CLINICAL MICROBIOLOGY REVIEWS, Oct. 1997, p. 611–636 Vol. 10, No. 4
0893-8512/97/$04.00+0

Interleukin-12 in Infectious Diseases

LUIGINA ROMANI,[1]* PAOLO PUCCETTI,[2] AND FRANCESCO BISTONI[1]

Microbiology Section, Department of Experimental Medicine and Biochemical Sciences, University of Perugia, 06122 Perugia,[1] and Pharmacology Section, Department of Experimental Medicine, University of Rome, 00133 Rome,[2] Italy

* Corresponding author. Mailing address: Microbiology Section, Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Via del Giochetto, 06122 Perugia, Italy. Phone: 39-75-585-3411. Fax: 39-75-585-3400. E-mail: iromani@unipg.it.

INTRODUCTION

Sporadic clinical reports since the early 18th century have indicated that spontaneous remission of tumors may occur in some patients with severe bacterial infections. Based on these observations, in 1891, William B. Coley began treating soft tissue sarcomas with bacterial preparations, or Coley's toxin, making use of gram-positive and gram-negative bacteria (74). Attempts to stimulate cellular immune responses with bacterial products have continued up to the present time and include the use of bacillus Calmette-Guérin (BCG) (229), complete Freund's adjuvant (123), and killed preparations of various organisms such as corynebacteria and streptococci. The immunological effects of these treatments have been interpreted as being the result of nonspecific activation of the phagocytic system and possible release of cytokines, which, in a tumor-bearing host, may effect direct antitumor activity, stimulate nonspecific effector mechanisms, or even trigger cytotoxic responses specific for the tumor antigens.

It is now clear that cytokines released during the initial contact of pathogens with cells of the innate immune system play a decisive role in shaping the subsequent cognate immune response orchestrated by T cells (302, 317, 378, 380). Interleukin-12 (IL-12), a product of the innate immune system, acts on cells of the acquired response and appears to meet the requirements as one of the most important links between natural and adaptive immunity (34, 416–422). The crucial relationship between these two types of response to infection, critical to an understanding of the biology of IL-12, is outlined in the following section.

INNATE AND ADAPTIVE IMMUNITY IN INFECTIONS: AN INTEGRATED VIEW

Vertebrates resist infection with pathogenic microorganisms through a combination of mechanisms of the innate (or natural) immunity and adaptive (or specific) immunity. The innate defense mechanisms preexist in all individuals and act within minutes of infection. For pathogens that do establish an infection, the innate response is crucial to control infections and hold them in check until an adaptive immune response can be generated. The early natural immune response to infection involves a wide variety of effector mechanisms directed at distinct classes of pathogens. Likewise, microorganisms encompass numerous components with the ability to interact selectively with different elements of the innate system. These responses are triggered by receptors that are either nonclonal or of very limited diversity, and the responses are distinguished from adaptive immunity by their failure to provide lasting immunity or immunological memory (109). Once considered merely a vestige of ancient antimicrobial systems that was made redundant by the evolution of acquired immunity, innate immunity is now considered to participate actively in determining the qualitative nature of the specific response to a pathogen (20, 109).

Different microbes require different types of response for their elimination. Infections by intracellular pathogens are best controlled by cell-mediated immunity, including phagocytosis and intracellular killing by macrophages, and lysis of infected cells by cytolytic T cells. In contrast, the host defense against extracellular pathogens, such as certain helminths, is associated with macrophage-independent responses, typically mediated by noncytotoxic antibodies, mast cells, and eosinophils. A combination of humoral and macrophage-dependent defenses are found in the defense against extracellular bacteria, while, in the case of bacterial toxin, production of antibodies of the appropriate isotype and function appears to be the proper opponent. Such diverse antimicrobial strategies demand highly specialized reactions that are controlled primarily by $CD4^+$ T helper (Th) cells. By producing different cytokines, $CD4^+$ T cells mobilize the most appropriate counteraction against invading pathogens.

The discovery that different subsets of cloned murine (282) or human (337) $CD4^+$ Th cells can be distinguished on the basis of the cytokines they produce has helped to explain why and how the immune system responds differentially to various pathogens in vivo (371, 378, 380). Th1 cells promote cell-mediated immune responses by secreting cytokines, such as gamma interferon (IFN-γ), lymphotoxin, and tumor necrosis factor alpha (TNF-α) (282, 283). These cytokines induce nitric oxide (NO) synthase in macrophages to increase their microbicidal activity, and IFN-γ causes murine B cells to switch their immunoglobulin (Ig) isotype to IgG2a (or IgG1 in humans), which promotes phagocytosis by activating the classical pathway of complement and binding to Fc receptors on macrophages. Th2 cells, by secreting the cytokines IL-4, IL-5, IL-6, IL-10, and IL-13, collectively mediate the growth and activation of mast cells and eosinophils, direct murine B-cell Ig switching to IgE and IgG1 (in humans, IgG4), and inhibit macrophage activation. Although interest in Th2 cells has been directed at their protective role in helminthic infections (243, 431) and pathogenic role in allergy (339), they may have important regulatory functions in limiting the tissue-damaging effects of Th1 cells and macrophages (368). Thus, the cross-regulatory properties of Th1 and Th2 cytokines are taken to explain the earlier observation made by Parish in 1972 (316) on the inverse relationship between cell-mediated and humoral immunity in response to antigen.

Recently, it has become evident that lymphocyte segregation into two subsets which produce different cytokine patterns is not restricted to $CD4^+$ T-cell receptor (TCR) $\alpha\beta$ cells alone. Rather, it appears to be a more general feature of the immune system. Both $CD8^+$ TCR $\alpha\beta$ and double-negative TCR $\gamma\delta$ cells appear as an IFN-γ-producing Th1-like subset or as an IL-4-producing Th2-like subset (40). In addition, several of the Th1 and Th2 cytokines are produced by multiple different leukocytes and even nonhematopoietic cells (246). For these reasons, a terminology of type 1 instead of Th1 and type 2 instead

TABLE 1. Microbial components that stimulate IL-12 production by phagocytic cells

Microbial component	Reference(s)
LPS of gram-negative bacteria	88
Teichoic acids of gram-positive bacteria	73
Spirochetal lipoproteins	250, 328
Bacterial DNA containing CpG motifs	157, 215
Prokaryotic heat shock proteins	301, 421
Bacterial superantigens	389
Mannoproteins of fungi	42
Leishmania antigen	391
T. gondii soluble antigen	135
gp120 of HIV	108

of Th2 has been recently suggested, to emphasize the function of a cytokine rather than its cellular source (71).

IL-12 BRIDGES THE INNATE AND ADAPTIVE IMMUNE SYSTEMS

Development of Th1 or Th2 cells from common precursor cells (317, 375) occurs in response to signals derived from the innate immune system (338). Cytokines produced in the local microenvironment profoundly influence the $CD4^+$ Th-cell differentiation (302, 317, 375). IL-12 produced by monocytes/macrophages and neutrophils as well as by different accessory cells (419), is required for Th1 development (242, 369), whereas IL-4, produced by basophils, mast cells, and an unconventional lymphocyte with a $CD3^+$ $CD4^+$ $NK1.1^+$ phenotype (462), is required for Th2 development (376, 403, 404). Thus, the early balance between IL-12 and IL-4 during an immune response most probably determines whether a Th1 or a Th2 type of response will develop (416–422). As stated above, microbial components exist which may selectively trigger the innate immune system at the very outset of infection to select quickly for the ensuing specific response. For IL-12 secretion, and hence Th1 development, these are listed in Table 1.

It is now accepted that the failure to control or resolve infectious diseases often results from inappropriate rather than insufficient immune responses (324). Therefore, development of a successful immune response with minimum pathology to an infectious agent is the desired goal of immunotherapy of infections. Cell-mediated immunity provides a major host defense against various infectious diseases, but if uncontrolled, it may lead to massive host tissue damage as a result of reactivity to self antigens. Several animal models of inflammatory autoimmune diseases suggest that preferential activation of Th1 responses is central to the pathogenesis of these diseases (303). Given the central role of IL-12 in the initiation of cell-mediated immunity (369), an understanding of the molecular and cellular basis of its actions may be critical in implementing a rational use of this cytokine in the prophylaxis and therapy of infectious diseases (Fig. 1).

MOLECULAR CHARACTERIZATION OF IL-12 AND ITS RECEPTOR

IL-12 was first described in 1989 as a product of B-cell lines capable of stimulating natural killer (NK) cell activity (natural killer stimulatory factor) (216) or cytotoxic lymphocyte maturation (cytotoxic lymphocyte maturation factor) (398). IL-12 is structurally unique among the interleukins in that it is a heterodimer cytokine composed of two covalently linked chains, a heavy chain of 40 kDa (p40) and a light chain of 35 kDa (p35), linked by a disulfide bond (323). Each chain is encoded by two separate and unrelated genes, which, in humans, map on chromosome 5 (p40 gene) and chromosome 3 (p35 gene) (153, 367, 382, 444). Structurally, p40 is composed of 306 amino acids, with 10 cysteine residues and 4 potential N-linked glycosylation sites; 10% of p40 is carbohydrate (153). The p35 chain is composed of 197 amino acids, with 7 cysteine residues and 3 potential N-linked glycosylation sites (153, 476). Approximately 20% of p35 is carbohydrate (323). The genes for the p40 and p35 subunits of murine IL-12 have also been cloned and expressed (367). The murine p35 and p40 genes map to chromosomes 3 and 11, respectively (415). Murine p40 has 70% identity to human p40, while murine p35 has 60% identity to human p35 (34, 367). Recombinant murine IL-12 is biologically active and has properties similar to those of human IL-12. In contrast to murine IL-12, human IL-12 is inactive in murine cells (34, 367). This species specificity is determined by the p35 subunit (394).

There is no sequence homology between the p40 and the p35 subunits of IL-12 (398). The p35 light chain has structure and sequence homology to the cytokines IL-6, granulocyte colony-stimulating factor, and chicken myelomonocytic growth factor (269). In contrast, the p40 heavy chain belongs to the hemopoietin receptor family and has homology to the extracellular portion of the ciliary neurotropic factor receptor (367) and of the IL-6 receptor (136). It has been postulated that IL-12 may have evolved from a cytokine/cytokine receptor that became covalently linked (136, 269, 367).

Neither subunit alone is active, nor are combinations of one subunit type (34). The biological activity of IL-12 has been demonstrated to be associated only with the p70 heterodimer (153, 323, 444). All the cell types producing IL-12 in vitro or in vivo secrete a 10- to 100-fold excess of free p40 chain over the biologically active heterodimer (88, 223, 398), which indicates that the production of p35 and p40 subunits is differentially regulated. This appears to be an important way of controlling the IL-12 biological activity. Indeed, the murine IL-12 p40 subunit, particularly in the form of disulfide-linked homodimer, can bind to the IL-12 β1 receptor subunit and block the binding of the IL-12 heterodimer, thus acting as an IL-12 receptor antagonist (140, 145, 264, 325). Like the murine counterpart, the human p40 homodimer appears to interact strongly with the human β1 subunit of the IL-12 receptor (60, 325). It has been speculated that production of p40 homodimer may be a physiological mechanism for limiting the actions of IL-12 (325). However, it is not yet clear whether the p40 homodimer is a physiological antagonist of IL-12 activity in vivo, although the data indicating that production of the p40 homodimer occurs independently or after that of IL-12 has ceased (325) suggest that this can be a realistic possibility.

