Interferon-γ in the Management of Infectious Diseases

**Moderator:** John I. Gallin, MD; **Discussants:** Joshua M. Farber, MD; Steven M. Holland, MD; and Thomas B. Nutman, MD

Interferon-γ has pleiotropic adjuvant effects on host defenses. These effects have made interferon-γ particularly useful for enhancing host defenses in patients with chronic granulomatous disease of childhood and thus for reducing the incidence of life-threatening infections in these patients. Increasingly, data suggest that interferon-γ will be useful for treating infections characterized by intracellular persistence in macrophages, such as toxoplasmosis, leishmaniasis, and mycobacteriosis. Interferon-γ is emerging as an important cytokine for use in the treatment of infectious diseases.

*Ann Intern Med.* 1995;123:216-224.

Dr. John I. Gallin (Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland): The interferons are a group of proteins and glycoproteins that are produced in response to infection. They are species-specific and can be induced by many viral and nonviral agents, including bacterial lipopolysaccharides and parasitic protozoa. Interferon-γ will induce both itself and interferon-β (1).

The history of interferons dates back to the 1950s, when they were discovered and named for their ability to interfere with viral growth (2, 3). Interferon-γ was the first T-cell-secretory product described (4) and the first T-cell product cloned (5). The inducer agents for interferon-α and -β are usually viruses. Specific antigens and mitogens induce interferon-γ production.

Three major types of cells produce interferon-γ: CD4+ T cells, natural killer cells, and CD8+ T cells. Interferon-γ induces many elements of host defenses, including the stimulation of antibody production by B cells. Interferon-γ activates natural killer cells and neutrophils and prolongs neutrophil survival in vitro (6). Similarly, interferon-γ stimulates macrophage microbicidal and tumoricidal activity by inducing production of cytokines, such as tumor necrosis factor-α, reactive oxygen and nitrogen intermediates, and indolamine 2,3-dioxygenase (7). In addition, interferon-γ stimulates the formation of granulomas, which are of particular importance in host defense against intracellular pathogens. Other macrophage products induced by interferon-γ are major histocompatibility complex (MHC) class II antigens, Fc receptors, the leukocyte adhesion protein LFA1, endotoxin binding sites, and the receptor for the endotoxin-lipopolysaccharide-binding protein complex (CD14). Interferon-γ also modulates CD4+ helper T-cell function by regulating interleukin-4, interleukin-5, and interleukin-10. Of particular interest is that interleukin-4 inhibits many activities of interferon-γ, such as production of reactive oxygen products and the inhibitory effects of interferon-γ on IgE synthesis.

Interferon-γ activates endothelial cells, fibroblasts, epithelial cells, hepatocytes, and macrophages to kill intracellular pathogens such as Mycobacterium, Leishmania, Toxoplasma, Rickettsia, and Chlamydia species. Recently, interferon-γ has been shown to reduce the incidence of infections in patients with chronic granulomatous disease and to be an important adjuvant for the treatment of certain intracellular parasites (7).

**Mechanisms of Action**

Dr. Joshua M. Farber (Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases): The biological effects of interferon-γ, like those of interferon-α and -β, result primarily from the enhanced expression of a collection of genes and proteins in responsive cells (8). Interferon-γ has a six-helix monomer structure and exists as a symmetric, antiparallel homodimer that induces dimerization of its receptor (Figure 1) (9). The interferon-γ receptor consists of at least two components, a 90-kd glycoprotein (α) that is able to bind ligands (10) and a structurally related putative transmembrane protein that is necessary for signaling (β) (11).

Signaling through the interferon-γ receptor requires Jak1 and Jak2 (12), two members of a family of tyrosine kinases. By analogy with other systems involving the Jak-family kinases, the interferon-γ receptor and the Jak kinases probably exist in a preformed complex before ligand binding. Binding of interferon-γ leads to the phosphorylation of the interferon-γ receptor (13) and of Jak1 and Jak2 on tyrosine residues; this is presumed to lead to their activation. Jak1 and Jak2 are each necessary for the phosphorylation of the other after interferon-γ binds to its receptor. This requirement is the basis for imagining the juxtaposition of the Jak kinases on receptor dimerization, although the details of the interactions among the kinases and the receptor subunits are not known (Figure 1).

Jak-kinase activation leads, either directly or indirectly, to the phosphorylation on tyrosine of the 91-kd latent cytoplasmic factor Stat1α [Signal transducer and activator of transcription (STAT) protein, which in turn leads to the formation of Stat1α homodimers, mediated through...
protein domains (Src homology 2 domains) that bind tyrosine-phosphorylated proteins (14). Once phosphorylated and dimerized, Stat1α moves from the cytoplasm to the nucleus, where it binds to regulatory regions of genes containing GAS (γ interferon activation site) sequences. The GAS sequence (consensus TTNCNNNAA) was the first well-defined promoter element identified as specifically related to interferon-γ–dependent gene activation (15), and GAS-like sequences typically have been found in interferon-γ–inducible genes and serve as binding sites for Stat1α. Nonetheless, sequences in addition to GAS are clearly important for the activation of some genes by interferon-γ (16, 17). Although it appears that Stat1α dimers are able to bind to a core GAS site without other proteins, evidence indicates that Stat1α does form complexes one or more other proteins, as yet unknown, when binding to the regulatory regions of interferon-γ–activated genes (17). The signaling events in response to interferon-γ rely solely on preformed components and constitute a pathway for direct and immediate communication between activated receptor and gene (Figure 1).

