Medical Progress

The Role of Phagocyte Function in Resistance to Infection

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MORE THAN ONE generation of physicians has placed its faith in "the Lord and the leukocytes" when visiting the sickbed of a patient with infection. Although the continued interest of the Lord has been questioned by some, and reinforced with antibiotics by others, phagocytic leukocytes remain a major determinant of our ability to survive exposure to pathogenic microorganisms. Recent investigations have increased our knowledge of the phagocytic process, and have led to the finding that several disorders of man are caused by or associated with defective phagocyte function. This paper will review some of this new information, especially as it relates to the function of phagocytes in human illness. The interested reader will find additional details in recent publications.[1-3]

Life Cycle of Leukocytes

Of the several types of phagocytic leukocytes, neutrophils have received the most extensive study. In structure and function this cell type shows numerous adaptations that equip it to respond rapidly and effectively to tissue invasion by microbes. The circulating pool of neutrophils, estimated roughly by a routine white blood cell count and a differential count, is continuously renewed by neutrophils that enter the blood from the bone marrow at a rate of 80 million cells per minute in the "average" adult.[4] This freely circulating pool is in equilibrium with an approximately equal number of mature neutrophils within the vasculature of certain organs. The latter are able to enter the circulation in response to various hormonal or metabolic stimuli.[4,5] Normally, at least four days elapse after the last occurrence of deoxyribonucleic acid (DNA) synthesis in a marrow precursor before the appearance of neutrophils in the circulation, but this may be considerably shortened in patients with acute infections and leukemoid reactions.[6] Under normal conditions, the half-time of a neutrophil in the peripheral blood of man is estimated to be approximately six and a half to seven hours.[4,5] Its subsequent life in the tissues is difficult to ascertain precisely, but is almost certainly short—probably no more than a day or two.

Our knowledge of monocytes, derived mainly from studies of laboratory animals, suggests several differences from the neutrophil model. Monocytes also are produced from rapidly dividing marrow precursors and enter the circulation quite promptly after final cell division. However, once in the circulation, they persist in the blood for a longer time than do neutrophils; the half-time of circulating mouse monocytes has been estimated at 22 hours.[7] From the circulation, monocytes enter various tissues where some may differentiate into larger phagocytic cells (macrophages or histiocytes) that may survive for several months.[8]

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Supported in part by U.S. Public Health Service research grant CA-11067.

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TABLE 1.—*Disordered Phagocyte Function—General Pathophysiology*

Defective Stage	*Illustrative Clinical Disorders*
Production of phagocytes	Agranulocytosis, acute leukemia
Migration to sites of inflammation	Neoplasia, steroid-treated patients
Chemotaxis	Hereditary disorders of complement function
Opsonization of microorganisms	Sickle-cell anemia, hypogammaglobulinemia
Killing of ingested microorganisms	Chronic granulomatous disease, hereditary myeloperoxidase deficiency

Unlike the short-lived neutrophil which enters the circulation equipped with its maximal supply of bactericidal and bacteriolytic components, mononuclear phagocytes may adaptively increase their microbicidal effectiveness after reaching tissue sites.[9,10]

Migration and Chemotaxis

The first facet of the phagocytic process to be considered is that of local accumulation of large numbers of these cells in areas of tissue damage or microbial invasion. Two test systems, the "skin-window" technique of Rebuck and Crowley[11] and the chemotaxis chambers of Boyden,[12] have provided considerable information about this aspect of phagocytic function.

A "skin-window" is made by placing a coverslip over a superficially abraded area of skin.[11] Leukocytes that migrate to this area can be examined by periodic removal and staining of the coverslips or, in some modifications, by emptying a small collecting chamber. In normal adults, the cells observed after two to four hours are almost exclusively neutrophils. By eight hours, one-third to one-half of the cells adherent to coverslips are mononuclear phagocytes and at 24 hours mononuclear phagocytes predominate. Studies in animals suggest that these mononuclear phagocytes are derived from blood monocytes.[8]

Drugs and some disease states can impair the ability of neutrophils or monocytes to respond in this test. Decreased migration of neutrophils has been reported after the administration of steroids[13] and ethanol[14] to physically normal subjects. Patients with acute leukemia[15] or diabetes mellitus and ketoacidosis[14,16] also have impaired migration of neutrophils.

