THE EOSINOPHIL

BEESON AND BASS

VOLUME

XIV

IN THE SERIES

MAJOR PROBLEMS IN INTERNAL MEDICINE

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FOREWORD

Eos was the Greek goddess of dawn, mother of Memnon. Transposed through a complex brominated dye ($C_{20}H_8Br_4O_5$), her name has been given to a cell that has both entranced and befuddled investigators for the past century. "Russia is a riddle, wrapped in a mystery, inside an enigma." This Churchillian phrase of October, 1939, applied to another Red phenomenon, has held equally true for the eosinophil.

Why study the eosinophil? Perhaps because "the complete ignorance of the function of this cell is one of the most humiliating and disgraceful gaps in all medical knowledge," as the authors have so aptly quoted Arnold Rich, who made the statement about the lymphocyte some 40 years ago. The lymphocyte has now emerged as the central component of the dispersed organ system of immunity with a remarkable diversity of function and interaction. Subtypes of lymphocytes with high degrees of specificity have been revealed, and selective defects in function are found in clinical medicine. In contrast, the eosinophil seems much too versatile for a serious function in the host defense system, and in fact no patient has been described with absence of eosinophils as a single defect. In some studies it resembles a rather effete neutrophil in chemotaxis, phagocytosis and bacterial killing function. Yet evidence (from genetic defects) suggests a different origin, and clear differences exist in control of production and distribution. Approximately one billion are in rapid transit (half-life of 3 to 8 hours) in blood at any one time, but 300 to 500 billion are thought to be in various tissue sites. The eosinophil is largely a tissue rather than a blood vessel inhabitant.

What is it doing there? This is far from clear. Possibly the eosinophil contributes to the restraint and repair of inflammation that have been set off by antigen-antibody interactions. It may inactivate histamine and the slow-reacting substance of anaphylaxis (SRS-A) for example. Systems for restraint are important in all defense mechanisms so that the response itself be not more injurious than the inciting agent. Witness the elaborate system that has evolved to circumscribe blood

coagulation. Recent studies show a direct attack of eosinophils on helminths, giving dramatic verification of utility for the long observed association of eosinophilia with parasitic infections. Perhaps the eosinophil is uniquely equipped to harass the metazoan invader, but the structural and chemical basis for this has escaped detection. Their granules do have some special components in core and matrix, including basic proteins that produce the tinctorial properties by which they were discovered and named. In a century of research no special functions for these granules have been established beyond their gratuitous "love for eosin." Even in death the eosinophil deposits a cryptic marker, the Charcot-Leyden crystal.

Although resembling a rather gaudy neutrophil and capable of simulating many of its functions, the eosinophil actually has much closer links to the immune system. In contrast to the neutrophil, it is dependent upon the T lymphocyte for its accelerated production and its tissue localization following contact with certain antigens. It has its own chemotactic factor or factors, including one that is a simple peptide of four amino acids. There are other intriguing differences, such as the presence of receptors for estradiol and the cyclic levels of eosinophils in the uterus. Noteworthy is the marked male predominance in the sex distribution of eosinophilic leukemia and most of the other infiltrative disorders of eosinophils. The response of the eosinophil to glucocorticoids obviously differs markedly from that of the neutrophil.

Is there a single eosinophil or, as in the case of lymphocytes, do we face heterogeneity of function in cells that seem structurally similar? Does a single cell phagocytize bacteria, erode helminths, buffer inflammation, counteract IgE-mediated immune responses, and receive information from such diverse sources as T lymphocytes and estradiol? Perhaps so, but this is asking a lot in a defense system characterized by specialization—even for a cell named for the goddess of dawn.