Just as interferon-γ has biological activities that are distinct from and yet overlap those of other immunomodulating factors, such as interferon-α, interferon-β, and lipopolysaccharide, so too does interferon-γ induce a set of genes and proteins that, although unique, overlaps the sets of genes and proteins induced by these other factors (18). These relations are reflected in shared components that participate in a combinatorial fashion in forming the protein complexes that transduce signals from ligand-activated receptors to the inducible genes. The Jak kinases and Stat1α (or closely related STAT proteins) have been shown to participate in signal transduction in response to a range of cytokines and growth factors (15). Major unanswered questions remain about how the specificity of the response to a given cytokine, such as interferon-γ, is determined.

The importance of the activation of specific genes by interferon-γ lies, of course, in the encoded proteins that are newly expressed and that alter the physiology of the target cells. Several host defense proteins are induced in response to interferon-γ, including products of immediate response (GAS-containing) genes and some proteins whose induction requires the previous synthesis of the protein products of the immediate response genes (Table 1). The inducible proteins include surface molecules, such as MHC antigens important for antigen presentation; enzymes, such as the components of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthase (important in generating reactive oxygen and nitrogen species, respectively, for pathogen killing); transcription factors, such as interferon regulatory factor-1 (an immediate response gene necessary for the induction of the nitric oxide synthase gene); and cytokines, such as tumor necrosis factor-α.

Although interferon-γ is a potent modulator of production of tumor necrosis factor-α, it is not sufficient to induce tumor necrosis factor-α; rather, it acts synergistically with other tumor necrosis factor-α inducers. This raises the general point that interferon-γ works not in isolation but in the context of an immune response involving a collection of cell-surface and secreted molecules. One model that places interferon-γ in the context of the overall immune response to pathogens is the helper T-cell Th1/Th2 paradigm (19). Studies of murine CD4+ T-cell clones in long-term culture have shown that a given clone expresses one of two mutually exclusive phenotypes: the Th1 phenotype (characterized by the production of interferon-γ, interleukin-2, and tumor necrosis factor-β) and the Th2 phenotype (characterized by the production of interleukin-4, interleukin-5, and other related lymphokines). Although first defined and best studied in murine systems, the Th1/Th2 paradigm, in its general outline, is clearly applicable to humans (20).

Interferon-γ plays a critical role both in inducing the differentiation of CD4+ T cells to the Th1 phenotype and as the major product of Th1 cells, which are important for activating macrophage against intracellular pathogens. As shown in Figure 2, after activation by a pathogen, the...
Table 1. Host Defense Proteins Induced by Interferon-γ

| Protein | Function |
|---------|----------|
| Surface proteins | |
| Major histocompatibility complex antigens | Antigen presentation |
| High-affinity Fc receptor for IgG | Binding and phagocytosis of opsonized particles |
| Enzymes | |
| (2'-5') oligo A synthetase | (2'-5') (A) synthesis with activation of ribonuclease L |
| Indolamine 2,3-dioxygenase | Tyrosine degradation |
| NADPH oxidase | Superoxide generation |
| Nitric oxide synthase | Nitric oxide generation |
| Transcription factors | |
| Interferon-stimulated gene factor-3γ | Part of interferon-stimulated gene factor-3, complex responsible for gene activation by interferon-α |
| Interferon regulatory factor-1 | Necessary for expression of nitric oxide synthase |
| Cytokines | |
| Tumor necrosis factor-α | Macrophage activation, granuloma formation |
| Interferon-γ inducible protein 10 | Lymphocyte chemotaxis |
| Monocyte chemotactic protein 1 | Monocyte chemotaxis |

* NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.

macrophage secretes interleukin-12. Interleukin-12 stimulates the production of interferon-γ by T cells and natural killer cells (21), and interleukin-12 and interferon-γ bias the differentiation of uncommitted antigen-stimulated CD4+ T cells into Th1 cells. Interferon-γ produced by the Th1 cells and the natural killer cells further activates macrophages by inducing the expression of proteins such as those listed in Table 1, resulting in enhanced killing of pathogens. Interferon-γ also has an inhibitory effect on the development of the Th2 phenotype. In contrast to interferon-γ, interleukin-4 and interleukin-10 inhibit Th1 responses and have direct inhibitory effects on the activation of macrophages. The development of effective cell-mediated immunity against intracellular pathogens has been shown in mouse models to depend on the predominance of the Th1 response over the Th2 response and on the production of interferon-γ, the signature cytokine of Th1 cells.

Given the complexity of the system within which interferon-γ operates and the redundancy in host defense mechanisms, it is reasonable to ask the following question: In which biological responses does interferon-γ play a unique and necessary role? The most unambiguous information about this comes from recent experiments that used mice with targeted disruptions of either the interferon-γ gene (22) or the gene for the binding (α) subunit of the interferon-γ receptor (23). These “knockout mice” are unable to control infections with intracellular pathogens in which macrophages are known to be important, such as infections with the mycobacteria Bacillus Calmette-Guérin (BCG) (24) and Mycobacterium tuberculosis and with Listeria species (23). When the knockout mice were experimentally infected with BCG, macrophages isolated from these mice showed a decreased ability to produce reactive oxygen species, a complete inability to produce reactive nitrogen species, and decreased expression of MHC class II antigens.

