Infections in Patients with Inherited Defects in Phagocytic Function

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INTRODUCTION

A characteristic of infections in patients with disorders of phagocytic cells is the frequency of infections at epithelial surfaces and the frequency of dissemination. The skin and the gastrointestinal tract harbor large numbers of potentially pathogenic organisms. Host defense at these sites relies pri-

marily on innate immunity because the constant exposure to microorganisms requires a very rapid response. Phagocytic cells are the cornerstone of the innate immune system. This review describes the pathophysiology of the primary disorders of phagocytic cell function. Primary defects in macrophage function and neutrophil function are not common in the general population but require very aggressive and specific management and lifelong prophylaxis in some cases. Recognition of the characteristic infections occurring in both types of disorders is important both from the perspective of diagnosis and for treatment. Studies of these disorders also provide im-

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portant insights into the role of phagocytic cells in host defense.

THE CELLS OF THE INNATE IMMUNE SYSTEM CONSTITUTE THE FIRST LINE OF DEFENSE

The cells of the innate immune system are monocytes/macrophages, neutrophils, and natural killer (NK) cells. NK cells are not phagocytic and are not discussed here. In some sense, the epithelial surfaces themselves contribute to host defense and could be considered a component of the innate immune system. The physical characteristics of epithelial surfaces assist in the defense against infection, and they typically produce soluble substances with antibacterial effects. Lysozyme, defensins, cryptidins, and surfactants are examples of antimicrobial substances produced by epithelial surfaces. There are data to support the concept that defects in these soluble mediators significantly compromise host defense (224, 225, 231); however, this review focuses on primary disorders of macrophage and neutrophil phagocytic function.

Pattern Recognition Receptors

The cells of the innate immune system utilize evolutionarily ancient pattern recognition receptors to distinguish among pathogens. These receptors are highly conserved among all multicellular eukaryotic species. They recognize a relatively small number of highly conserved structures which are common to large numbers of microorganisms. Microbial structural motifs are sometimes referred to as pathogen-associated molecular patterns, and the receptors which recognize them are called pattern recognition receptors (181). The advantages of this type of innate system are its heritability and the immediacy of the response. The overall goal of the innate immune system is the recognition of pathogens, recruitment of the requisite cells, and eradication of the pathogens. Pattern recognition receptors are involved in the initial stages.

There are three functional categories of pattern recognition receptors. Secreted pattern recognition molecules typically function as opsonins, and the best known examples of this category are the proteins of the alternative complement pathway, the lectin activation pathway of the complement cascade, surfactants, C-reactive protein, serum amyloid protein, and lipopolysaccharide (LPS) binding protein (95, 125, 250, 296). Through their actions as opsonins, they can influence the uptake of antigen by phagocytic cells (56, 230). The second category of pattern recognition receptors is the endocytic category. Their main function is to mediate the uptake of pathogens; examples of this category include the macrophage mannose receptor and the macrophage scavenger receptor. Defects in these molecules have not been described in humans, but their importance has been demonstrated in mice. Mice deficient in type I/II macrophage scavenger receptors show defective killing of *Listeria monocytogenes*, clearance of malaria, and regulation of responses to endotoxin (134, 146, 203). The last category, and the one most relevant to the disorders discussed in this review, are the signaling receptors. The best characterized set of receptors that perform a direct signaling function are the toll-like receptors (TLRs). These are extremely highly conserved throughout evolution and were orig-
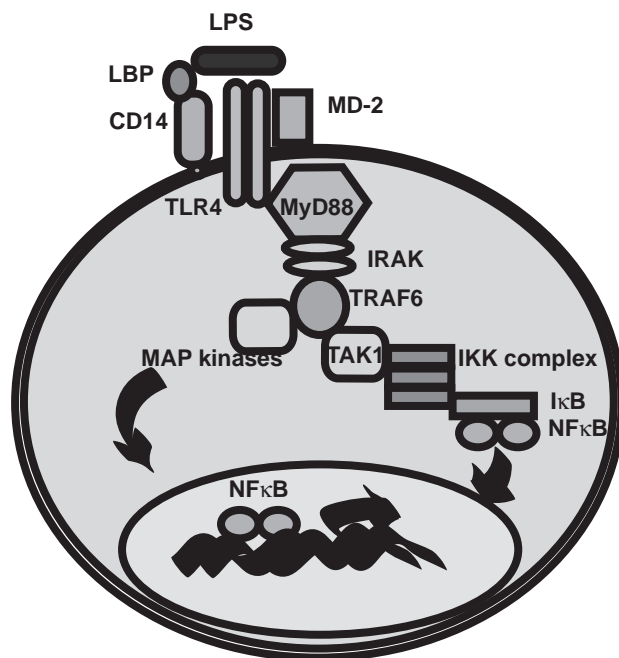

FIG. 1. Signaling through TLR4. TLRs are dimers which signal Myd88 and TIRAP (not shown) to induce the MAP kinase cascade and activation of NF-κB. These molecules induce the transcription of a variety of inflammatory mediators. Certain TLRs are known to require soluble cofactors for recognition, such as LPS binding protein (LBP), CD14, and MD-2.

inally identified in *Drosophila* (115). There are 10 TLRs in humans; they recognize different pathogen-associated molecular patterns (182). All share a conserved leucine-rich extracellular domain and a cytoplasmic domain with homology to the interleukin-1 (IL-1) receptor. The TLRs may not recognize pathogens directly. In the case of bacterial lipopolysaccharide (LPS), at least three additional proteins appear to be required for receptor engagement (Fig. 1) (229, 256). Recognition of peptidoglycan and gram-negative bacteria by toll in *Drosophila* also requires a soluble cofactor, suggesting that this may be a common feature of this class of receptors (165, 166, 183).

The TLRs all have a common signaling pathway involving NF-κB. As shown in Fig. 1, phosphorylation of IκB by IKK and release of active NF-κB is a final common pathway for all known TLRs (281). This is significant not only for the generation of inflammatory mediators such as IL-12 but also for the induction of expression of T-cell costimulatory receptors. The importance of this pathway in activating NF-κB is shown by the profound immunodeficiency that occurs in people with defective IKK, the kinase that phosphorylates IκB (discussed below). The TLRs also activate mitogen-activated protein (MAP) kinases, and this group of signaling molecules is important in the activation of macrophages and phagocytosis (168).

A second category of signaling receptors has recently been described. These receptors are unusual in that they are completely intracellular. They also activate NF-κB and the MAP kinases but are thought to participate primarily in the regulation of inflammatory responses. The best known examples are the members of the nucleotide-binding oligomerization do-

TABLE 1. Neutrophil-mediated microbial killing

Microbicidal substance	Action
Defensins	Cause gram-negative bacterial permeability
Proteinase 3	Amplifies inflammation
Elastase	Degrades outer membrane protein of gram-negative bacteria
PLA2	Has potent bactericidal activity against *S. aureus*
Myeloperoxidase	Converts H_2O_2 to HOCl
Metalloproteinases	Gelatinase and collagenase may activate chemokines in addition to cleaving matrix proteins
Reactive oxygen species	Cause oxidation of bacterial proteins and nucleic acids

main (NOD) family of caspase recruitment domain. proteins and the double-stranded RNA-activated protein kinase (35, 132). NOD mutations have been implicated in Crohn's disease and infantile-onset sarcoidosis.

Opsonization

Opsonization refers to the "tagging" of a pathogen by serum proteins such that it is more likely to be phagocytosed. Many proteins participate in this process, and many are activated as part of the acute-phase response. Mannose-binding lectin, C-reactive protein, C3, and antibody are all potent opsonins which act to facilitate the uptake of pathogens by phagocytic cells. Receptors for each opsonin are present on the macrophage surface. Fc receptors on neutrophils are the primary receptors for opsonins present.

Mechanisms of Neutrophil-Mediated Killing

Neutrophils are capable of recognizing bacteria directly, often via TLRs. In addition, the neutrophil integrins, CD11b/CD18 (Mac-1) and CD11c/CD18 (p150), recognize and bind *Leishmania* spp., *Bordetella* spp., *Candida* spp., and *Histoplasma capsulatum* directly (48). Most frequently, microbes are coated with antibody or complement. Receptors recognize complement activation products and facilitate engulfment, as do the immunoglobulin Fc receptors. Cross-linking of these surface receptors activates the respiratory burst that is unique to myeloid cells and activates the phagocytic pathway (51). On phagocytosis of the microbe, reactive oxygen species are released into the primary phagosome. A charge differential, generated during the respiratory burst, leads to neutrophil granules releasing their contents into the phagosome, enhancing killing (44, 112, 235, 254). Table 1 shows the main microbicidal substances released into the phagosome to promote killing.

The respiratory burst is critical, and patients with defective NADPH oxidase (chronic granulomatous disease [CGD]) have frequent infections with *Staphylococcus aureus* and other catalase-positive organisms (295). The NADPH oxidase system is part of a larger biochemical pathway regulating the flow of electrons to various substrates. There are five subunits comprising NADPH oxidase proper (Fig. 2) and a regulatory subunit termed Rac-2. gp91^{phox} and p22^{phox} (cytochrome b_{558}) are embedded primarily in the membrane of specific granules, with scattered complexes in the plasma membrane and in secretory
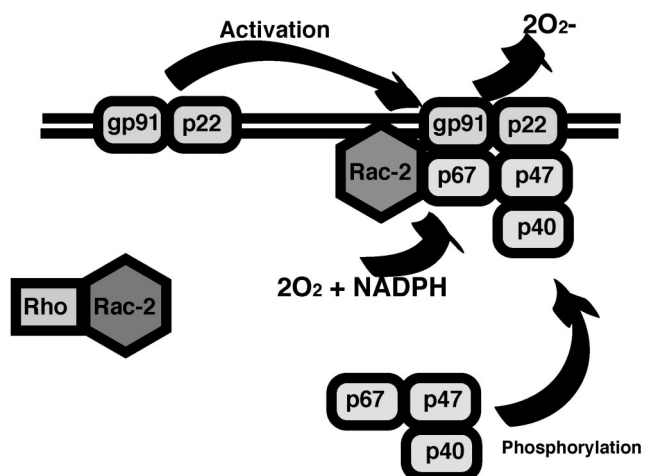

FIG. 2. NADPH oxidase. The NADPH oxidase complex consists of five structural components and Rac-2, which serves to regulate activation of the NADPH oxidase complex. Superoxide (O_2^-) is produced by the complex and released extracellularly or into the primary phagosome.

granules. These two membrane-bound subunits are constitutively associated (214, 251). Cell surface signaling events lead to GTP binding on Rac-2 in the cytoplasm (2). Rac-2 then binds and stabilizes the cytoplasmic protein p67^{phox}, which is phosphorylated by protein kinase C. Phosphorylation of p47^{phox} leads to its interaction with the cytoskeleton and translocation to the membrane (197). The entire complex is required for the production of superoxide, O_2^-.

Superoxide itself is a weakly microbicidal agent. Metabolism to H_2O_2 by superoxide dismutase results in a more microbicidal compound, and H_2O_2 can be converted to HOCl by myeloperoxidase. Both H_2O_2 and HOCl are strongly microbicidal. Additional biochemical reactions produce peroxynitrite anion and nitryl chloride, which contribute additional microbicidal activities (49).

Mechanisms of Macrophage-Mediated Killing

Macrophages are important antigen-presenting cells and thus participate both directly in killing microorganisms and indirectly by cueing of the adaptive lymphocyte responses. Macrophage activation and granuloma formation depend on both tumor necrosis factor alpha (TNF-α) and gamma interferon (53, 93, 145, 171, 184, 237), and these two cytokines influence each other's expression (199). In humans with gamma interferon receptor 1 deficiency, one of the first immunologic defects identified was a lack of gamma interferon enhancement of macrophage production of TNF-α. Nearly all other tests of immunologic function were normal (162). The patients had no detectable granulomas or poorly formed granulomas, depending on the severity of the mutation.

