Analytic Review: Disorders of Phagocyte Function

By Steven D. Douglas

Recent clinical and laboratory investigations have led to the description of a group of syndromes related to impaired bactericidal functions of neutrophils and monocytes. Although the pathophysiology of this group of disorders is unknown, detailed immunologic, biochemical and morphologic studies have elucidated some clues to the basic defects leading to impairment of phagocyte function. The complex biology of the polymorphonuclear neutrophil and the mononuclear phagocyte (blood monocyte and tissue macrophage) will be considered in relation to phagocytosis and bactericidal capacity. The role of extracellular factors in host defense including properdin, interferon, complement, plasma factors and kinins will not be considered in detail; these subjects have been extensively reviewed by others and will be mentioned only in relation to possible pathophysiologic significance in phagocyte dysfunction. The cellular mechanisms of host resistance to viral infection, which are for the most part unknown in man, are not discussed in this review.

Although it may be premature to make such a comparison, it seems apparent that the diseases of the phagocyte, in some respects similar to the erythrocyte, will involve membrane abnormalities, genetically determined and acquired enzyme deficiencies, alterations in cytoplasmic proteins (specifically proteins with antibacterial activity), defects secondary to immunologic factors involved in the opsonization of organisms, and abnormalities related to various humoral mediators. Thus far, three types of clinical syndromes have been described: (1) A defect involving neutrophil chemotaxis; (2) defects in the ingestion phase of phagocytosis, involving plasma opsonizing ability; and (3) defective intracellular killing of bacteria by both neutrophils and monocytes. The third type has been shown to have several distinct genetic and clinical forms.

Physiological Aspects

Chemotaxis

The initial events in the inflammatory response include a series of sequential steps which involve the migration of phagocytic cells into an area which contains some type of inflammatory stimulus. There are several humoral factors...
including the local release of histamine, bradykinin and other components of
the plasminogen–kinin system which contribute to vascular dilatation and
concentration and margination and emigration of leukocytes. Using the micropore
diffusion chamber devised by Boyden,\textsuperscript{15} four different factors which are chemotactic for polymorphonuclear neutrophils have been elucidated.\textsuperscript{16,17} In this
system chemotaxis is defined as “the specific unidirectional migration of PMN’s
in the direction of a gradient of increasing concentration of attractant.”\textsuperscript{17}
These factors include: (1) “Activated trimolecular complex,” namely, the fifth
(C5), sixth (C6), and seventh (C7) components of complement\textsuperscript{18}; (2)
plasmin-split C3 fragment, a heat labile, dialyzable substance of molecular
weight of about 6000\textsuperscript{19}; (3) chemotactically active fragments which are found
following cleavage of C3 by tissue protease\textsuperscript{20}; and (4) bacterial chemotactic
factors which have been prepared from filtrates of \textit{Diplococcus pneumoniae},
\textit{Staphylococcus aureus}, \textit{Staphylococcus albus}, \textit{Streptococcus faecalis}, alpha and
beta hemolytic streptococcus, \textit{Escherichia coli}, \textit{Proteus mirabilis}, \textit{Proteus
rettgeri} and \textit{Pseudomonas aeruginosa}.\textsuperscript{21}

Mononuclear phagocytes respond chemotactically in vitro to plasmin-treated
fresh serum and to soluble bacterial factors. However, in contrast to neutro-
phils, mononuclear cells also respond to two additional factors: a factor in
serum treated with immune complexes (this factor is not C5, C6 or C7) and
to lysates of neutrophils, which may be related to the cationic peptides of
lysosomal granules.\textsuperscript{23} These in vitro observations are evidence for mechanisms
whereby cells accumulate in the inflammatory response. The demonstration of
the factors required for mononuclear cell chemotaxis is consistent with the
clinical observation that prior appearance of neutrophils is requisite for the
accumulation of mononuclear cells in Rebuck skin-windows. A decrease in
the accumulation of mononuclear cells has been observed in Rebuck windows
in patients with cyclic neutropenia.\textsuperscript{24}

