Disorders of polymorphonuclear leukocytes relevant to infection

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The idea that phagocytic cells protect the host against attack by microorganisms is a very old one, first expounded clearly by Metchnikoff. Much of our detailed knowledge of the mechanisms by which phagocytes accomplish this function and the ways in which these mechanisms can be deranged, however, has been obtained in the past several years. The neutrophil, in particular, has been the subject of extensive investigation, which has yielded a mass of complex and sometimes conflicting data. In this paper, I review some of the important ways in which impairment of neutrophil function can lead to increased susceptibility to infection.

General properties of mature neutrophils

Some of the important structural features of the mature neutrophil are illustrated in *Figure 1.* This is an electron micrograph of a cell which has been subjected to a cytochemical technique, so that intracellular sites of peroxidase activity are marked by a dense black reaction product. The cytoplasm of the cell contains numerous granules, which first were shown to be lysosomes by Cohn and Hirsch.[1] It now is known that there are at least two distinct types of granules, differing both in morphologic appearance and in the nature of the enzymes and other substances within them. The *primary* or *azurophilic* granules are formed

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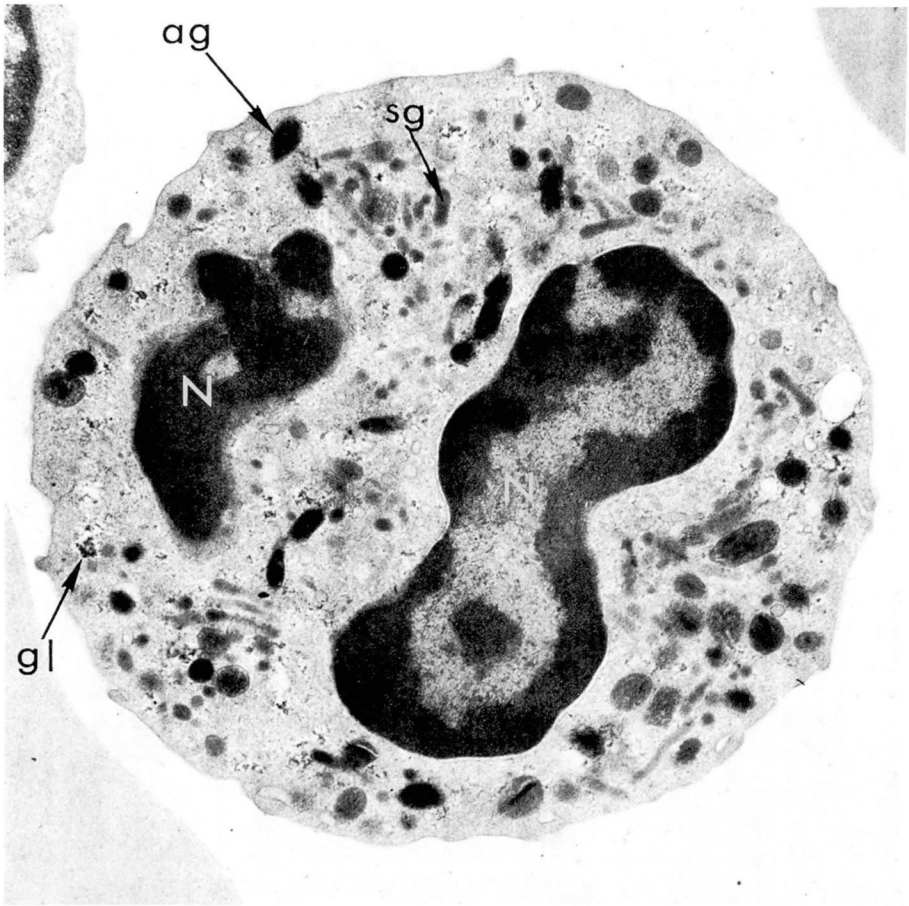