The mechanism by which gamma interferon elicits the killing of intracellular organisms in mice is well defined. Gamma interferon induces superoxide and nitric oxide synthase. TNF-α then triggers NO production. Mice deficient for inducible nitric oxide synthase or components of NADPH oxidase are uniformly more susceptible to infection with intracellular

Activated macrophage   **T cell**   **Activated macrophage**

IL-12   **IL-4**

Th1   **Th2**

Interferon-γ
IL-2
TNFα
Macrophage activation
IgG1, IgG3
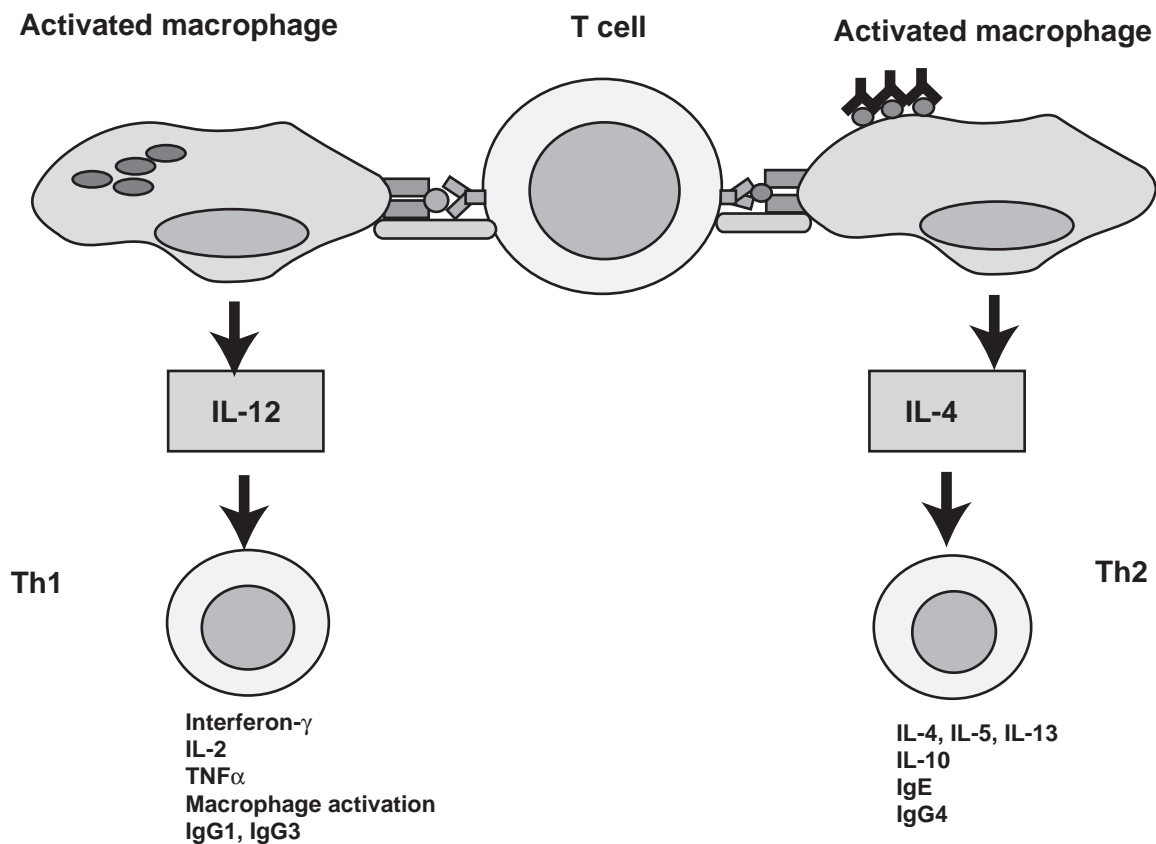
IL-4, IL-5, IL-13
IL-10
IgE
IgG4

FIG. 3. T cells become polarized toward Th1 by macrophages activated by microbes. T cells generally can be categorized as Th1 or Th2 depending on the cytokines produced by the individual cell. Th1 cells predominantly activate macrophages to enhance killing through the release of gamma interferon and TNF-α. In mice they can stimulate B cells to make opsonizing antibodies of the IgG1 and IgG3 subclasses. Th2 cells predominantly activate B cells through the secretion of IL-4 and IL-5. They can also activate eosinophils and are important in defense against parasites. The infected macrophage acts to determine the fate of the naive T cell by producing IL-12, which is produced in response to engagement of TLRs by microbes. In the absence of IL-12, IL-4 from other cells can direct a Th2 response. The response then ultimately directs effector functions listed at the bottom of the figure.

organisms such as *Mycobacterium* spp., *Listeria* spp., *Salmonella* spp., *Aspergillus* spp., and *Toxoplasma gondii* (41). Human macrophages, in contrast, produce little NO, and inducible nitric oxide synthase is induced by IL-4 and cross-linking of the immunoglobulin E (IgE) receptor on macrophages (85, 217, 278, 279). The role of TNF-α and gamma interferon in humans may be to augment this pathway.

Interfacing with Adaptive Immunity

The innate immune system interfaces with and directs the subsequent responses of the adaptive immune system. There is ample evidence for the concept that exposures of mice and humans to microbes or microbial products directs a Th1-skewed immune system (22, 126). A common model for this phenomenon is that stimulation through TLRs leads to the production of IL-12, which is a Th1-polarizing cytokine (Fig. 3). Engagement of TLRs also leads to the expression of costimulatory molecules, which would allow the T cells to support an antimicrobial response. There is also evidence to support the concept that regulatory T cells are affected by exposures to pathogens (7, 301, 302).

INHERITED NEUTROPHIL DISORDERS

Many of the inherited neutrophil disorders are associated with neutropenia. This review does not focus on pure congenital neutropenias because they have recently been reviewed elsewhere (17). Instead, it focuses on disorders of phagocytic function. Neutrophils are cells with a complex functional program that is executed in response to an array of cues from the environment. The final common process is usually phagocytosis, but neutrophils can infiltrate and release inflammatory mediators in the absence of phagocytosis.

Neutrophils are derived from pluripotent progenitors in the bone marrow. Production is increased in response to granulocyte-monocyte colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) (116, 119). As neutrophils mature, they proceed through the myeloblast, promyelocyte, and myelocyte stages as actively dividing cells. Metamyelocytes and fully differentiated neutrophils are nondividing cells. Once released from the bone marrow, neutrophils have a short half-life and circulate for 8 to 24 h before undergoing constitutive apoptosis (284). The life span is extended in inflammatory conditions and is shortened by active
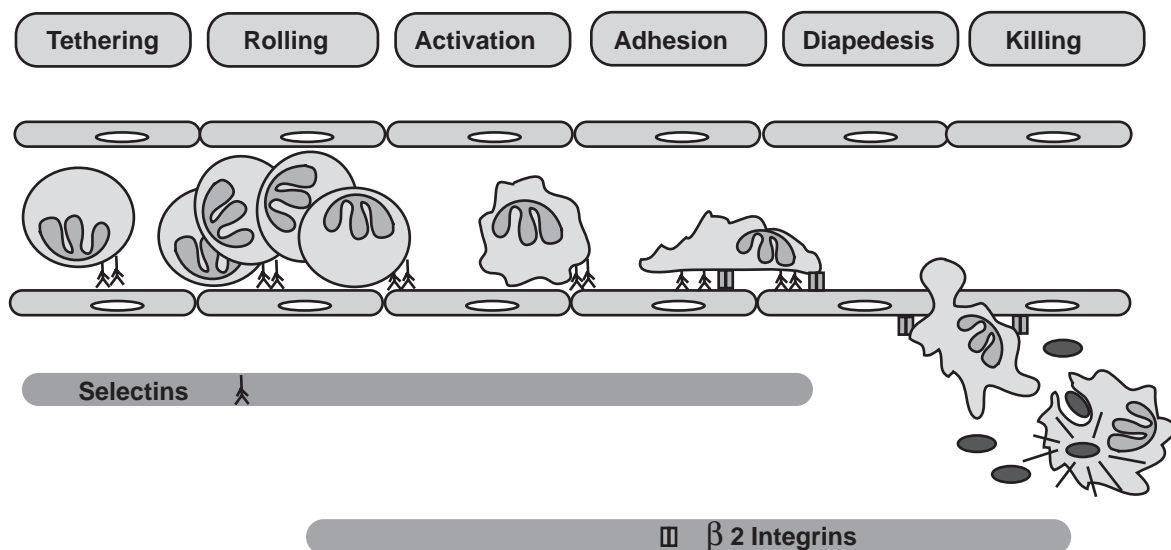
FIG. 4. Neutrophil responses to infection. Initial interactions are mediated by P-selectin, which is released from Weibel-Palade bodies in endothelial cells on exposure to C5a, leukotriene B_4, TNF-α, or LPS. E-selectin is expressed subsequently, and together they bind fucosylated glycoproteins on the tips of neutrophil surface villi. This initial interaction is often termed rolling. IL-8 and other chemokines cause a conformational change in neutrophil surface integrins and allow binding to ICAM-1 and ICAM-2, which are induced on inflamed endothelial cells. Extravasation requires the β_2-integrins and PECAM (CD31). Migration toward C5a, bacterial peptides, or a chemokine gradient is mediated by interactions with cell surface receptors and cytoskeletal changes. Resident tissue macrophages produce chemokines in response to pathogen recognition receptor engagement. Phagocytosis is activated by the binding of complement receptors, immunoglobulin receptors, or TLRs. Once engulfed, bacteria are killed by the combined actions of granule contents and reactive oxygen species. Rolling is defective in LAD 2, tight adhesion is defective in LAD 1, and chemotaxis is defective in Chédiak-Higashi syndrome, specific granule deficiency, Schwachman syndrome, myelokathexis, and glycogen storage disease type Ib. Phagocytosis is defective in LAD 1, and intracellular killing is defective in CGD, specific granule deficiency, Chédiak-Higashi syndrome, myeloperoxidase deficiency, myelokathexis, and glycogen storage disease type Ib.

phagocytosis (297, 298). While circulating, the cells are attracted to sites of inflammation by complement component C5a, various chemokines, leukotrienes, and bacterial peptides. Travel from the circulation to the issue requires a coordinated interaction of adhesion molecules (Fig. 4).

Once at the site of inflammation, neutrophils bind to the pathogen by means of pathogen recognition receptors or receptors for opsonins. Following phagocytosis, the respiratory burst is activated as described above and the granule contents are released into the primary phagosome. In this review we broadly considers defects in phagocytic function to be defects that impair chemotaxis, adhesion, and/or killing. Certain of the primary neutrophil disorders are associated with a mild to moderate neutropenia due to impaired survival or production. These are considered separately from the others.

Neutrophil Disorders Associated with Neutropenia

After infancy, neutrophil counts lower than $1,500 \times 10^9$/liter are considered to be abnormal and neutrophil counts lower than 500×10^9/liter are associated with significant risk of serious infection (289). The causes of neutropenia encompass drug effects, infection, autoimmune processes, congenital disorders, and malignancy. In some cases, the neutropenia is indicative of an underlying defect in neutrophil function. Many metabolic disorders are associated with neutropenia on the

TABLE 2. Inborn errors of metabolism associated with neutropenia

Disorder	Clinical features	Infections and causes
α-Mannosidosis	Dysostosis multiplex, hepatomegaly, facial coarsening, developmental delay	Recurrent bacterial infections due to neutrophil chemotaxis defect
Glycogen storage disease 1b/c	Hepatomegaly, hypoglycemia, seizures	Recurrent mucous membrane ulcers, recurrent infections due to neutropenia and neutrophil dysfunction
Transcobalamin II deficiency	FTT,[a] vomiting, megaloblastic anemia, increasing neurologic dysfunction	Oral ulcers, frequent infections; pancytopenia and hypogammaglobulinemia
Branched-chain organic acidurias	16 types with variable clinical features; typically include acidosis, neurologic signs, and cardiomyopathy; may present with a Reye's-like syndrome	Accumulation of toxic metabolites diminishes leukocyte function; 3-methylglutaconic aciduria type II (Barth syndrome) is associated with neutropenia

[a] FTT, failure to thrive.

basis of accumulation of toxins detrimental to neutrophil survival (Table 2). Generally, these resolve as the metabolic derangement is addressed. This section reviews primary neutrophil disorders associated with neutropenia.

Chédiak-Higashi syndrome. Chédiak-Higashi syndrome is diagnosed clinically in patients with mild neutropenia, peripheral nerve conduction defects, pigmentary dilution with partial oculocutaneous albinism, easy bruising, and frequent infections (25, 144, 220). The syndrome is due to mutations in *LYST*, which encodes a cytoplasmic protein involved in vacuole formation and transport of proteins (26, 192, 219). While Chédiak-Higashi syndrome is usually considered an immunodeficiency, all cells with lysosomes are affected. Giant inclusions due to fusion of cytoplasmic granules are seen in hematopoietic cells, renal tubular cells, neurons, Schwann cells, melanocytes, and fibroblasts (290, 293). A common diagnostic strategy is to observe the giant inclusions in neutrophils or hair under high power. There is a spectrum of severity including a few adults who present with isolated peripheral neuropathy; however, the most common presentation involves recurrent infections due to the defective neutrophil function (144). The neutrophil inclusions are due to fusion of azurophilic and specific granules (233, 291). These giant granules fuse poorly with the primary phagosome, and intracellular killing is delayed on this basis (241). In addition, chemotaxis is inefficient due to impaired assembly of microtubules (99). For reasons that remain to be elucidated, the cells are also deficient in cathepsin G and elastase (102). Diminished elastase amounts may contribute to the neutropenia since elastase mutations have been found to underlie most cases of congenital neutropenia and cyclic neutropenia (17).