Diminished mononuclear cell response has been reported in untreated patients with advanced neoplasms and in patients receiving certain cytotoxic drugs to treat both neoplastic and non-neoplastic disorders.[17-19] If these abnormal neutrophil and monocyte responses also occur in areas of microbial challenge, they could serve to provide the invading organisms with a critical head start in causing disease.

The term *chemotaxis* refers to the directional motion of a cell toward a substance in its environment. Certain bacteria have been shown to be chemotactic for neutrophils,[20] and antigen-antibody complexes also generate chemotactic substances when added to fresh serum.[12] Many contemporary studies of chemotaxis *in vitro* utilize a chamber, devised by Boyden, that contains two adjacent compartments separated by a Millipore filter that has pores just large enough to permit a leukocyte to wriggle through.[12] If a suspension of leukocytes is placed in one compartment and the test substance in the other, the number of leukocytes that migrate through the filter may provide a measure of the substance's chemotactic activity. Keller and Sorkin have analyzed some of the recent work on such chemotactic mediators.[21]

Ward and his associates have described several mediators of chemotaxis that are generated in rabbit or guinea pig serum by reactions involving components of complement. One, a trimolecular complex composed of the fifth, sixth and seventh components of complement, is generated after the addition to serum of antigen-antibody precipitates.[22] Other chemotactic factors of lower molecular weight are generated as a result of the cleavage of C3* by plasmin[23] or of C5 by trypsin.[24] Additional factors, generated from serum or present in lysates of neutrophils, may exert chemotactic effects that are specific for certain macrophage populations.[25] Recently, it has been reported that sera from patients with deficiencies of C3 or C5 have impaired ability to generate chemotactic stimuli *in vitro* (Table 1).[26,27]

*C3 and C5 are symbols for the third and fifth components of complement.

Opsonization

Although certain bacteria may be ingested by leukocytes in the absence of serum, phagocytosis of many potential pathogens requires, or is facilitated by, the action of serum factors called opsonins.[28] By specific attachment or nonspecific adsorption to the bacterial surface, opsonins modify microorganisms so that they are readily ingested by leukocytes.

Antibodies

Although early workers concentrated on heat-labile serum opsonins, opsonizing properties have been detected in several moieties of serum. The opsonizing activity of specific antibodies, arising from previous vaccination or natural infection with the challenging organism or with one sharing some of its antigenic determinants, is of prime importance for phagocyte function. The repeated infections incurred by patients with hypogammaglobulinemia result in large part from their deficiencies of such heat-stable opsonins and are ameliorated by replacement therapy with gamma globulin. Recent studies suggest that the capability of immune IgG to combine with a specific microorganism depends on the Fab portion of the antibody molecule, whereas its ability to act as an opsonin depends on its Fc portion.[29] The opsonic ability may be related to the presence of Fc-attachment sites on the cell surface of certain phagocytes.[30]

Complement Factors

Since the early studies of Wright and Douglas,[31] it has been recognized that the phagocytosis of certain microorganisms is enhanced by heat-labile substances in the serum.[32] The studies of Hirsch and Strauss suggested that heat-labile opsonins were distinct from antibodies and from the complete series of complement factors causing immune hemolysis.[28] Recent investigations by Wood and his collaborators have provided evidence that certain complement factors, specifically the third and fifth components, are involved in the phagocytosis of pneumococci by leukocytes suspended in rat serum.[33,34] Binding sites for complement components have been detected on the surfaces of neutrophils and macrophages[35] and, in mononuclear phagocytes, these sites may show specificity for C3.[36]

Complement Deficiencies in Man

Deficiencies of C3 or C5 may be associated with an increased susceptibility to bacterial infection in man.[26,27] Alper et al studied a young adult with Klinefelter's syndrome and a lifelong history of infections by various bacteria.[26] The concentration of C3 (β_{1C} globulin) in his serum was less than one-third of normal and, of that, most was present in an inactive form. *In vitro,* his serum had decreased hemolytic complement activity and exerted poor bactericidal power against certain Gram-negative organisms. It failed to support optimal phagocytosis of pneumococci or to generate normal amounts of chemotactic activity. These serum deficiencies could be corrected *in vitro* by addition of small amounts of normal serum, but not by addition of purified C3. It was suggested that the patient might lack a serum factor, as yet uncharacterized, required for normal stability and function of C3.