The structure of the cellular receptor for IL-12 (IL-12R) has recently been elucidated. The IL-12R is a member of the β-type cytokine receptor (397) and, as such, is structurally related to gp130-like members of the cytokine receptor superfamily. Two or more binding affinities are observed on IL-12-responsive human (59, 325, 446) and murine (58, 325) cells. The functional high-affinity IL-12R is composed of at least two independent, β-type receptor subunits, β1 and β2, that individually exhibit low affinity for IL-12 (326). High-affinity binding of IL-12 appears to require multiple points of interaction between IL-12 and the two IL-12R subunits (325). However, expression of the IL-12Rβ subunit is necessary but not sufficient for expression of a functional IL-12R, thus suggesting the existence of an as yet unidentified receptor component (325, 446). The genes encoding human and mouse IL-12 receptor subunits have been isolated by expression cloning (65, 66). The

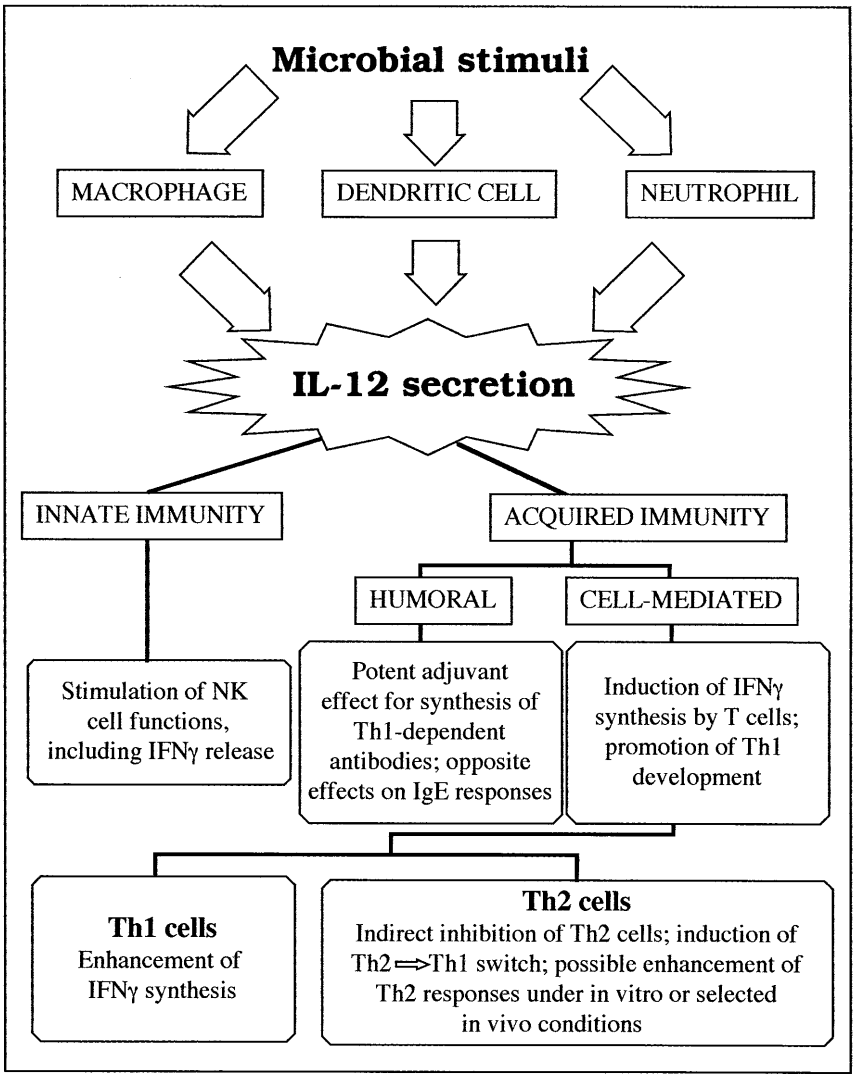

FIG. 1. The central role of IL-12 in the initiation of cell-mediated immunity. IL-12 enhances innate immunity via recruitment of NK cells, which produce IFN-γ and are involved in resistance to acute microbial infections. IL-12 is also an essential cytokine governing the differentiation of Th cells into Th1 cells, resulting in the development of type 1 responses, mediated by $CD4^+$ and $CD8^+$ T cells.

deduced amino acid sequences of the mouse IL-12R β1 and β2 proteins show 54 and 68% amino acid identity, respectively, to the human protein (66, 326). Although IL-12R was found to be expressed on several lymphoid cells (446), the expression of both components of the receptor is upregulated, albeit to a low level, upon cellular activation of NK and T cells, with a concomitant increase in IL-12 responsiveness. However, complementary studies with humans (336) and mice (406) have recently demonstrated the differential expression of the β2 chain in Th1 and Th2 cells. Continuous expression of both components occurs in Th1 cells, whereas selective loss of the IL-12 β2 subunit correlates with extinction of the IL-12 signaling in Th2 cells (336, 406). Continued stimulation with antigen in the presence of selected cytokines (336, 406, 447) is required for maintenance of the expression of the β2 chain.

Binding to both β1 and β2 subunits mediates IL-12 signaling, despite the absence of tyrosine in the cytoplasmic tail of the β1 subunit. In contrast, the cytoplasmic region of the IL-12 β2 chain contains three tyrosine residues, suggesting an important role for this subunit in IL-12 signal transduction (475). The IL-12R appears to signal through the recently recognized Janus family kinase/signal transducers and activators of transcription (JAK/Stat) pathway. The β1 subunit interacts with JAK2, and β2 interacts with TYK2 and with Stat3 and Stat4 (12, 184, 185, 407, 413).

PRODUCTION OF IL-12 AND ITS REGULATION

Although IL-12 was discovered as a product of B-cell lines, B lymphocytes do not appear to be the most important physiological producers of bioactive IL-12, which in vivo and in vitro appears to be produced mainly by phagocytic cells (monocytes, macrophages, and neutrophils) (41, 88, 249, 345, 347) and cells with antigen-presenting capabilities, including dendritic cells (46, 219, 251). Other cell types capable of producing IL-12, albeit at low levels, are keratinocytes (286) and nonmucosal mast cells (392). The production of IL-12 by macrophages and dendritic cells is mediated either by a T-cell-independent pathway that is induced by microbes or microbial products and enhanced by IFN-γ or by a T-cell-dependent

pathway that is induced primarily by the interaction of CD40 ligand (CD40L) on activated T cells with CD40 on IL-12-producing cells (408).

A number of infectious agents (or their components) induce IL-12 synthesis in phagocytic cells both in vitro and in vivo (Table 1). Although pathogens have evolved a complex array of strategies to evade the counteracting host immune response, there appears to be a remarkable ubiquitous ability among diverse types of pathogens to induce the production of IL-12 through a variety of mechanisms (91, 389, 408). Microbial components that promote IL-12 release include lipopolysaccharides (LPS) of gram-negative bacteria (88) and teichoic acids of gram-positive bacteria (73), spirochetal lipoproteins (250, 328), bacterial DNA containing CpG motifs (157, 215), bacterial superantigens and heat shock proteins (301, 389), mannoproteins of fungi (42), leishmanial antigen (391), *Toxoplasma* soluble antigens (135), and glycoprotein gp120 of human immunodeficiency virus (HIV) (108) (Table 1). Remarkably, the presence of these components on a pathogen cannot be taken to indicate that IL-12 is actually produced in vivo during an infection. In fact, some pathogens, such as HIV or the protozoan parasite *Leishmania major*, although containing molecules with IL-12-inducing activity, are nevertheless able to inhibit the induction of IL-12 synthesis in vivo in the infected host (39, 53, 331, 410). Differences in IL-12 production are also related to the ability of a pathogen to persist and multiply within the macrophage (389). Although still a controversial issue (125), it appears that phagocytosis alone may be insufficient for IL-12 release by phagocytic cells (346, 389). Moreover, both intracellular and extracellular pathogens are endowed with the ability to induce IL-12 production by phagocytic cells. It appears that microbial components may be essential for IL-12 induction. This issue is particularly relevant to the design of candidate vaccines that would be capable of stimulating sufficient production of endogenous IL-12 or would benefit from the adjuvant effect of exogenous IL-12.

Production of IL-12 by dendritic (46, 219) and phagocytic (200, 208) cells can be induced by cognate interaction with activated Th1 cells, which provide costimulatory signals via molecules such as the CD40L (150). These signals appear to be essential, because their inhibition will abrogate IL-12 production, particularly in dendritic cells, whose IL-12 production is poorly or not at all triggered by microbial agents and LPS (46, 408). Th1 cells, activated by TCR ligation with peptide antigen-major histocompatibility complex class II, will both express CD40 ligand on their surface and upregulate, through cytokines, CD40 expression on macrophages and dendritic cells. However, on macrophages, only the antigen-driven but not the LPS-driven IL-12 production requires triggering of CD40 (91). The CD40-CD40 ligand interaction leads to IL-12 production and eventually to the IL-12-dependent production of IFN-γ by $CD4^+$ Th1 cells. Priming with IFN-γ is known to upregulate the ability of macrophages (161, 223, 248) and neutrophils (41) to produce IL-12. Thus, IL-12-induced IFN-γ acts as a potent feedback mechanism in inflammation, a condition where a sustained IL-12 production may even represent a potentially dangerous mechanism, possibly leading to the uncontrolled production of cytokines and to shock (422). Also, because of the Th1-promoting activity of IL-12 (259, 373), the enhancing effect of IFN-γ on IL-12 production may represent one mechanism whereby Th1 responses are maintained in vivo. Recently, the ability of human Th2 clones to induce IL-12 production by dendritic cells has also been reported (434).

Due to the noticeable proinflammatory and immunoregulatory functions of IL-12, its production needs to be tightly regulated. Cytokines and other soluble mediators may regulate the ability of phagocytic cells to produce IL-12. IFN-γ and granulocyte-macrophage colony-stimulating factor priming of monocytes or neutrophils upregulates their ability to release IL-12 in response to LPS or *Staphylococcus aureus* (41, 161, 420). In contrast, transforming growth factor β (TGF-β), IL-4, IL-10, and IL-13 are potent inhibitors of IL-12 production (86, 389, 408, 420). The ability of IFN-γ to enhance IL-12 production may be particularly relevant in infections with agents that are rather poor inducers of IL-12 production (114, 118).

The finding that IL-12 is able to induce IL-10 production both in vivo (279, 349, 452) and in vitro (142) indicates that IL-12 can regulate itself paracrinally, by inducing factors that enhance (IFN-γ) or suppress (IL-10) its own production. Despite their ability to inhibit the production of IL-12 by phagocytic cells when present simultaneously with the inducing stimulus (87), IL-4 and IL-13 priming of human peripheral blood mononuclear cells was found to enhance IL-12 production in response to LPS or *S. aureus* (52). This finding is particularly surprising because of the antagonistic roles of IL-12 and IL-4 in the respective induction of Th1 and Th2 cell development (416). Among the mediators capable of affecting IL-12 release, prostaglandin E_2 is a potent inhibitor of human IL-12 production (433) whereas NO upregulates IL-12 p40 gene expression (352).

Activation of phagocytic cells by the appropriate stimuli induces the accumulation of IL-12 p40 mRNA and requires active protein synthesis (420). Expression of IL-12 p40 transcripts is restricted to the cell types producing IL-12 and is usually observed only upon activation of the cells (88, 249). In contrast, expression of the p35 transcripts is constitutive in many different cell types, including all types of leukocytes. However, p35 expression is upregulated during activation of IL-12-producing cells (88) and may determine the level of bioactive IL-12 production (394). The induction of p40 expression is controlled largely at the transcriptional level (249, 420). There are several binding motifs for known transcription factors in the promoter of the gene encoding the p40 chain. Motifs that are critical for responsiveness to both IFN-γ and LPS are the ets-2 (248) and NF-κB-binding (290) motifs.

BIOLOGICAL ACTIVITY OF IL-12

The major cellular targets of IL-12 include T and NK cells, in which IL-12 induces cytokine production, stimulates proliferation, and enhances cytotoxic activity (127, 216). Among the cytokines induced by IL-12, IFN-γ predominates, due to the ability of IL-12 to induce IFN-γ gene transcription and to synergize with other inducers (50, 51). However, other cytokines including TNF-α, granulocyte-macrophage colony-stimulating factor, and IL-2 are also induced. IL-12 acts as a mitogenic factor for preactivated T- or NK-cell blasts and is required for optimal proliferation of mitogen- or antigen-stimulated T cells (322). The enhancing effects of IL-12 on cell-mediated cytotoxicity involve stimulation of NK cell-mediated cytotoxicity as well as increased generation of lymphokine-activated killer cells and cytotoxic T lymphocytes (55, 127, 216, 398). In addition to T and NK cells, B cells, particularly B1 ($CD5^+$) cells, considered to be critically involved in autoimmunity and chronic lymphocytic leukemia (213), are cellular targets of IL-12. Human and mouse B cells express the IL-12R β1 subunit and directly bind IL-12 (437). IL-12 inhibits B-cell functions while enhancing the conventional, B-cell-dependent antibody response (271). IL-12 also has a direct stimulatory effect on hematopoietic progenitor cells (182, 183). This effect, however, may be antagonized by the hematopoietic inhibitory effect of the IL-12-induced cytokines, IFN-γ and TNF-α (19,

106). Via IFN-γ, IL-12 may also act as an antiangiogenetic agent (436), an activity which may contribute to the antitumor effect of exogenous IL-12 (34, 35, 474).