\textbf{Opsonization}

Following chemotaxis and preceding the engulfment of bacteria, the phe-
nomenon of opsonization occurs. Opsonins generally operate through their
interaction with the particles and not the phagocyte. The factors involved in
particle recognition are complex, and in vitro models may not be entirely
representative of the in vivo phenomena. Opsonins include IgG and IgM
antibodies, complement components, noncomplement thermolabile factors and
possibly basic polypeptides, including lysozyme and basic polyamino
acids.\textsuperscript{4,5,25,26} There are different requisites for opsonization of different types
of particles, and for different bacterial species.\textsuperscript{26} Despite these differences,
present available evidence suggests that the initial events of attachment and
engulfment during phagocytosis are dependent upon the recognition of either
antibody alone (IgG) or antibody (IgM)-complement complexes (C-1, 4, 2,
3).\textsuperscript{26} Our studies\textsuperscript{27,28} and those of others,\textsuperscript{29,30} using erythrocytes coated with
an IgG antibody, anti-Rho, have demonstrated that mononuclear phagocytes
Fig. 1.—Human peripheral blood monocytes incubated with anti-Rho coated red cells. Rosette formation and ingested red cells seen. Assay system demonstrates IgG receptor on monocytes (× 6000).

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have receptor sites for IgG (Fig. 1). This system preferentially interacts with IgG1 and IgG3, and is inhibited by small amounts of free IgG in the fluid phase.27 In addition, the monocyte has been shown to have a receptor for C3.31-33 In contrast to the monocyte, the neutrophil requires both complement (C1, 4, 2, 3) and IgG for rosette formation and erythrophagocytosis.28 The specific requisites for opsonization of different organisms involve the interaction of a multiplicity of factors and warrant further analysis.34 Studies by Quie, et al.35 of the opsonic properties of immune IgG from patients with chronic septicemic conditions, principally subacute bacterial endocarditis, showed that opsonization, at least with macrophages, is related to the Fc region of IgG and is lost with pepsin digestion. They35 also showed that colostral IgA, which had agglutinating antibacterial antibodies and lacked complement fixing activity, had no opsonic activity. The possible role of opsonins in subsequent intracellular events during phagocytosis is unknown.

Phagocytic Events

Following appropriate opsonization, a sequence of events ensues which involves surface attachment, engulfment, and formation of a phagocytic vacuole, followed by degranulation (the lysis of leukocyte granules which release their contents into the phagocytic vacuole). The morphodynamics of
the process were first studied by Hirsch using cinemicrophotography of neutrophils.\(^{36}\) This complex sequence of events involves several morphologic and biochemical phenomena. Although there appear to be basic similarities, there are several differences in the events for neutrophils and mononuclear phagocytes, the former having been investigated much more intensively. The initial trigger mechanism following entry of a phagocytosed particle or organism is the interiorization of the phagocyte cell membrane.

**Biochemical Events**

The most extensive studies of the metabolic pathways in leukocytes have been done using guinea pig cells\(^{37}\); recent studies using rat\(^{38}\) and human cells\(^{39}\) have demonstrated several similarities, as well as differences, between cells of these species. Ingestion of particles can be dissociated from the subsequent events of degranulation by agents such as colchicine, which inhibit only the latter events.\(^{40}\) Available evidence indicates that the primary energy supply for the neutrophil is through the glycolytic pathway and increased glycolysis has been shown to occur during phagocytosis.\(^{41}\) The citric acid cycle is less active, an observation which correlates with the presence of few mitochondria.\(^{37}\) Although phagocytosis occurs efficiently under either aerobic or anaerobic conditions, significant increases in oxygen consumption, glucose utilization and lactate production occur. These events are linked to stimulation of the hexose monophosphate shunt pathway (HMP). The limiting factor in HMP shunt activity is the existing glucose 6-phosphate and the amount of glucose 6-phosphate dehydrogenase which regulates entry into the pathway. HMP stimulation is insensitive to cyanide.\(^{37,41}\) In addition, the availability of oxidized TPN\(^+\) (NADPH) is critical. Whether regeneration of TPN is dependent on DPNH (NADH) oxidase\(^{42}\) or on myeloperoxidase\(^{43}\) is still a controversial issue. Concomitant with phagocytosis is the production of hydrogen peroxide (2-to-4-fold increase) and increased formate oxidation.\(^{44}\)