Miller and Nilsson described an infant with severe eczematoid dermatitis who experienced repeated cutaneous and systemic infections caused by Staphylococcus aureus and various Gram-negative bacteria.[27] Sera from the patient, her mother and numerous relatives were markedly deficient in their ability to generate chemotactic activity or to promote ingestion of yeast particles by leukocytes. The defective function could be corrected *in vitro* by normal sera or purified C5, but not by (rat) sera deficient in C5. Attribution of this patient's infectious diathesis solely to the deficiency of C5 is tempered somewhat by the lack of reported infections in numerous other similarly affected relatives.

Other Opsonin Deficiencies in Man

From an historical standpoint it is instructive to recall that in 1904 Wright and Douglas noted that the incubation of human blood with viper venom reduced its opsonic activity, and they suggested that this could explain "the reduced resistance to septic infection which supervenes upon viper bites."[31] More recently, the sera of patients with sickle cell anemia have been reported to have diminished amounts of heat-labile opsonins for Type 25 pneumococci,[37] and it has been suggested that this deficiency, in conjunction with the functional asplenia of such individuals,[38] may underlie the unique susceptibility of these patients to pneumococcal sepsis and meningitis.

Phagocytosis

The term *phagocytosis* refers to events associated with the envelopment and subsequent disposition of particles by certain cells. It is useful to consider the phagocytosis of microorganisms by leukocytes as composed of three sequential phases: (1) ingestion, the incorporation of extracellular organisms into cytoplasmic vacuoles; (2) the killing or inactivation of the ingested organisms; and (3) the digestion of killed organisms.

Metabolic Events

Contemporary biochemical and metabolic analyses of the phagocytic process are based on the contributions of Karnovsky, Quastel and their colleagues.[39,40] Neutrophils derive the energy required for particle ingestion from glycolysis;[41] therefore, inhibitors of oxidative metabolism (cyanide, dinitrophenol, oxygen-free atmosphere) do not block particle uptake *in vitro* by these cells. In contrast, killing of ingested organisms is greatly impaired under anaerobic conditions.[42] The metabolic changes that follow particle ingestion by neutrophils include increased rates of lactate production, phospholipid turnover and ribonucleic acid (RNA) synthesis.[39,40] Most importantly in relation to neutrophil microbicidal activity, phagocytosis triggers a burst of oxygen consumption associated with greatly increased oxidation of glucose via the hexose monophosphate shunt; this reaction results in the intracellular generation of hydrogen peroxide.[40]

Morphologic Events

During phagocytosis, cytoplasmic granules of leukocytes enter and release their contents into the phagocytic vacuoles containing ingested organisms.[43] Recent studies of rabbit "neutrophils" indicate that these granules are heterogeneous; subpopulations of intact granules have differences in their enzymatic constituents.[44-46] Substances detected in neutrophil granules from various mammalian species include numerous acid hydrolases, alkaline phosphatase, peroxidase, and a group of cationic proteins.[47,48] How are the various granule proteins related to the ability of leukocytes to kill and digest engulfed organisms?

Proteins with antibacterial activity have been extracted from the neutrophils of certain mammalian species. Important contributions to this research were made by Hirsch.[49] More recently this approach has been pursued vigorously by Zeya and Spitznagel,[48,50,51] who have isolated and partially purified a group of cationic proteins from the granules of rat and guinea pig neutrophils and have demonstrated that these substances kill various bacteria *in vitro*. After fractionation, they found that the proteins differed in their amino-acid composition and in their ability to kill various species of bacteria.[48,50] More recently these authors have assigned the granule-associated cationic proteins to a specific subpopulation of neutrophil granules, which also exhibits eosinophilic staining characteristics.[51] It is not known whether similar cationic proteins are present in human neutrophils. Earlier attempts by these investigators to detect bactericidal cationic proteins in human granulocytes antedated techniques for obtaining pure monospecific cell populations, and the cationic proteins they detected in extracts of human leukocytes could have come from inadvertant contamination by eosinophils.[52]