Fig. 1. Electron micrograph of normal human neutrophil. Two lobes of the nucleus (N) are visible; the thin cytoplasmic strands connecting them cannot be seen in this plane of section. The cytoplasm contains multiple granules of various sizes and shapes. The large, dense structures are primary, or azurophilic granules (ag), whereas most of the smaller ones are secondary, or specific granules (sg). Glycogen particles (gl) are scattered throughout the cytoplasm (×12,000).

only during the promyelocyte stage of neutrophil development,[2] and are present in relatively small numbers in the mature neutrophil. These granules, which qualify as lysosomes by virtue of their content of acid hydrolytic enzymes, also contain myeloperoxidase, a variety of basic proteins with microbicidal and inflammatory activities, and lysozyme (muramidase), an enzyme which lyses the cell walls of certain gram-negative bacteria.[2-4] The *secondary* or *specific* granules form only during the myelocyte stage of neutrophil development.[2] These granules are lacking in acid hydrolases, but contain an alkaline phosphatase, some lysozyme, and lactoferrin, an iron-binding protein with microbicidal activity.[2, 5]

Another feature seen in *Figure 1* is the familiar multilobed nucleus. The functional advantage conferred by this unique nuclear configuration is not

certain, but may be related to the extreme plasticity of the mature neutrophil. The cell indeed can force itself through surprisingly narrow openings, such as the junctions between venular endothelial cells.[6]

The mature neutrophil is a highly motile cell, its motility being expressed both as random, ameboid movement and as directed migration in response to chemical stimuli (chemotaxis). Normal motility is required for certain essential functions which are discussed below.

Normal expression of neutrophil function in response to infection obviously requires the delivery of adequate numbers of neutrophils to the site of microbial invasion. This involves, sequentially, production of neutrophils in the bone marrow, migration of mature neutrophils from the marrow to the intravascular space, emigration of neutrophils from vessels into tissue and, finally, migration of the cells within the tissues to the site of their ultimate function. Disorders of any of these steps can result in increased susceptibility to infection, particularly by bacteria and certain fungi such as Candida and Aspergillus.

Neutropenia is defined as a deficiency of functional neutrophils in the circulating blood. Failure of the bone marrow to produce adequate numbers of mature neutrophils is the most common reason for neutropenia. The many causes of inadequate marrow neutrophil production[7] are outside the scope of this review. Neutropenia also can result from failure of mature neutrophils to leave the bone marrow, from increased peripheral destruction of neutrophils, and from greatly increased demand for neutrophils in massive infections.

That severe neutropenia is associated with increased risk of infection has long been recognized by clinicians. More recent data indicate that only when the absolute neutrophil count falls below 1500 per cubic millimeter does the risk of infection increase significantly.[8] Risk of infection increases proportionally with further decrease in the neutrophil count and with duration of neutropenia. Neutropenias of this magnitude are associated with reduction of neutrophil migration into tissue.[9] The risk of infection at a given level of neutropenia appears to be lessened if there is a compensatory monocytosis.[9]

Neutrophil motility

The mature neutrophil is a highly motile cell, its motility being expressed both as random ameboid movement and as directed migration in response to chemical stimuli (chemotaxis). Although the cellular mechanisms underlying neutrophil motility are incompletely understood, recently there have been several interesting observations relating to these mechanisms. It has been known for a long time that actively migrating neutrophils are surrounded by a clear rim of cytoplasm which contains no granules. This clear zone of cytoplasm is greatest in the direction that the cell is moving. When examined by electron microscopy, this clear cytoplasm has been found to contain glycogen particles and fine filaments approximately 60 Å in diameter.[10] Similar filaments have been observed in other cell types and appear to be composed of actin polymers. Myosin, structurally similar to that of muscle and capable of hydrolysing ATP has been isolated from neutrophils.[11] These findings suggest the pos-

sibility that in neutrophils the interaction of actin, myosin, and ATP may result in a contractile mechanism similar to that of skeletal muscle.[10] Cytoplasmic microtubules are probably also important in the complex process of cellular motility. This subject is well discussed in the review by Stossel.[10]