Figure 2. Interferon-γ (IFN-γ) in the cytokine network. A macrophage (Mφ*) that has been activated by encountering a pathogen secretes interleukin-12, which stimulates T cells and natural killer (NK) cells to secrete interferon-γ and biases the differentiation of CD4+ cells into the Th1 phenotype. Interferon-γ produced by natural killer cells and Th1 cells activates macrophages for pathogen killing through the production of mediators such as superoxide (O2·), nitric oxide (NO·), and cytokines such as tumor necrosis factor-α (TNF-α). Interferon-γ inhibits the production of CD4+ Th2 cells. These cells are characterized by the production of interleukin-4, interleukin-10, and related cytokines. Interleukin-4 inhibits the development of Th1 cells; interleukin-10 inhibits cytokine production by natural killer and Th1 cells; and interleukin-4 and interleukin-10 both antagonize the effects of interferon-γ on macrophage activation. Although this scheme is based on data from studies in mice, the Th1/Th2 paradigm is applicable to humans.
necrosis factor-a is probably one of the important mediators of the action of interferon-γ in such infections and has been shown to play a role both in granuloma formation and in the direct control of mycobacterial infections. In addition, the knockout mice could not deal with vaccinia virus (23), although they had no difficulty in controlling infections with lymphocytic choriomeningitis virus or vesicular stomatitis virus. Therefore, even though interferon-γ is generally regarded as much less important in antiviral defense than interferon-α and -β, it plays a key role with vaccinia virus. Further studies with these mice will probably show additional unexpected defects in their ability to deal with specific pathogens.

Because many of the biological findings described above derive from studies in mice, the data may not apply to humans in every detail. For example, the role of nitric oxide as a host defense mechanism in humans remains unsettled because substantial production of nitric oxide by human macrophages has not been shown. Nonetheless, good evidence shows that, as the clinical data below will illustrate, the animal data generally delineate a mechanism of action for interferon-γ that applies to humans.

**Chronic Granulomatous Disease**

Dr. Gallin: Chronic granulomatous disease is an inherited, life-threatening pediatric immunodeficiency state characterized by recurrent pyogenic infections with catalase-positive microorganisms, excessive granuloma formation, and deficient bactericidal activity by neutrophils and mononuclear phagocytes (25). The abnormality in chronic granulomatous disease relates to a defect in NADPH oxidase, an enzyme essential for the conversion of molecular oxygen to hydrogen peroxide by phagocytic cells. This enzyme is a complex of at least five proteins; an abnormality in any of four of the proteins accounts for all forms of chronic granulomatous disease (26). Thus, chronic granulomatous disease is a group of disorders of oxidative metabolism in phagocytic cells, in which different genetic mutations of components in a complex enzyme system result in a common phenotype.

Current therapy for chronic granulomatous disease includes antibiotic prophylaxis with trimethoprim-sulfamethoxazole, prolonged courses of parenteral antibiotics for infections, and aggressive surgical intervention for drainage of abscesses. Some centers, including the National Institutes of Health Warren G. Magnuson Clinical Center, use leukocyte transfusions for life-threatening infections. In 1991, partly because of a multicenter, double-blind study done in the United States and Europe in which interferon-γ reduced the frequency of infection by more than 70% in patients with chronic granulomatous disease (27), the Food and Drug Administration approved the prophylactic use of subcutaneous interferon-γ in patients with chronic granulomatous disease. As a consequence, most physicians have begun using interferon-γ as a prophylactic agent in the management of chronic granulomatous disease.

Curnutte and colleagues (28) reported that 30 patients with chronic granulomatous disease, who were evaluated for 12 months while receiving interferon-γ after completion of the above study (27), had an incidence of 0.13 infections per patient-year. This was substantially less than the rate of 1.16 infections per patient-year seen in the placebo group in the double-blind study. The major reported adverse effects (fever, mild liver enzyme abnormalities, and mild neutropenia) were transient and resolved with dose reduction. Curnutte and colleagues concluded that interferon-γ therapy was effective and did not have unexpected toxicities.

We followed 34 patients at the National Institutes of Health Warren G. Magnuson Clinical Center who received interferon-γ for 3 years after the above-described double-blind study (27) was completed. Twenty-six of the patients with chronic granulomatous disease were children. No unexpected side effects were noted; normal growth and development occurred in the 25 children receiving the subcutaneous interferon-γ injection (50 μg/m² body surface area) three times per week. The major toxicities seen were headache, fever, and myalgias. In most patients, these side effects were relieved by pretreatment with acetaminophen. In a few patients, it was necessary to halve the dose of interferon-γ to achieve tolerance.

During the 3 years since the above-mentioned study (27), it has been our impression that patients with chronic granulomatous disease who are receiving interferon-γ have more pronounced clinical and febrile reactions to infections. Thus, interferon-γ helps the family and the physician recognize when a clinical event is serious and warrants an extensive work-up.