What role is played by the enzymes contained in neutrophil granules? Some neutrophil granules are lysosomes—that is, they contain acid phosphatase and other hydrolytic enzymes with acid pH optima in an inactive, structurally latent form.[47] When the granule contents are released into phagocytic vacuoles, the enzymes become active and can participate in the degradation of bacterial macromolecules.[53,54] Muramidase (lysozyme) is also a component of neutrophil granules and acts to cleave the chemical bond linking two of the molecular constituents of bacterial cell walls. A few Gram-positive organisms, whose cell walls are stabilized principally by susceptible bonds, can be completely lysed by muramidase. However, like the other hydrolases, its major function is presumed to be the enzymatic digestion of organisms killed by other components of the leukocyte rather than primary bactericidal activity.

Defects in Microbicidal Activity

Two recently appreciated "experiments of nature," chronic granulomatous disease and hereditary myeloperoxidase deficiency, have provided insights into molecular mechanisms employed by normal human leukocytes to kill bacteria and fungi (Table 2). Chronic granulomatous disease (CGD) was originally described as a familial disorder with X-linked inheritance, affecting only male children.[55] However, cases affecting females, with alternate modes of hereditary transmission,

TABLE 2.—*Comparison of Two Hereditary Disorders of Leukocyte Function*

	Chronic Granulomatous Disease	*Myeloperoxidase Deficiency*
Symptoms	Repeated infections, especially by staphylococci and organisms of limited intrinsic pathogenicity	Increased susceptibility to opportunistic mycoses (*Candida, Aspergillus*), but compatible with good health
Age at onset of infections	Infancy, childhood	May be delayed until adulthood
Sex incidence	Males predominate	Probably equal (few cases)
Genetic pattern	X-Linked inheritance (most male patients), other patterns (affected females and sporadic male cases)	Autosomal recessive inheritance
Cellular defect	Impaired H_2O_2 production (specific underlying defects may vary)	Impaired H_2O_2 utilization due to absence of myeloperoxidase
Clinical variants	With associated immunologic defects	Mosaic myeloperoxidase deficiency
	Job's syndrome	—with refractory megaloblastic anemia
	Leukocyte glucose-6-phosphate dehydrogenase deficiency	—with acute leukemia
Diagnostic leukocyte studies	Familial lipochrome histiocytosis NBT test Microbicidal assay	Peroxidase stain of blood smear Candidacidal assay

have recently been recorded.[56-58] CGD is manifested by a great susceptibility to severe infections which are often caused by microorganisms of limited intrinsic virulence.[59,60] Symptoms generally develop during the first two years of life, often in infancy. Lymphadenopathy with suppurative adenitis, repeated pneumonias, hepatosplenomegaly and skin infections are characteristic, and other sequelae may include rhinitis, conjunctivitis, osteomyelitis, meningitis and septicemia.[60,61] Eighteen of the 28 affected boys whose histories were reviewed by Johnston and McMurry died before their seventh birthday.[61] Although staphylococci and various coliform bacilli are the predominant causes of infection in these children, resistance to actinomycetes and certain fungi, especially Candida species, is also impaired.[60,61] Routine laboratory studies usually reveal anemia, leukocytosis, an accelerated sedimentation rate and hypergammaglobulinemia.

Quie and associates established a basis for the impaired resistance of affected children by demonstrating that leukocytes from CGD patients, although normally phagocytic, were deficient in bactericidal activity.[62] CGD leukocytes have a remarkable metabolic defect as well—they fail to develop the burst of oxidative metabolism and hydrogen peroxide generation that follows ingestion of particles by normal leukocytes[63] (Chart 1).