Most of the infectious manifestations are due to the neutrophil defect. The severe form of Chédiak-Higashi syndrome frequently presents with recurrent infections in infancy. Infections usually involve the skin and respiratory system and include cellulitis, abscess, otitis media, pneumonias, pyoderma, and periodontal disease. Skin abscesses can be particularly problematic, requiring frequent surgical intervention (24). Infections with *S. aureus* are common. Other bacterial pathogens include beta-hemolytic *Streptococcus* spp. and aerobic gram-negative rods (39). Periodontal disease can be severe, leading to alveolar bone loss and tooth exfoliation (72).

While bacterial infections are the most common feature of the immunodeficiency, the most dangerous feature is a hemophagocytic process that arises as a consequence of NK cell dysfunction in response to a viral infection (25, 61, 133, 241). These viruses are typically members of the *Herpesviridae* family, although other types of viruses have been recovered, and in one case *Rickettsia* was thought to be the trigger. This hemophagocytic process is sometimes termed the accelerated phase and is characterized by fever, hepatosplenomegaly, adenopathy, and pancytopenia (39, 232). The age of onset of the hemophagocytic process is variable, but onset is usually seen before adulthood and is ultimately seen in 85% of patients with Chédiak-Higashi syndrome.

Miscellaneous. Glycogen storage disease type Ib, myelokathexis, and Schwachman syndrome are all associated with defects in neutrophil function and neutropenia. The neutropenia in glycogen storage disease type Ib ranges from mild to severe, and patients experience very frequent infections as a consequence of the combined effects of the neutropenia, impaired expression of adhesion molecules, impaired mobilization from the bone marrow, impaired chemotaxis, diminished calcium mobilization, and dysfunction of microbial killing (77, 105, 275, 276, 287). Many of these defects are reversed by G-CSF administration (50). The typical clinical manifestations include colitis, abscesses, gingivitis, and frequent skin infections (276). There is a spectrum of severity, but most patients present in infancy with hypoglycemia. The defect is in one member of the glucose-6-phosphatase system, which functions to maintain glucose homeostasis (58).

Myelokathexis is a rare disorder which occurs as an isolated defect or as part of complex with hypogammaglobulinemia and warts, sometimes called the WHIM syndrome (warts, hypogammaglobulinemia, infection, and myelokathexis) (20, 42, 127). The relationship between the two disorders is not understood, and the gene defect(s) is not known. Defects in the chemokine receptor CXCR4 have been found in some patients with WHIM. Both disorders appear to be inherited in an autosomal dominant fashion. Affected individuals have neutrophils that are hypersegmented with condensed nuclear lobes, which may be due to accelerated apoptosis (16). There may also be defective release from the bone marrow (210). Many defects in neutrophil function have been described, including defective chemotaxis, superoxide production, and Fc receptor expression (226, 288). The neutropenia and infections improve with administration of G-CSF; however, the defects in cell morphology are not altered (288).

Schwachman syndrome (or Schwachman-Diamond syndrome) is another poorly defined disorder. It is the second most common cause of pancreatic insufficiency in children. The manifestations are dysostosis multiplex, pancreatic insufficiency, and neutropenia with defective chemotaxis (60, 236, 246). Patients have an increased risk of leukemia, and there have been reports of increased chromosome breakage. G-CSF is not usually required, and its use must be balanced against the theoretical possibility of increasing the risk of leukemia (272).

Functional Neutrophil Disorders

The functional disorders of neutrophils are all characterized by recurrent infections of surfaces. In some cases the predisposition to infection is mild, while in others the infections may be life-threatening. Most of the disorders considered in this section are pure disorders of neutrophils. Only Gaucher's disease and α-mannosidosis have organ involvement unrelated to neutrophil dysfunction.

Chronic granulomatous disease. CGD is the prototypic functional neutrophil disorder for most immunologists. It has a frequency of 1:100,000 to 1:200,000 people. Patients generally are normal in all other respects, although there may be mildly diminished T-cell numbers (120). The NADPH oxidase complex is expressed at its highest levels in neutrophils, although it is also seen in monocytes, B cells, and fibroblasts. Monocyte defects in NADPH oxidase may predispose to mycobacterial disease which is found with increased frequency in patients with CGD; however, the majority of infections are thought to be due to defective production of superoxide by neutrophils. In CGD, all other aspects of neutrophil function are normal (66, 67). As described above, there are five structural components

in NADPH oxidase and a regulatory subunit called Rac-2 (Fig. 2) (253). Defects in all of the subunits except p40^{phox} have been found to cause CGD (295). Approximately two-thirds of patients with CGD have defects in the X-linked gene, encoding gp91^{phox}. Most of the mutations in the X-linked form are associated with a complete null phenotype, although there are reports of dysfunctional proteins produced in normal or near normal levels (295). Approximately 5% of patients with CGD have defects in the gene encoding the p22^{phox} subunit. These are also generally associated with a complete absence of superoxide production. Similarly, defects in the gene encoding p67^{phox} are also found in approximately 5% of patients, and nearly all patients with this gene defect have absent production of superoxide. In contrast to the diverse mutations seen in the other genes, the defects in p47^{phox} are often due to a 2-bp deletion causing a premature stop codon. Defects in p47^{phox} are seen in approximately 20% of patients with CGD (62, 295).

All patients with CGD, regardless of the genotype, suffer from recurrent infections with catalase-positive organisms. Catalase-negative organisms are not often medically significant in patients with CGD because these organisms provide their own H$_2$O$_2$, which is converted by the neutrophils to HOCl and other potent microbicidal reactive oxygen species. In essence, the microbes carry their own killing mechanism. In contrast, catalase-positive organisms eliminate their own H$_2$O$_2$, and in patients with CGD, there is no eukaryotic production of H$_2$O$_2$, and the pathogens survive and multiply. While all catalase-positive organisms have the potential to cause serious infection, there are a few pathogens which dominate the infection pattern. This is probably due to the increased exposure to certain organisms (*S. aureus*) and to the differential effects of microbicidal peptides or NO (*Aspergillus nidulans*). For example, *Pseudomonas aeruginosa* is a catalase-positive organism not frequently seen in patients with CGD whereas *Burkholderia cepacia* causes much morbidity and mortality in these individuals (152). Neutrophils from patients with X-linked CGD show reduced in vitro killing of *Burkholderia cepacia*, while *Pseudomonas aeruginosa* killing is intact (262). These studies suggest that other virulence factors or aspects of neutrophil killing contribute to the infection pattern in CGD.

(i) Infections in patients with CGD. A national registry for patients with CGD in the United States was established in 1992 (295). The most common organisms, in order of frequency, are *Staphylococcus* spp., *Aspergillus* spp., *Serratia* spp., *Nocardia* spp., *Burkholderia* spp., *Klebsiella* spp., and *Candida* spp. A comparison with a previous report from 1989 shows an increasing frequency of recovering *Aspergillus* spp. (187). Other trends identified by the review of the national registry include an increasing frequency of *Burkholderia cepacia* and *Nocardia* infections and a decreasing frequency of *Salmonella* infections.

Pneumonia is the most frequent type of infection in CGD patients, affecting approximately 80% of patients (Table 3). *Aspergillus* spp. (41%) are the microorganisms most frequently recovered, followed by the bacteria *Staphylococcus* spp. (12%), *B. cepacia* (8%), and *Nocardia* spp. (8%). Abscesses are the second most frequent type of infection in patients with CGD, and the location of the abscess may suggest the microorganism responsible for the infection. Table 4 summarizes the pathogens most frequently causing infections in CGD patients by location in the body (295).

Osteomyelitis has been specifically examined in two separate studies. In the first study, *Aspergillus* spp. were the causative organisms in 38% of the cases and *Serratia* spp. were the causative organisms in 30% (263). The remainder of the cases were due to *Nocardia* spp., *Mycobacterium* spp., or *Staphylococcus* spp. In the second study, *Serratia* spp. and *Aspergillus* spp. each caused approximately 30% of the cases of osteomyelitis, with the remainder due to *Paecilomyces* spp., *Staphylococcus* spp., *Nocardia* spp., *B. cepacia*, or other gram-negative bacteria (295).

Nocardia species, including *N. asteroides*, *N. farcinica*, *N. nova*, and *N. otitidiscaviarum*, have frequently been identified as causing infections in patients with CGD (138, 255). A retrospective review of 28 episodes of *Nocardia* infections in CGD patients noted that all episodes involved pulmonary infection with dissemination occurring in one fourth of the episodes. Dissemination was less likely in patients receiving prophylaxis with gamma interferon or a sulfonamide (84).

Liver abscesses caused by *Staphylococcus* spp. or *Serratia* spp., as well as osteomyelitis caused by *Serratia* spp., are very suggestive of CGD, since these infections rarely occur in patients without an underlying immunodeficiency. Unusual infections such as these are suggestive of an underlying immunodeficiency and warrant an evaluation when encountered. Other unusual pathogens that have been identified infrequently in

TABLE 3. Clinical features in patients with CGD[a]

Feature	% of patients affected
Penumonia	79
Liver abscess	27
Lung abscess	16
Perirectal abscess	15
Brain abscess	3
Adenitis	53
Osteomyelitis	25
Inflammatory bowel disease	17
Idiopathic thrombocytopenia purpura	1
Lupus-like syndrome	3

[a] Adapted from reference 294.

TABLE 4. Organisms causing infection in patients with CGD

Location or infection type	Organisms (listed in order of frequency)
Subcutaneous	*Staphylococcus* spp., *Serratia* spp., *Aspergillus* spp., *Klebsiella* spp.
Liver	*Staphylococcus* spp. *Serratia* spp., *Steptococcus* spp., *Nocardia* spp.
Lung	*Aspergillus* spp., *Nocardia* spp., *Staphylococcus* spp., *Burkholderia* spp.
Brain	*Aspergillus* spp., *Staphylococcus* spp.
Osteomyelitis	*Serratia* spp., *Aspergillus* spp., *Paecilomyces* spp., *Staphylococcus* spp.
Adenitis	*Staphylococcus* spp., *Serratia* spp., *Candida* spp., *Klebsiella* spp.
Perirectal abscesses	*Staphylococcus* spp., *Klebsiella* spp., *Escherichia* spp.
Bloodstream	*Salmonella* spp., *Burholderia* spp., *Candida* spp., *Staphylococcus* spp.

[a] Adapted from reference 295.

TABLE 5. Features of LAD

Clinical and laboratory feature	LAD I	LAD I variant	LAD II
Diagnosis	Diminished CD11b/CD18 expression	Functional analyses	Bombay blood type, absent Lewis sialyl X
Typical white cell count (μl^{-1})	20,000–100,000	35,000–96,000	20,000–70,000
T-cell function	Diminished delayed-type hypersensitivity	Normal except diminished proliferation to CD2	Absent cutaneous lymphocyte antigen, and diminished delayed-type hypersensitivity
Binding defect	Fails to bind ICAMs and complement opsonized particles	Normal binding, failure to signal	Fails to bind endothelial selectins
Types of infections	Necrotic skin infections, cellulitis, periodontal disease, pneumonia, spontaneous peritonitis, frequent sepsis	Recurrent skin infections, periodontitis, otitis media, pneumonia	Pneumonia early in life, periodontitis in later childhood, severe recurrent sepsis early in life in one patient Pneumonia early in life periodontitis in later childhood, severe recurrent sepsis early in life in patient
Types of bacteria	*S. aureus, Psuedomonas* spp., *Enterococcus* spp., *E. coli, Klebsiella* spp. many mixed bacterial infections	*S. aureus, Psuedomonas* spp., *Streptococcus* spp., *Enterococcus* spp., *E. coli, Bacteroides* spp.	Not reported
Other infections	*Candida* spp., *Aspergillus* spp., two deaths from viral infections	*P. carinii*	Not reported
Other features	Abnormal NK cell function; colitis seen in 50% of severely affected individuals; 87% of severely affected individuals have delayed separation of the umbilical cord	Myelodysplasia in one case, hypogammaglobulinemia in one case, and diminished platelet activation in two cases	Developmental delay (in 5 of 5 patients), overlapping toes (in 2 of 5), response to oral fucose (in 1 of 5), no response to oral fucose (in 2 of 5)

CGD patients include *Chromobacterium violaceum, Mycobacterium* spp., and *Legionella* spp. (59, 172, 173, 207, 218, 261).