Abnormal neutrophil motility may lead to subnormal egress of mature neutrophils from the bone marrow, resulting in neutropenia. Neutrophils which do manage to enter the vascular compartment subsequently may demonstrate defective ability to emigrate into tissues and to respond to chemotactic substances. Both congenital and acquired examples of defective neutrophil motility have been observed. Recognized congenital disorders of neutrophil motility appear to be rare. In the "Lazy Leukocyte Syndrome," [12] there is neutropenia, apparently because of inability of mature neutrophils to leave the bone marrow. In addition, circulating neutrophils are subnormal in migrating to inflammatory sites. In

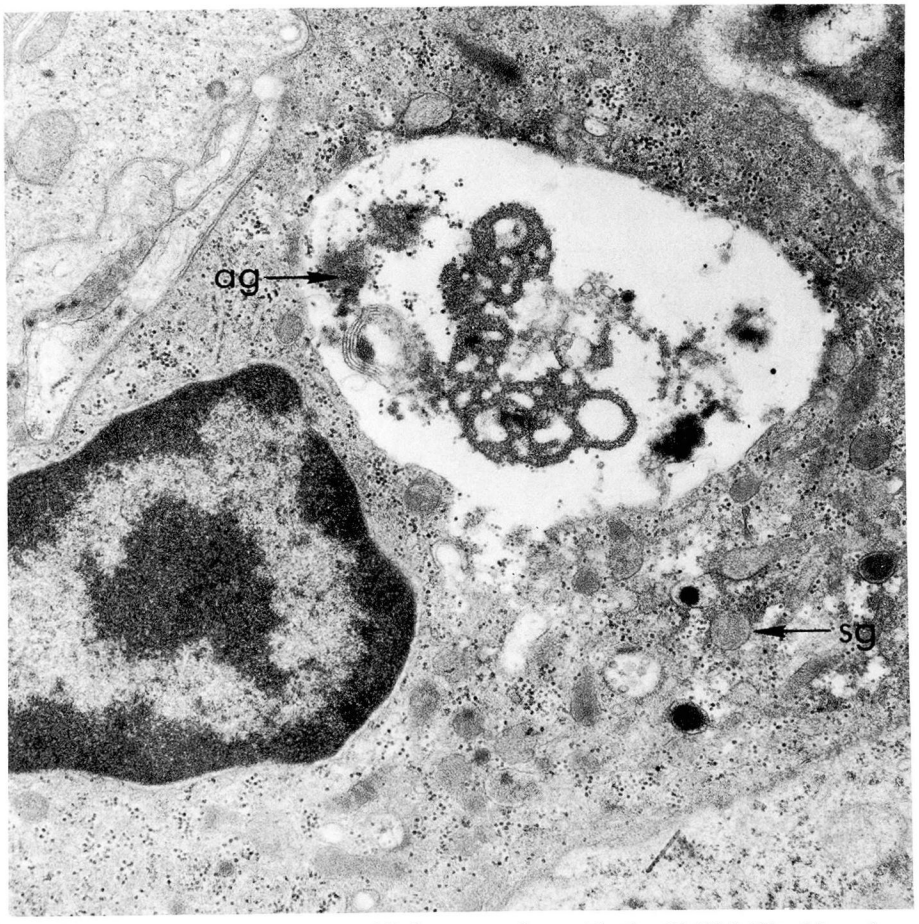

Fig. 2. Electron micrograph of neutrophil from a patient with the Chédiak-Higashi syndrome. A typical giant azurophilic granule (ag) contains a variety of membranous and other material. Specific granules (sg) are normal in size and structure (×23,000).