Several lines of evidence suggest that this metabolic deficiency is the cause of the bactericidal

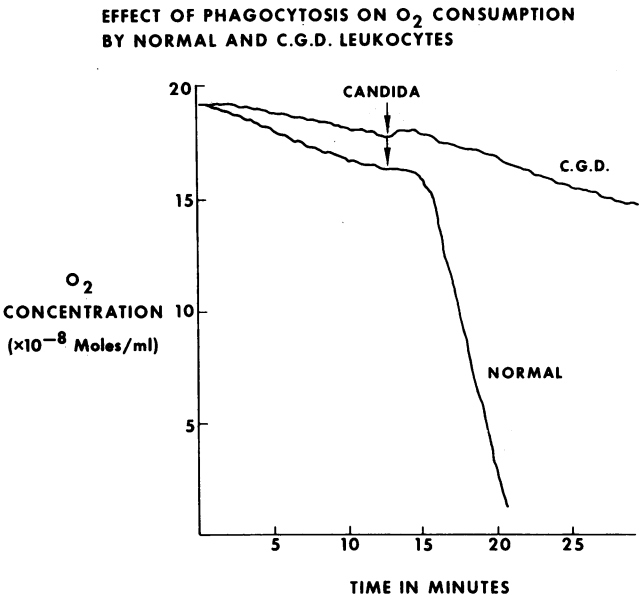

Chart 1.—Different rates of oxygen consumption by normal and CGD leukocytes (1×10^7 neutrophils per ml) after they have phagocytosed heat-killed Candida albicans cells (3×10^7 per ml). The recordings, made with a Gilson model KM oxygraph with a Clark electrode (Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio) show the concentration of oxygen remaining in solution.

defect. The bactericidal and fungicidal activity of CGD leukocytes *in vitro* can be improved by providing an exogenous source of hydrogen peroxide[64] or by stimulating endogenous oxidative metabolism with redox dyes.[65] Moreover, CGD leukocytes kill certain hydrogen peroxide-producing bacteria (streptococci, lactobacilli and

pneumococci) relatively effectively, presumably because the bacteria supply the ingredient missing from these cells.[66,67]

At present, the diagnosis of CGD requires two observations: that the patient's leukocytes display deficient oxidative metabolism after particle ingestion, and that they exert defective microbicidal activity. The metabolic response to phagocytosis can be measured in several ways. Some, such as the method illustrated in Chart 1, are relatively direct but require special equipment that may not be readily available. Consequently, many investigators have favored the use of some variant of the nitro blue tetrazolium (NBT) test, which utilizes the fact that, after ingestion of particles in the presence of the essentially colorless NBT, normal leukocytes reduce it to an insoluble blue substance that accumulates in the cytoplasm. Although CGD leukocytes ingest particles normally, little of the NBT is reduced and consequently little blue color is formed.[57] The extent of NBT reduction can be measured spectrophotometrically after appropriate chemical extraction;[57] alternatively, the proportion of phagocytic cells containing the reduced NBT can be established by microscopic examination.[68,69]

Microbicidal activity is most often measured by some modification of the *in vitro* assay of Maale[70] as adapted by Hirsch and Strauss.[28] Known numbers of bacteria and leukocytes are combined under standardized conditions and serial colony counts are done on samples of the mixtures to record the rate of decline in viable bacteria. More recently described methods of determining leukocyte candidacidal activity may provide a somewhat simpler way to establish the presence of a microbicidal defect in leukocytes from children suspected of having CGD.[71,72] Although the standard tests of microbicidal activity measure neutrophil function, monocytes from the peripheral blood of CGD patients also exert impaired bactericidal[73,74] and candidacidal activity.[75]

The demonstration of disordered leukocyte function has provided for the more precise diagnosis of CGD; it also has resulted in expanding our clinical picture of the disorder. Cases fulfilling the criteria for CGD have been reported in girls[56-58] and diagnosed in children in their late teens.[76] The leukocyte defects of CGD have also been reported in association with other abnormalities, such as impaired leukotaxis[77] and selective immunoglobulin deficiency.[78]

A variant of CGD, manifested by recurrent cold staphylococcal abscesses from birth and occurring in fair-skinned, red-haired girls, was described by Davis, Schaller and Wedgwood, who named the condition Job's syndrome.[79] Bannatyne et al demonstrated defective NBT reduction and impaired bactericidal activity against staphylococci by leukocytes from a child with this disorder. Like leukocytes from male children with CGD, her leukocytes killed streptococci normally.[68]

In contrast, normal leukocyte bactericidal activity has been reported in studies of patients or animals with the Chediak-Higashi syndrome,[80,81] who also have frequent severe infections starting in infancy or childhood. This inherited abnormality is associated with oculocutaneous hypopigmentation and may terminate with the development of an atypical lymphoma.[82,83] Large cytoplasmic granules are present in various cell lines of affected patients, and the disorder may be diagnosed by finding the characteristic giant granules in leukocytes on conventionally stained blood smears.