A. fumigatus and *A. nidulans* are the most common fungi in patients with CGD at any site except the meninges and lymph nodes, where *Candida* spp. predominate (295). *Candida* spp. also frequently cause fungemia in patients with CGD. *A. fumigatus* and *A. nidulans* occur with similar frequency; however, *A. nidulans* is more virulent (252). The reason behind the increased virulence of *A. nidulans* in this population is unknown. In surveys of non-CGD patients with invasive *Aspergillus* infection, *A. fumigatus* is the most common and *A. flavus* is the next most common (73). *A. nidulans* is an uncommon pathogen outside of the CGD population. Unusual fungi have been occasionally reported in patients with CGD; these include *A. sydowi, Penicillium chrysogenum, Paecilomyces varioti, Wangiella dermatitidis, Sarcinosporon inkin, Acremonium strictum, Trichoderma* spp., *Pseudoallescheria boydii*, and *Mucormycosis* spp. (186, 295).

Two studies have recently shown that the most common cause of death in CGD patients is fungal infection. Advances in antifungal treatments may lead to improvement; however, at this time, fungal disease remains life-threatening. Deaths due to *Aspergillus* spp. comprised approximately 35% of the deaths in two separate studies (164, 295). *Candida* spp./*Torulopsis* spp. were a less common cause of death (6%). While other infections may be nearly as common, fungal infections require more sustained treatment, and recurrence and relapse are distressingly frequent. The limited armamentarium and the development of resistance to multiple antifungal drugs have limited the ability to effectively treat serious fungal disease in patients with CGD (283).

Patients with CGD would be expected to develop viral and parasitic infections at the same rate as the general population. There is no reason to conclude that viral infections would be any more severe in patients with CGD or other pure neutrophil disorders. The chance of bacterial superinfection is greater, but viral processes should be cleared normally. Nevertheless, significant infections with respiratory syncytial virus and adenovirus have been reported (295). This could reflect the diminished T-cell numbers seen in patients with CGD (120).

Leukocyte adhesion deficiency. Leukocyte adhesion deficiency (LAD) refers to a number of defects in adhesion molecule expression and function (Table 5). The nomenclature for the LADs has not always been straightforward, but there is a trend toward more consistency. Traditionally, LAD I is due to mutations in the gene encoding CD18 (*ITGB2*). This is the common β subunit for all β$_2$-integrins. Thus, expression of all β$_2$-integrins is deficient. There are four members in this family of adhesion molecules: LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, CR3), p150 (CD11c/CD18, CR4), and CD11d/CD18 (131, 260). All four molecules participate in the tight adhesion of neutrophils to endothelial cells, although the functions of LFA-1 and Mac-1 are the best characterized. In the absence of this tight adhesion step, transendothelial migration to the site of inflammation is markedly deficient (14). The disorder is characterized by a high resting neutrophil count and recurrent infections with frequent dissemination and sepsis. The infections are necrotic rather than pustular because neutrophils are unable to migrate to the site of infection. The mutations within the gene encoding CD18 are diverse, and there is substantial heterogeneity in the clinical presentation. Patients with 1 to 10% residual expression have a milder course than those who

have completely absent expression of β_2-integrins (13). Heterozygous carriers have no clinical manifestations, suggesting that a modest level of expression is sufficient for full function.

"LAD 1 variant" refers to small number of patients with normal or near normal expression of β_2-integrins on the neutrophil surface, but clinical features consistent with LAD 1 and dysfunction of β_2-integrins when tested in adhesion or signaling assays (114, 122, 150). The three patients identified with this variant have been consistent in having high circulating neutrophil counts and poor extravasation of neutrophils into sites of infections. Two of the patients developed a bleeding diathesis that may be due to impaired signaling through β_3-integrins on platelets.

LAD 2 is due to a defect in fucosylation and leads to a more complicated syndrome (170). It is part of a family of glycosylation defects and is also termed carbohydrate-deficient glycoprotein IIc disease. Six patients are known, and they have all demonstrated significant infections early in life and developmental delay (90, 91, 121, 177). Other features include growth delay, leukocytosis, and the Bombay blood phenotype. In two patients, the infection pattern improved with age (90), and in another two patients, biochemical and clinical improvement was noted after fucose supplementation (121, 169).

Initial interactions between neutrophils and endothelium are mediated by membrane glycoproteins called selectins (Fig. 4). They are induced on the endothelium by TNF-α and other inflammatory mediators and bind to fucosylated oligosaccharides on leukocytes (98). LAD 2 patients cannot initiate adhesion via this process, although in situations where blood flow is reduced, the cells are able to engage integrins. Tight adhesion is mediated by intercellular cell adhesion molecules (ICAMs) on the endothelium, binding to members of the integrin family on neutrophils (76). LFA-1 binds ICAM-1 and Mac-1 binds ICAM-2. Binding is enhanced by induction of a conformational change in the integrins in response to chemokines and upregulation of ICAM expression in response to inflammatory mediators (55). Following integrin binding, the neutrophil arrests and undergoes a morphologic change such that it orients toward the endothelium. Diapedesis requires PECAM in addition to the molecules involved in tight adhesion (57). Loss of the common β_2-integrin chain renders the neutrophils unable to form tight adhesion to endothelium because all three members of the β_2-integrins participate in this process. This is one of the mechanisms underlying the chronically elevated neutrophil counts. Mac-1 and p150 are also found on monocytes and NK cells, and there is evidence for in vitro dysfunction of NK cells, although there has been little clinical evidence of NK cell dysfunction, suggesting that it may not be medically significant (148, 245).

Clinical manifestations of LAD include delayed umbilical cord separation, leukocytosis, poor wound healing, and recurrent infection with pyogenic bacteria (271). In severely affected individuals, infections can appear shortly after birth with omphalitis and delayed cord separation (38, 118). Necrotizing and ulcerative soft tissue infections, often requiring surgical drainage, are common. Pyoderma gangrenosum has been found in patients with LAD 1 (29). Periodontal disease may be severe, leading to bone erosion requiring dental extractions. Other sites of infection include the meninges, peritoneal cavity,

pericardium; in an older individual with a milder form of LAD, bronchiectasis was found (178).

(i) Infections in patients with LAD. The most common bacterial pathogens include *S. aureus* and *Streptococcus* spp. Other pathogens reported to cause infections include *Escherichia coli*, *Proteus mirabilis*, *Enterococcus* spp., and *P. aeruginosa* (14, 193, 238). The most common sites of infection are the skin, gingiva, oral mucosa, respiratory tract, and sepsis. Spontaneous peritonitis and sepsis are relatively frequent due to an inability to contain even mild infections.

Candida spp. are the primary fungi isolated from patients with LAD 1. Candidal skin infections were seen in approximately 16% of patients. *Candida* esophagitis has also been frequently described (14). LAD 1 variant patients have a broad spectrum of severity. One of the three reported patients had *Candida* skin and pulmonary infections.

Six patients with LAD 2 have been identified to date, and recurrent episodes of pneumonia, periodontal disease, otitis media, and localized cellulitis have been observed (89, 90, 121). One of the identified patients suffered several sepsis-like episodes and required prophylaxis with antibiotics to prevent further episodes (177). The initial patients described with LAD 2 showed less severe and less frequent infections as they matured, suggesting that compensation can occur (90).

Patients with LAD have not had serious viral infections or parasitic infections in general. This is surprising, given the defects in T cells and NK cells which have been demonstrated in vitro (148). Nevertheless, a few serious viral infections have been noted. Significant herpesvirus and picornavirus infections and aseptic meningitis due to presumed viruses have all been reported (13). The most severely affected LAD 1 variant patient was hospitalized for respiratory syncytial virus, parainfluenza virus, and *Pneumocystis carinii* infections (114).

Myeloperoxidase deficiency. Congenital myeloperoxidase deficiency is seen in 1:4,000 individuals (216). Acquired forms are even more common. Most patients have a missense mutation in the *MPO* gene which leads to failure to incorporate heme into the mature molecule (198). Neutrophils deficient in myeloperoxidase produce superoxide and H_2O_2 properly but are unable to convert H_2O_2 to HOCl. Myeloperoxidase is a constituent of the azurophilic granule and is responsible for the greenish tinge seen in dense neutrophilic infiltrates. As a consequence of the deficient myeloperoxidase, neutrophil killing of some organisms is diminished early but is normal late in killing assays (64). HOCl is a potent microbicidal compound, but H_2O_2 and granule contents may be primarily responsible for neutrophil killing in standard laboratory assays. In contrast, neutrophil-mediated killing of *Candida* spp. and *Aspergillus* spp. is significantly impaired in neutrophils from myeloperoxidase-deficient individuals (216). This is consistent with the clinical picture. Patients are generally asymptomatic; however, those who have symptoms generally experience *Candida* spp. infections (156). Myeloperoxidase deficiency is associated with a mild predisposition to infection, and its effects are usually seen when the patients develop another defect in host defense. For example, *Candida* infections in patients with diabetes are more frequently seen in patients with concomitant myeloperoxidase deficiency (154, 156, 196).

Specific granule deficiency. Specific granule deficiency is a rare disorder of neutrophils, although an acquired form is seen

in a number of preleukemic states (101). The disorder is characterized by a nuclear morphologic alteration called the Pelger-Huët anomaly, which is characterized by a bilobed nucleus instead of the normal trilobed neutrophil nucleus. The neutrophils appear to have a ground-glass appearance on Giemsa stain due to an absence of specific granules. Interestingly, mRNAs for the constituents of the specific granules are absent, which was the first suggestion that the defect is developmental (139). The azurophilic granules are relatively normal, although they lack defensins, and eosinophils and platelets have abnormal granules (102, 242). Functional studies of neutrophils from patients with specific granule deficiency have demonstrated impaired chemotaxis, impaired disaggregation, reduced respiratory burst, and deficient bactericidal activity (100, 101, 107). The gene defect was identified as C/EBP epsilon, and a knockout mouse has been produced (106, 157, 159). C/EBP epsilon is a transcription factor with both inhibitory and activation roles. In mice, the transcription factor is relevant for TNF-α downregulation and the induction of expression of several adhesion molecules (157). Therefore, the phenotype of recurrent infections may be due to multiple biochemical defects.

Patients with specific granule deficiency present in infancy with recurrent deep and superficial skin infections. Respiratory infections, otitis, and mastoiditis are common, and abscesses frequently require surgical drainage. Skin lesions are often indolent, requiring months to heal. *S. aureus* is responsible for most infections, and *P. aeruginosa* is occasionally identified in cases of mastoiditis (12, 101, 149, 265). *Candida* infections have been seen, but invasive fungal disease has not (46, 101, 149, 215).

Miscellaneous. Papillon-Lefèvre syndrome is due to cathepsin C deficiency (155). Patients develop hyperkeratosis and juvenile periodontitis. With very aggressive dental care, the secondary teeth may be preserved, but it is more typical to have complete loss of the teeth by adulthood (23, 270). Generally, the infections are limited to gingivitis; however, there are several reports of recurrent skin infections and deep abscesses in patients with Papillon-Lefèvre syndrome, which is consistent with the role of cathepsin C (34, 45, 113, 176). Phagocytosis and chemotaxis have been demonstrated to be aberrant (104, 167), although the current understanding of the role of cathepsin C is that it cleaves granzymes and serine proteases (3, 37). The typical gingivitis organisms are *Actinobacillus actinomycetemcomitans*, *Capnocytophaga* spp., *Streptococcus constellatus*, *S. oralis*, and *S. sanguis*. *Neisseria* spp., *Bacillus* spp. and *Prevotella* spp. have also been recovered (239, 273).

The phagocytic defects in α-mannosidosis and Gaucher's disease have not been well characterized, and the predisposition to infection appears to be mild (4, 75). Patients with both disorders appear to have an increased predisposition to infection, but there have been no comprehensive studies of prevalence.