It is difficult to assess the benefit of interferon-γ in a phase IV follow-up study, because there can be no randomization of patients in such a study. This is particularly relevant because some participants in the original study (27) believed that they had less severe disease and declined to receive the agent during the phase IV follow-up. Furthermore, compliance was a problem in the phase IV study, especially among persons in adolescent populations. Nonetheless, 34 patients had well-documented periods of receiving and not receiving interferon-γ during the phase IV study. The incidence of infection when the patients were receiving or not receiving interferon-γ was assessed, allowing for a 1-month washout period when the patients were not receiving interferon-γ. In this group of patients, there were 1189 patient-months receiving and 648 patient-months not receiving interferon-γ. The incidence of bacterial infections was 0.528 per patient-year receiving interferon-γ and 0.372 per patient-year not receiving the drug; the difference was not significant ($P = 0.24$). Similarly, the incidence of fungal infection did not differ significantly between those receiving and those not receiving interferon-γ. The incidence per patient-year was 0.144 receiving interferon-γ and 0.168 not receiving interferon-γ ($P > 0.05$). Thus, the incidence of infections in patients with chronic granulomatous disease who received interferon-γ for 3 years after the completion of the double-blind trial was lower than that in the group receiving placebo in the double-blind trial (27), as noted by Curnutte and colleagues (28). However, there was no significant difference in infection rates in patients who stopped receiving interferon-γ after prolonged use. This finding suggests that patients receiving interferon-γ regularly for 1 August 1995 • Annals of Internal Medicine • Volume 123 • Number 3 219

Downloaded From: http://annals.org/ on 07/20/2018
1 to 3 years have a sustained benefit after therapy with the agent is discontinued, as originally suggested by Sechler and coworkers (29). The possibility that the effects of interferon-γ are sustained warrants further investigation to determine the appropriate frequency and duration of interferon-γ administration for prophylactic use in diseases such as chronic granulomatous disease.

**Mycobacteria**

Dr. Steven M. Holland (Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases): To date, two types of mycobacterial infections have been treated with interferon-γ: leprosy and infection with *M. avium* complex. Leprosy is caused by *M. leprae*, the Hansen disease bacillus, and afflicts about 12 million persons worldwide. It is probably transmitted from human to human, although not efficiently. Initial infection with *M. leprae* results in an indeterminate lesion that may progress into one of several subtypes of leprosy, the two polar forms of which are tuberculoid and lepromatous. Tuberculoid disease is characterized by circumscribed, contained infection; good immune response to *M. leprae* antigens; good granuloma formation; and few organisms seen in biopsy specimens. In contrast, lepromatous disease is characterized by diffuse, destructive tissue infiltration; no immune response to *M. leprae* antigens; no granuloma formation; and abundant organisms seen in biopsy specimens. During treatment for lepromatous leprosy, many patients have exacerbations of immune responses, including erythema nodosum leprosum, in which painful erythematous, subcutaneous plaques erupt and may ulcerate. These findings conform to the T<sub>H1</sub> and T<sub>H2</sub> phenotypes predicted from mouse models (Figure 2). The relative abundance of interferon-γ and interleukin-2 messenger RNAs were more abundant in tuberculoid lesions, whereas interleukin-4, interleukin-5, and interleukin-10 mRNAs were more abundant in lepromatous lesions. These findings conform to the T<sub>H1</sub> and T<sub>H2</sub> phenotypes predicted from mouse models (Figure 2). The relative abundance of interferon-γ in contained, circumscribed (tuberculoid) disease and its relative paucity in diffuse, disseminated (lepromatous) disease help provide a pathophysiologic rationale for the use of interferon-γ in the treatment of lepromatous leprosy.

Most studies of the treatment of leprosy with interferon-γ have used short-term intradigital administration (31). In general, the studies have used 3 to 6 doses of 10 to 20 μg each for 3 to 10 days. These studies have followed bacillary counts, lesional histology, cellular activation markers, and superoxide production. One study gave somewhat higher doses for 6 to 10 months after an induction period (32). The results have been encouraging. In studies in which interferon-γ was given in combination with antimycobacterial agents, bacillary counts in lesions in patients receiving combination therapy clearly decreased more than they did in patients receiving drug therapy alone. Lesional granuloma formation was enhanced, as was monocyte superoxide generation. Intraderal administra-

...
pathways are also augmented; these include the release of antimicrobial granule proteins, the degradation of tryptophan, prostaglandin synthesis, T-cell development, cytokine production, and antigen processing and presentation (1). In vitro, interferon-γ increases the intracellular concentration of certain antibodies, particularly macrokines (38). This may help to explain the importance of the simultaneous administration of interferon-γ and antimicrobial agents.

Protozoal Infections and Hyper-IgE States

Dr. Thomas B. Nutman (Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases): The practice of using interferon-γ in parasitic protozoal infections and in states associated with extreme elevations of IgE is based on two distinct, important actions of interferon-γ. For protozoan parasites, for which the infection is intracellular (primarily within macrophages), interferon-γ provides one of the major signals for activation of the macrophage, a process required for killing the parasite. Interferon-γ also appears to enhance the accumulation of chemotherapeutic agents within the macrophage, so that higher levels of a specific antiprotozoal agent are delivered to the site where the parasite lives (39). In hyper-IgE states (such as atopic dermatitis or the hyper-IgE recurrent infection [Job] syndrome), interferon-γ is used because it can down-regulate the production of IgE either by acting directly on the B lymphocyte itself or by modulating the expression of interleukin-4, the major cytokine involved in antibody class switch recombination to IgE.

Protozoal Infections

Toxoplasmosis and leishmaniasis are caused by obligate intracellular protozoa. In both infections, the production of interferon-γ has been shown, at least experimentally, to be absolutely critical for clearance of the parasite (39). Thus, it is in these two protozoal infections that interferon-γ has been either used (40-48) or considered for use in human infection.