IL-12 as a Proinflammatory Cytokine

Within hours of infection, phagocytic cells and antigen-presenting cells produce IL-12. Resting NK cells expressing IL-12R are likely to be the first target for IL-12. Upon stimulation with IL-12, NK cells produce high levels of IFN-γ (51) as well as other cytokines, which then act on phagocytic cells by potentiating their microbicidal activity, phagocytosis, oxidative burst capability, and production of NO and IL-12 itself (420). Thus, IL-12 acts as a proinflammatory cytokine in response to infection. IFN-γ production by NK cells is transient compared with that by T cells and appears to be important in controlling pathogens during the early stages of infection. Thus, before the establishment of T-cell-mediated immunity, IL-12 and IFN-γ comprise a paracrine positive feedback loop between macrophages and NK cells, resulting in maximal macrophage activation. This powerful amplifying mechanism is probably at work in pathogens which by themselves are unable to efficiently induce IL-12 production (114, 118, 331). However, IL-12-independent mechanisms of IFN-γ production, including that from Th1 cells (220), have been proposed (26). Other cytokines (such as TNF-α and IL-1), released by macrophages upon stimulation by microbial products, synergize with IL-12 to induce IFN-γ secretion by NK cells (130, 175, 426). The importance of this pathway in resistance to in vivo infection is revealed by studies with mice with severe combined immunodeficiency (SCID mice), which lack mature T and B cells. The susceptibility of these mice to infections with some intracellular pathogens is dramatically increased after neutralization of endogenous IL-12 or IFN-γ or after depletion of NK cells (130, 131, 133, 423). Although these proinflammatory effects of IL-12 are of primary importance in the innate resistance to infectious microorganisms, they may also have pathological consequences. If uncontrolled, the exaggeration of the physiological response may result in an endotoxic shock type of pathology due to cytokine dysregulation (314, 455) or in gastrointestinal damage due to excessive sensitization to local microbial stimuli (299, 342). Negative stimulators of IL-12 production, such as IL-4, IL-10, IL-13, and TGF-β, also counteract the proinflammatory functions of IL-12 (41, 86, 87, 420). TGF-β is probably the most effective inhibitor of the IL-12 system, by inhibiting both IL-12 production and IL-12 effects on T and NK cells (87, 173).

IL-12 as a Th1-Promoting Cytokine

The production of IL-12 during the early inflammatory response to pathogens profoundly influences the characteristics of the ensuing adaptive immune response against the pathogen. This IL-12 activity is mediated by its ability to drive the differentiation of Th cells into a specific phenotype. In contrast to NK cells, resting T cells do not express the IL-12R (129, 325). Before differentiation into Th1 or Th2 cells, undifferentiated Th precursor cells, activated by peptide antigen-major histocompatibility complex class II and costimulatory signals, initiate the synthesis of IL-2 and express the IL-12R. IL-12, if locally present, will then induce the generation of Th1-type cells producing IFN-γ and IL-2 and favoring cell-mediated immunity, macrophage activation, and production of the opsonizing IgG2a isotype. At the same time, IL-12 will inhibit the generation of Th2 cells, which produce IL-4, IL-5, and IL-10, and favor humoral immunity with the production of IgG1, IgE, and IgA. These activities of IL-12 have been clearly documented both in vivo and in vitro in mice and in humans (1, 25, 129, 162, 172, 259, 260, 418). Mice deficient for the p40 subunit are defective in IFN-γ but not IL-2 production and in mounting Th1 and delayed-type hypersensitivity (DTH) responses (256, 265). At the molecular level, these activities appear to correlate with tyrosine phosphorylation of Stat3 and Stat4, such that mice with a disrupted Stat4 gene are impaired in IL-12-dependent functions (196, 413).

While IL-12 can directly endow T cells with the capacity to produce IFN-γ (373), inhibition of Th2 cell development occurs, at least in part, through the inhibitory effect of IFN-γ (128, 259, 421). Paradoxically, IL-12 also induces T cells to produce the counteracting cytokine, IL-10 (142, 279, 349), and this may be taken to indicate the existence of a negative-feedback mechanism of IL-12 production. However, it appears that IL-12 can also promote the development of Th2 cells (28, 139, 141, 190, 366, 443, 445, 452) and serve as a potent adjuvant for humoral immunity (138, 141). In inducing cytokine production by and proliferation of Th1 cells, IL-12 strongly synergizes with costimulators expressed on antigen-presenting cells (224, 291). Once differentiated, Th1 cells no longer require IL-12 as a costimulatory molecule to maintain their pattern of cytokine secretion and to mediate resistance against pathogens such as *Toxoplasma gondii* (135, 359), *Histoplasma capsulatum* (374), and *Listeria monocytogenes* (424). Therefore, IL-12 appears not to be an absolute requirement for maintenance of a Th1 response in vivo. Recently, the absolute requirement of IL-12 for Th1 development has been questioned, and it has been suggested that IL-12 is required for the occurrence of a functional Th1 response by quantitatively increasing the amount of IFN-γ produced (374). One important observation may be that the Th1 phenotype is reversible and can be converted to Th2 by exposure to IL-4 (320, 321, 407). This finding may have important implications for recrudescence in chronic infection or transient loss of protection against a pathogen in coinfection. Also important is the finding that IL-12 can reverse the established Th2 responses, which could be helpful in treating certain infectious diseases and allergies. The reversal of an established Th2 response has been demonstrated in experimental leishmaniasis (294). While many immunological manipulations are effective in the early but not late phases of leishmanial infection, administration of IL-12 in combination with a leishmaniacidal drug switches a dominant Th2 response to a Th1 response during an active *L. major* infection, resulting in healing and resistance to reinfection (294). Similarly, IL-12 can suppress the Th2 response induced by schistosome eggs (449, 450, 454).

IL-12 as an Adjuvant

Because IL-12 can influence the differentiation of precursor Th cells to the Th1 phenotype, its use as a vaccine adjuvant to promote beneficial Th1 responses is of great interest. The first demonstration of the efficacy of IL-12 as a vaccine adjuvant was obtained in experimental leishmaniasis (1). A protective Th1 cell response to infection with *L. major* was induced in susceptible mice by vaccination with parasite extracts in combination with IL-12. The induction of Th1 cell development following vaccination with leishmanial antigens and IL-12 requires NK cell activation and IFN-γ production (1), thus mimicking the induction of resistance seen in resistant mice infected with *L. major* (357, 358, 360). Likewise, administration of nonviable bacterial antigens with IL-12 generates protective Th1 immunity against *L. monocytogenes* (275) and *Bordetella pertussis* (257). One very recent application of IL-12 is its use as a component of vaccines directed against pathology rather

than the pathogen itself (449). In murine schistosomiasis, cotreatment with parasite eggs and IL-12 not only enhances resistance but can also ameliorate the pathology associated with schistosome granulomas (449). The effective use of IL-12 as an adjuvant has now been demonstrated with several other pathogens (210, 240, 268) and nominal (28) and tumor (474) antigens. The advantage of using IL-12 as an adjuvant is that the actual cytokine dose required for an effect is rather low, thus avoiding possible side effects due to prolonged treatment. Moreover, the successful use of an adenovirus vector to deliver IL-12 to the site of infection (147, 459) suggests that compartmentalized expression of IL-12 may also contribute to its adjuvant activity while minimizing undesirable systemic toxicity.

IL-12 Toxicity

The primary toxicities of IL-12 in mice include hepatotoxicity, as well as an IFN-γ-dependent inhibition of hematopoiesis causing anemia, neutropenia, and lymphopenia (106, 127, 182, 183, 354). These toxic effects of IL-12 are observed mainly at high doses and after continuous treatment. Due to the ability of IL-12 to directly stimulate hematopoiesis (183), its toxicity may also include stimulation of extramedullary hematopoiesis, resulting in splenomegaly (127). At a dose of 10 μg per mouse per day for more than 1 week, IL-12 treatment induced lethal effects (127). The toxicity of IL-12 may also derive from interaction and/or synergism with endogenously produced cytokines. In acute viral or fungal infections, the immunotoxicity of relatively low doses of IL-12 was associated with the uncontrolled production of proinflammatory cytokines, such as TNF-α and IFN-γ, thus resulting in septic shock-like pathology or excessive sensitization to microbial stimuli (26, 44, 299, 307, 340).

INTERMEZZO

A comprehensive discussion of the role of the different Th-cell subsets and their cytokines in infections is beyond the scope of this article. For in-depth analysis, the reader is referred to extensive reviews on the subject (89, 162, 189, 244–246, 258, 330, 351), and we will limit our discussion to the rapidly expanding information on the production, roles, and effects of IL-12 in experimental and human infections. Much of the current work in this field is still explorative and evolving. The emerging paradigm involves interactions of pathogens with cells of the innate immune system, which lead to IL-12 production, activation, and IFN-γ production by NK cells and subsequent Th1-cell development. However, although applicable to different degrees in different infections, the paradigm provides only a framework of what occurs in the early phases of an infection. Questions such as the relative dependency of the early IL-12 production from other regulatory cytokines, e.g., IFN-γ, still remain to be answered. The clue to solving this problem may be rather pathogen dependent. For instance, there is a wide diversity in the ability of pathogens to induce IL-12 production. Some pathogens stimulate IL-12 production by resting macrophages (118) as well as by IFN-γ-deficient mice (118, 361), while others require priming with IFN-γ (114). Since a positive amplification loop involving IL-12 and IFN-γ seems to occur in vitro and in vivo, it may be difficult to determine which of these cytokines actually initiates the response. Also, an as yet unresolved issue concerns the identification of positive and negative regulators of the IL-12-driven response. Cytokines and mediators exist that can both enhance and inhibit IL-12 activity. However, the relative roles played by each mediator in vivo in each infection is far from known. For instance, during HIV infection, a decreased IL-12 production has been observed, which was associated with either increased (62) or unaltered (52) IL-10 production. In murine models of viral infections, a role for IL-12 in inducing protective antiviral responses was observed in some but not all viral infections examined (26). It is implicit that the answers to these and other questions and, more generally, a better understanding of IL-12 biological relevance may lead to major conceptual advances in basic and clinical immunology.

We will review the rapidly expanding literature on the production and activities of IL-12 in experimental and human infections, with a perspective of conceptualizing novel therapeutic approaches aimed at restoring an appropriate balance between Th1 and Th2 responses.

IL-12 IN EXPERIMENTAL INFECTIONS

Bacterial Infections

L. monocytogenes. Infection of mice with *L. monocytogenes* has been used extensively as a model to study the role of Th1-dependent cell-mediated immunity in the control of infection by intracellular pathogens (89, 156, 160). *L. monocytogenes* is able to live and replicate inside resting macrophages but is rapidly destroyed as a result of macrophage activation (156). Although macrophages represent the ultimate effector cells, the presence of T cells is essential for effective control of infection (103). The contribution of T cells to an optimal antibacterial defense is operative at two levels, i.e., in the activation of the antibacterial potential of phagocytes (252) and in the lysis of infected cells (75, 203). The predominance of Th1 responses in listeriosis has been attributed to innate, nonspecific immune responses at the onset of infection. *L. monocytogenes*-infected macrophages (172) produce IL-12, which effectively activates NK cells (425, 426) and γδ T cells (390) to secrete IFN-γ, which is capable of activating microbial effectors and favoring the development of the appropriate $CD4^+$ Th1 subset (172, 425). Administration of recombinant IL-12 (rIL-12) enhanced, and its neutralization decreased, resistance to infection (423, 438). Cytokines, such as TNF-α and IL-1β, also produced by infected macrophages (335), act as positive regulators of IL-12-induced IFN-γ production by NK cells (175, 426). Viable, but not killed, bacteria stimulate significant IL-12 production by macrophages (395), which is relatively independent of priming with IFN-γ (118). IL-12 neutralization in vivo markedly reduces IFN-γ expression in infected mice, thus implying that IL-12 production precedes and directs IFN-γ production (241). Thus, the positive amplification loop exerted by IFN-γ on IL-12 production appears to be superfluous when sufficient IL-12 is produced. Cytokines such as IL-4 (172) and IL-10 (395, 426) act as negative regulators of IL-12 production. In the case of IL-4, neutralization of IL-4 prior to infection increases resistance to *L. monocytogenes* infection (155). Hsieh et al. have suggested that IL-4 may be involved in IL-12-mediated induction of Th1 cells (172). $CD4^+$ $NK1.1^+$ T cells, producing IL-4, disappear in infected mice soon after infection, a phenomenon that is partially reversed by neutralization of IL-12 and is mimicked by the administration of rIL-12 (104). Therefore, it appears that the production of IL-4 is actively impaired as a result of IL-12 release by infected macrophages. The production of IL-10 was found to inhibit IL-12 production and responsiveness (425, 426) and to account for the failure of killed bacteria to induce IL-12 p40 expression in macrophages of infected mice (395). However, nonviable bacteria or soluble bacterial antigens could elicit protective Th1 responses when administered together with rIL-12 (275).