Hyper-IgE syndrome is a poorly understood immunodeficiency which is thought by many to be due to abnormal neutrophil function. The basis of the disease is not known, and the affected cell type is often disputed, with various studies suggesting abnormal macrophage function, others documenting abnormal neutrophil chemotaxis, and still others describing defects in T cells. Recent evidence suggests that the defect may occur very early in the recognition of microbes. Cytokine and

TABLE 6. Diagnostic algorithm for the inherited susceptibility to mycobacteria[a]

Diagnostic evaluation	Type of patient
High priority for diagnostic evaluation	Patients with disseminated or recurrent infections with poorly pathogenic mycobacteria
	Patients with infection with poorly pathogenic mycobacteria and a positive family history for either disseminated non-typhi *Salmonella* or nontuberculous mycobacteria
	Patients with persistent or recurrent infection with non-typhi *Salmonella*
Consider a diagnostic evaluation	Patients with extraintestinal *Salmonella* enterica serovor Typhi or Paratyphii
	Patients with *M. tuberculosis* who have persistence or recurrence in spite of adequate therapy
	Patients with systemic symptoms compatible with mycobacterial disease and a history of either *Salmonella* or severe herpesvirus infections
	Patients with atypical histiocytosis X

[a] Adapted from reference 153.

chemokine release after stimulation with microbial products is aberrant (43, 54). The infections are characteristic of neutrophil disorders, with recurrent staphylococcal abscesses being a prominent feature (160). An unusual feature of the abscesses is that they engender little pain and warmth. Often, the patient has little or no fever, suggesting that the ability to incite the early inflammatory changes is lacking in this syndrome. Other clinical features include abnormal dentition, scoliosis, pneumatoceles, mild facial dysmorphia, and osteopenia (109). The serum IgE level is usually extremely high, although it can fall with age (109). Other laboratory examinations are usually normal, although abnormal neutrophil chemotaxis is seen in a majority of patients. The infections are not exclusively due to *S. aureus*, but the vast majority of abscesses are due to that organism. There seems to be a mildly increased risk of fungal disease and infections with other bacteria.

PATHOPHYSIOLOGY OF INHERITED DISORDERS OF MACROPHAGE FUNCTION

The primary defects in macrophage function are all defects of intracellular killing. They all have the common phenotype of increased susceptibility to infections with intracellular organisms. They are sometimes collectively referred to as disorders with Mendelian susceptibility to mycobacteria because of the frequency with which mycobacterial disease occurs (Tables 6 and 7).

In spite of multiple distinct genetic defects, primary functional macrophage defects all have a common presentation: all are associated with an increased susceptibility to mycobacterial disease (Tables 6 and 7). In this section, we review the pathophysiologic basis for the susceptibility to mycobacterial disease.

TABLE 7. Infections in patients with macrophage activation disorders

Disorder	Mycobacterial infections	Other types of infections	References
EDA-ID	*M. avium*, *M. kansasii*, *M. chelonae*, *M. tuberculosis*, *Mycobacterium* spp.	*C. parapsilosis*, *P. carinii*, *S. enterica* serovar Enteriditis, *S. pneumoniae*, *S. aureus*, *E. faecalis*, *P. aeruginosa*	18, 47, 79, 87, 175
IFN-γR1 deficiency	*M. bovis* BCG, *M. avium*, *M. kansasii*, *M. chelonae*, *M. fortuitum*, *M. smegmatis*, *M. peregrinum*, *M. szulgai*, *M. gordonae*, *M. margaritense*, *M. tuberculosis*	*S. enterica* serovar Enteriditis, *Salmonella* spp., *L. monocytogenes*, *Legionella* spp., *M. pneumoniae*, *H. capsulatum*, respiratory syncytial virus, herpesvirus, parainfluenza virus	6, 9, 65, 83, 123, 140, 143, 201, 223, 240, 243
IFN-γR2 deficiency	*M. bovis* BCG, *M. avium*, *M. fortuitum*, *M. abscessus*		78, 81, 124
STAT-1 deficiency	*M. bovis* BCG, *M. avium*		86
IL-12Rβ1	*M. bovis* BCG, *M. avium*, *M. fortuitum*	*Salmonella* spp.	5, 8, 11, 71, 88, 247, 274
IL-12p40	*M. bovis* BCG, *M. tuberculosis*, *M. chelonae*	*Salmonella* spp. varicella-zoster virus *Candida*, *N. asteroides*	10, 88, 221

The disorders discussed include anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID), defects in the gamma interferon receptor complex, defects in STAT1, and defects in IL-12 and its receptor. These disorders all result in mycobacterial infection and other types of intracellular infections. All the genes involved encode proteins involved in a circuit which culminates in intracellular killing of bacteria (Fig. 5). These disorders have only recently been described, and the true prevalence is not known, nor is the phenotypic spectrum fully appreciated.
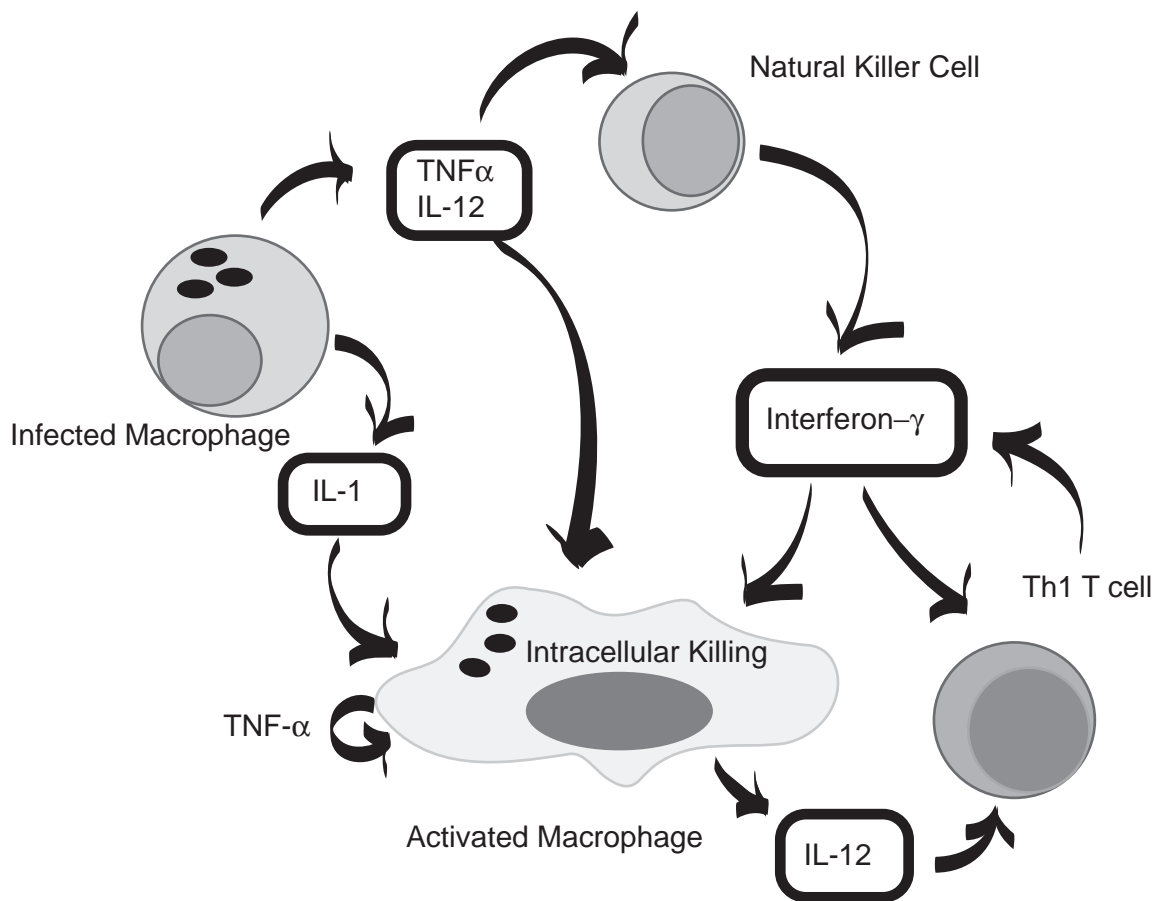

FIG. 5. Macrophage killing of intracellular pathogens. An infected macrophage produces cytokines which stimulate NK cells (TNF-α and IL-12) and which activate macrophages (IL-1, TNF-α, and IL-12). Gamma interferon produced by the NK cell further activates the macrophage and acts to amplify the T-cell response.

Mycobacterium spp. are recognized and killed via a complex multicellular pathway. Once the macrophage is activated, the molecules which actually participate in the killing are not completely understood. NO may play a role, as may H_2O_2; however, there are probably mechanisms yet to be defined which play a dominant role. What is clear is that *Mycobacterium* spp. and *Salmonella* spp. are killed in a fashion distinct from that used to kill *T. gondii* and *L. monocytogenes*. Macrophage killing of mycobacteria and *Salmonella* spp. appears to be completely due to gamma interferon, while the intracellular killing of *L. monocytogenes* and *T. gondii* in human cells is mediated equally by gamma interferon and TNF-α (137). This is consistent with what is seen in patients with defects in the gamma interferon receptor complex, who have markedly increased susceptibility to *Mycobacterium* spp. and *Salmonella* spp. but not to *L. monocytogenes* and *T. gondii*. In fact, several patients with IFNGR1 mutations have had confirmed exposures to *T. gondii* without experiencing overt disease (137).

Initially, *Mycobacterium* spp., *Salmonella* spp., *L. monocytogenes*, and *T. gondii* are bound by TLRs. For mycobacteria, these TLRs appear to be primarily TLR2 and TLR4. Once the mycobacteria are taken up by macrophages, the NF-κB and MAP kinase pathways are activated. This leads to upregulation of costimulatory molecules on the macrophage, which in turn activates T cells. TNF-α, gamma interferon, and IL-12 are released, which further enhances containment and killing (195). Gamma interferon leads to improved antigen presentation, increased expression of TLRs, and further activation of the macrophage. Activation of macrophages leads to increased production of lytic enzymes, chemokines, reactive oxygen species, and an increased metabolic rate. At the extreme, macrophages become epithelioid giant cells comprising granulomas. The final activation of the macrophage elicits the production of NO and other reactive oxygen species. NO has been directly demonstrated to be required for mycobacterial killing in murine cells (41), while killing of mycobacteria appears to be NO independent in human monocytes and alveolar macrophages (267). This, coupled with the finding that patients with CGD develop mycobacterial disease only infrequently, has led to speculation that the killing mechanism may be less dependent on reactive oxygen species in human cells than in mice. The recent identification of intracellular molecules with pattern recognition potential, such as NOD2, may allow further definition of the final pathway responsible for killing mycobacteria in humans (130, 205, 206).

Immunity to mycobacteria represents a concerted effort by a number of cells. The role of the T cell has long been recognized, and T cells play a significant role in the containment of mycobacteria within granulomas (211). It is thought that cytotoxic T cells contribute to mycobacterial stasis through the secretion of perforin and granulysin (264).

The circuit shown in Fig. 5 relies heavily on the coordinated interactions of cells and cytokines. The three main cytokines involved in this circuit are gamma interferon, TNF-α, and IL-12. Gamma interferon is secreted as a homodimer primarily by Th1 T cells and NK cells (Fig. 6) (40). The receptor is composed of two gamma interferon receptor 1 chains and two gamma interferon receptor 2 chains. These are already bound to inactive JAK1 and JAK2, respectively. On ligand binding, the receptor subunits approximate and JAK1 and JAK2 are
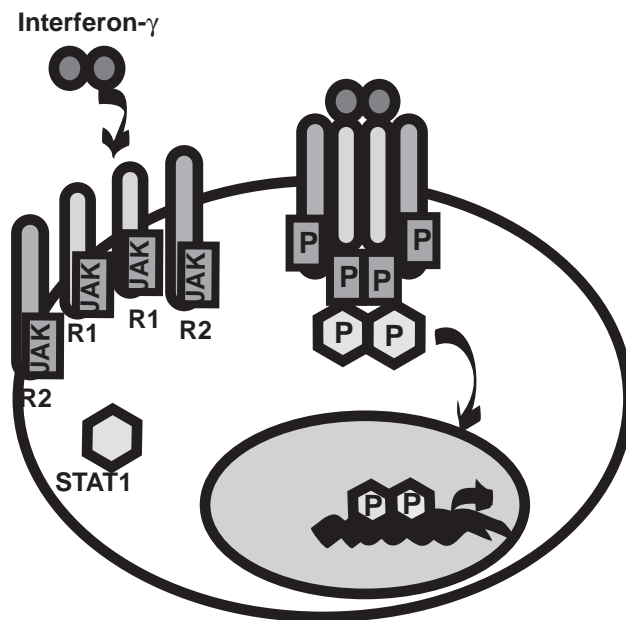

FIG. 6. Gamma interferon binds its receptor and activates STAT1. It acts as a dimer and binds to the receptor chains. Once the complex is formed, STAT1 is recruited to the receptor complex, where it is phosphorylated (P) and dimerizes. The STAT1 dimer is a potent transcription factor which activates transcription of an array of inflammatory mediators.

activated by phosphorylation. This act leads to recruitment from the cytoplasm of STAT1 monomers, which bind to the complex and are themselves phosphorylated (40). Phosphorylation is a prerequisite for homodimerization of STAT1 and translocation to the nucleus, where a broad range of STAT1-inducible genes are upregulated.