the Chédiak-Higashi syndrome, in which the neutrophils have abnormally large primary granules (*Fig. 2*), one of the functional abnormalities is subnormal motility, resulting in decreased accumulation of neutrophils at sites of inflammation.[13] The cellular basis for these congenital abnormalities of motility is unclear. Acquired disorders of neutrophil motility may be somewhat more common. For example, antigen-antibody complexes from patients with rheumatoid arthritis inhibit neutrophil motility.[14]

Chemotaxis

Chemotaxis is defined as the directed migration of a phagocyte in response to a concentration gradient of a substance, known as a *chemotactic factor*. That the phenomenon of chemotaxis exists has been suspected for many years on the basis of observations of the accumulation of phagocytes around microorganisms and other foreign materials in tissues. More recently, quantification has become possible on the basis of in vitro assays, the prototype of which is the chamber designed by Boyden.[15] In this assay and its subsequent modifications, a chamber is used which consists of two compartments separated by a Millipore filter. Phagocytes are placed in one compartment and a chemotactic factor is introduced into the other. In response to the concentration gradient of the chemotactic factor so established, phagocytes migrate through the interstices of the filter toward the opposite chamber. The number of phagocytes migrating through the filter can be evaluated conveniently by microscopy.

When evaluated in assays of the Boyden type, a number of substances have been found to have chemotactic factor activity (*Table 1*). The complement-derived chemotactic factors may be of particular importance, since they are generated both when complement is activated by antigen-antibody complexes[16] and during complement activation by nonimmunologic means, mediated by the properdin or alternate pathway.[17] Properdin pathway activation can be initiated by endotoxins and other bacterial products.[18] In addition, C3a and C5a can be released directly by proteases released by bacteria and damaged host cells.[19] Both congenital and acquired defects of the complement system can have as one of their manifestations deficiency in complement-related chemotactic factors. Deficiency of C2 is associated with decreased serum chemotactic factor activity.[20] Deficiency of C3 because of congenital hypercatabolism, or other causes of underproduction or overutilization of C3 is associated with subnormal development of chemotactic factor activity in plasma.[21, 22] A familial disorder in which C5 is dysfunctional, leading to diminished generation of chemotactic factor activity, also has been described.[23]

Table 1. Chemotactic activity of biological substances

1. Substances with in vitro chemotactic activity
Complement-related factors C3a, C5a, $\overline{C567}$
Kallikrein
Bacterial products
2. Substances without in vitro chemotactic activity
Bradykinin
Histamine
5-Hydroxytryptamine

Neutrophils with abnormal motility, as described above, respond sub-

normally to chemotactic stimuli. Deficiency in chemotaxis has been reported in children with eczema, recurrent skin infections, and abnormally high IgE levels.[24] Histamine inhibits the ability of neutrophils to respond to chemotactic factors in vitro, and it was postulated that excessive release of histamine or other mediator substances might be responsible for the chemotactic abnormality in these patients. Hypophosphatemia, occurring as a complication of parenteral hyperalimentation, is associated with neutrophils which respond poorly to chemotactic stimuli.[25] Hypophosphatemia is associated with decreased neutrophil ATP, a deficiency which may inhibit the cellular contractile mechanisms.

Phagocytosis—recognition and ingestion

Once the neutrophil has migrated to the site of an invading microorganism, it is called upon to carry out its ultimate function, phagocytosis and killing of the microbial intruder. In the first step of this process, the neutrophil must recognize the invader as foreign. The way in which this occurs is uncertain, and presumably involves subtle physicochemical properties of the microbial surface. Many microorganisms, particularly those which are encapsulated, are quite resistant to phagocytosis, a factor which contributes to their virulence. Phagocytosis of such organisms is greatly facilitated if their surfaces are coated with certain host proteins, or *opsonins*. Specific antibody of the IgG_1 or IgG_3 class has opsonizing capacity.[26] Such opsonizing capacity is weak unless the individual has been hyperimmunized.[27]

The third component of complement, when activated, gives rise to a fragment with potent opsonizing capacity. Activation of C3 can be initiated either by specific antibody by means of the classic complement pathway, or by nonimmunologic mechanisms through the properdin pathway.[28-30] The latter mechanism is of considerable importance because of the ability of endotoxins and other microbial cell wall components to activate the properdin pathway.