In contrast to primary infection, the anamnestic response to *Listeria* appears to be less dependent on the presence of IL-12 (424). This finding may have implications for immunotherapy, by suggesting that IL-12, as a therapeutic agent or vaccine adjuvant, may be useful in the initial phases of *Listeria* infection but less useful in an established disease.

***Mycobacterium* species.** The role of IL-12 has been investigated in several murine models of infection with pathogenic mycobacteria, including *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and *Mycobacterium avium*. Experimental infection of mice with *M. tuberculosis* or *M. bovis* BCG results in long-lasting, chronic infection (27). Although specific T cells effectively activate macrophage antibacterial functions, they do not provide the host with sterilizing immunity, so that a balance typically follows between host immunity and persistence of the pathogen. Any impairment in host immune surveillance may be followed by fatal dissemination of infection (201). Activation of infected macrophages and blood monocytes is crucially dependent on IFN-γ (92, 115). Mutant mice with disrupted IFN-γ or IFN-γ receptor genes are highly susceptible to *M. tuberculosis* and *M. bovis* BCG infections and develop disseminated disease (78, 85, 119, 194). Protective immunity against mycobacteria depends on the presence of specific Th1 cells of the $CD4^+$ TCR αβ, $CD8^+$ TCR αβ, and double-negative TCR γδ subsets (181, 201, 228), which are capable of producing IFN-γ and lysing mycobacterium-infected target cells (202, 205, 310, 311, 412). Although protection against mycobacterial infections is controlled predominantly by Th1 cells (6, 90, 93, 119, 179, 311), Th2 cytokines have been detected during infection with *M. tuberculosis* or *M. bovis*, although at low levels (179, 311, 412). Both beneficial and detrimental effects have been associated with Th2 cytokines (89, 116, 117). The current paradigm of Th1/Th2-cell dichotomy in tuberculosis holds that the two types of responses do not occur simultaneously. The predominance of a Th1 response would occur in the early phases of *M. tuberculosis* infection, eventually leading to asymptomatic infection. In contrast, a shift toward Th2 cell activation may lead to detrimental effects, as is seen in the late phases of a severe disseminated infection (201). Development of cell-mediated, Th1 protective immunity to mycobacteria is considered a two-edged response, contributing to both clearance of infecting agents and tissue damage (100). The emergence of a protective Th1 response was found to be dependent on the early production of IL-12, so that rIL-12 administration increased and IL-12 neutralization decreased the resistance to *M. tuberculosis* (79, 120) or *M. avium* (43, 217, 218, 356) infection. Treatment with rIL-12 also delayed lung pathology in *M. tuberculosis*-infected mice (120), which highlights a possible beneficial effect of IL-12 in reducing pathology in infection. Neutralization of IL-12 late in the course of *M. avium* infection did not change the outcome of infection (43), thus implying a role for IL-12 in the initiation of a protective Th1 response in the early phases of mycobacterial infection. However, the mechanisms regulating early IL-12 production as well its Th1-promoting activity remain to be clarified.

IL-12 is produced by macrophages both in vitro (upon exposure to *M. bovis* BCG) and in vivo, in *M. bovis* BCG-infected mice (114). Interestingly, expression of IL-12 was found to correlate with genetic and nongenetic patterns of susceptibility and resistance to mycobacterial infections. The level of IL-12 p40 mRNA was decreased in the lungs of old susceptible *M. tuberculosis*-infected mice compared to young resistant mice (77) and also in the spleens of genetically susceptible *M. avium*-infected mice compared to genetically resistant mice (218). rIL-12 could improve the course of infection in both old and genetically susceptible mice (77, 218). In *M. bovis* BCG infection, production of IL-12 occurs only in the presence of IFN-γ or TNF-α, thus indicating that IL-12 may not be the initial cytokine produced upon contact with the infectious agent (114). However, the results obtained with mice were not confirmed by the use of *M. tuberculosis* or its antigens in a human system (125). Therefore, whether a positive amplification loop is required for IL-12 to be sufficiently produced in mycobacterial infections remains an open question. Again, this notion could be important in the development of vaccine-based therapeutic strategies. The Th1-promoting effect of IL-12 in vivo was found to be dependent on the presence of IFN-γ (125) and for full expression required the presence of T cells and perhaps that of an as yet unknown cofactor in *M. tuberculosis*-infected mice (79). Yoshida et al. (461) recently reported that regulation of NO synthase in macrophages of *M. bovis* BCG-infected mice may be important for complete expression of IL-12-dependent acquired immunity to BCG infection.

***Salmonella* species.** Experimental models of murine salmonellosis include infection with either typhoid or nontyphoid *Salmonella* given systemically or orally. The severity and outcome of *Salmonella* infections are determined by multiple bacterial and host factors. Among the latter, different alleles of the susceptibility gene, *Nramp*, mapping to the *Ity* locus, determine the relative resistance and susceptibility to *Salmonella* infections (105, 388) and other intracellular pathogens. The gene is expressed in murine and human macrophages (47, 48, 388), which are the most important effector cells against *Salmonella* spp. Several cytokines, including IFN-γ and TNF-α, are important regulators of antibacterial effector functions of macrophages, such that their neutralization in vivo increases the severity of *Salmonella* infection whereas their systemic administration mitigates pathology (193, 280, 281, 289, 296–298, 414). T-cell-deficient mice are initially resistant to *Salmonella typhimurium* infection but fail to control disease in the late phases of infection (297). Therefore, the innate immune system plays an important role in the early control of infection.

Mice infected orally with the attenuated *Salmonella dublin* strain produce increased levels of IL-12 mRNA in Peyer's patches and in mesenteric lymph nodes (33) and are protected against subsequent challenge (61). IL-12 depletion increases and rIL-12 administration decreases the severity of *S. dublin* oral infection in vivo (211). Viable but not killed bacteria immunize mice against reinfection, and this is associated with increased and sustained production of IL-12 (61). In a murine model of *S. dublin* systemic infection, expression of the IL-12 p40 mRNA increased upon infection in both *Salmonella*-susceptible and *Salmonella*-resistant mice, indicating that IL-12 expression in vivo is independent of alleles at the *Ity* locus (99). Peritoneal macrophages from mice infected intraperitoneally with *Salmonella choleraesuis* also express the IL-12 p40 mRNA (7). Neutralization of IL-10 increases IL-12 p40 expression and the number of γδ T cells, suggesting that IL-10 may act as a negative regulator of IL-12 production and activity in *Salmonella* infection. Because IL-12 neutralization decreases IFN-γ production in *S. typhimurium*-infected resistant mice (262), it appears that *Salmonella* spp. are endowed with the ability to drive IL-12-dependent Th1 immune responses. This may explain the ability of recombinant *S. typhimurium* organisms expressing a leishmanial surface protein to induce protective antileishmanial Th1 responses (457).

***Y. enterocolitica*.** Although *Yersinia enterocolitica* is an extracellular pathogen, it is known that a specific T-cell-mediated host response is required to overcome infection (8–10). In a murine model of infection, protection against lethal *Yersinia* challenge was obtained by adoptive transfer of *Yersinia*-specific $CD4^+$ Th1-cell clones (10). Furthermore, neutralization of

TNF-α or IFN-γ abrogates resistance in infected mice, suggesting that activated macrophages are important effector cells against this pathogen (8, 9). It has been suggested that the susceptibility of BALB/c mice to infection is due to a weak and delayed *Yersinia*-specific T-cell response, including IFN-γ production, compared to that of the resistant strains (8). IL-12 gene expression in vivo is similar in the spleens and livers of susceptible and resistant mice, and bone marrow-derived macrophages from either type of mice produce comparable levels of bioactive IL-12 in vitro in response to several stimuli (31). Interestingly, killed bacteria are as effective as viable bacteria in inducing IL-12 production, which is enhanced by the presence of IFN-γ (31). However, while IL-12 neutralization decreased resistance in both strains of mice, administration of rIL-12 increased resistance in susceptible mice, thus suggesting that a functional IL-12 deficiency occurs in these mice. Whether this is due to insufficient IL-12 production or defective IL-12 responsiveness in vivo or to the production of antagonistic cytokines is unclear, and all of these possibilities seem to be plausible. However, anti-IL-10 increased IFN-γ production in infected susceptible mice, indicating that IL-10 is one possible IL-12 antagonist at work in *Yersinia* infection (31). The activity of IL-12 in promoting protective immunity appears to be mediated by the production of IFN-γ from T and non-T cells. Thus, IFN-γ appears to be required for both the production and biological activity of IL-12 in *Yersinia* infection. Surprisingly, IL-12 seems to play only a minor role in the generation of local protective immunity in Peyer's patches of orally infected mice (31). Recently, protective Th1-dependent immunity against *Y. enterocolitica* infection was elicited by vaccination with *Yersinia* heat shock protein 60 (HSP 60) in combination with IL-12 (301). This again emphasizes both the capacity of microbial HSP to induce IL-12 synthesis and the use of IL-12 as a promising adjuvant in vaccine preparations. In humans, *Yersinia*-specific Th1 cells may be both protective and harmful, in that *Y. enterocolitica*-reactive T-cell clones obtained from synovial fluids of arthritis patients are of the Th1 type, producing IFN-γ but not IL-4 (230, 365). Therefore, the potential application of IL-12 as an adjuvant in human *Yersinia* infections awaits further studies.

B. abortus. Resistance to the facultative intracellular pathogen *Brucella abortus* depends on the generation of protective IFN-γ-producing Th1 cells (110, 273, 402, 464). IFN-γ plays a crucial role in the resolution of *B. abortus* infection through its ability to activate antibacterial functions in infected macrophages (191, 192). In addition, IFN-γ administration and neutralization increased and decreased, respectively, resistance to infection in vivo (400, 466). IL-12 clearly contributes to resistance to *B. abortus* infection (467, 468). IL-12 neutralization in infected mice exacerbates infection and reduces the production of IFN-γ. Production of NO by macrophages was also reduced by IL-12 neutralization, which further points to a defective macrophage activation in these mice (467). These data indicate, although indirectly, that *B. abortus* may be endowed with the ability to induce IFN-γ-dependent protective immunity through the induction of IL-12 from cells of the innate immune system. Direct evidence indicating that this may be the case comes from in vitro studies with human monocytes. Stimulation of these cells with heat-inactivated *B. abortus* or its LPS resulted in the activation of monocytes and the secretion of biologically relevant quantities of IL-12 (465). Induction of IL-12 synthesis did not require priming with IFN-γ but was associated with upregulation of expression of important costimulatory molecules, such as B7.1 and B7.2. Thus, through IL-12 and by facilitating costimulation of Th precursor cells, *B. abortus* may provide optimal conditions for the activation of Th1 cells.

F. tularensis. In a murine model of *Francisella tularensis* infection, development of protective immunity to challenge with an attenuated live vaccine strain (LVS) depends on stimulation of specific IFN-γ-producing T cells (199, 387). Both T-dependent and T-independent host immune mechanisms contribute to the generation of immunity to *F. tularensis* (76, 101), with cytokines such as IFN-γ playing an important role in the activation of microbicidal macrophages (121, 234). Recently, IL-12 p40 mRNA expression was found in the livers of mice infected with viable but not killed vaccine strains (146). The biological relevance of this IL-12 expression and its regulation in tularemia are presently unknown.