The production of gamma interferon is regulated by IL-12 (52, 103, 174, 249). This cytokine is produced primarily by antigen-presenting cells and consists of a heterodimer of 40- and 35-kDa subunits. IL-23 shares the p40 subunit from IL-12 (208). IL-12 binds a receptor which is also a heterodimer of IL-12Rβ1 and IL-12Rβ2. The β1 subunit is also shared by the receptor for IL-23 (213). The fact that no patients with Mendelian inherited susceptibility to mycobacteria have had IL-12 p35 or IL-12Rβ2 deficiencies perhaps suggests that IL-23 plays an important role in mycobacterial killing.

TNF-α is critical for granuloma formation, and its relevance in mycobacterial killing has been demonstrated in patients who receive therapeutic TNF-α inhibitors. Approximately 300,000 people have received these drugs, and 8 cases of nontuberculous mycobacterial disease, >100 cases of *M. tuberculosis* infection, 9 to 16 cases of *H. capsulatum* infection, 12 to 17 cases of *L. monoctogenes* infection, 8 to 11 cases of *Aspergillus* infection, and 17 to 21 cases of *P. carinii* infection have occurred (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3779b2.htm). The patients who receive TNF-α inhibitors are often also receiving other immunosuppressive drugs, which could magnify the effect; however, mycobacterial disease is infrequently seen in immunocompromised patients outside of the transplant setting, suggesting that these infections are due primarily to the inhibition of TNF-α.

Pathogens Found in Patients with Disorders of Macrophage Function

Mycobacteria. Mycobacteria are the most common infectious agents in patients with disorders of macrophage activation. Nearly all of the patients with the macrophage activation disorders described above presented with mycobacterial disease (Table 7). There may be some selection bias toward evaluating patients with unusual mycobacterial infections as opposed to *M. tuberculosis.* Nevertheless, nontuberculous mycobacteria are the most common causes of infection seen in patients with inherited defects of macrophage function. Rapidly growing nonpigmented pathogenic species in the *M. fortuitum* complex are frequently seen (*M. fortuitum, M. peregrinum, M. chelonae, M. abscessus,* and *M. mucogenicum*). *M. smegmatis* may be either pigmented or nonpigmented and has been seen infrequently. The rapidly growing pigmented species have not caused infection in this unique patient population to date. The slowly growing *M. avium* complex (*M. avium* and *M. intracellulare*) is another group which is frequently found in patients with defective macrophage activation. The remainder of the mycobacterial species are fairly evenly divided between the photochromagen species and the scotochromagen species. The frequency of *M. avium* complex infections in patients with human immunodeficiency virus (HIV) and CD4 counts of <100 cells/mm^3 suggests that defense against this subgroup may be subtly different from that against other mycobacteria (202).

The mycobacterial disease is nearly always disseminated, and positive cultures have been obtained from draining fistulae, lymph nodes, and liver biopsy specimens. Patients from Europe with *M. bovis* BCG infections often report that the inoculation site never healed and the process evolved into a generalized lymphadenopathy with continued drainage from the inoculation site (212). Many patients have had unusual presentations requiring multiple biopsies before the diagnosis was established. Fever and adenopathy were occasionally confused with proliferative processes. A diagnostic algorithm may be used as a guide (Table 6); however, the limited number of patients known makes it likely that other presentations are possible.

Other intracellular bacteria. *Salmonella* spp. are typically ingested through contaminated food or water, and they must pass through the acid barrier of the stomach. The organisms interact with M cells that overlie the Peyer's patches, where they are rapidly internalized (147) and transported into the submucosal lymphoid tissue, from where they can enter the general circulation. The *Salmonella*-containing primary phagosome fuses rapidly with the lysosomal compartment in both macrophages and neutrophils (286). Just as for mycobacteria, a complex interplay of T cells, macrophages, and cytokines is required to eradicate *Salmonella* spp. Humoral immunity may offer protection from initial infection by acting as an opsonin and encouraging uptake by neutrophils (163). It is not surprising, based on the mechanism of host defense, that patients with macrophage activation disorders experience a high frequency of *Salmonella* infections. These infections are seen in 34% of patients with IL-12 or IL-12 receptor defects and in 7% of patients with defects in the gamma interferon receptor complex (80).

L. monocytogenes has been found in a single individual with complete gamma interferon receptor 1 deficiency (240). The frequency of infection may be low because exposures are infrequent. *L. monocytogenes* is a small, facultatively anaerobic, nonsporulating, catalase-positive, oxidase-negative, gram-positive bacillus. It typically enters the gastrointestinal tract and may be aided by concomitant infection with other organisms. Once it is in the bloodstream, hematogenous dissemination occurs. Both T cells and macrophages are important in the host defense against *L. monocytogenes* (258). Thus, defects in macrophage activation would be expected to increases susceptibility to *L. monocytogenes*.

Legionella spp. have been found in a single patient with a partial gamma interferon receptor 1 defect (141). This may have been a coincidental finding, but our understanding of the mechanisms of host defense against *Legionella* spp. suggests that there may be an increased susceptibility in patients with defects in macrophage activation. Organisms enter and replicate within respiratory epithelial cells. Alveolar macrophages phagocytose *Legionella* spp. avidly in the presence of antibody (194). The primary phagosome does not fuse with lysosomes, and the organisms proliferate until the cell ruptures. Macrophages activated with gamma interferon inhibit the proliferation of *Legionella* spp. (36). This suggests that patients with defects in macrophage activation could be at increased risk for *Legionella* infections even though only a single infection has been noted clinically.

Other causes of infection. Histoplasmosis was seen in a single patient with a partial defect in gamma interferon receptor 1 (212). *H. capsulatum* is present at various densities in soil around the world. It is not known if the low frequency in patients with macrophage activation defects is due to lack of exposure or lack of increased susceptibility. Infection begins with aspiration of conidia and uptake by neutrophils and macrophages via CD11/CD18 receptors. The conidia transform to yeast forms, which proliferate in macrophages (180, 200). T cells and macrophages provide active defense, and neutrophil antimicrobial peptides can inhibit the yeast forms. As with mycobacteria, granuloma formation is thought to be critical for containment. Therefore, it is likely that patients with inherited defects in macrophage activation are at increased risk of *H. capsulatum* infection.

Herpesvirus, parainfluenza virus, and respiratory syncytial virus infections have been found in single patients with complete gamma interferon receptor 1 defects (212). Varicella was found in a single patient with IL-12p40 deficiency. One could hypothesize that lack of an effect of gamma interferon on T cells led to poorer Th1 responses and impaired responses to viruses. It could also be hypothesized that lack of an effect of gamma interferon on NK cells could lead to increased susceptibility to herpesviruses. While all of these are theoretical reasons for these patients to have an increased risk of severe viral disease, it is striking how few patients have had severe viral infections, given the high rate of exposure.

Disorders Associated with Defective Responses to Gamma Interferon

The first genetically defined primary immunodeficiencies associated with Mendelian inherited susceptibility to mycobacte-

ria were defects in the gamma interferon receptor complex. Defects in the gamma interferon receptor 1 chain were the first described (Fig. 6). In 1996, four children from Malta were found to have multiple mycobacterial infections (201). All four children carried homozygous mutations leading to a truncated protein. Simultaneously, another child in France was reported to have fatal disseminated *M. bovis* BCG infection (140). She also had a mutation in the gamma interferon receptor 1 chain. Since the initial descriptions, over 50 patients with mutations in the gamma interferon receptor 1 chain have been described (6, 9, 65, 83, 123, 143, 223, 240, 243). Gamma interferon and TNF-α are the final common mediators of granuloma formation and intracellular killing. Thus, defects at this distal point are difficult to overcome therapeutically. This is borne out clinically, since nearly 20% of the patients with gamma interferon receptor 1 defects have died prematurely from infection. Demonstrating the importance of the macrophage specifically, the patients had detectable anti-mycobacterial antibodies and mycobacterially responsive T cells (140). In patients with gamma interferon receptor defects, *M. avium* was the most common infectious agent, occurring in 55% of the patients. Disseminated *M. bovis* BCG was seen in 43% of the patients, and *M. fortuitum*, *M. tuberculosis*, and *M. chelonae* were each seen in two patients (3% each). The remainder of the mycobacterial species were seen in single patients (212).

There is a spectrum of severity, and the severity of the biochemical defect correlates well with clinical severity. Both autosomal recessive (43%) and autosomal dominant (57%) forms exist (212). The autosomal dominant forms are generally somewhat leaky, and those patients have some ability to form granulomas. In addition, certain of the autosomal recessive mutations are associated with residual function. Patients with some residual receptor function do better clinically. In fact, in patients with residual function, treatment with gamma interferon is possible and can be beneficial (162). There is a mutational hot spot which typically leads to the production of one chain which is truncated in the cytoplasmic domain. While the mutant chain is unable to bind JAK1, the wild-type chain is competent. Over half of the children with gamma interferon receptor 1 mutations have this leaky autosomal dominant mutation with an attenuated phenotype, and few of these patients have died. In contrast, nearly 50% of those with complete absence of receptor function have died. Interestingly, the severity of the defect did not seem to affect the type of mycobacteria infecting the patients.

Only three patients with gamma interferon receptor 2 mutations have been described, and they all suffered from multiple mycobacterial infections (78, 81, 124). Two mutations led to premature stop codons, and the third was a partial defect due to a single amino acid substitution. All three patients had autosomal recessive patterns of inheritance.

STAT 1 is the primary effector of gamma interferon signaling (Fig. 6). The STAT1-deficient patients resembled those deficient in the gamma interferon receptor. The two patients both had recurrent infections with mycobacteria: one with *M. bovis* BCG and one with *M. avium* (86).

The clinical phenotypes of the human disorders were initially surprising. The gamma interferon and the gamma interferon receptor knockout mice had been studied for some years. These mice were known to have an increased susceptibility to viruses, intracellular and extracellular bacteria, and certain parasites (69, 129). The explanation for the more limited phenotype seen in humans may have to do with the type and size of inoculum typically used in murine experiments. There is also evidence that the effect of the mutations in humans is more limited with respect to Th1 T-cell differentiation (69, 140).

Disorders Associated with Defective Production of Gamma Interferon

Nearly 40 patients with defects in either IL-12 or the IL-12 receptor have been described. Interestingly, all cases have been due to defects in the subunit that is shared with IL-23. All of the IL-12 defects have been in the IL-12p40 subunit, and all of the receptor defects have been in the IL-12Rβ1 subunit. This has suggested that the effects of IL-23 are at least as important in the defense against mycobacteria as are those of IL-12. IL-12 and IL-23 have many overlapping functions, although IL-23 induces a profound systemic inflammatory disorder and appears to have a more potent inducing effect on dendritic cells (30, 292). IL-23 and IL-12 both act on T cells, but IL-23 directs the proliferation of memory T cells while IL-12 acts predominantly on naive T cells to polarize their subsequent cytokine production (Fig. 3) (97). How these actions could be relevant to host defense against mycobacteria is not known. It may be that the actions of IL-23 on T cells are significant in granuloma formation.

The IL-12p40-deficient individuals have thus far had complete defects inherited in an autosomal recessive fashion (10, 88, 221). Similarly, all but one of the cases of IL-12Rβ1-deficient individuals have had complete deficiencies, which have been inherited in an autosomal recessive fashion (5, 8, 11, 71, 88, 247, 274). One leaky mutation in the IL-12Rβ1 gene has been described, and the only manifestation in this patient was recurrent *M. bovis* BCG infections (212). It is of interest that deaths are more frequent in the IL-12-deficient individuals (44%) than in the IL-12 receptor-deficient individuals (19%) (212). It is also noteworthy that *Salmonella* infections are more common in the patients with defects in IL-12 and the IL-12 receptor (34%) than in the patients with gamma interferon receptor defects (7%) (212). Both of these clinical observations may have to do with the fact that IL-12 can act to promote intracellular killing independently of gamma interferon (190). In addition, IL-12 plays an important role in the induction of chemokine expression, which serves to regulate the migration of immunologically competent cells (266, 282). Patients with defects in IL-12 or the IL-12 receptor have a similar distribution of mycobacterial species, and the infections are nearly always disseminated. *M. bovis* BCG has been seen in 68% of these patients, and *M. avium* has been seen in 16%. Other mycobacterial species were seen in single patients (212).