Leishmanial Infection

The leishmaniases are caused by several genetically distinct intracellular parasites of Leishmania species, which are found worldwide. Both the clinical and the immunologic manifestations of leishmaniasis cover a wide spectrum, from localized cutaneous disease, with its associated strong delayed-type hypersensitivity reactions to leishmanial antigen, to the visceral form of the disease (kala-azar), which is associated with an inability to respond immunologically to leishmanial antigen.

The localized cutaneous form and the mucocutaneous form of leishmaniasis (in which both the skin and mucosal surfaces are involved) are characterized by the development of single or multiple ulcerating lesions that are initially found on exposed areas of the skin. Cutaneous leishmaniasis usually heals spontaneously. In Central and South America, where mucocutaneous disease occurs in as many as 2% to 5% of infected patients, spontaneous healing is somewhat less common. Both forms of leishmanial infection are associated with strong parasite-specific immune responses, including the production of interferon-γ (49), but in some situations the infection is neither self-limited nor sensitive to available chemotherapy. In single cases (Table 2) of patients with cutaneous or mucocutaneous leishmaniasis who were refractory to standard chemotherapy (pentavalent antimony), adding interferon-γ to the pentavalent antimony caused remission (44). Adding interferon-γ to the antimony regimen has been shown to allow a shorter duration (10 rather than 20 days) of antileishmanial drug administration (47). In one patient with refractory cutaneous leishmaniasis, adding interferon-γ to a regimen that included antimony induced healing (46).

Visceral leishmaniasis (kala-azar) is characterized by fever, massive hepatosplenomegaly, profound anemia, leukopenia, and thrombocytopenia, and it is often fatal without therapy. Visceral leishmaniasis and the diffuse cutaneous form of leishmaniasis, in which skin lesions are widely disseminated (plaques, papules, and nodules), are forms of the infection that are associated with profound immunologic defects. Patients with diffuse cutaneous leishmaniasis do not mount a delayed-type hypersensitivity response to intradermally administered leishmanial antigen or to recall antigens, such as Candida albicans or purified protein derivative. Lymphocytes from these patients cannot produce either interleukin-2 or interferon-γ in response to leishmanial antigen (50). Finally, this lack of interferon-γ, the cytokine responsible not only for inducing macrophages to kill leishmanial parasites but for concentrating the chemotherapeutic agents (such as pentavalent antimony [39] within macrophages), led to its use as an adjuvant to standard chemotherapy for these forms of leishmaniasis (Table 2).

Toxoplasmosis

Evidence indicates that the administration of cytokines, particularly interferon-γ, could be useful as adjuvant ther-

Table 2. Use of Systemic Interferon-γ with Pentavalent Antimony in Human Leishmanial Infection

| Condition                          | Patients, n | Patients Having Remission, n(%) | Reference       |
|-----------------------------------|-------------|---------------------------------|-----------------|
| Previously untreated visceral leishmaniasis | 23 (66)     | 6 (100)                         | 41-43           |
| Refractory visceral leishmaniasis  | 27 (69)     | 6 (100)                         | 40-43, 45       |
| Refractory diffuse cutaneous leishmaniasis | 1 (100)     | 1 (100)                         | 46              |
| Refractory mucocutaneous leishmaniasis | 1 (100)     | 1 (100)                         | 44              |
| Refractory cutaneous leishmaniasis | 22 (100)    | 22 (100)                        |                 |

**Annals of Internal Medicine** • Volume 123 • Number 3 • 1 August 1995
apy in the treatment of toxoplasmosis. Both interferon-\(\gamma\) and interleukin-2 have been shown to be important in controlling toxoplasmosis (42). Interferon-\(\gamma\) can inhibit the replication of *Toxoplasma gondii* in vitro. Indeed, in animal models of acute toxoplasmosis, administration of either interferon-\(\gamma\) (51) or interleukin-12, a cytokine that induces interferon-\(\gamma\) (52), has been shown to increase survival. Conversely, administration of neutralizing antibodies to interferon-\(\gamma\) has been shown to decrease survival (50). Finally, in several cases of persons with HIV infection who were receiving interferon-\(\gamma\) or interleukin-2, monocytes obtained during cytokine administration had a greater ability to inhibit the growth of *T. gondii* than did those obtained earlier or later (53, 54). Studies are under way to examine the utility of interferon-\(\gamma\) as an adjunct to chemotherapy.

Hyper-IgE States.

The use of interferon-\(\gamma\) in states associated with extreme elevations of serum IgE levels derives from the ability of interferon-\(\gamma\) to regulate the production of IgE by B lymphocytes. Interferon-\(\gamma\) acts directly on appropriately differentiated B cells to induce them to produce antibody isotypes other than IgG4 or IgE (namely, IgG1, IgG2, and IgG3). In addition, because interferon-\(\gamma\) is a potent inhibitor of T-cell interleukin-4 production, less interleukin-4 is available to induce B-cell switching to IgE. Thus, theoretically, interferon-\(\gamma\) acts at several levels (B cells and T cells) to downregulate IgE production.