B. burgdorferi. *Borrelia burgdorferi* is a gram-negative spirochete, which causes Lyme disease in humans. Lyme disease is characterized by several stages, ranging from the initial erythema migrans to meningitis and reactive arthritis (377). Studies in a murine model of Lyme disease suggest that spirochete persistence correlates with the severity of pathologic changes and may be responsible for localized inflammation (18, 458). Susceptible mice develop severe disease, including arthritis associated with an intense inflammatory and immune response (17). Lymph node cells from resistant mice produce IL-4, while those from susceptible mice produce IFN-γ (206, 207, 266), which suggests that Th1 cells may be involved in the genesis of the pathology caused by *B. burgdorferi* (463). Because of the proinflammatory and Th1-promoting activities of IL-12, it would not be surprising to find that *B. burgdorferi* is a potent inducer of IL-12 and that production of IL-12 may play a detrimental role in Lyme disease. Indeed, *B. burgdorferi* stimulates IL-12 production by human dendritic cells (112), and the outer surface lipoproteins of *B. burgdorferi* stimulate the production of IL-12 and other inflammatory cytokines by cultured macrophages from resistant and susceptible strains of mice (250). In vivo, IL-12 neutralization results in a reduction of the early inflammatory and subsequent Th1 responses and mitigates the severity of acute Lyme arthritis in susceptible mice (5). It appears that cellular Th1 reactivity exerts a disease-promoting role in Lyme disease. However, the role of Th1-dependent antibodies, including those favoring opsonization and complement lysis, in the control of *Borrelia* infection has yet to be defined.

K. pneumoniae. Mice challenged intratracheally with the gram-negative bacterium *Klebsiella pneumoniae* develop a clinical picture and inflammatory response similar to those seen in acute bacterial pneumonia in humans (147–149). In this model, an effective antibacterial host defense requires the generation of vigorous inflammatory responses, which involves recruitment and activation of phagocytic cells, including neutrophils and macrophages (149). The recruitment and/or activation of leukocytes in the setting of bacterial challenge involves the coordinate expression of both pro- and anti-inflammatory cytokines and chemokines (147–149). Upon intratracheal infection of mice with *K. pneumoniae*, bioactive IL-12 is rapidly produced mainly by alveolar macrophages but also by pulmonary epithelial cells and neutrophils. IL-12 neutralization impairs bacterial clearance from the lungs and increases mortality after *K. pneumoniae* infection. Overexpression of IL-12 in the lungs by the use of an adenovirus vector (see above) results in a beneficial effect that requires the presence of IFN-γ and TNF-α (147).

Other bacteria. As one leading bacterial agent of neonatal sepsis and meningitis (111), the extracellular pathogen group B streptococcus (GBS) has been used in experimental models of infection involving SCID mice. Exposure of macrophages to

type III GBS, as well as other extracellular bacterial agents of neonatal sepsis including staphylococci and enterococci, results in the production of bioactive IL-12, which, together with TNF-α, probably stimulates IFN-γ production by NK cells (96). Should IL-12 production be reduced in human neonates, the exogenous supply of IL-12 would enhance the innate resistance to infection. The early activation of NK cells and IFN-γ release may be a critical event in promoting the functions of immature neutrophils and macrophages necessary for defense against infection by GBS. In an experimental model of group A streptococcal infection, treatment with rIL-12 increased survival after infection, an effect possibly mediated via enhancement of innate immunity (270). In a recent study, the expression of IL-12 was not modified upon exposure to products of enteropathogenic *Escherichia coli* (214).

Septic shock. In a murine model of LPS-induced endotoxic shock, IL-12 neutralization protects mice from death (455). Protection was also observed upon neutralization of IFN-γ and TNF-α, suggesting dysregulated production of proinflammatory cytokines in the pathology of endotoxic shock (422).

Protozoan Infections

***Leishmania* species.** Experimental *L. major* infection in mice provides a prototypic example of Th1 and Th2 predominance associated with either resistance (Th1) or susceptibility (Th2) to this protozoan parasite. Protective mechanisms include both suppression of deleterious Th2 responses and amplification of beneficial Th1 cell activities (244, 330, 370). *L. major* multiplies within macrophages, and therefore the innate immune system actively participates in the early containment of infection (30). IFN-γ production by NK and Th1 cells represents a key event in the activation of leishmaniacidal activity of macrophages (357). Production of IFN-γ by NK cells and development of Th1 responses in resistant mice are dependent on IL-12 production (358, 360). Endogenous IL-12 is also required for control of Th2 cytokine production in both resistant and susceptible mice (163, 164). Indeed, genetically resistant mice lacking IL-12 are susceptible to *L. major* infection and mount Th2 responses (265), whereas in susceptible mice, the early production of IL-4 is downregulated by IL-12 and IFN-γ (122, 233).

Production of IL-12 in response to *L. major* has been documented both in vivo (331, 435) and in vitro (122, 331). Production of IL-12 followed that of IFN-γ (235, 331), and induction of IL-12 p40 mRNA was essentially absent in IFN-γ-deficient mice (441). Thus, it appears that early production of IFN-γ is important for optimal IL-12 priming in vivo. In vitro, the induction of IL-12 expression in macrophages by *L. major* was dependent on the stage of the parasite (331). Infective promastigotes were found to inhibit selectively IL-12 induction (39), an effect possibly related to the pathway of entry into macrophages (331). In this regard, there is substantial evidence that leishmanial infection selectively impairs protein kinase C-dependent signal transduction in host macrophages, suggesting that this may be an essential pathway for the induction of IL-12 (97, 278, 304). In contrast, amastigotes rapidly induce the expression and production of functional IL-12 (122). This finding may indicate that a stage-specific evasion of IL-12 could be of biological relevance in *L. major* infection (122, 331), although infection initiated by amastigotes remains fully progressive (405). Importantly, IL-12 induction was comparable in macrophages from both resistant and susceptible mice, suggesting that a functional IL-12 inactivation, rather than defective production, may occur in genetically susceptible mice.

Recently, impaired T-cell responsiveness to IL-12 has been proposed to account for the failure of susceptible mice to mount protective Th1 responses (154). Treatment of susceptible mice with rIL-12 mediates curing of the infected animals, associated with both suppression of Th2 cytokine production and amplification of Th1 responses (165, 405), while neutralization of IL-12 leads to an adverse outcome in resistant mice (164, 405). Exogenous IL-12 appears to bypass the capacity of the promastigotes to evade IL-12 induction during the establishment of natural infection. However, when given later in the course of *L. major* infection, IL-12 alone was unable to alter the course of infection in susceptible mice and even enhanced IL-4 production under certain circumstances (165, 171, 405, 442). This effect appeared to be IFN-γ independent, presumably reflecting the loss of proximal signaling components of IL-12R by committed Th2 effector cells (407). Interestingly, treatment with IL-12 was instead effective in an established visceral infection with *Leishmania donovani* (292, 411). However, failure to effectively control this latter infection appears to be due to multiple host defense defects, including impaired IFN-γ production and IL-12 responsiveness (293). Therefore, if defective Th1 reactivity, not associated with a predominant Th2 cell response, occurs in this infection, this could explain the beneficial effect of IL-12 in the late phases of infection.

Recent evidence indicates the efficacy of IL-12 in alternative therapeutic strategies. Vaccination with *Leishmania* antigens and IL-12 was capable of inducing protective Th1 responses in otherwise susceptible mice (1, 284). Likewise, in contrast to IL-12 alone, the combination of IL-12 with suboptimal chemotherapy induced curing of mice with an established infection (294). These results indicate the feasibility of successful parasitic vaccines composed of a dominant antigen(s) and IL-12 or an adjuvant capable of inducing endogenous IL-12. Moreover, the fact that an established Th response could be redirected to an appropriate one by chemotherapy plus IL-12 offers new perspectives in the treatment of chronic infectious diseases, whether caused by protozoan parasites or not.

***T. gondii*.** The quiescent nature of chronic toxoplasmosis in immunocompetent hosts is attributed to the induction of strong cell-mediated immunity, which actively controls parasite replication in acute infection and prevents cyst reactivation during chronic infection. In contrast, toxoplasmosis in SCID mice is characterized by unrestricted parasite replication in the brain and the presence of parasites in other tissues, thus mimicking the disease in immunocompromised patients (332). IL-12 plays a crucial role in establishing protective immune responses (176, 359), primarily through induction of IFN-γ from NK and T cells (133, 174, 176, 359) but also through IFN-γ-independent mechanisms (209). TNF-α (381) and IL-1 (175) appear to be important cofactors for IL-12-induced IFN-γ synthesis. IFN-γ production by NK cells during the innate immune response is associated with early control of pathogen replication and subsequent differentiation of IFN-γ-producing Th1 cells (133). IL-12 neutralization in vivo blocks production of IFN-γ by NK cells and reduces the survival of both conventional and SCID mice (133, 135, 174, 209). Treatment with rIL-12 has beneficial effects in both conventional and SCID mice (133, 174–176, 209). The activation of NK cells to produce IFN-γ early after infection appears to be the primary mechanism of IL-12-dependent resistance in *T. gondii*-infected SCID mice (133). In contrast to the effects observed early in acute infection, IL-12 neutralization during chronic infection fails to alter the course of disease, suggesting that the maintenance and expression of acquired immunity to *T. gondii* is relatively IL-12-independent (135, 359).

A soluble tachyzoite extract was found to elicit IL-12 production by macrophages from both conventional and IFN-γ-

deficient mice (135, 361), which indicates that *T. gondii* is capable of inducing IL-12 synthesis in the absence of IFN-γ. Interestingly, the chemical nature of the IL-12-inducing molecule appears to be similar to that of the IL-10-inducing molecule, which indicates that both cytokines may be coordinately induced in host macrophages (359). In keeping with this finding is the observation that IL-10 (178, 359) and TGF-β (173) antagonize IL-12 functions in infected mice.

***Plasmodium* species.** T-cell-mediated immunity is clearly required for protection from malaria (170, 225, 232, 460). Possible mechanisms of T-cell protection include lysis of infected hepatocytes by cytotoxic T cells and release of cytokines capable of priming hepatocytes to produce substances toxic to the parasite or of controlling parasite growth during the blood stage of infection (83). Given the protective effect of IFN-γ in malaria (186, 187), IL-12 might be expected to cure infected mice. Indeed, prophylactic treatment with rIL-12 resulted in 100% protection of *Plasmodium yoelii*-infected mice (372) or *P. cynomolgy*-infected monkeys (169), an effect possibly related to IFN-γ-dependent production of NO that kills intrahepatic parasites.

Exogenous IL-12 also had protective effects against blood-stage *Plasmodium chabaudi* infection, an effect that required IFN-γ and TNF-α but not NO. This effect was observed in both resistant and susceptible mice (401). However, ablation of IL-12 did not impede clearance of infection in resistant mice, thus suggesting that IL-12 is necessary but not sufficient for the development of resistance to malaria (460). The ability of IL-12 to protect against the liver-stage parasites would be particularly attractive for the purpose of using IL-12 as a prophylactic or therapeutic agent against infection with dormant liver forms (83). However, the recent finding that resistance to cerebral malaria in TNF-α/β-deficient mice is associated with reduced IL-12 expression in the brain (353) indicates that IL-12 may have both protective and nonprotective effects in malaria.

***C. parvum*.** Infection by *Cryptosporidium parvum* can be acutely severe in immunocompetent hosts but may be chronic and life-threatening in immunocompromised subjects. Experimental models of cryptosporidiosis include infection of suckling or adult mice, the former being highly susceptible to infection (429, 430). Both IFN-γ and $CD4^+$ cells play roles in protecting mice against infection (430). Treatment with IL-12-neutralizing antibodies greatly exacerbated the severity of infection, suggesting that endogenous IL-12 may act to limit infection (432). Treatment of neonatal and SCID mice with rIL-12 before oral infection with oocysts of *Cryptosporidium* prevented or greatly reduced the severity of infection. However, late treatment with rIL-12 did not improve the course of an established infection. The protective effect of IL-12 occurred through the induction of IFN-γ (432). Thus, it appears that the ability of IL-12 to exert beneficial effects through IFN-γ is a common mechanism shared by other protozoa of the subphylum *Apicomplexa*, such as *T. gondii* and *P. yoelii*.

***T. cruzi*.** Infection with the hemoflagellate protozoan parasite *Trypanosoma cruzi* causes Chagas' disease, which is characterized by acute and chronic phases, the latter associated with pathology in several organs. In a murine model of experimental *T. cruzi* infection, host resistance to the pathogen depends on both innate and acquired immunity, requiring the combined effects of NK and T cells and cytokines (38, 329). By inducing NO synthesis in activated macrophages, IFN-γ plays an important role in controlling intracellular parasite replication; in contrast, IL-10 and TGF-β have been associated with susceptibility to infection by inhibiting IFN-γ-mediated macrophage activation (38, 329, 384, 385). In vitro studies indicate that IL-12 is an IFN-γ inducer in infection (3). Exposure of macrophages to *T. cruzi* results in the production of IL-12. This production was found to be dependent on the parasite stage, as observed on exposure to the trypomastigote but not the epimastigote forms (3). In vivo, administration of rIL-12 reduced parasitemia but only modestly increased the survival of infected mice, an effect that was both IFN-γ and TNF-α dependent (177). Likewise, IL-12 neutralization increased parasitemia in infected mice without significantly affecting mortality (3, 177).