It is thought that the clinical similarity of the gamma interferon receptor defects and the IL-12 and IL-12 receptor defects in humans is because they all lead to impaired production of intracellular moieties which kill pathogens. In this model, the main effect of IL-12 and IL-12 receptor deficiencies may be the impaired stimulation of gamma interferon production. A few patients have been treated with gamma interferon in an effort to bypass the defect, with limited success (10, 153), providing support for the concept that it is the integrity of the

TABLE 8. Phenotypic features in EDA-ID patients[a]

Phenotypic feature	No. of patients affected/total no. (%)
Ectodermal dysplasia	24/24 (100)
Osteopetrosis	6/24 (25)
Lymphedema	3/15 (20)
Bronchiectasis	2/2 (100)
Mycobacterial infections	8/24 (33)
Severe bacterial infections	23/24 (96)
Severe viral infections	1/14 (7)
Severe fungal infections	2/22 (9)
Hypogammaglobulinemia	7/9 (78)
Elevated IgM Levels	4/7 (57)
Elevated IgA Levels	5/9 (56)
Poor antibody responses to polysaccharide antigens	6/7 (86)
Increased B-cell counts	2/5 (40)
Decreased	13/24 (54)

[a] Compiled from references 1, 18, 19, 79, 136, 175, 210, and 300.

circuit which is critical for the defense against intracellular organisms.

EDA-ID is a disorder of males which is allelic with the female disorder incontinentia pigmenti (18, 175). The clinical features of incontinentia pigmenti are a streaky vesicular rash in early infancy, which resolves with hyperpigmentation. Patients also have abnormal retinal vessels, missing and deformed teeth, and neurologic symptoms. Incontinentia pigmenti is generally lethal in males and is caused by defects in the regulatory subunit of IKK, which is encoded on the X chromosome (259). The regulatory subunit is referred to as IKK-γ or NF-κB essential modulator. Most patients with incontinentia pigmenti bear a frameshift mutation leading to premature termination and failure to produce active protein (19). Recently, four male patients with dysgammaglobulinemia, frequent infections that did not improve after administration intravenous gammaglobulin, abnormal dentition, and ectodermal dysplasia were described (300). These patients had mutations in IKK-γ which allowed the production of dysfunctional protein. The mutations identified to date have been diverse but have been consistent in allowing the production of partially functional protein.

The phenotype (Table 8) is easily explainable on the basis of impaired activation of NF-κB (151). The dysgammaglobulinemia is probably due in part to impaired signaling through CD40, which directs isotype switching via an NF-κB-dependent pathway (33). Two patients have had osteopetrosis due to defective osteoclast differentiation which is NF-κB dependent, and this mechanism is probably the basis for the abnormal dentition (94, 128).

The immunodeficiency is more pleomorphic in this disorder than in the other macrophage function defects being described. While mycobacterial infections are a prominent feature, other infections and bronchiectasis are common findings. The macrophage dysfunction is probably due to impaired activation of NF-κB; however, it appears to be stimulus specific. In one study, IκBα was normally degraded in monocytes of EDA-1D patients after LPS stimulation and was abnormal after CD40L stimulation (136). This suggests that monocyte responses to T cells are critically affected in EDA-ID patients. Monocytes typically produce IL-12 and gamma interferon after CD40L

stimulation, and these cytokines were not seen in supernatants of cultures of patient cells (136). Cytokine production after stimulation through TLRs was preserved. NF-κB is also required for responses to IL-1, IL-18, and TNF-α, which may contribute to the severity of the immunodeficiency and the inability to compensate with intravenous gamma globulin (79). B-cell defects have been demonstrated, with a failure to signal through CD40 and a picture similar to X-linked hyper-IgM syndrome, with elevated IgM levels and normal or depressed IgG levels (136). T-cell function appears to be largely normal in patients with EDA-ID, although NK cell function is impaired (209). This population does not have many severe viral infections, but prolonged or recurrent herpesvirus infections have been seen.

The patients with EDA-ID have a marked predisposition to bacterial infections. Specific bacteria described in this population are *S. pneumoniae*, *S. aureus*, *Enterococcus faecalis*, *P. aeruginosa*, and *H. influenzae* (1, 18, 79, 136, 175, 209, 300). Some of the infections are probably due to the compromise in forming antibody to polysaccharide antigens. In most (but not all) cases where it was examined, the patients either failed to develop isohemagglutinins or antibodies to polysaccharide pneumococcal antigens. This doubtless contributes to the high frequency of penumococcal disease in this population. The mycobacterial infections are similar to what is seen in patients with the other macrophage defects, with a preponderance of atypical mycobacteria.

MANAGEMENT ISSUES

Neutrophil Disorders

Management of neutrophil disorders is complex. Diagnosis of the immunodeficiency provides important insights into the types of infections to which the patient is susceptible. It also defines a therapeutic strategy in some cases. For example, patients with Chédiak-Higashi syndrome usually receive a stem cell transplant near the time of diagnosis in an effort to prevent the accelerated phase, which has a high mortality rate (25, 74). Similarly, patients with the severe form of LAD, in which there is no detectable expression of the β2-integrins, should receive a stem cell transplant soon after the diagnosis is established (13). Supportive and conservative measures for these patients are insufficient, and the risk of stem cell transplantation is low compared to the risk of death in the absence of that intervention.

Patients with neutropenia have an improved quality of life when treated with G-CSF to stimulate neutrophil production and survival. Patients with myelokathexis and glycogen storage disease type Ib have benefited from G-CSF treatment (50, 127). In addition to improved neutrophil counts, the G-CSF improves function.

Initial therapy. The initial therapy for any infection in patients with a neutrophil disorder should be tailored to the specific organism and its susceptibility pattern. The possible infecting organisms are legion, and culture of significant infections is essential. Complicating the management is the fact that infections in patients with neutrophil defects often present in atypical ways. In CGD patients, fever is often delayed and symptoms may be nonspecific. Fungal infections can be indo-

lent, and in some cases a rising erythrocyte sedimentation rate and mild discomfort are the only indication. In patients with LAD, the infections may progress very rapidly from an innocuous skin papule to a large necrotic ulcer with dissemination. A general strategy is to treat infections in patients with neutrophil defects aggressively and for a longer period than what would be typical for a host without these defects. For example, fungal infections are usually treated for at least a month after radiologic evidence of cure and the erythrocyte sedimentation rate and C-reactive protein have normalized or plateaued at a low level. The more severe neutrophil defects such as Chédiak-Higashi syndrome, glycogen storage disease type Ib, myelokathexis, CGD, LAD, and specific granule deficiency nearly always require prolonged antibiotic therapy for infections. White cell transfusions have a history of success in CGD and LAD patients and would be expected to be beneficial in serious infections arising in any patient with a neutrophil disorder (277, 299). Several of the neutrophil disorders benefit from the use of immunomodulatory agents, and two of the disorders, LAD and Chédiak-Higashi syndrome, are usually treated by stem cell transplantation soon after the diagnosis of the immunodeficiency is established.

Nearly all of the neutrophil disorders are associated with gingivitis, and this can be the major management issue faced by patients with mild LAD and Papillon-Lefèvre syndrome. There is little consensus; however, aggressive dental scaling and hygiene are thought to be beneficial for the gingivitis as well as for the prevention of disseminated disease from the gingiva. Here too, culture can be instructive. *A. actinomycetemcomitans* is often an important pathogen. Treatment with systemic amoxicillin and metronidazole or amoxicillin and a quinolone is usually effective, but in infections with multiple organisms, different combinations may be required (23, 270). Treatment is prolonged and may be lifelong.

Patients with neutrophil disorders are often predisposed to deep abscesses, which require surgical treatment in addition to prolonged antibiotics (189, 228). In the absence of adequate neutrophil killing, antibiotics are insufficient to kill large accumulations of infection. Female carriers of X-linked CGD with as few as 10% normal neutrophils have no increase in infections, suggesting that granulocyte transfusions, although imperfect, can provide a significant increase in microbicidal activity and clinical benefit. For serious infections, granulocyte transfusions are appropriate. Concern about side effects and alloimmunization in a population potentially treated by stem cell transplantation limits the use of granulocyte transfusions to seriously ill patients.

Chédiak-Higashi syndrome occasionally presents in the accelerated phase. There is no evidence that treatment of potential viral triggers modifies the process. In fact, the mainstay of treatment is immunosuppression. Most of the current protocols involve the use of steroids, cyclosporin A, and VP-16 in combination. Intrathecal therapy is required if there is central nervous system involvement. Once remission is established, a stem cell transplant should be arranged. Transplants undertaken during the accelerated phase are associated with particularly high risk.

Empiric therapy. Empiric therapy in patients with neutrophil defects is unsatisfying because of the broad range of potential infecting organisms. Nevertheless, it is sometimes un-

avoidable because of the tenuous clinical condition of the patient or the inaccessible nature of the infection. Biopsies in CGD patients will occasionally be unrevealing in spite of ample evidence of infection, perhaps because the exuberant granulomas encase the infection. In LAD patients, cultures of surface infections often contain multiple organisms, and colonization versus infection can be difficult to distinguish. Fortunately, the majority of infections in patients with LAD and CGD are limited to a few organisms, and it is often possible to devise a strategy that addresses many of the potential organisms. The five most common pathogens in CGD patients are *S. aureus*, *B. cepacia*, *S. marcescens*, *Nocardia* spp., and *Aspergillus* spp. (253). Most physicians would not undertake empiric therapy for fungal infections unless there was strong supportive evidence. Therefore, initial empiric therapy is usually directed at *S. aureus* and gram-negative organisms. CGD patients with suspected fungal disease are often initially given amphotericin or voriconazole. The unpredictable absorption of itraconazole makes it a poor choice for treatment of an acute infection. Patients with LAD most often suffer from infections with *S. aureus*, *P. aeruginosa*, and enteric gram-negative organisms. The potential range of infections is broader than what is seen in CGD patients, and there have been no systematic studies of the organisms causing infection at different sites. Dissemination, sepsis, and progressive necrosis are terrible consequences of infections that often begin innocuously. Therefore, empiric therapy is often extremely broad spectrum. Fungal infections are less common than what is seen in CGD patients, and therefore empiric therapy for fungi is needed less frequently. *Candida* spp. are the major fungal pathogens.

The less severe neutrophil disorders are associated primarily with *S. aureus* and *Pseudomonas* infections. Gingivitis again requires special consideration. Many institutions do not offer the special cultures required to define the infecting species. Empiric therapy with tetracyclines, amoxicillin plus metronidazole, metronidazole, clindamycin, or quinolones may be attempted if culture is not available (280).

Immunomodulatory therapy. Stem cell transplantation is the most radical immunomodulatory intervention. Most caregivers would agree that it is clearly indicated for severe LAD and Chédiak-Higashi syndrome (110, 268). It is, in principle, an effective therapy for all of the neutrophil disorders. The risk associated with stem cell transplants limits their use to patients at high risk of morbidity or mortality. It has also been performed for CGD and Schwachman syndrome, although there is no consensus about patient selection (21, 27, 161).

Immunomodulatory therapy more typically refers to cytokine therapy. Gamma interferon has been used to both treat and prevent infections in patients with CGD. There is controversy about its mechanism of action, but a large multicenter study showed a 70% reduction in infections (132a). The usual dose is 50 $\mu g/m^2$ subcutaneously three times a week. Side effects seem to be less of an issue in children than in adults and consist of flu-like symptoms and fever. Premedication with acetaminophen is beneficial. There has been concern that one long-term consequence of the use of gamma interferon would be an increase in inflammatory disorders. This has not been noted thus far in patients (31). Gamma interferon has also been used acutely in patients with active infection. It has also

been infused via catheter topically to treat liver abscesses (111, 158).

G-CSF has a long history of use for congenital neutropenia. It improves neutrophil counts in patients with disorders associated with neutropenia and improves function in patients with myelokathexis and glycogen storage disease type Ib (50, 127, 287). It is used cautiously in patients with Schwachman syndrome and significant morbidity from infections. Myelodysplasia and malignancy have been seen in patients receiving G-CSF; however, patients with congenital neutropenia and Schwachman syndrome are known to have an increased predisposition to these disorders. It is not known whether G-CSF increases the risk. The side effects of G-CSF are generally manageable. Acutely, it is associated with musculoskeletal pain. Splenomegaly occurs with sustained use, and hypersplenism has led to splenectomy in some cases. Bone density should be monitored in patients receiving significant doses.