Following recognition and adherence of the microorganism to the plasma membrane of the neutrophil, ingestion of the organism may take place. Pseudopods extend from the neutrophil to surround the organism. The pseudopods eventually fuse at the distal side of the microbe, encasing it in a phagocytic vacuole, the lining of which is composed of inverted neutrophil plasma membrane. Ingestion is an energy-requiring process; in neutrophils, ATP is generated by glycolysis and glycogenolysis.[31] There is evidence suggesting that ingestion involves an actin-mycin type of interaction and that microtubules are involved, mechanisms similar to those that may be involved in neutrophil migration.[10]

Disorders of recognition mainly involve deficiencies in plasma opsonic activity. Any derangement in the complement system resulting in diminished ability to activate C3 will have this effect. Disorders of the properdin pathway are much more likely to give rise to severe recurrent infections than are defects in the early components of the classic complement pathway. Defects in the properdin system have been identified in some newborn infants[32] and in patients with sickle cell anemia,[33] resulting in decreased opsonic capacity and increased susceptibility to infection in these patients.

Susceptibility to infection with encapsulated, virulent bacteria is particularly increased. Immunoglobulin deficiencies also result in diminished plasma opsonic activity and increased susceptibility to bacterial infections.

Defective ingestion most commonly results from a disorder of recognition caused by subnormal plasma opsonic capacity. Contact with immune complexes may inhibit ingestion[34] as well as decrease neutrophil motility. Hyperosmolarity inhibits ingestion,[35] and the neutrophils of poorly controlled diabetics with high glucose levels exhibit subnormal ingestion.[36] Some patients with severe bacterial infections have neutrophils with depressed capacity for ingestion.[37]

Degranulation

During formation of the phagocytic vacuole, neutrophil granules migrate to, and fuse with the limiting membrane of the phagocytic vacuole.[38, 39] This results in the emptying of the enzymes and other contents of the granules into the phagocytic vacuole.[40, 41] Both primary and secondary granules participate in this process, with fusion of secondary granules occurring more rapidly.[42] Granule contents also are released to the outside of the cell during degranulation.[43, 44] External release probably results from leakage from incompletely fused phagocytic vacuoles, and from attempts to ingest particles too large to permit phagocytosis. Both the actin microfilaments and microtubules appear to be involved in degranulation. The microfilaments may form a barrier preventing fusion of granules with the plasma membrane; cytochalasin B, an agent which disrupts microfilaments, enhances extracellular degranulation.[45] Agents such as colchicine, which disrupts microtubules, also inhibit degranulation.[43]

Disorders of degranulation include deficiences of various granule constituents. Absence of secondary granules results in diminished bactericidal capacity of the involved neutrophils,[46] although the reason for this is not understood. Myeloperoxidase deficiency will be discussed in a subsequent section. In the Chédiak-Higashi syndrome, the giant primary granules have no enzyme deficiency, but fusion with the phagocytic vacuole is retarded, leading to functional enzyme deficiency and impaired bactericidal capacity.[13] Corticosteroids may impede degranulation, perhaps because of their stabilizing effect on lysosomal membranes.[47] There is no concensus, however, that corticosteroids stabilize lysosomal membranes in human neutrophils.[48]

Hydrogen peroxide formation and microbial killing

Phagocytosis is accompanied by a complex series of metabolic events, an important feature of which is the reduction of oxygen to hydrogen peroxide. Other observations include increased oxygen consumption, increased glucose utilization, and increased glucose metabolism via the hexose monophosphate pathway.[31] These metabolic events are not required for phagocytosis and degranulation per se, the energy for which is derived from glycolysis. The onset of these metabolic changes appears to occur at the time of recognition, presumably on the basis of some alteration in the plasma membrane of the neutrophil.[49] Actual phagocytosis is not required, similar metabolic altera-

tions occurring upon contact of the neutrophil membrane with endotoxin or other surface-active agents.[50]