In parallel with the changes in carbohydrate metabolism is the stimulation of lipid biosynthesis from acetate, and conversion of lysolecinith into lecithin and lyosphatidylcholine into phosphatidylethanolamine.\(^{45}\) This evidence indicates about a five per cent net increase in membrane synthesis by neutrophils during phagocytosis. Several additional enzymatic processes accompany these biochemical events; however, these will be considered in relation to the granules and their composition.

In general, macrophages and monocytes undergo a sequence of metabolic events comparable to neutrophils; however, these cells have been studied less extensively. There is some evidence that the citric acid cycle is more efficient in these cells and, although stimulated, HMP shunt activity is less prominent.\(^{46}\) Moreover, a greater phagocytic potential of cells of the reticuloendothelial system has been shown when these cells have had prior exposure to bacteria, endotoxin or inert materials.\(^{37}\) Cohn has recently reviewed the structure and function of mononuclear phagocytes.\(^{46}\)
Morphologic and Cytochemical Studies

Neutrophils

Investigations of neutrophils have, for the most part, been concerned with the rabbit heterophil; studies of human granulocytes are more limited. Extensive studies of the morphogenesis of the granulocyte have demonstrated the formation of two distinct granule types which originate from different parts of the Golgi complex.\textsuperscript{48-50} The neutrophil granules in the mature cell differ in size, in electron density,\textsuperscript{48,50-52} in sedimentation properties by ultracentrifugation\textsuperscript{53} and in enzyme content.\textsuperscript{53-57} The granule content of the mature neutrophil is made up of about 10\%-20\% per cent primary or azurophil granules which have been shown to contain acid hydrolases, DNAase, RNAase, beta-glucuronidase, myeloperoxidase and lysozyme,\textsuperscript{50-52} and 80\%-90\% per cent secondary or specific granules which contain nonspecific alkaline phosphatase,\textsuperscript{55,56} a high concentration of cation (probably sodium)\textsuperscript{50} and some lysozyme. Recent zonal centrifugation studies have demonstrated a third granule type which contains several acid hydrolases and increased amounts of beta-glycerophosphatase and N-acetyl-6-glucosaminidase;\textsuperscript{53} this smaller, morphologically heterogeneous granule may correspond to the tertiary granule which Spicer and co-workers\textsuperscript{49,50,54} described by electron microscopy. Primary neutrophil granules have been shown to contain sulfated acid mucosubstances and strongly basic proteins.\textsuperscript{58} These cationic proteins constitute about 50\% per cent of the soluble lysosomal proteins, have specific antibacterial activities, and appear to be associated with a unique granule type.\textsuperscript{60,61} These cationic components were not found in either normal or stimulated rabbit macrophages.\textsuperscript{46} Other features of the neutrophil include large amounts of glycogen which is depleted during phagocytosis and a small number of mitochondria.\textsuperscript{52}

Monocytes

The morphologic features of the peripheral blood monocyte are characterized by little glycogen, moderate amounts of rough-surfaced endoplasmic reticulum, some slim mitochondria and a well-developed Golgi complex (Fig. 2).\textsuperscript{46,51,62} Monocyte granules, although less thoroughly characterized than neutrophil granules, appear to be primarily of one type. They contain acid hydrolases and lysozyme, and no conclusive role of either hydrogen peroxide or antibacterial proteins have been demonstrated in mononuclear phagocytes.\textsuperscript{46} The high content of lysozyme in these granules has been shown to be the basis for the elevated serum and urinary lysozyme which occurs in monocytic leukemia.\textsuperscript{63}