The two conditions associated with extreme elevations in serum IgE levels in which interferon-\(\gamma\) has been used therapeutically are the hyper-IgE recurrent infection syndrome (the Job syndrome) and atopic dermatitis. The hyper-IgE recurrent infection syndrome is characterized clinically by eczematoid rashes, a particular facial appearance, recurrent deep and subcutaneous infections, and kyphoscoliosis. Atopic dermatitis is an inflammatory skin disease characterized by dermatitis and severe pruritus. Both the hyper-IgE syndrome and atopic dermatitis are associated with immunologic defects and produce serum IgE levels that are among the highest recorded. In atopic dermatitis, the elevated IgE levels have reflected both overproduction of interleukin-4 (55) and a defect in the production of interferon-\(\gamma\) (56, 57). Because good therapeutic methods do not exist for either of these clinical conditions, and because interferon-\(\gamma\) was believed to be capable of reversing several of the associated immunologic abnormalities, interferon-\(\gamma\) has been administered for these two conditions (Table 3). In the hyper-IgE syndrome, interferon-\(\gamma\) reduced IgE production both in vitro and in vivo in most patients, although no clear clinical improvement was seen. In contrast, in most patients with atopic dermatitis, many of whom had severe manifestations refractory to standard therapy, interferon-\(\gamma\) was clinically beneficial. Interestingly, the clinical benefit was not related to IgE reduction in this group of patients.

Thus, the systemic administration of interferon-\(\gamma\) is clearly shown to have clinical benefit in persons with atopic dermatitis, but its utility in the hyper-IgE recurrent infection syndrome remains to be established. In neither of these conditions and in none of the diseases mentioned above have controlled trials been done to optimize the dosage, the intervals between doses, or the duration of therapy needed to sustain continued benefit from the administration of interferon-\(\gamma\).

### Table 3. Use of Interferon-\(\gamma\) in States Associated with IgE Overproduction*

| Condition                                      | Patients | Duration of Interferon-\(\gamma\) Therapy | Serum IgE Decrease | In Vitro IgE Decrease | Clinical Improvement | Study (Reference)       |
|-----------------------------------------------|----------|------------------------------------------|--------------------|-----------------------|----------------------|-------------------------|
|                                               |          | wk                                       | n (%)              | n/n (%)               | n (%)                |                         |
| Atopic dermatitis                             |          |                                          |                    |                       |                      |                         |
|                                               | 14       | 6                                        | None               | 6/10 (60)            | 8 (57)               | Reinhold et al. (58)    |
|                                               | 40       | 12                                       | None               | ND                    | 18 (45)              | Hanifin et al. (59)     |
|                                               | 2        | 6-12                                     | None               | ND                    | 2 (100)              | Pung et al. (60)        |
|                                               | 22       | 3-6                                      | None               | 10/14 (71)           | 22 (100)             | Boguniewicz et al. (61) |
|                                               | 3        | 4                                        | 3 (100)            | 3/3 (100)            | 3 (100)              | Reinhold et al. (62)    |
| The hyper-IgE recurrent infection (Job) syndrome | 5        | 2-6                                      | 2 (40)             | 5/5 (100)            | None                 | King et al. (63)        |
|                                               | 1        | 20                                       | 1 (100)            | ND                    | 1 (100)              | Pung et al. (60)        |

ND = not determined.

### Conclusion

Dr. Gallin: Interferon-\(\gamma\) is currently licensed for only one indication: the reduction of life-threatening infections in chronic granulomatous disease. However, increasing evidence indicates that interferon-\(\gamma\) is important in the therapy for certain intracellular infections, such as leishmaniasis, toxoplasmosis, and infections by atypical mycobacteria and *M. leprae*. Interferon-\(\gamma\) exerts its effects through pleiotropic modulation of the host defenses. Understanding the molecular mechanisms of interferon-\(\gamma\) action may lead to the ability to enhance or inhibit specific subsets of the effects of interferon-\(\gamma\). A 3-year follow-up of patients with chronic granulomatous disease who have received interferon-\(\gamma\) suggests that the beneficial effects of this drug may be sustained. Future studies of interferon-\(\gamma\) need to focus on several points. First, the mechanisms of the drug's therapeutic and prophylactic effects must be understood. Addressing these mechanisms in human models of disease will probably not be possible. The development of mouse models of chronic granulomatous disease will allow dissection of the critical pathways involved in prophylaxis for infections. Second, other modes of delivery may be more effective than the subcutaneous route; we currently use aerosolized interferon-\(\gamma\) for pulmonary infections. The roles for interferon-\(\gamma\) therapy in multi-
drug-resistant tuberculosis and fungal infections are also being explored. The role of interferon-γ in the prevention and treatment of opportunistic infections in patients with AIDS has not been prospectively explored, and more work is clearly needed in this area. Finally, optimal dose and duration of therapy are unknown and require prospective study.

Requests for Reprints: Dr. Gallin: Warren G. Magnuson Clinical Center, National Institutes of Health, Building 10, Room 2C146, 10 Center Drive, MSC 1504, Bethesda, MD 20892-1504.

Current Address: Dr. Gallin: Warren G. Magnuson Clinical Center, National Institutes of Health, Building 10, Room 2C146, MSC 1504, 10 Center Drive, Bethesda, MD 20892-1504.

Dr. Farber: Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, Building 10, Room 1N1228, 10 Center Drive, Bethesda, MD 20892-1504.

Dr. Holland: Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, Building 10, Room 2N103, 10 Center Drive, MSC 1886, Bethesda, MD 20892-1886.

Dr. Nutman: Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Building 4, Room 126, Bethesda, MD 20892-0425.

Multiple defects of immune cell function in mice with disrupted interferon-γ genes. Science. 1993;259:1-79-42.

