subcutaneous angiolymphoid hyperplasia is a similar condition with eosinophilic lym-

Table 2—Pulmonary Eosinophilic Syndromes With Associated Immediate Hypersensitivity

Syndrome	Essential features	Evidence for involvement of immediate hypersensitivity	Specific examples
Persistent eosinophilic pneumonitis	Constitutional manifestations Altered pulmonary function	IgG and/or IgE antibodies in some patients	Hypersensitivity pneumonitis
Nodular eosinophilic pneumonitis	Bronchoconstriction Recurrent pneumonia and atelectasis	Increased mast cells in airway walls Specific IgE antibodies	Allergic bronchopulmonary aspergillosis
Tropical eosinophilia	Bronchoconstriction Finely nodular infiltrates Endomyocardial fibrosis	Very high levels of serum IgE Specific IgE antibodies	Filariasis
Disseminated invasive eosinophilia	Multisystem disease with limited forms Frequent endomyocardial fibrosis Eosinophil cellular abnormalities	High levels of serum IgE (1/3) Cutaneous urticaria and angioedema	

Table 3—Pulmonary Eosinophilic Syndromes Without Evidence of Immediate Hypersensitivity

Syndrome	Essential features	Specific examples
Transient pulmonary eosinophilic infiltrates	Benign course Bronchoconstriction in some patients Spontaneous resolution	Löffler's syndrome
Granulomatous angiitis	Bronchoconstriction Pulmonary infiltrates, nodules, and cavities Multisystem disease	Churg–Strauss variant of polyarteritis nodosa
Pulmonary malignant tumors with eosinophilia	Tumor and pulmonary tissue eosinophilia Endomyocardial fibrosis	Anaplastic large cell tumors

phoid nodules, containing foci of capillary hyperplasia, on the head and neck.[157] Patients with bullous pemphigoid, a condition quite distinct from the various forms of pemphigus, develop IgG antibodies to constituents of the dermal–epidermal junction, that can be detected both in the circulation and at the bases of the bullous lesions.[158,159] IgE is found at the dermal–epidermal junction in a minority of patients, but the serum level of IgE is elevated in over 70% of the cases. Further, degranulated mast cells are found at the bases of the bullous lesions; and mast-cell–derived mediators, including specific eosinophil chemotactic factors, have been identified in the bullous fluid.[114] Substantial fever, chills, myalgia, and arthralgia are typical of both recurrent granulomatous dermatitis, or Well's disease,[160] and eosinophilic fasciitis, or Shulman's syndrome.[161] The two disorders present acutely, follow a subacute or relapsing course, demonstrate serum polyclonal hypergammaglobulinemia and the occasional presence of IgG and C3 in the cutaneous lesions, but lack features of immediate hypersensitivity reactions.[162] Approximately a third of the patients with systemic invasive eosinophilia and cutaneous involvement have abnormally elevated serum concentrations of IgE, but the frequency of high IgE lev-

Table 4—Cutaneous Eosinophilic Syndromes

A. No systemic involvement
   1. Eosinophilic lymphofolliculosis of the skin (Kimura's disease)
   2. Subcutaneous angiolymphoid hyperplasia with eosinophilia
   3. Bullous pemphigoid

B. Constitutional manifestations
   1. Recurrent granulomatous dermatitis with eosinophilia (Well's disease)
   2. Eosinophilic fasciitis (Shulman's syndrome)

C. Systemic disease: Inflammation and fibrosis of the heart and possibly other organs
   1. Papular–nodular lesions
   2. Urticaria and angioedema

els is no higher in association with urticaria and angioedema than with the papular-nodular lesions.[163]