The purpose of the monographs that are being published in the series *Major Problems in Internal Medicine* is to present a personal critical analysis of an area of medicine by an authority or authorities in a field. *The Eosinophil* meets that criterion admirably. Only those who are themselves eosinophilophilic could have undertaken the awesome task of analyzing the vast literature that has sedimented out concerning this baffling cell. There are few areas of medicine where the signal to noise ratio is so abysmally low. Only those who have made many personal contributions to the field could so skillfully sort out the margin where fact and fancy blur. We are indebted to Drs. Beeson and Bass for this scholarly analysis, which combines cytology, cell biology and clinical medicine. This authoritative monograph will be the point of departure for future investigators who pursue this interesting cell.

LLOYD H. SMITH, JR., M.D.

PREFACE

The function, or purpose, of the eosinophil has puzzled students of the white blood cells for over 100 years. It still remains elusive. Our interest in the subject began in 1967 when, with Antony Basten, Markley Boyer, Christopher Spry and Ronald Walls, we undertook a series of experimental studies on mechanisms of eosinophilia and eosinopenia in the laboratories of the Nuffield Department of Clinical Medicine, University of Oxford. Our background reading for that work and numerous informal discussions kept directing our thoughts to possible functions of the eosinophil. We undertook the assembly of this book in the hope that a detailed review of observations made in clinic and in research laboratory might bring out some linkages or associations that would provide clues to eosinophil functions.

We have surveyed a substantial part of the vast literature concerning eosinophils, but neither this book nor any other conceivable work could now claim to be a complete catalog of all writing in which the eosinophil is mentioned. As early as 1914, E. Schwarz compiled a review in which more than 2700 references were cited;[4] since then many more thousands have appeared. From 1960 onward the emphasis has been on experimental work, and we have dealt with that more thoroughly. We do not pretend to be expert in all the areas covered, but have tried to quote the works and interpretations of others accurately, with the aim of providing entry points into the relevant literature that would assist an interested student to find further information. Our book is based predominantly on articles published in English, mainly because we have felt more competent to read them critically.

Parts of the huge literature of the eosinophil appear contradictory. Where possible, we have attempted to suggest reasons for contradictions and to indicate the most attractive interpretation. From time to time we have pointed to particular areas we believe especially suitable for further investigation and have also speculated at times on the implications of data at hand.

Phylogenetically, the eosinophil has been found in all species of animals above the most primitive vertebrates. It does not seem to be present in the hagfish or the lamprey.[2, 3] Cooper's studies of comparative immunology indicate that eosinophils make their appearance at about the same time as sophisticated lymphocyte-mediated immune systems can be identified.[1] Above that evolutionary stage we know of no animals that lack this cell.

In all animals the number of eosinophils in the blood in proportion to other leukocytes is about the same. In many clinical situations the behavior of the eosinophil is predictable and uniform. There are complex mechanisms that accelerate or curtail its production, or that change the rate and direction of its movement. We think that such uniformity of behavior in all animal and human models studied is one basis for postulating that the cell serves some useful function or functions. Its universal presence in health could also be used as an argument that it plays a role in the body economy. At present, evidence is accumulating to suggest not one but several functions for the cell. It probably helps to maintain homeostasis by interactions with a variety of endogenous products. It seems unimportant in defense against invading microorganisms, although it may assist the host in defense against some metazoan helminths. Eosinophil behavior often mimics that of cells known to be part of the immunologic apparatus. It may be involved in the action of certain hormones. Finally, as is true of other leukocytes, the eosinophil appears to be capable of liberating products that can damage the tissues of its host.

In discussing various aspects of eosinophil behavior we have found it necessary to describe some observations more than once in order to make each section of the book more readable. We hope this work will be useful as a reference, that it will stimulate interest in specific studies, and that the "riddle" of the eosinophil will, before too long, be of interest only to historians.