Morphodynamics

Following the engulfment of the particles and formation of phagocytic vacuoles, fusion of the granules with the vacuole occurs. Electron microscopic examination of these cells suggests that all three neutrophil granule types fuse with the phagocytic vacuole.\textsuperscript{50,52,64,65} Following fusion is degranulation, the release of granule content into the phagocytic vacuoles. This has been demonstrated cytochemically for acid and alkaline phosphatase\textsuperscript{65} and per-
oxidase. The enzymes thus released can act upon the phagocyted organism or particle within the phagocytic vacuole. There are specific requisites for cellular killing of different types of organisms. In general, the morphologic events of vacuolization and degranulation appear to be quite similar for PMN and mononuclear phagocytes. However, the monocyte may have the capacity for continued synthesis of new granules in its active Golgi complex, the capacity to rid itself of bacterial products by exocytosis, and perhaps the ability to survive a phagocytic act, in contrast to the neutrophil which usually dies. Further detailed electron-microscopic and cytochemical studies of the morphologic events and participation of various granule types during phagocytosis by normal and abnormal human phagocytes are necessary.

**Clinical Aspects**

Intensive studies of patients with normal or elevated immunoglobulins and a propensity toward recurrent bacterial and mycotic infections have demonstrated a diversity of clinical syndromes related to impairment of phagocyte function involving chemotaxis, opsonization and intracellular bactericidal capacity.
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Chemotactic Defect

Ward and Schlegel have recently described a child who had recurrent cutaneous and respiratory infections primarily due to klebsiella and Escherichia coli. They demonstrated a defect in leukotactic responsiveness of the patient's cells in vitro and in a skin-window in vivo. The study suggested that the defect was at least in part related to an inhibitor of neutrophil chemotaxis present in the serum. The parents of the child had no detectable abnormality; however, a clinically unaffected sibling had an intermediate defect. Two children with chronic granulomatous disease (CGD) were studied and found to have normal leukotactic responsiveness in vitro. In addition, neutrophils from the child were found to have impaired bactericidal capacity for certain gram negative bacteria. The interrelationship between the leukotactic defect and intracellular defect is unknown.

Opsonization Defects

Miller et al. reported an infant whose neutrophils showed a defect in the ingestion of yeast particles, rice-starch, and staphylococci. Serum B1C/B3A levels and whole complement were normal. Phagocytosis became normal when the patient's cells were incubated with pooled normal plasma, and conversely the patient's plasma inhibited phagocytosis by normal cells. Impaired phagocytosis was also demonstrated for cells from the patient's mother and maternal grandparents. The factor involved in this familial defect appeared to be related to a deficiency of an opsonin component or possibly an activator of the complement system.

Winkelstein and Drachman demonstrated a defect in heat-labile serum opsonizing activity for Pneumococcus Type 25, but not for Salmonella choleraesuis in patients with sickle cell disease. Huber et al. have shown a normal IgG receptor system on mononuclear phagocytes of patients with chronic granulomatous disease, "acquired" agammaglobulinemia, and Wiskott-Aldrich syndrome; the integrity of this system is presumably a requisite for opsonization. Undoubtedly, detailed analysis of the factors involved in opsonization will demonstrate further defects; the physiologic role of the complement system in opsonization has recently been reviewed.