Eventually, it should prove possible to classify CGD syndromes on the basis of their specific metabolic (enzymatic?) defects. Unfortunately, the studies designed to elucidate the mechanism that triggers the normal burst of postphagocytic oxidative metabolism and to discern the reason for its failure in CGD have produced a wealth of often conflicting information. Although detailed consideration of these studies is beyond the scope of this review, there are indications that CGD may be the expression of more than one specific cellular defect. Several recent papers can launch the interested reader into this interesting but controversial area.[63,84-86]

If defective production of hydrogen peroxide underlies the CGD syndrome (or syndromes), it is reasonable to consider how H_2O_2 achieves its bactericidal activity. Klebanoff's studies indicate that the effectiveness of H_2O_2 as an antimicrobial agent may be considerably augmented by its combination with a peroxidase. In a series of *in vitro* experiments with peroxidase enzymes derived from saliva, milk and leukocytes, he has shown that effective antimicrobial activity results from and requires the interaction of the peroxidase enzyme with H_2O_2 and an appropri-

ate halide cofactor.[67,87,88] In his studies with H_2O_2, iodide and myeloperoxidase (MPO), the peroxidase of neutrophils and monocytes, bactericidal activity was associated with iodination of the bacteria.[87] Iodination of intracellular bacteria was demonstrated if normal leukocytes ingested microorganisms in the presence of low concentrations of extracellular iodide.[67,87] The extent of iodination was much diminished within CGD leukocytes, but could be demonstrated when viable, H_2O_2-generating organisms (lactobacilli) were ingested.[67] These observations, and studies by Sbarra and his associates,[89] strongly implicated MPO in the microbicidal activity of normal mammalian leukocytes.

The detection of hereditary myeloperoxidase deficiency, a syndrome characterized by the complete absence of peroxidase activity in neutrophils and monocytes, has permitted extensive evaluation of the role of MPO in the microbicidal affairs of human leukocytes.[90,91]

Hereditary MPO deficiency is readily diagnosed by examination of a peroxidase-stained smear of peripheral blood. In contrast to the characteristic deposition of dark reaction product on the cytoplasmic granules of normal neutrophils, monocytes and eosinophils (Figure 1), only the eosinophils of affected patients show peroxidase activity (Figure 2). The persistence of eosinophil peroxidase in this condition is in accordance with other observations indicating that the eosinophil enzyme is structurally and chemically distinct from MPO.[92] Thus far, five patients with hereditary MPO deficiency have been reported, including two pairs of siblings.[90,93,94] Its true incidence is unknown, and its apparent rarity may only reflect the paucity of attempts to detect it. Indeed, the first three reported subjects were discovered essentially by chance.[93,94]

In addition to the hereditary form of MPO deficiency, there have been reports of presumably acquired forms of the disorder; these forms are characterized by an enzymatic mosaicism of the peripheral blood neutrophils. In such patients, peroxidase - containing and peroxidase - deficient lines of cells coexist in the bone marrow and peripheral blood,[95,96] and additional hematologic abnormalities may be present. We have recently observed such a patient. Almost all of his neutrophils lacked peroxidase, and he died as a result of systemic fungal infection.

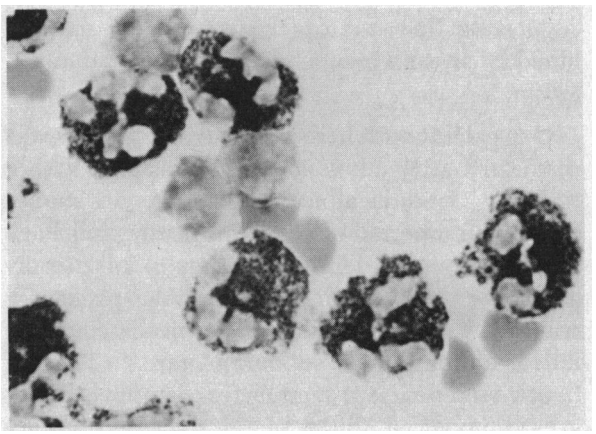

Figure 1.—Normal neutrophils, stained for peroxidase and counterstained with Giemsa. The peroxidase-containing granules are stained black and fill the cytoplasm of the cells. Original magnification X1250.