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CONTENTS

Part I

STRUCTURE AND BEHAVIOR

CHAPTER 1

LIFE CYCLE

The great majority of eosinophils are produced in the bone marrow, although occasional eosinophil mitoses may be observed in extramedullary sites such as the thymus.[5] Their cell of origin is unknown. The many similarities of the polymorphonuclear leukocytes prompted the hypothesis of a pluripotent, undifferentiated stem cell as the common origin of all granulocytes. As the genetic, biochemical and physiologic differences between the granulocytes become more clearly defined, this hypothesis seems progressively less tenable. For example, selective genetic absences of either eosinophil or neutrophil peroxidases have been reported.[25, 27–29, 33] Children with congenital neutrophil agranulocytosis may have normal or elevated eosinophil production,[16] an event that has also been observed in drug-induced neutrophil agranulocytosis.[10] Recent studies by the group at the Walter and Eliza Hall Institute have provided further evidence for a distinctive eosinophil precursor cell. Bone marrow cultures *in vitro*, stimulated with human placental conditioned medium, formed eosinophil colonies between days 10 and 14 , at a time when neutrophil colonies are diminishing. Moreover, the eosinophil colonies contained only eosinophils; no example of mixed colonies was found.[13] Thus it appears that the eosinophil and neutrophil leukocytes are under separate genetic control and are produced separately from unidentifiable precursor cells, which may or may not have a common cell of origin.[11]

STUDIES OF EOSINOPHIL KINETICS: PROLIFERATION

The development of autoradiographic techniques for studying the kinetics of leukocyte production by Cartwright et al.[8] has been followed by several studies on eosinophil production and mobilization in the

rat.[1, 6, 15, 35, 36] The eosinophil arises from an unidentified precursor and proceeds through several cell divisions before maturing and entering the bloodstream. Eosinophils in the unstimulated rat bone marrow were found to have a mitotic index of 0.44 to 0.74 per cent, [14, 35] a cell cycle time of 22 to 30 hours[1, 35] and a total marrow transit time (from unidentified precursor to marrow egress) calculated to be 5.5 days. The effect of a stimulus to eosinopoiesis was studied by intravenous injection of *Trichinella spiralis* larvae by Spry.[35] There was a delay of 23 hours, part of which was undoubtedly due to the time required for induction of DNA synthesis. With stimulation, all phases of the cell cycle were shortened, the total cell cycle time being reduced to 9 hours. With the shortened cell cycle time, an additional 16- to 64-fold increase in eosinophil production could occur during the calculated shortened marrow transit time of 3.6 days.

Data regarding eosinophil kinetics in human bone marrow are exceedingly scarce. Greenberg and Chikkappa[17] studied a patient with hypereosinophilia with a pulse of tritiated thymidine followed by serial sampling of marrow and peripheral blood. The first labeled eosinophil metamyelocytes were seen after 3¾ hours, suggesting this to be the G_2 + M phase of the cell cycle, the time between the end of DNA synthesis and the end of mitosis. This compares to a corresponding determination of 3.9 hours for the rat.[35] Labeled eosinophil band forms were observed after 32 hours, suggesting a metamyelocyte maturation time of less than 29 hours. Labeled blood eosinophils appeared after 63 hours, indicating this to be the emergence time. Stryckmans et al.[38] studied two patients but reported no quantitative data. They felt that the eosinophil maturation or storage time in the bone marrow was less than reported for neutrophils and shorter during a stimulus to eosinophilia; however, they did not observe a shortened generation time in the eosinophil proliferating compartment. This observation is in disagreement with the detailed animal studies reported above.

MATURATION AND RELEASE

The factors controlling release of mature eosinophils are poorly understood. The studies of Spry[35, 36] suggest that the release of marrow eosinophils in rats continues to follow the normal sequence of development (although more rapidly) following stimulus for eosinophilia.

The site of final maturation of the eosinophil may be either the bone marrow or the spleen, depending upon the species examined. There are few data on the site of maturation of human eosinophils, yet the long postmitotic maturation time noted by Herion et al. would suggest that it occurs in the bone marrow. The reports of Parwaresch et al.[26] and Herion et al.[20] assert sufficient eosinophils in the nondividing