Intracellular Defects

The syndrome now commonly known as chronic granulomatous disease (CGD) was first reported in 1957 and is characterized by eczema, lymphadenopathy, hepatosplenomegaly, recurrent suppurative infections often with mild pathogens and granuloma formation without hypogammaglobulinemia. The neutrophils from these children were demonstrated to have a normal capacity to ingest bacteria, but a marked impairment of bactericidal capacity. These patients frequently have characteristic roentgenographic features including chronic pneumonias, hilar node enlargement and calcified granulomatous lymph nodes in the abdomen and neck. A major pathologic feature is the presence of lipid laden histiocytes in liver, lungs, spleen and lymph nodes. Recent studies have demonstrated that there are several different
Table 1.—Comparative Neutrophil and Monocyte Bactericidal Studies and NBT-Tests

<table>
<thead>
<tr>
<th>Cell Donor</th>
<th>Bactericidal Capacity</th>
<th>O.D. Resting</th>
<th>O.D. Phagocytosing</th>
<th>Δ O.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls *</td>
<td>&gt; 2.0 &gt; 2.0</td>
<td>0.10</td>
<td>0.31</td>
<td>0.22</td>
</tr>
<tr>
<td>Family B:</td>
<td>M.B.</td>
<td>&lt; 0.5</td>
<td>0.04</td>
<td>0.10</td>
</tr>
<tr>
<td>Family D:</td>
<td>D.D.</td>
<td>0.3</td>
<td>0.09</td>
<td>0.17</td>
</tr>
<tr>
<td>Family T:</td>
<td>R.T.</td>
<td>0.3</td>
<td>0.15</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>&lt; 0.5</td>
<td>(0.05-0.15)</td>
<td>(0.21-0.50)</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>&lt; 0.5</td>
<td>(0.14-0.37)</td>
<td></td>
</tr>
<tr>
<td>WB (75 yr.)</td>
<td>0.2</td>
<td>—</td>
<td>0.12</td>
<td>0.35</td>
</tr>
<tr>
<td>One mo. later</td>
<td>2.0</td>
<td>—</td>
<td>0.23</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Twenty normal adult subjects were tested.
† Logarithm difference of number organisms killed per two hours (Logarithm initial number of viable organisms—final number).
‡ Optical density at 515 mμ against a pyridine blank. Results for $2.5 \times 10^9$ phagocytes per 15 minutes.

clinical and laboratory manifestations of neutrophil and monocyte bactericidal dysfunction. We have proposed a tentative classification of these syndromes. Most investigators have utilized two test systems for studies of these patients and their families, namely, bactericidal assays and the nitroblue tetrazolium test (NBT), a measure of hexose monophosphate shunt activity. We have shown defective bactericidal function of peripheral blood monocytes, a finding which has been confirmed. However, cultured macrophages from a patient with this syndrome have been reported to have normal bactericidal ability. Results of bactericidal studies of purified mononuclear phagocyte populations using the albumin gradient separation method of Bennett and Cohn have generally agreed with neutrophil bactericidal assays; however, some difficulties have been encountered in demonstrating heterozygosity using the NBT test. Comparative results for the bactericidal tests with mixed leukocytes, mononuclear phagocytes and NBT tests are shown in Table 1.

Earlier studies suggested that neutrophils from boys with typical CGD had impaired bactericidal capacity for staphylococci, Serratia marcescens and several other gram negative organisms, but had a normal capacity to kill beta-streptococcus, Streptococcus viridans and pneumococcus. Further studies have shown that, whereas neutrophils from some of these patients have a normal capacity to kill these organisms, those from others do not. In addition, impaired fungicidal capacity of neutrophils from these patients has been shown. A selective defect limited to inability to kill staphylococci has been demonstrated in one boy and heterozygosity was not detectable in his parents cells. A reversible bactericidal defect has been demonstrated in a 75-year-old man who had a mixed cryoglobulin and a high titer rheumatoid factor.
with typical CGD has, in addition, selective absence of IgA. Some of these findings of heterogeneity of organisms with which there was impaired function are shown in Table 2. Although many cases have been shown to have a typical X-linked mode of inheritance, in other families no heterozygotes were detectable. Recently, Soothill and his co-workers have detected abnormalities in neutrophils from the fathers of their patients and have proposed a sex-limited autosomal recessive mode of inheritance; these findings have not been confirmed. At least eight females with neutrophil bactericidal defects have been reported. A red-haired girl with a syndrome characterized by recurrent cold staphylococcal abscesses, Job's syndrome, and her asymptomatic sister have been shown to have neutrophil bactericidal defects; both parents had normal in vitro studies.