The exact nature of the process which results in hydrogen peroxide production is still unclear. The process is not inhibited by cyanide,[31] indicating that the critical enzyme is not a heme protein. Presumably, the enzyme involved is a flavoprotein that oxidizes reduced pyridine nucleotides. Evidence for this presumption includes the observation that neutrophils totally deficient in glucose-6-phosphate dehydrogenase, which reduces NADP to NADPH, are unable to generate hydrogen peroxide.[51] Karnovsky[31] originally proposed that NADH was the hydrogen donor for the critical oxidase. Since then it has been suggested that because of transhydrogenase reactions, both NADH and NADPH are subnormal in glucose-6-phosphate dehydrogenase deficiency.[52] The concept that hydrogen peroxide is generated by an NADH oxidase has not been universally accepted, however, and other investigators believe that the critical enzyme is an NADPH oxidase.[53] The resolution of this dispute must await purification of the enzyme. Whether NADH or NADPH is directly involved, the oxidation of the reduced pyridine nucleotide is coupled to the reduction of molecular oxygen to superoxide ion.[54] Whether superoxide (O_2^-), a highly reactive substance, itself participates in a major way in microbicidal processes is unclear. Superoxide, however, can be further reduced, either spontaneously or catalyzed by the enzyme superoxide dismutase, yielding hydrogen peroxide. Hydrogen peroxide has microbicidal activity alone, and this activity is greatly augmented in the presence of myeloperoxidase and certain co-factors, such as halide ions.[55] The exact mechanism of hydrogen peroxide-myeloperoxidase microbicidal activity in the intact cell is uncertain, but it probably involves oxidation of the cofactor to form reactive intermediates, which then react with and damage the microorganism. For example, it has been shown that when the hydrogen peroxide-myeloperoxidase mechanism is activated, iodide anion becomes covalently linked to bacterial protein.[55] Evidence suggesting that hydrogen peroxide, rather than superoxide, is the actual bactericidal compound has come from a recent study of staphylococcal virulence.[56] In these experiments, the virulence of a given staphylococcal strain correlated with its content of catalase, which catalyzes the breakdown by hydrogen peroxide, but was unrelated to its content of superoxide dismutase, which catalyzes the reduction of superoxide to hydrogen peroxide. Further, the administration of exogenous catalase to mice at the time of infection caused avirulent strains of staphylococci to behave as virulent ones.

There are a number of disorders in which the normal augmentation of hydrogen peroxide production during phagocytosis does not occur (*Table 2*). The prototype of these is chronic granulomatous disease.[57] This disorder which affects young boys, is inherited as an X-linked recessive trait. Affected patients have frequent, recurrent bacterial and fungal infections and usually die of sepsis before reaching adulthood. The infecting organisms usually are staphylococci, aerobic gram-negative bacilli, and certain fungi such as Candida or Aspergillus, all of which possess catalase. Infections with cata-

lase-negative bacteria, such as streptococci and pneumococci, appear to be no more frequent than in normal individuals. Neutrophils and mononuclear phagocytes of such patients are morphologically normal, and in most cases carry on phagocytosis at a normal rate. Metabolically, however, these cells are abnormal in that the phagocytosis-associated increase in oxygen consumption, hexose-monophosphate pathway metabolism, and production of superoxide and hydrogen peroxide do not occur.[58, 59] The specific enzyme deficiency responsible for the metabolic abnormalities of X-linked chronic granulomatous disease remains uncertain. Neutrophils from such patients are defective in killing catalase-positive microorganisms such as staphylococci, many enteric gram-negative bacilli, and Candida.[60] In contrast, catalase negative bacteria, such as pneumococci and streptococci, are killed at a normal rate. This selective killing defect corresponds well to the clinical observation that patients with chronic granulomatous disease are highly susceptible to infection only by catalase positive microorganisms. The explanation of this selective defect relates to the fact that bacteria generate hydrogen peroxide as a product of their own metabolism. In bacteria which possess catalase, this hydrogen peroxide, once formed, is rapidly broken down, so that little or none of it escapes to the outside of the bacterial cell. Thus, for normal microbicidal activity against catalase positive organisms, hydrogen peroxide must be supplied by the phagocyte. Catalase negative bacteria lack the means to destroy the hydrogen peroxide they generate, and substantial amounts of it escape to the outside. Thus, a phagocytic vacuole surrounding a catalase negative organism contains significant amounts of hydrogen peroxide even if little or none is contributed by the phagocyte, and bacterial killing can proceed.