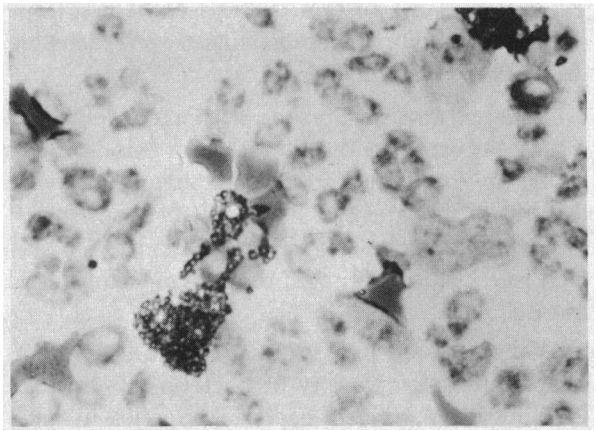

Figure 2.—Peroxidase stain of peripheral blood leukocytes from a patient with hereditary MPO deficiency. An eosinophil contains granules that are outlined by the peroxidase reagent. Neutrophils and monocytes all lack peroxidase activity. Original magnification X1000.

We have studied the leukocytes of three MPO-deficient subjects: a brother and sister with hereditary MPO deficiency, and a man with mosaic MPO deficiency in whom more than 99 percent of the circulating neutrophils were peroxidase-deficient. Peroxidase - deficient neutrophils were found to have an impaired ability to kill certain bacterial species. For example, the neutrophils of a patient with hereditary MPO deficiency required three to four hours to kill Staphylococcus aureus 502A or Serratia marcescens to the extent achieved by normal neutrophils in 45 minutes.[91] Curiously, as with CGD cells, the ability of MPO-deficient neutrophils to kill Streptococcus fecalis is relatively intact,

suggesting that this organism normally may be killed by an MPO-independent microbicidal mechanism.

Our patient with hereditary MPO deficiency was diagnosed after admission to the hospital with a systemic Candida albicans infection. In studies made over a period of years, his neutrophils have had a profoundly depressed ability to kill that organism[72,90] and certain other Candida species. In contrast, a strain of Candida tropicalis could be killed, although at a subnormal rate.[97] The patient's MPO-deficient monocytes also have had a greatly impaired ability to kill ingested Candida albicans.[75] The patient's sister has MPO-deficient neutrophils and monocytes and equally defective leukocyte candidacidal activity *in vitro;* she has, however, always been in good health and has remained free of infection. Likewise, the first three cases of hereditary MPO deficiency were detected in otherwise healthy adults.[93,94]

Thus, of the six persons with MPO deficiency either reported in the literature or known to us fully at this time, four have been otherwise healthy adults and two have had serious systemic mycoses. This may signify that MPO plays a special role in the antifungal defense mechanisms of normal man.[98]

Although MPO may increase the ability of neutrophils to kill a variety of bacteria,[90,91] the lack of clinically significant bacterial infection in many MPO-deficient individuals suggests that the residual leukocytic bactericidal activity can, in most circumstances, compensate for the lack of MPO. Comparison of the severity of the clinical manifestations of CGD, presumably caused by a deficiency in H_2O_2 production, with that of hereditary MPO deficiency suggests that H_2O_2 may activate leukocyte components other than MPO to produce bactericidal activity.

An attempt has been made to survey a rapidly expanding area of medical research. As the patterns of infectious disease in our hospitals have gradually changed under the influences of medical and socioeconomic factors, infections in "impaired hosts" have assumed greater importance. Studies such as those surveyed here not only increase our knowledge of factors that govern susceptibility or resistance to infection, but may eventually enable physicians to cope more successfully with the increasing challenge of opportunistic infections.

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