Helminth Infections

***S. mansoni*.** There is still considerable debate concerning the immunological effector mechanisms responsible for protection to *Schistosoma mansoni* infection (247), with evidence supporting a function for humoral Th2-based responses (37) as well as for Th1-dependent cell-mediated immunity (188). In murine schistosomiasis, a strong Th2 response dominates the immunopathogenetic response of the host to the parasite eggs (57, 152, 456) whereas immunity induced by attenuated cercariae of *S. mansoni* is highly dependent on IFN-γ production by Th1 cells (379, 393). In vaccinated mice, an elevated expression of IFN-γ, TNF-α, and IL-12 was observed (451, 453); IFN-γ-activated effector cells exhibited potent killing activity against schistosomula (312). IL-12 administered alone had no effect on the protective immunity elicited by attenuated cercariae; however, if administered with attenuated cercariae or larval antigens, IL-12 enhanced Th1 cytokine production and protection and decreased Th2 cytokine and IgE productions (285, 451, 453). IL-12 also decreased IgE synthesis by peripheral blood mononuclear cells from helminth-infected individuals (212).

An additional important role for IL-12 in this infection and its pathology concerns the ability to regulate pulmonary schistosome egg granuloma formation. Schistosome eggs elicit an eosinophil and macrophage granulomatous immune response, which in turn causes tissue damage in nearly every organ of the human host (247). Granuloma formation, particularly its growth and maintenance, is largely associated with the production of Th2 cytokines (56, 152). Macrophages from egg granulomas had impaired IL-12-producing capacity, which could be reversed by IL-4 and IL-10 inhibition (56). Neutralization of endogenous IL-12 enhanced granulomatous inflammation and the corresponding Th2 cytokine expression, while injection of rIL-12 decreased both functions (450). The beneficial effect of exogenous IL-12 was dependent on the production of IFN-γ, since no such effects were observed in IFN-γ-deficient mice (452). Actually, in the absence of IFN-γ, IL-12 exacerbated rather than suppressed Th2-dependent granuloma formation and pathology. In addition to affecting granuloma formation, IL-12 inhibited the anamnestic granulomatous response of animals presensitized with eggs, and this suppression was associated with a decreased expression of Th2 cytokines (450). The ability of IL-12 to suppress both primary and secondary egg-induced Th2 responses suggests the possibility of strategies aimed at preventing schistosoma egg-induced pathology by the use of IL-12. Elegant experiments by Wynn et al. (449) demonstrated that this indeed may be the case. Sensitization with eggs plus IL-12, while partially inhibiting granuloma formation, dramatically reduced the tissue fibrosis that is induced by infection with *S. mansoni*.

Other helminths. Resistance to several other helminths is associated with strong humoral Th2 responses (102, 318, 431). It has recently been proposed that Th2 cells provide "help for helminths" (243). In *Nippostrongylus brasiliensis* infection, treatment with IL-12 suppresses eosinophilia and IgE production but prolongs parasite survival and increases egg produc-

tion (113). Interestingly, all these effects, except eosinophilia, were dependent on IFN-γ production. IL-12 loses the ability to inhibit Th2-associated responses when administered in the course of an established infection. Thus, IL-12 may be more useful as an adjuvant for inducing Th1 responses during initial immunization than for converting established Th2 responses to Th1 responses.

In a murine model of *Brugia malayi* infection, IL-12 treatment suppresses the induction of pathogen-driven Th2 responses in both naive and immunized mice without affecting the clearance in vivo of microfilariae (318). Different tissue location and/or effector mechanisms of parasite rejection may account for the different effects of IL-12 in different helminth infections.

Fungal Infections

C. albicans. In mucosal colonization and systemic infection of mice with *Candida albicans*, Th1 cells mediate phagocyte-dependent protection and are the principal mediators of DTH reactions. In contrast, production of inhibitory cytokines, such as IL-4 and IL-10, by Th2 cells and high levels of IgE are associated with disease progression (327, 341, 342, 344, 351). Th2-like reactivity is frequently observed in patients with *Candida*-related pathology, such as in symptomatic infections, allergy, and asthma. Th1-type responses may thus characterize the carriage of saprophytic yeasts and the resistance to disease seen in healthy humans, whereas yeast-specific Th2 responses are associated predominantly with pathology (327). The mechanisms responsible for the preferential expansion of *Candida*-reactive Th1 cells in mice are now beginning to be clarified. Th1 differentiation in vivo requires the combined effects of different cytokines acting on several cell types, including IL-12, in the relative absence of counterregulatory cytokines, such as IL-4 and IL-10, which are per se necessary and sufficient for Th2 polarization. Although deficient IFN-γ (343), TGF-β (396), and IL-6 (348) responses may each block the induction of protective immunity, none of these cytokines correlates with Th1 development as IL-12 does (340, 349, 350). IL-12 transcripts are persistently expressed by macrophages from healer but not nonhealer mice (350). Combined with the finding that IL-12 also plays an obligatory role in *Candida*-driven Th1 differentiation in vivo upon challenge with a yeast LVS (349), these observations indicate that IL-12 is necessary for the development of a Th1 response to *Candida*. Subsequent studies indicated that exogenously administered IL-12 can increase the Th1-mediated vaccinating potential of a mannoprotein fraction of *C. albicans* (268). The occurrence of early and sustained levels of IFN-γ in *Candida*-driven Th2 development makes it unlikely that IL-12 plays only an indirect role in Th1 differentiation by providing, soon after infection, the IFN-γ that acts as an essential requirement for $CD4^+$ cell priming for IFN-γ production. In vivo data based on serologic ablation of either cytokine suggest that irrespective of whether high or low levels of IFN-γ are present early in infection, it is the availability of IL-12 at the level of the antigen recognition triad (accessory cells, antigen, $CD4^+$ cells) that allows the $CD4^+$ cells to utilize IFN-γ, initiate their own production of IFN-γ, and differentiate into Th1 cells. Although IL-12 is both required and prognostic for Th1-cell development in murine candidiasis, administration of rIL-12 did not improve the course and outcome of nonhealing systemic infections caused by virulent challenge (349). Even more striking, however, was the observation of an exacerbating effect of IL-12 in the mucosal infection model, where the spontaneous development of Th1-associated acquired resistance was somewhat impaired, to the benefit of an emerging Th2-biased reactivity. An IFN-γ-dependent priming of mucosal tissue to local damage by inflammatory stimuli might contribute to the exacerbating effects of IL-12 in gastrointestinal infection (340, 349).

Early in infection and as a result of IL-12 exposure, an increase in the circulating levels of not only IFN-γ but also IL-4 and IL-10 was found. Thus, these latter cytokines may act to overshadow the Th1-promoting effect of rIL-12 administered to infected mice (340). Indeed, in a pathogen-free animal model of vaccination, in the absence of counterregulatory cytokines, exogenous IL-12 could fully exhibit its Th1-promoting potential (268). As a possible source of IL-12 in candidiasis, macrophages are clearly the primary candidates. Upon exposure to *Candida* cells in vitro, splenic macrophages produce bioactive IL-12 and require the presence of IFN-γ (345). Recently, by examining IL-12 production by neutrophils in vitro in response to *Candida* cells, we have obtained direct evidence that neutrophils can produce both IL-12 and IL-10 (341, 345–347). Most importantly, IL-12 appeared to be released only in response to a *Candida* LVS that initiates Th1 development in vivo but IL-10 was released in response to a virulent strain. The quantitative production of IL-12 (p40 and p70) was similar to that observed in vitro with established cellular sources of the biologically relevant cytokine, such as activated macrophages, dendritic cells, keratinocytes, and Langerhans' cells.

Production of IL-12 by neutrophils occurs in response to live *Candida* cells and does not seem to be dependent on phagocytosis or on the addition of IFN-γ (346). However, priming with IFN-γ increases cytokine production in response to fungal cells (346). Human neutrophils also produced bioactive IL-12 in response to a mannoprotein fraction that is capable of inducing Th1 cytokine expression in peripheral blood mononuclear cells (42). The production of IL-12 by neutrophils also occurs in vivo in infected mice. Cytokine gene expression patterns of early neutrophils from healer and nonhealer mice are consistent with a selective association of IL-12 with the healing response and of IL-10 with progressive disease (347). In line with previous data (351), early neutropenia in *C. albicans* infection, while greatly exacerbating infection, would also change the cytokine gene expression and secretion patterns of $CD4^+$ cells. Because of the large number of neutrophils present in the blood or inflammatory tissues of infected mice (345, 351), it is likely that neutrophil production of cytokines may influence the early development of the T-cell response in mice infected with *C. albicans*. More importantly, administration of IL-12 to neutropenic infected mice alters both the outcome of disease and the phenotype of the T-cell response, with a reversion from a Th2 to a Th1 type of reactivity (341, 346, 347). Thus, replacement therapy with IL-12 will restore protective Th1 reactivity in otherwise susceptible neutropenic mice infected with a yeast LVS.

Besides identifying a potentially critical source of endogenous IL-12 in Th1 development to *Candida* cells, these studies may provide some insight into the mechanisms governing Th2 differentiation in nonhealer mice. If neutrophil-derived IL-12 plays a role in Th1-associated anticandidal protection, it is also possible that production of IL-10 by neutrophils contributes to Th2 development. The finding of therapeutic efficacy of IL-12 treatment in neutropenic mice with candidal infection not only strengthens the previous suggestion that the induction of IL-10 may serve as a regulatory response to challenge with IL-12 (340, 349) but also suggests that neutrophils may represent a major source of IL-10 induced by IL-12 in nongranulocytopenic hosts. IL-12 induction of IL-10 production by neutrophils may be only one of the possible mechanisms whereby exogenous IL-12 exerts detrimental or immunotoxic activity in ex-

perimental candidiasis. In otherwise healer mice infected with yeast LVS, relatively high doses of IL-12 result in acute pathology and mortality, suggesting the onset of fungal septic shock associated with neutrophil dysregulation (340). While neutrophils may not be the only source of IL-10 in mice with candidiasis, the finding that IL-10 neutralization improves the outcome of infection in neutropenic but not in nongranulocytopenic mice strongly indicates that neutrophils contribute to the overall secretion of IL-10 in mice with candidiasis (345, 346).

In humans, risk factors for invasive fungal infections are not the same in all neutropenic patients (439) and chronic systemic candidiasis initiated by neutropenia may persist in spite of normal neutrophil counts and adequate antifungal therapy (29). Therefore, it is possible that neutrophils have additional functions other than antifungal effector activity. Together, these data suggest that IL-12 therapy could benefit neutropenic individuals with a responsive T-cell compartment. In addition, they may provide important insights into the general mechanisms of immunoregulation in invasive fungal infections. The ability of murine granulocytes to secrete cytokines that affect either directly or indirectly their own function supports a general function of IL-12 in regulating the neutrophil compartment in inflammation and infection, thus adding to the crucial role of this cytokine in bridging innate and adaptive immunity.

C. neoformans. Cryptococcosis is considered to be controlled primarily by cell-mediated immunity, suggesting a predominant role of Th1 responses (222). In a murine model of pulmonary cryptococcosis, protection against *Cryptococcus neoformans* infection correlates with the production of Th1 cytokines; however, susceptible mice do not show an elevated production of IL-4 and IL-10 (168). Recent studies have examined the potential of immunomodulation of the host immune response by IL-12. Administration of rIL-12 to intratracheally infected mice reduces fungal burden and fungal dissemination and increases survival (204). Treatment with IL-12 also induces the expression of IFN-γ mRNA in the lungs of infected mice. IL-12 is effective when administered in the early stages of pulmonary cryptococcal infection (204). In addition, because conventional antifungal chemotherapy may not be curative in the treatment of the human infection, IL-12 was also given in conjunction with a suboptimal (noncurative) dose of an antifungal agent to assess its possible utility as an adjunctive therapy (67). The results showed that IL-12, given alone or in combination with chemotherapy, is an effective therapy in systemic, particularly brain, cryptococcosis. The mechanisms underlying the therapeutic activity of the exogenous cytokine were interpreted as involving primarily IFN-γ-mediated stimulation of the phagocytic and cytotoxic potential of antifungal effectors, including microglial cells in the brain (67).