Huang S, Hendriks W, Alhage A, Hemmi S, Bluethmann H, Kamijo R, et al. Immune response in mice that lack the interferon-γ receptor. Science. 1993;259:1-79-42.

Kamijo R, Le J, Shapiro D, Havett EA, Huang S, Aguet M, et al. Mice that lack the interferon-γ receptor have profoundly altered responses to infection with Bacillus Calmette-Guerin and to subsequent challenge with lipopolysaccharide. J Exp Med. 1993;178:1455-40.

Gallin JI. Malech HL. Chronic granulomatous disease of childhood. Immunotherapy and potential for gene therapy [Clinical conference]. JAMA. 1990;263:1333-7.

Malech HL. Phagoctytic oxidative mechanisms. Curr Opin Hematol. 1993;1:123-12.

A controlled trial of interferon-gamma to prevent infection in chronic granulomatous disease. The International Chronic Granulomatous Disease Cooperative Study Group. N Engl J Med. 1991;324:589-16.

Kaplan G, Rossie JT, Boreman R, Boreman KM, Bemiller LS. Safety and efficacy of prolonged interferon gamma use in patients with chronic granulomatous disease [Abstract]. Sixth International Congress for Infectious Diseases. Prague, 1994;42.

Sechter JM, Malech HL, White CJ, Gallin JI. Recombinant human interferon gamma reconstitutes defective phagoctytic function in patients with chronic granulomatous disease of childhood. Proc Natl Acad Sci U S A. 1988;85:8478-8.

Shama AM, Yuen J, Deans RJ, Westberg K, Ren TH, Bloom BR, et al. Defining protein responses to pathogens: cytokine profiles in leprosy lesions. Science. 1991;254:277-9.

Kaplan G. Recent advances in cytokine treatment in leprosy. J Infect Dis. 1993;169(Suppl):S128-9.

Samadio EP, Moreira AL, Sarno EN, Malta AM, Kaplan G. Prolonged treatment with recombinant interferon gamma induces erythema nodosum leprosum in lepromatous leprosy patients. J Exp Med. 1992;175:1279-37.

Horsburgh CR Jr, Mason UC 3d, Farber DC, Isman MD. Disseminated infection with Mycobacterium avium-intracellulare. A report of 13 cases and a review of the literature. Medicine (Baltimore). 1985;64:336-44.

Benecke CA. Disease due to Mycobacterium avium complex in patients with AIDS: epidemiology and clinical syndrome. Clin Infect Dis. 1994;18(Suppl):S218-222.

Holland SM, Eisenstein EM, Kohas DB, Turner ML, Fishlee TA, Strober W, et al. Treatment of refractory disseminated nontuberculosis mycobacterial infection with interferon gamma. A preliminary report. N Engl J Med. 1990;334:1348-55.

Squires KE, Murphy WF, Madoff LC, Murray HW. Interferon-gamma and Mycobacterium avium-intracellulare infection. J Infect Dis. 1989;160:59-60.

Squires KE, Brown ST, Armstrong D, Murphy WF, Murray HW. Interferon-gamma treatment for Mycobacterium avium-intracellulare complex bacilluria in patients with AIDS [Letter]. J Infect Dis. 1992;166:686-7.

Bermudez IE, Inderlied C, Young LS. Stimulation with cytokines enhances penetration of azithromycin into human macrophages. Antimicrob Agents Chemother. 1994;38:2629-34.

Murray HW, Berendt JD, Wright SD. Immunomodulation for intracellular Leishmania donovani infection: gamma interferon plus pentavalent antimonial. J Infect Dis. 1993;168:573-83.

Homs G, Chehade A, Roegiers A, Mouaakil A, Rosenkaimer F, et al. Randomized trial comparing pentavalent antimonial drug and recombinant interferon-gamma in the local treatment of cutaneous leishmaniasis. Trans R Soc Trop Med Hyg. 1991;85:214-6.

Badaro R, Falcoff E, Badaro FS, Carvalho EM, Pedral-Sampaio D, Barral A, et al. Treatment of visceral leishmaniasis with pentavalent antimonial and interferon gamma. N Engl J Med. 1990;322:16-21.

Badaro R, Johnson W Jr. The role of interferon-gamma in the treatment of visceral and diffuse cutaneous leishmaniasis. J Infect Dis. 1993;167:513-7.

Squires KE, Rosenkaimer F, Sherwood JA, Forni AL, Were JB, Murray HF. Immunomodulation for intracellular Leishmania donovani infection: gamma interferon plus pentavalent antimonial. Am J Trop Med Hyg. 1992;47:1455-7.

Gallin JI. Malech HL. Phagoctytic oxidative mechanisms. Curr Opin Hematol. 1993;1:123-12.

A controlled trial of interferon-gamma to prevent infection in chronic granulomatous disease. The International Chronic Granulomatous Disease Cooperative Study Group. N Engl J Med. 1991;324:589-16.

Kaplan G, Rossie JT, Boreman R, Boreman KM, Bemiller LS. Safety and efficacy of prolonged interferon gamma use in patients with chronic granulomatous disease [Abstract]. Sixth International Congress for Infectious Diseases. Prague, 1994;42.

Sechter JM, Malech HL, White CJ, Gallin JI. Recombinant human interferon gamma reconstitutes defective phagoctytic function in patients with chronic granulomatous disease of childhood. Proc Natl Acad Sci U S A. 1988;85:8478-8.