Table 2. Disorders of hydrogen peroxide-dependent microbicidal mechanisms

1. Disorders of hydrogen peroxide production
Classic (X-linked) chronic granulomatous disease
Glutathione peroxidase deficiency
Severe deficiency of leukocyte glucose-6-phosphate dehydrogenase
Myeloid dysplasias
Corticosteroids
2. Myeloperoxidase deficiency
Congenital or acquired

Defects other than that of X-linked chronic granulomatous disease can result in failure of phagocytes to produce hydrogen peroxide, leading to a similar clinical syndrome (*Table 2*). Several girls with "chronic granulomatous disease" have been shown to be deficient in leukocyte glutathione peroxidase activity.[61] A few individuals with almost total absence of leukocyte glucose-6-phosphate dehydrogenase have been shown to have neutrophils with defective hydrogen peroxide production and bacterial killing.[51] It should be emphasized that almost all individuals with red cell glucose-6-phosphate dehydrogenase deficiency have enough of this enzyme in their leukocytes to support normal hydrogen peroxide production and microbial killing. Disorders of leukocyte hydrogen peroxide production also can be encountered as acquired disorders. For example, a patient has been reported in whom the leukocyte abnormality appeared to

arise as the result of dysplastic myelopoiesis.[62] Many patients with "preleukemic" myeloid dysplasias are unusually susceptible to infection, and it is possible that more patients with disorders of leukocyte hydrogen peroxide production will be found when this group of patients is appropriately studied. High dose corticosteroids also can suppress leukocyte hydrogen peroxide production,[63] another of the multiple ways in which these agents interfere with leukocyte function and the inflammatory response.

In addition to the disorders of leukocyte hydrogen peroxide production, patients with congenital[64] and acquired[65] neutrophil myeloperoxidase deficiency have been identified. Although some of these individuals have had recurrent infections, particularly with fungi, others have been asymptomatic. The reason for the mildness of the clinical syndrome in myeloperoxidase deficiency is not entirely clear, but it is possible that in the absence of this enzyme, unusually high levels of hydrogen peroxide, which are microbicidal by themselves, accumulate in the phagocytic vacuole.[66]

Clinical and laboratory evaluation of suspected disorders of neutrophil function

Persons with a history of repeated, severe infections with bacteria or fungi or both, or with less serious infection of such frequency as to be disabling, should be considered for evaluation for possible neutrophil dysfunction. To some extent, the nature of the infecting organisms is of value in predicting the most likely nature of the disorder. If infection with pneumococci or streptococci comprises a significant part of the problem, immunoglobulin deficiency or a complement disorder should be suspected. If most of the infections involve staphylococci, gram-negative bacilli, Candida or Aspergillus, a primary leukocyte dysfunction, particularly one involving subnormal production of hydrogen peroxide, is a possibility. Visceral (not purely mucocutaneous) infection with Candida or Aspergillus in an otherwise well person suggests myeloperoxidase deficiency. These distinctions are, of course, not absolute, but they may serve as a guide to priorities in the evaluation of patients with recurrent infection.