***Aspergillus* species.** Invasive aspergillosis is often observed as a secondary infection and is associated with high mortality, particularly in immunocompromised patients. In a murine model of allergic bronchopulmonary aspergillosis, exposure to particulate fungal antigens elicits a strong Th2 response (227); however, fungal allergens may contain epitopes capable of inducing selective Th1 or Th2 cytokines (226). Recent studies indicate a protective role for endogenous and exogenous IFN-γ and TNF-α in murine invasive aspergillosis (295). IFN-γ was also found to be beneficial in human aspergillosis (22, 333). Cenci et al. have recently reported that susceptibility and resistance to invasive aspergillosis in mice are associated with the preferential expansion of $CD4^+$ Th1 and Th2 cells, respectively, so that inhibition of endogenous IL-4 but not administration of exogenous IL-12 will cure infected mice (49).

H. capsulatum. In the immunocompetent host, specific T-cell-mediated immunity develops within a few weeks of infection and controls disease caused by *Histoplasma capsulatum*; however, in individuals with immune deficiency, histoplasmosis is a severe and potentially fatal disease (36). Resistance to infection is due primarily to T cells and macrophages, with IFN-γ being the critical cytokine in activating macrophages to kill the organism (448). A recent study has examined the regulation of cytokine induction in mice with pulmonary (4) or disseminated (472) histoplasmosis and the effect of IL-12 administration or neutralization on the course of disease (4, 472). Depletion of IL-12 greatly increased the severity of infection, whereas treatment with IL-12 early in infection resulted in a substantial decrease in fungal burden and an improved clinical course and survival. Again, these effects were dependent on the production of endogenous IFN-γ and were seen in the course of a primary but not established infection (4, 374). A recent study demonstrates that IL-12, given alone or in combination with amphotericin B, significantly increases the survival of SCID mice infected with *H. capsulatum* (473).

C. immitis. Coccidioidomycosis may develop as a severe progressive and often fatal condition in immunocompromised individuals. Cell-mediated immunity is crucial for host defense against *Coccidioides immitis* infection, so that impaired T-cell reactivity is associated with the development of a severe, progressive disease (399). According to a pattern that appears to be similar yet inverse to that of experimental candidiasis, DBA/2 mice are genetically resistant to infection and develop Th1-associated protective immunity whereas BALB/c mice exhibit Th2-associated susceptibility to systemic challenge with *C. immitis* (82, 253). A recent study showed that IL-12 neutralization increased the severity of an intraperitoneal infection in a resistant strain (254). Conversely, administration of rIL-12 to the susceptible mouse strain before and after challenge significantly improved the course of infection and was associated with a Th1 cytokine secretion profile (254). It will be of interest to ascertain whether IL-12 retains its beneficial effects in a mouse model of aerogenic infection.

Viral and Retroviral Infections

Lymphocytic choriomeningitis virus. Experimental infection of immunocompetent mice by lymphocytic choriomeningitis virus (LCMV) is characterized by the activation of NK, $CD4^+$, and $CD8^+$ T cells, but clearance of the virus is mediated by virus-specific, histocompatibility-restricted $CD8^+$ cytotoxic T lymphocytes (24). Production of bioactive IL-12 is impaired in LCMV-infected mice (26, 80), and, indeed, IL-12 neutralization does not affect viral replication and T-cell responses in infected mice (26, 305). Thus, an IL-12-independent mechanism for IFN-γ production and CTL activation appears to occur in LCMV infection. In the absence of IFN-α and IFN-β, expression of IFN-γ and IL-12 was increased in LCMV-infected mice, suggesting a novel mechanism of IL-12-dependent immune responses during viral infections (80). Both detrimental and beneficial effects were observed following rIL-12 administration to LCMV-infected mice, depending on the treatment dose, endogenous immune response, and genetic sensitivity to IL-12 (307, 309). The toxic effects included a TNF-α-dependent reduction of cytotoxic T-lymphocyte function and increased virus titers, whereas enhancement of late $CD8^+$ T-cell expansion and virus clearance were observed with lower dosages of IL-12.

Murine cytomegalovirus. In contrast to the role and effects of IL-12 in LMCV infection, in murine cytomegalovirus (MCMV)-infected mice bioactive IL-12 is readily detectable

soon after infection both in vivo and in vitro (26, 305, 306). In vivo, IL-12 neutralization increased susceptibility to acute MCMV infection and abrogated NK-cell-dependent IFN-γ production. Thus, early IL-12 production is responsible for the activation of NK cells to release IFN-γ and contributes to the NK-cell-mediated antiviral defense during early MCMV infection in immunocompetent and immunodeficient mice (308). Administration of low doses of rIL-12 increases the resistance to MCMV infection, an effect that is dependent on IFN-γ production by NK cells (440). Thus, at low doses, IL-12 enhances protective NK-cell responses to viral infections (25, 26).

Vesicular stomatitis virus. In a murine model of vesicular stomatitis virus infection of the central nervous system, exogenously administered IL-12 was found to have beneficial dose-dependent effects (23). Peripheral administration of rIL-12 resulted in a local decrease of viral titers and increased class I- and class II-dependent immune responses. Expression of inducible NO synthase in the central nervous system was also increased (23).

Respiratory syncytial virus. In a mouse model of vaccination against respiratory syncytial virus, administration of rIL-12 at the time of immunization with a formalin-inactivated respiratory syncytial virus preparation greatly improved the resistance to subsequent virulent challenge and increased the expression of IFN-γ and IL-12 and the utilization of IgG2a-specific antibodies (409).

Pseudorabies virus. Virulent pseudorabies virus (PRV) is highly neurotropic in mice and produces lytic infections of cells in the central nervous system, leading to fatal encephalitis. Immunization with inactivated PRV leads to Th1 protective immunity in mice, mediated mainly by antibody-dependent virus neutralization (363). Exogenous IL-12 increased the vaccinating potential of inactivated PRV, an effect which was dependent on the production of IFN-γ and antiviral IgG2a antibodies (362).

Herpes simplex virus type 1. Two recent studies of experimental herpes simplex virus type 1 (HSV) infections illustrate the opposite roles that IL-12 may play in the outcome of infection and/or associated immunopathology. In a mouse model of HSV infection of the eye, sustained expression of IL-12 in corneal and inflammatory cells was induced by the virus (195). This local IL-12 production was considered to bias virus-specific immunity to a Th1 reactivity, ultimately leading, in the environment of the eye, to an immunopathologic disease (166). In contrast, the ability of IL-12 to promote virus-specific Th1 responses was considered to be of benefit in HSV-1-infected, thermally injured mice (263). Indeed, exogenous IL-12 increased the resistance to infection in these mice, an effect possibly due to inhibition of Th2 cytokine production.

Other viruses. It has been suggested that a predominance of hepatitis B e antigen (HBeAg)-specific Th2 cells may contribute to chronicity in hepatitis B virus infection (261). In transgenic mice overexpressing the HBeAg, low doses of exogenous IL-12 significantly inhibited autoantibody production and increased IFN-γ production by shifting the Th2 response toward Th1 predominance (45, 274). A crucial role for IL-12-dependent IFN-γ production in the induction of protective antiviral responses has recently been demonstrated in a mouse hepatitis virus model (364). Therefore, the potential clinical application of IL-12 in the treatment of chronic viral hepatitis has recently been suggested (126). Exogenous IL-12 was also protective in mice infected with encephalomyocarditis virus (313), and its expression by macrophages was induced upon infection with lactate dehydrogenase-elevating virus, hepatitis virus, and adenovirus (81).

LP-BM5 murine leukemia viruses. Murine AIDS develops in susceptible strains of mice infected with the LP-BM5 mixture of murine leukemia viruses (144). The patterns of cytokine gene expression upon infection are different in resistant and susceptible mice, with a predominant production of Th2 cytokines being observed during progression of retrovirus-induced immunodeficiency in susceptible mice (134). IFN-γ appears to be a key mediator of disease in this infection, being associated with both protection and pathology (144, 427). Therefore, IL-12 could be expected to play a complex role in murine AIDS. Transcripts for IL-12 p40 are induced within 1 week of infection of either resistant or susceptible mice, and their numbers continue to increase slowly in susceptible but not resistant strains (144). Chronic treatment of susceptible mice with an appropriate dose of rIL-12, initiated at the beginning of infection, reduces the severity of the disease and the immune system abnormalities associated with its progression (132). These effects are dependent on the production of IFN-γ. However, neutralization of IL-12 and IFN-γ did not induce disease in resistant mice (144). Thus, neither IFN-γ nor IL-12 is essential for controlling the infection of resistant mice. In contrast, in susceptible mice, they could contribute to both immunopathology and protection, a phenomenon possibly related to the levels of endogenously produced cytokines.

IL-12 IN HUMAN INFECTIONS

Viral Infections

Human immunodeficiency virus. The roles of different Th cytokines in regulating the immune responses in HIV infection and in AIDS have recently been reviewed in detail (246). Therefore, we will deal only with the role and effects of IL-12. Although the gp120 glycoprotein of HIV will induce IFN-γ-dependent production of IL-12 in cultured macrophages (108), production of IL-12 by monocytes/macrophages in response to *S. aureus* and other pathogens was found to be impaired in HIV-positive individuals (52, 53, 62, 64, 95, 130, 180). Decreased expression of the IL-12 p35, but not p40, gene appeared in one study to correlate with defective production of bioactive IL-12 in the early stages of infection (64), thus confirming previous observations on the biologically relevant role of p35 chain expression (394). Impaired production of IL-12 was associated with a decreased p40 gene expression at later stages of the disease, possibly as a result of overproduction of Th2 cytokines, such as IL-10 (62, 64, 72, 84), IL-4, and IL-13 (52, 87), and of prostaglandin E_2 (63). Although complex relationships probably operate in the reciprocal regulation of IL-12 and IL-10 production (272), it appears that these two cytokines are the major immunoregulatory cytokines that control progression to AIDS (62, 70, 71). Both IL-10 neutralization (72, 231) and IL-12 addition to cultured peripheral blood mononuclear cells from HIV-positive individuals restore Th1 responses to recall (68, 428) and nonrecall (300) antigens. On its own, IL-12 may exert its effects at both the immunological and virological levels. T and NK cells from HIV-infected patients have been shown to produce IFN-γ and to become activated in response to IL-12 (52, 54, 315, 386, 418). However, IL-12 also protects $CD4^+$ Th1 cells from antigen-induced apoptotic death (69, 107), a finding that expands our knowledge of the biological activities of this cytokine. Because Th1 clones appear to be less permissive than Th2 clones for HIV replication (255), it is possible that, through its anti-apoptotic effect, IL-12 contributes to decreased viral replication. In this regard, it has recently been shown that IL-12 is capable of down-regulating HIV replication in human macrophage cultures,

either directly or indirectly, through the induction of inhibitory cytokines (2, 319). This latter mechanism may account for the different effects of IL-12 on HIV replication seen at the different clinical stages of infection (319).

Although much remains to be learned about the possible sources and regulation of IL-12 production in HIV infection and AIDS, it seems that administration of exogenous IL-12 or maneuvers aimed at restoring endogenous IL-12 production could be a promising therapeutic approach in this infection. Phase 1 trials in HIV patients have shown modest and tolerable toxicity (14).

Measles virus. A marked suppression of cell-mediated immune responses, such as skin DTH, T-cell proliferation, and NK-cell activity, associated with predominant production of Th2 cytokines and elevated levels of IgE in plasma, is observed during and after measles (151, 167). Infection of primary monocytes with measles virus selectively impairs the expression and production of IL-12 without affecting other cytokines and chemokines (197). Evidence for a role of inhibitory cytokines could not be demonstrated. Interestingly, decreased IL-12 production was found to be dependent on the activation of the measles virus cellular receptor CD46, a cell surface member of the regulators of complement activation gene cluster (98). The ligation of CD46 by its endogenous complement ligand also leads to decreased IL-12 production by macrophages (197). This finding provides the first evidence that the complement system not only augments humoral immune responses but also inhibits cellular immune responses. Again, IL-12 is the link between the complement natural system and adaptive cellular immunity.