GM-CSF has been used topically for patients with nonhealing ulcers. This is primarily a problem in LAD patients; however, it has been used to treat other conditions with success (227, 257). The GM-CSF promotes healing, and its role in infection per se is not known. It is administered as a sterile 5-μg/ml solution in water. The ulcer dressing is soaked with GM-CSF four times a day.

Prophylaxis. Most patients with one of the severe neutrophil disorders require antimicrobial prophylaxis to prevent infections. Antimicrobial prophylaxis plays an important role; however, the risk of microbial resistance is a growing threat. Some centers use a rotating series of antibiotics for prophylaxis in an effort to prevent the emergence of resistance. There is no evidence that this is beneficial on an individual patient basis; however, it decreases population resistance in an intensive care setting (234). There have been only a few studies evaluating the role of antimicrobial prophylaxis for immunodeficient patients. The use of co-trimoxozole is standard practice for patients with CGD, and the prophylactic use of itraconazole is often advocated (188, 285). In addition, most CGD patients receive gamma interferon as a prophylactic agent because of its ability to reduce the frequency of hospitalizations (132a). CGD patients often benefit from education regarding high-risk exposures. Marijuana contains fungal spores that could be problematic, and stagnant water could also potentially lead to infection. Other settings where exposure to mold or fungus is likely should be avoided.

Prophylaxis for LAD is usually required and is often based on the assumption that *S. aureus* is the dominant pathogen for the skin. This does not address periodontitis, but some patients can tolerate local therapy for the gingiva. Prophylaxis for LAD often uses co-trimoxazole or dicloxacillin. Patients with significant infections by gram negative bacteria could benefit from metronidazole prophylaxis. No controlled trials have been performed to elucidate the role of prophylaxis for this patient population. Antifungal prophylaxis has not been widely used in this patient population.

The other neutrophil disorders often require prophylaxis with co-trimoxazole or another antibiotic with a restricted spectrum of activity. The risk of bacterial resistance must be weighed against the benefit to the patient of minimizing infections.

Aberrant inflammatory responses. Two of the neutrophil disorders demonstrate aberrant healing or aberrant inflammatory responses which can cause significant morbidity. One of the major chronic issues for patients with CGD are the granulomas (28, 63, 244). These can cause obstruction of the gastrointestinal tract, urinary tract, or airways. It is sometimes difficult to determine whether there is an underlying infectious component. Generally, a short course of steroids does not exacerbate genuine infection and can provide significant relief from obstruction. Two exceptions are diffuse pulmonary granulomas and Crohn's-like colitis. Pulmonary disease may require very prolonged steroid therapy. Crohn's-like colitis also often requires a prolonged course or even administration of a second immunosuppressive agent. The colitis causes significant morbidity and occurs in approximately 30% of patients with CGD. One case of Crohn's-like colitis responded to G-CSF administration (191). For patients who are not receiving antimicrobial prophylaxis, immunosuppression warrants the administration of both co-trimoxazole and itraconazole. Gamma interferon may drive the formation of granulomas, and management of granulomatous disease in patients receiving gamma interferon may require dose modification if the granulomas persist after a course of steroids.

CGD patients and mothers of CGD patients with the X-linked form have a markedly increased risk of discoid lupus erythematosus and systemic lupus erythematosus (295). The mechanism underlying this association is not known. It is another example of aberrant inflammation, and the lesions often respond to topical approaches rather than systemic immunosuppression.

Patients with LAD experience a type of ulcerative colitis which is distinct from that seen in CGD patients (68, 238). This colitis has generally responded to intensive antibiotic therapy and white cell transfusions. Immunosuppression has not been used. The basis of this complication is not understood but may relate to the abnormal healing seen in this disorder. Cutaneous ulcers often heal slowly, poorly, and with an atrophic scar which is susceptible to further infection (13). Topical administration of GM-CSF can be of benefit, as described above.

Macrophage Disorders

Initial therapy. Accurate diagnosis of mycobacterial infection through biopsy and culture is essential. The antimycobacterial agents may be best selected on the basis of in vitro sensitivities. There are imperfections in the current analyses being used for determining antimycobacterial sensitivities, and certain in vitro sensitivities do not translate to clinical efficacy. With that caveat, in vitro sensitivities can be used to help guide therapeutic options for the less well known mycobacteria. Mycobacteria from the *M. fortuitum* group are often sensitive to amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, sulfonamides, or imipenem (179). *M. abscessus* and *M. chelonae* are often sensitive only to amikacin, cefoxitin, imipenem, and clarithromycin or only amikacin, imipenem, tobramycin, and clarithromycin. Treatment of *M. avium* involves a multidrug regimen including clarithromycin and ethambutol (70, 108). Rifabutin does not appear to enhance eradication of the mycobacteria but does protect against the development of cla-

rithromycin resistance (32). Rifamycin may play a role, but this requires additional study.

The case reports detail many difficulties in diagnosing the initial mycobacterial infections. For patients who present with disseminated *M. bovis* BCG infections, there is usually persistent drainage from the inoculation site. Even those cases have occasionally required multiple biopsies before the diagnosis was established (140, 162, 223). Two patients were initially diagnosed with histiocytosis X, and initial staining did not reveal mycobacteria (142). Other patients have had biopsies which showed chronic inflammatory changes but no evidence of mycobacteria. Two patients with complete gamma interferon receptor 1 deficiency were treated with immunosuppressive drugs for presumed autoimmune disease and on subsequent biopsy were found to have acid-fast bacilli within the chronic inflammatory infiltrates (162, 223). In acknowledgement of the difficulty in establishing a diagnosis of the mycobacteria and the underlying immunodeficiency, a diagnostic algorithm was recently developed in an effort to assist in the prioritization of patient evaluations (Table 4). The diagnostic studies are not widely available and are not performed in a standard fashion at present. It is therefore critical to define the patient population most likely to benefit from this labor-intensive analysis. On the other hand, timely diagnosis of the underlying immunodeficiency is important to deliver the appropriate aggressive care required in this patient population.

Once the diagnosis of an inherited susceptibility to mycobacteria has been established and the infecting mycobacteria have been identified, it becomes important to determine whether a biological agent could augment therapy. Gamma interferon is unquestionably beneficial, although patients with complete deficiencies of gamma interferon receptor 1 or gamma interferon receptor 2 would not be expected to respond (153). Treatment with antimicrobials with or without gamma interferon is usually tailored to the individual, but long courses of therapy (up to 2 years) are common (142). Relapses are frequent, and there may be a role for lifelong prophylaxis in patients particularly at risk. High-risk patients would include those with any type of complete deficiency or those with a history of recurrent disease.

Salmonella infection is the other common type of infection in patients with inherited defects in macrophage function. Approximately 25% of patients develop an infection with a *Salmonella* sp. (153). The infections are more frequently either disseminated or extraintestinal than in the general population. As with mycobacterial disease, recurrences and relapses are common. Cultures of abscesses, blood, intestinal secretions, and bone marrow should be considered to establish the diagnosis. A prolonged course of therapy should be considered.

Antimicrobial resistance among human nontyphoidal *Salmonella* isolates is increasing worldwide due to the widespread use of antimicrobial agents in humans and domesticated animals. High rates of resistance to chloramphenicol, trimethoprim-sulfamethoxazole, and ampicillin have been reported in Africa, Asia, and South America and are seen with increasing frequency in North America and Europe (269). Some nontyphoidal *Salmonella* infections are resistant to third-generation cephalosporins. Therefore, culture is essential to define sensitivities. A treatment regimen developed for patients with AIDS is to initiate treatment with 1 to 2 weeks of intravenous antimicrobial therapy followed by 4 weeks of oral quinolone therapy (135). AIDS patients who relapse after 6 weeks of quinolone therapy are usually treated with long-term suppressive therapy with a quinolone or trimethoprim-sulfamethoxazole. This strategy could be used as a starting point for treating *Salmonella* infections in patients with a functional macrophage defect. Particular care seems warranted for focal *Salmonella* infections which seem to require both drainage and very aggressive antimicrobial therapy. Persistent carriage is a significant risk in patients with impaired immunity, and patients may benefit from treatment of long-term carriage to prevent recurrences or relapses (96, 204, 248). Amoxicillin, trimethoprim-sulfamethoxazole, ciprofloxacin, and norfloxacin are effective in eradication of long-term carriage. The high concentrations of amoxicillin and quinolones in bile are theoretical advantages.

A few cases of significant herpesvirus infections have been found in patients with gamma interferon receptor 1 deficiency (82). The mechanism underlying this predisposition is not known. The observation that it was limited to a very small number of patients with gamma interferon receptor 1 deficiency, while many others had normal courses of varicella or measles, suggests that it may have to do with the influence of background genes or concomitant infection which may influence an abnormal immune response. For patients with a severe herpesvirus infection, antiviral therapy should be considered. For patients with EDA-ID, standard antiviral therapy plus IL-2 has been successful in treating one case of chronic cytomegalovirus infection (209).

Empiric therapy. Empiric therapy for mycobacterial infections is undesirable, and it is worthwhile to obtain additional samples for culture rather than to attempt an empiric treatment regimen. This is largely because the mycobacterial species vary so drastically in their sensitivities. Broad-based empiric therapy is undesirable because each of the drugs is associated with significant side effects. If necessary, empiric therapy in patients who received *M. bovis* BCG should include rifampicin, isoniazid, ethambutol, and clofazimine. Patients with suspected mycobacterial disease who have not been vaccinated with *M. bovis* BCG and have no known exposures to *M. tuberculosis* should receive a combination including rifampicin or rifabutin, clarithromycin or azithromycin, and a quinolone. Empiric therapy for *Salmonella* spp. is not usually required because these bacteria are easily cultured even when associated with extraintestinal disease.

Immunomodulatory therapy. Therapy with gamma interferon is currently the only available immunomodulatory therapy. It has been used successfully for acute therapy (3 to 50 $\mu g/m^2$ initially, with stepwise increases if necessary) but could be considered for prophylaxis in patients at risk of recurrence or relapse of mycobacterial disease (10, 81, 140). It would not be expected to benefit patients with complete gamma interferon receptor 1 defects because that receptor is necessary to transduce signals from gamma interferon. IL-12 therapy has not been attempted.

IL-2 therapy for chronic cytomegalovirus infection has been attempted in a single patient with EDA-ID (209). IL-2 has been used to treat selected patients with primary immunodeficiencies and defective NK cell function. It is thought to induce NK cell activity.

Prophylaxis. Preventive strategies for *L. monocytogenes* and *Salmonella* infections should be instituted. Immunization with the inactivated Typhoid Vi vaccine could be considered in areas where typhoid is endemic. The numbers of *M. avium* infections can be reduced by the use of prophylactic antimicrobials in the HIV-positive population. Rifabutin (300 mg daily), clarithromycin (500 mg twice daily), and azithromycin (1,200 mg weekly), either alone or in combination with rifabutin, have all been shown in controlled trials of HIV-positive adults to be effective as prophylactic agents for the prevention of *M. avium* infections (117, 185, 222). While unproven in this population with an inherited susceptibility to mycobacteria, it is likely that rifabutin would have similar clinical efficacy. For patients with a clinical response to gamma interferon, it could be considered a prophylactic agent. In patients with CGD, long-term prophylaxis with gamma interferon has been well tolerated (31).

CONCLUDING REMARKS

Many of the disorders described in this review are uncommon. Nevertheless, some generalizations can be drawn from this diverse set of uncommon disorders. Treatment of infections in patients with these primary immunodeficiencies requires sustained and aggressive antimicrobial therapy. Often, adjunctive treatment with cytokines or white cell transfusions is required. Another generalization is that many of the disorders increase the susceptibility of the host to a very limited number of organisms. For example, the macrophage disorders, with the exception of EDA-ID, all lead to increased susceptibility to *Mycobacterium* spp. and *Salmonella* spp. Only a few other infections are problematic. This allows the caregiver to focus on the diagnosis and therapy of a relatively small number of types of infections. The list is slightly longer for patients with CGD; however, the number of organisms most likely to cause infection at given site is still very limited.

The recent identification of the gene defects responsible for the macrophage function disorders has led to a new appreciation of the role of the innate immune system in the eradication of intracellular bacteria. Study of these disorders has also illuminated new cytokine-based treatment strategies which could be exploited to enhance the eradication of intracellular bacterial in competent hosts in the future.

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