Specific Pathways Mediating Tissue Eosinophilia in Human Diseases

The availability of sensitive *in vitro* assays for the assessment of eosinophil chemotactic factors has permitted the identification and characterization of such factors in biologic fluids and extracts of tissues from patients with eosinophilic diseases.[2] The predominant eosinophil chemotactic factors in lesional fluid of bullous pemphigoid resemble those derived from mast cells and are composed of peptides with a molecular weight of 300–500, which are as highly acidic as the tetrapeptides of ECF-A, and of peptides with a molecular weight of 1500–3000 that were not characterized further.[114] An analogous diversity of eosinophil chemotactic peptides has been recognized in relation to the elicitation of physical allergic attacks, such as cold urticaria and cholinergic urticaria, and of asthmatic episodes by bronchial challenge. Cold urticaria is a mast-cell–dependent disease that can be transferred passively by the IgE in the serum of some affected subjects.[164] Analyses of paired serum samples from the venous effluents of the cold-challenged and control arms of several subjects with cold urticaria showed transient elevations in the concentrations of eosinophil chemotactic activity, as well as histamine and neutrophil chemotactic activity.[165–168] A comparable array of mediators was found transiently in the serum of subjects with cholinergic urticaria after challenge by running on a treadmill in a plastic occlusive suit.[169] The rises in the serum levels of eosinophil and neutrophil chemotactic activities were similar to those in cold urticaria, but the peak elevation of the concentration of histamine was less in cholinergic urticaria. In both instances, the eosinophil chemotactic activity was resolved by gel filtration into at least two families of peptides with a molecular weight of 400–600 and 1500–3000, respectively, that were separated from the neutrophil chemotactic activities of greater than 10,000 mol wt. In contrast, the challenge of asymptomatic asthmatics by inhalation of aerosolized allergen or by isocapnic hyperventilation was not accompanied by a consistent rise in the circulating levels of eosinophil chemotactic activity or of histamine, while the serum concentration of neutrophil chemotactic activity rose after hyperventilation, but not inhalational challenge.[170] The differences in quantities of eosinophil chemotactic peptides detected in the circulation after the elicitation of physical allergies and the physical challenge of asthmatics may relate in part to differences both in the regions of the circulation that were monitored and in the techniques for processing the samples. Nonetheless, each disorder was characterized by the elaboration of an ap-

parently unique profile of mast-cell–derived chemotactic factors, many of which attracted eosinophils preferentially.

The eosinophil infiltration of tumor and adjacent normal tissues in some patients with undifferentiated squamous cell carcinoma of the lung [171,172] or histiocytic lymphoma of the central nervous system [173] is attributable to uniquely specific peptide or polypeptide chemotactic factors that have not been recognized in normal tissues. The eosinophil chemotactic factor (ECF-LSC) extracted from lung squamous cell carcinomas of three patients and elaborated by long-term dispersed cell cultures of two of the tumors is a peptide with a molecular weight 300–400, by filtration on Sephadex G-25, and is moderately acidic, as assessed by elution from Dowex-1 at pH 5.0–5.3, as compared with 3.2–2.2 for the ECF-A tetrapeptides.[171] The eosinophil chemotactic factor derived from a histiocytic lymphoma of the brain (ECF-HL) and the cerebrospinal fluid of the same patient is a polypeptide with a molecular weight of 13,000–14,000 on Sephadex G-50 and is highly acidic, since it elutes from a high-pressure anion-exchange liquid chromatography column at pH 2.3–2.1.[173] In addition to eosinophil chemotactic activity of similar specificity, both ECF-LSC and ECF-HL have the capacity to chemotactically deactivate eosinophils *in vitro*. Further, serial studies of one patient demonstrated that high circulating concentrations of ECF-LSC resulted in eosinophil chemotactic deactivation *in vivo* without impairment of other functions.[171] Not only do the results confirm the importance of specific chemotactic factors in the selective accumulation of eosinophils in tissue eosinophilias, but they suggest further that high local concentrations of eosinophil chemotactic factors may trap the eosinophils at the sites of tissue response without altering the capacity of the eosinophils to perform other functions.

Eosinophil Cellular Abnormalities in Human Eosinophilic Diseases

Extensively hypogranulated and vacuolated eosinophils are observed in the circulation in some hypereosinophilic syndromes associated with allergic,[174] parasitic,[175] or idiopathic [176] diseases, but the characteristics of the degranulation have not been analyzed in terms of specific enzymatic constituents. The tissue eosinophils of patients with Hodgkin's disease contain increased numbers of vesiculotubular and other membranous structures,[46] which are morphologic alterations analogous to those that develop in rat eosinophils that have been exposed to colloidal gold or fetal calf serum [46] and presumably reflect augmented microendocytic function. Further, the tissue eosinophils in Hodgkin's disease, in comparison with the corresponding circulating eosinophils, have more arylsulfatase- and acid phosphatase-positive small granules, which normally appear late in the devel-