The diversity of clinical and genetic patterns thus far observed suggest that there are several forms of impaired phagocyte bactericidal function. Recently Lehrer and Cline have reported an adult with absent neutrophil myeloperoxidase activity and disseminated candidiasis; abnormalities were also detectable in several first-degree relatives. These findings further extend the spectrum of intracellular defects. The antibacterial effect of myeloperoxidase, halides such as iodide, bromide or chloride and hydrogen peroxide on E. coli and Lactobacillus acidophilus has been shown. Although defective iodination occurs in CGD, this appears to be secondary to other underlying metabolic defects. Methimazole, which inhibits iodination, has been shown to inhibit bactericidal function.

Thus far there have been extensive studies of leukocytes from these patients and their families, yet the fundamental defect remains unknown. The initial electron microscopic studies suggested failure of degranulation and vacuolization.

### Table 2—Neutrophil Bactericidal Capacity

<table>
<thead>
<tr>
<th>Family</th>
<th>Individual</th>
<th>Tested</th>
<th>Staph. aureus</th>
<th>Serratia marcescens</th>
<th>Test E. coli</th>
<th>Strept. pyogenes</th>
<th>Strept. viridans</th>
<th>Normal Relatives Tested</th>
</tr>
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<tbody>
<tr>
<td>D</td>
<td>DD</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>B</td>
<td>MB</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>T</td>
<td>RT</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>M</td>
<td>KM (18 yr.)</td>
<td></td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td></td>
<td></td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Mei</td>
<td>DM</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Mer</td>
<td>TM (9)</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>0</td>
<td>+</td>
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<tr>
<td></td>
<td>Mother</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>0</td>
<td>0</td>
<td>+</td>
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<tr>
<td>WB</td>
<td>(75 yr.)</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>One month later</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

NOTE: + = Defective bactericidal capacity; 0 = Normal bactericidal capacity.

* All propositi are males except where indicated.
† All propositi are under 10 years of age except where indicated.
‡ The fathers of patients DD, MB, RT, KM, DM and TM were tested, and all had normal bactericidal capacity.
Fig. 3.—Monocyte from CGD patient incubated for five minutes with *Escherichia coli*. Phagocytic vacuole formation and degranulation have occurred (× 11,000).

Biochemical studies of CGD leukocytes have shown normal lysosomal enzymes and normal conversion of lysolecithin to lecithin during phagocytosis. Bactericidal function is improved by lysosomal labilizers, such as filipin. Metabolic studies reveal a decreased respiratory burst, decreased HMP shunt activity, decreased peroxide activity, as well as reduced NADH oxidase activity. The defect can be reversed in vitro by providing a peroxide...
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generating system. This has been done using streptonigrin, an agent which also facilities lysosomal “unzipping” and glucose oxidase coated latex spherules. The precise identification of the defect may offer an approach to specific therapy.

SUMMARY

The physiologic aspects of neutrophil and monocyte function as related to bactericidal capacity have been reviewed. Recent studies have demonstrated clinical syndromes involving defects in chemotaxis, opsonization, and a spectrum of intracellular neutrophil and monocyte defects. The present concepts of the pathophysiology of these syndromes have been considered. The elucidation of the basic defects awaits the development of new approaches to the study of phagocyte function.

ACKNOWLEDGMENT

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Fig. 5.—Phagocytic vacuole containing *E. coli*. Note fusion of neutrophil granules with vacuole (× 42,000).

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