All such patients should have a complete blood count, with examination of the peripheral blood smear for differential count and leukocyte morphology. Repeated blood counts often are necessary to detect cyclic neutropenias.[7] If the above examinations reveal neutropenia or other significant abnormality, consultation with a hematologist should be requested. Immunoelectrophoresis and quantitative immunoglobulin levels should be obtained. The level of serum total hemolytic complement should be determined, but a normal result does not totally exclude a defect in the complement system.[23]

If the above examinations are unrevealing, evaluation of leukocyte function should be considered. Unfortunately, some of the studies needed for complete evaluation of leukocyte function are rather complex, and only a few are presently within the scope of the usual clinical laboratory. Leukocyte myeloperoxidase activity can be assessed with a simple and rapid cytochemical staining procedure.[67] Nitroblue tetrazolium (NBT) reduction provides a relatively simple means of

assessing phagocytosis-associated metabolic stimulation and, by inference, hydrogen peroxide production.[58] NBT is a soluble yellow redox dye which is reduced to an insoluble blue-black formazan in the phagocytic vacuoles of normal neutrophils. Although the exact biochemical events leading to NBT reduction are unclear, NBT reduction correlates well with the other metabolic events that normally accompany phagocytosis. A qualitative NBT slide test[68] is relatively simple to perform and will detect chronic granulomatous disease and other disorders in which hydrogen peroxide production is severely impaired. Patients whose neutrophils fail to reduce NBT during phagocytosis should be referred for further studies as described below.

The above simple screening procedures, unfortunately, will detect only a minority of cases of leukocyte dysfunction. At present, further, more detailed evaluation of leukocyte function is practical only in specialized laboratories conducting research in this area. Referral to such a center should be considered if recurrent infections are of such frequency and severity that they constitute a major clinical problem. Such patients often appear chronically ill and, in children, subnormal growth and development frequently are present. It has been our experience that investigation of patients with relatively minor problems with presently available techniques uncommonly yields useful information. When there is doubt whether detailed evaluation of leukocyte function is likely to be productive, discussion of the problem with a physician experienced in this area often is helpful.

Management of patients with neutrophil dysfunction

Therapy for most of the disorders of leukocyte function still is much less than satisfactory, and this constitutes a major challenge to investigators working in this area. Antimicrobial therapy should be begun promptly, and agents which are bactericidal rather than bacteriostatic should be chosen if possible. In patients whose infections are mostly streptococcal and pneumococcal, chronic low dose oral penicillin therapy is worthy of trial.

If leukocyte dysfunction is caused by an exogenous agent, such as corticosteroids or ethanol, avoidance of the agent, if possible, will result in improvement. Immunoglobulin deficiencies are benefitted by periodic administration of gamma globulin. When complement disorders are complicated by life-threatening sepsis, infusion of fresh plasma may be temporarily helpful.

In the severe, cellular disorders of leukocyte function, leukocyte transfusion might be helpful during episodes of major sepsis. This procedure is best performed, however, in institutions equipped to perform histocompatibility typing and repeated leukophoresis. Bone marrow transplantation theoretically might be of value in some of these patients, but it has not yet been successfully applied to patients with leukocyte dysfunction syndromes. One would be reluctant to add the burden of immunosuppression to host defenses already severely compromised.

Conclusions

Neutrophil function may be impaired by intrinsic cellular abnormalities, by drugs and other exogenous

agents, by immune complexes, and by deficiencies in plasma factors promoting phagocytosis, such as complement components and immunoglobulins. Dysfunction may occur at the stages of bone marrow production, mobilization, migration and chemotaxis, recognition, ingestion, degranulation, or intracellular killing. In many patients, however, the abnormalities are complex, and more than one stage is found to be abnormal. Although therapy of many of these disorders as yet is inadequate, accurate definition of the defect may facilitate management of the patient.

In this paper, I have attempted to present a reasonably concise survey of the complex and rapidly expanding information about neutrophil dysfunction. For those readers with further interest in the subject, excellent and more detailed reviews are available.[10, 58, 69]

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