Shama AM, Yuen J, Deans RJ, Westberg K, Ren TH, Bloom BR, et al. Defining protein responses to pathogens: cytokine profiles in leprosy lesions. Science. 1991;254:277-9.

Kaplan G. Recent advances in cytokine treatment in leprosy. J Infect Dis. 1993;169(Suppl):S128-9.

Samadio EP, Moreira AL, Sarno EN, Malta AM, Kaplan G. Prolonged treatment with recombinant interferon gamma induces erythema nodosum leprosum in lepromatous leprosy patients. J Exp Med. 1992;175:1279-37.

Horsburgh CR Jr, Mason UC 3d, Farber DC, Isman MD. Disseminated infection with Mycobacterium avium-intracellulare. A report of 13 cases and a review of the literature. Medicine (Baltimore). 1985;64:336-44.

Benecke CA. Disease due to Mycobacterium avium complex in patients with AIDS: epidemiology and clinical syndrome. Clin Infect Dis. 1994;18(Suppl):S218-222.

Holland SM, Eisenstein EM, Kohas DB, Turner ML, Fishlee TA, Strober W, et al. Treatment of refractory disseminated nontuberculosis mycobacterial infection with interferon gamma. A preliminary report. N Engl J Med. 1990;334:1348-55.

Squires KE, Murphy WF, Madoff LC, Murray HW. Interferon-gamma and Mycobacterium avium-intracellulare infection. J Infect Dis. 1989;160:59-60.

Squires KE, Brown ST, Armstrong D, Murphy WF, Murray HW. Interferon-gamma treatment for Mycobacterium avium-intracellulare complex bacilluria in patients with AIDS [Letter]. J Infect Dis. 1992;166:686-7.

Bermudez IE, Inderlied C, Young LS. Stimulation with cytokines enhances penetration of azithromycin into human macrophages. Antimicrob Agents Chemother. 1994;38:2629-34.

Murray HW, Berendt JD, Wright SD. Immunomodulation for intracellular Leishmania donovani infection: gamma interferon plus pentavalent antimonial. J Infect Dis. 1988;157:573-83.

Homs G, Chehade A, Roegiers A, Mouaakil A, Rosenkaimer F, et al. Randomized trial comparing pentavalent antimonial drug and recombinant interferon-gamma in the local treatment of cutaneous leishmaniasis. Trans R Soc Trop Med Hyg. 1991;85:214-6.

Badaro R, Falcoff E, Badaro FS, Carvalho EM, Pedral-Sampaio D, Barral A, et al. Treatment of visceral leishmaniasis with pentavalent antimonial and interferon gamma. N Engl J Med. 1990;322:16-21.

Badaro R, Johnson W Jr. The role of interferon-gamma in the treatment of visceral and diffuse cutaneous leishmaniasis. J Infect Dis. 1993;167:513-7.

Squires KE, Rosenkaimer F, Sherwood JA, Forni AL, Were JB, Murray HF. Immunomodulation for intracellular Leishmania donovani infection: gamma interferon plus pentavalent antimonial. Am J Trop Med Hyg. 1992;47:1455-7.

Gallin JI. Malech HL. Phagoctytic oxidative mechanisms. Curr Opin Hematol. 1993;1:123-12.
fractory visceral leishmaniasis in India using antimony plus interferon-y. J Infect Dis. 1994;170:659-62.

49. Locksley RM, Louis JA. Immunology of leishmaniasis. Curr Opin Immunol. 1992;4:413-8.

50. Reed SG, Scott P. T-cell and cytokine responses in leishmaniasis. Curr Opin Immunol. 1993;5:524-31.

51. Suzuki Y, Orellana MA, Schreiber RD, Remington JS. Interferon-gamma: the major mediator of resistance against Toxoplasma gondii. Science. 1998;280:516-518.

52. Gazzinelli RT, Hieny S, Wynn TA, Wolf S, Sher A. Interleukin 12 is required for the T-lymphocyte-independent induction of interferon gamma by an intracellular parasite and induces resistance in T-cell-deficient hosts. Proc Natl Acad Sci U S A. 1993;90:6135-9.

53. Murray HW, Squier KE, Gassel-Botev E, DePamphilis JK. Interleukin-2 treatment, interferon-gamma induction, and AIDS monocyte activation [Letter]. Am J Med. 1992;93:234.

54. Delemare FC, Stevenhagen A, Snojek F, Kroon FP, van Er M, Reiss P, et al. Restoration of the toxoplasmastatic activity of monocytes from AIDS patients during in vivo treatment with interferon-gamma [Letter]. J Infect Dis. 1993;168:516-8.

55. Reinhold U, Kukel S, Kreysel HW. Systemic interferon gamma treatment in severe atopic dermatitis. J Am Acad Dermatol. 1993;28:39-43.

56. Hanifin JM, Schneider LC, Leung DY, Ellis CN, Jaffe HS, Izu AE, et al. Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol. 1993;28:189-97.

57. Boguniewicz M, Jaffe HS, Izu AE, Sullivan M, York D, Geha RS, et al. Recombinant interferon gamma in treatment of patients with atopic dermatitis and elevated IgE levels. J Am Acad Dermatol. 1993;28:1282.

58. King CL, Gallin JJ, Malech HL, Abrams SL, Nutman TB. Regulation of immunoglobulin production in hyperimmunoglobulinemia E recurrent-infection syndrome by interferon gamma. Proc Natl Acad Sci U S A. 1990;86:10085-9.