opment of the eosinophils.[85] Such biochemical and morphologic characteristics are presumed to reflect *in vivo* stimulation and activation of the eosinophils that are attributable to exposure to chemotactic factors and other eosinophil-directed mediators. In contrast, the developmental defects are exemplified by chromosomal aberrations analogous to those seen in some cases of eosinophilic leukemia.[177] This contention is supported by the documentation of specific eosinophil chemotactic deactivation *in vivo* with or without lysosomal degranulation in three clinical settings. Eosinophils obtained from two patients with bronchogenic carcinomas that produced peptide eosinophil chemotactic factors exhibited reduced responses to the homologous chemotactic factor and to C5a but had normal chemokinetic responses to sodium ascorbate.[171] Serial studies of eosinophils from one of the patients revealed the loss of chemotactic responsiveness at a time in the course of the disease when the circulating levels of the eosinophil chemotactic factor were maximal, as assessed by the appearance of the factor in the patient's urine.[171] Eosinophils that were harvested from the lesional fluid of three patients with bullous pemphigoid showed striking chemotactic deactivation and the intracellular contents of arylsulfatase B, an enzyme contained preferentially in eosinophils, were reduced to 29–52% of the corresponding level in the circulating eosinophils of the same patients.[114]

Significant alterations in the eosinophil content of arylsulfatase B were found in the course of diethylcarbamazine chemotherapy of 21 patients with Bancroftian filariasis.[178] The level of arylsulfatase B, assessed as micrograms of p-nitrocatechol generated from p-nitrocatechol sulfate/hr/10^6 eosinophils, decreased significantly from a mean of 36 μg prior to therapy, to 26 μg on the eighth day of therapy and then rose significantly to a mean of 47 at 10–14 days after the completion of therapy. The changes in the eosinophil content of arylsulfatase B were not due to diethylcarbamazine itself, were unrelated to the quantitative changes in blood eosinophilia, and were not accompanied by concurrent changes in the eosinophil content of peroxidase and β-glucuronidase, which suggests that selective degranulation of circulating eosinophils accompanies antifilarial chemotherapy.

It is not clear to what extent the normal regulation of maturation of specific properties of tissue eosinophils and the apparent accentuation of some aspects of the maturation process in disease states may be attributable to the effects of tissue-derived mediators on the eosinophils. For example, the increased expression of some receptors on eosinophils of patients with hypereosinophilic syndromes may be mediated by mast-cell-derived principles. Both complement receptors and receptors for het-

erologous and homologous IgG are increased in number on eosinophils of some patients, and the extent of the increase is related generally to the level and duration of the eosinophilia.[89,155] Histamine and the ECF-A tetrapeptides may contribute to the augmented density of the eosinophil C3b receptors in some of the hypereosinophilic syndromes.[91,94] Although the origins of disease-related cellular abnormalities of eosinophils have not been elucidated, both the density of C3b receptors and the extent of degranulation of circulating eosinophils correlate with the severity of tissue injury and the incidence of development of endomyocardial fibrosis in some series of hypereosinophilic patients.[89,149] A recent analysis of the frequency of endomyocardial fibrosis in the setting of eosinophilia associated with a malignant tumor indicated that all of the patients who developed endomyocardial fibrosis had at least 1000 degranulated eosinophils per cubic millimeter in the peripheral blood.[179]

VII. Concluding Comments

Eosinophils differ from other leukocytes of the polymorphonuclear (PMN) series not only in terms of genesis, morphologic features, and biochemical constituents, but also by a greater adaptability of expression of plasma membrane receptors and membrane and lysosomal enzymes. Because the eosinophils are normally positioned predominantly in the tissues, with a preferential localization beneath the body surfaces, immunologically specific challenges rapidly lead to the accumulation of eosinophils and the mobilization of their special functional capabilities. Considerable evidence suggests that eosinophils possess unique capacities to contain and terminate immediate-type hypersensitivity reactions and to suppress helminthic infections. While the hypereosinophilic syndromes are characterized by intense tissue eosinophilia in association with organ dysfunction and fibrosis, a causal relationship of the infiltrating eosinophils to the tissue damage has not been established.

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