Bacterial Infections

***Mycobacterium* species.** Human tuberculosis is considered a prime example of a disease controlled by cell-mediated immunity and not by humoral immunity (287). However, cell-mediated immunity is also responsible for tissue damage to the host. Depressed peripheral Th1 responses are a prominent feature of human tuberculosis (267, 469–471), even though the immune response at the site of infection is characterized by enhanced production of IFN-γ by T cells (239). Actually, the local production and expression of IFN-γ were similar in patients with pleural (16) and pulmonary (334) tuberculosis, as well as in tuberculosis patients with and without HIV infection (239). This may imply that the levels of IFN-γ produced in tissues contribute more to local inflammation or immunopathology than to protective immunity. In contrast, Th2 responses are not enhanced either systemically or at the sites of disease (239, 469–471).

IL-12 plays an important role in the generation of cell-mediated immunity to mycobacterial infection (277). In patients with tuberculous pleuritis, IL-12 expression and production were higher in pleural fluid than in blood (469) and the numbers of IL-12-producing peripheral blood cells in these patients were larger than those in healthy subjects (288). rIL-12 enhanced and IL-12 neutralization inhibited *M. tuberculosis*-induced proliferation of pleural fluid and peripheral blood cells from tuberculosis patients, with or without HIV coinfection (469, 470). IL-12 also enhanced the cytolytic activity of $CD4^+$ T cells and NK cells against human monocytes infected with *M. tuberculosis* (32, 94). In vitro, live *M. tuberculosis* cells and, to a lesser extent, soluble mycobacterial proteins were able to induce production of IL-12 by monocytes, an effect potentiated by phagocytosis (125). Monocytes also produce IL-10 upon exposure to *M. tuberculosis* (15, 469), suggesting that the balance of these cytokines may influence the T-cell cytokine profile. Indeed, the addition of anti-IL-10 antibodies to *M. tuberculosis*-stimulated peripheral blood mononuclear cells from tuberculosis patients increased the T-cell production of IFN-γ and monocyte production of IL-12 (469, 470). In *M. avium* infection, IL-12 increased the pathogen-induced proliferative responses of peripheral blood lymphocytes from HIV-infected patients (300) and stimulated the antibacterial activity of macrophages through an action on NK cells (21). In addition, defective IL-12 production was associated with increased familial susceptibility to disseminated *M. avium* infections (124).

Human leprosy forms a spectrum in which the clinical manifestations correlate with the level of cell-mediated immunity to the pathogen *Mycobacterium leprae*. At one pole, patients with tuberculoid leprosy are able to restrict the growth of the pathogen and their skin lesions are characterized by a predominance of $CD4^+$ Th1 cells producing IFN-γ and IL-2. At the opposite pole, patients with lepromatosy leprosy are unable to contain infection and their skin lesions are characterized by a predominance of $CD8^+$ T cells producing IL-4 and IL-10 (276, 277, 355). The expression and production of IL-12 were higher in tuberculoid than lepromatous lesions, indicating that the level of IL-12 expression correlates with the presence of cell-mediated immunity (383). In vitro, comparable levels of bioactive IL-12 were produced by *M. leprae*-stimulated adherent cells from tuberculoid and lepromatous leprosy patients. Both IL-4 and IL-10 abrogated this production, indicating the existence of negative regulators of IL-12 production in lepromatous lesions (238). IL-12 stimulated the proliferation of $CD4^+$ Th1 clones from tuberculoid lesions but not $CD8^+$ Th2 clones from lepromatous lesions. Moreover, anti-IL-12 antibody inhibited the T-cell proliferative response to *M. leprae* in tuberculoid leprosy patients.

Other bacteria. In diseases caused by bacterial superantigens, such as atopic dermatitis, production of IL-12 and levels of IL-12R expression were normal in peripheral blood monocytes, despite the inability to generate a normal IFN-γ response (236). Bacterial superantigens induce T-cell expression of the skin-selective homing receptor via stimulation of IL-12 production, suggesting that IL-12 may contribute to the development of skin rashes in superantigen-mediated diseases (237). A possible involvement of IL-12 has also been suggested in the expression of local immune response to periodontal bacteria (137), to *Helicobacter pylori* (198), or in bacterial meningitis (221).

Protozoan Infections

***Leishmania* species.** Elevated levels of inhibitory Th2 cytokines are thought to be responsible for the lack of protection against these parasitic diseases (13). Addition of IL-12 restores the proliferative and IFN-γ-producing ability of peripheral blood mononuclear cells from patients with visceral leishmaniasis (11, 143). A recombinant *Leishmania* antigen has recently been found to elicit IL-12 production and Th1 cytokine production in patients with chronic mucosal leishmaniasis as well as in uninfected individuals (391). Therefore, IL-12 may play an important role in the regulation of the cellular immune responses in human leishmaniasis.

Fungal Infections

A recent study has examined IL-12 expression in peripheral blood mononuclear cells in response to *C. neoformans* and *C. albicans*, as well as the effect of IL-12 on cellular proliferative responses to fungal antigens (158). Exposure to either fungal pathogen induced comparable expression of IL-12 p40 mRNA

and production of bioactive IL-12 in monocytes from both HIV-seronegative and HIV-seropositive donors. Moreover, rIL-12 did not restore the lymphoproliferative activity of mononuclear cells from HIV-seropositive donors. These results indicate that the ability of monocytes to synthesize IL-12 in response to fungal stimuli is preserved during HIV infection. Therefore, it will be of interest to examine the role of T-cell-derived cytokines in the regulation of IL-12 gene expression and release in response to fungal stimulation in the course of HIV infection. In this regard, it has recently been shown that priming with IFN-γ can increase IL-12 production in response to fungi in HIV-infected patients (159).

CONCLUSIONS

The crucial role of endogenous IL-12 production in resistance to experimental and human infections with many bacteria, protozoa, fungi, and viruses can be traced to its proinflammatory activity and ability to promote type 1 or phagocyte-dependent responses. Although many of the effects initiated by IL-12 may be attributable to the induction of IFN-γ, several aspects of the relationship between these two cytokines remain to be elucidated, and recent evidence suggests that they could be different according to the type of pathogen and experimental conditions. Major unresolved questions in this regard include whether IL-12 is an absolute requirement for Th1 development and maintenance of reactivity, whether IFN-γ is necessary for the initial production of IL-12, and to what extent IFN-γ induced by IL-12 regulates Th1 cells, besides acting as a primary effector molecule of their functional activity. However, common to most models of experimental infections may be the finding that IL-12 regulates the extent of the IFN-γ response at the time of infection but is not required to sustain the Th1 response once it has been established. On the other hand, overproduction of IL-12 and IFN-γ in response to an acute infection may play a significant role in the pathogenesis of septic shock syndromes, whereas sustained IL-12 release may initiate or worsen immunopathology and autoimmunity in chronic infection.

The clinical implications of these findings for infectious diseases and for therapy or prophylaxis of these conditions are manifold. Although it is as yet unclear whether IL-12 can modify established responses in humans, IL-12 appears to be an excellent candidate to help restore immunity to a variety of opportunistic intracellular pathogens that require IFN-γ for effective control and could be used as an adjunct to chemotherapy. This could be particularly important in patients with cellular immunodeficiencies, who are at high risk for developing opportunistic infections, because the exogenous IL-12 would either enhance protective memory responses (e.g., in AIDS, by residual $CD4^+$ cells) or compensate for the loss of a major cellular source of endogenous IL-12 (e.g., in systemic mycoses of neutropenic hosts). Because of its Th1-promoting effects, IL-12 also has great potential as a vaccine adjuvant for diseases requiring primarily cellular immunity and possibly for infections requiring a combination of cell-mediated and humoral immunity, since the cytokine has been shown to increase antibody responses as well. Since the qualitative nature of the T-cell response following vaccination may depend on the ability of the antigenic stimulus to induce IL-12 by antigen-presenting cells, the development of appropriate adjuvants or specific antigens might even obviate the need for exogenous IL-12. If recombinant IL-12 is administered with immunization or sufficient IL-12 is induced by the use of these adjuvants or antigens, it is likely that a protective memory response can be generated that will not require repeated immunization or continuous IL-12 exposure. In some infections (e.g., by helminths), IL-12 could be used as an adjuvant to a vaccine to modulate detrimental Th2 responses, representing primarily an anti-pathology rather than an anti-parasite prophylactic approach. In contrast, the use of IL-12 antagonists could be useful in septic shock syndromes or when the endogenous cytokine helps to sustain immunopathology or autoreactivity mediated by Th1 cells.

In addition to these therapeutic perspectives, already supported by a considerable amount of data in experimental models of infection, several possibilities can be envisioned that could carry the exploitation of the action of IL-12 one step further than the simple administration or neutralization of the cytokine. Once the chemical nature of the microbial products triggering IL-12 production has been established, such products could be modeled artificially and used as adjuvants for cell-mediated immunity. Likewise, an understanding of the nature of those products capable of selective inhibition of IL-12 synthesis might lead to the availability of specific immunosuppressors for pathogenetic cell-mediated responses. Elucidation of the signaling pathways for IL-12 induction in phagocytes and of IL-12 signal transduction in target cells might allow for the development of specific regulators of IL-12 synthesis or activity. A deeper understanding of the structural basis for the functional activity of the IL-12 receptor on different cell types could result in the design of ligands that would act specifically and could perhaps dissociate the beneficial from the detrimental effects of IL-12. Although some of these perspectives may still seem remote, the expectations that IL-12 can be used successfully in the prophylaxis or therapy of infectious diseases in humans are high. Undoubtedly, the results obtained in this area will have far-reaching implications for the development of novel approaches in a variety of therapeutic areas.

ACKNOWLEDGMENTS

We thank Eileen Mahoney Zannetti for superb and invaluable editorial and secretarial assistance.

This work was supported by IX Progetto AIDS, 9404-31, Italy.

REFERENCES

1. **Afonso, L. C. C., T. M. Scharton, L. Q. Vieira, M. Wysocka, G. Trinchieri, and P. Scott.** 1994. The adjuvant effect of interleukin-12 in a vaccine against *Leishmania major*. Science **263:**235–237.
2. **Akridge, R. E., and S. G. Reed.** 1996. Interleukin-12 decreases human immunodeficiency virus type 1 replication in human macrophage cultures reconstituted with autologous peripheral blood mononuclear cells. J. Infect. Dis. **173:**559–564.
3. **Aliberti, J. C. S., M. A. G. Cardoso, G. A. Martins, R. T. Gazzinelli, L. Q. Vieira, and J. A. Silva.** 1996. Interleukin-12 mediates resistance to *Trypanosoma cruzi* in mice and is produced by murine macrophages in response to live trypomastigotes. Infect. Immun. **64:**1961–1967.
4. **Allendoerfer, R., G. P. Biovin, and G. S. Deepe, Jr.** 1997. Modulation of immune responses in murine pulmonary histoplasmosis. J. Infect. Dis. **175:** 905–914.
5. **Anguita, J., D. H. Persing, M. Rincon, S. W. Barthold, and E. Fikrig.** 1996. Effect of anti-interleukin 12 treatment on murine lyme borreliosis. J. Clin. Invest. **97:**1028–1234.
6. **Appelberg, R., A. G. Castro, J. Pedrosa, R. A. Silva, I. M. Orme, and P. Minóprio.** 1994. Role of gamma interferon and tumor necrosis factor alpha during T-cell-independent and -dependent phases of *Mycobacterium avium* infection. Infect. Immun. **62:**3962–3971.
7. **Arai, T., K. Hiromatsu, H. Nishimura, Y. Kimura, N. Kobayashi, H. Ishida, Y. Nimura, and Y. Yoshikai.** 1995. Effects of in vivo administration of anti-IL-10 monoclonal antibody on the host defence mechanism against murine *Salmonella* infection. Immunology **85:**381–388.
8. **Autenrieth, I. B., M. Beer, E. Bohn, S. H. E. Kaufmann, and J. Heeseman.** 1994. Immune responses to *Yersinia enterocolitica* in susceptible BALB/c and resistant C57BL/6 mice: an essential role for gamma interferon. Infect. Immun. **62:**2590–2599.
9. **Autenrieth, I. B., and J. Heeseman.** 1992. In vivo neutralization of tumor necrosis factor alpha and interferon-gamma abrogates resistance to *Yersinia*

enterocolitica in mice. Med. Microbiol. Immunol. **181:**333–338.
10. **Autenrieth, I. B., A. Tingle, A. Reske Kunz, and J. Heeseman.** 1992. T lymphocytes mediate protection against *Yersinia enterocolitica* in mice: characterization of murine T-cell clones specific for *Y. enterocolitica*. Infect. Immun. **60:**1140–1149.
11. **Bacellar, O., C. Brodskyn, J. Guerreiro, M. Barral-Netto, C. H. Costa, R. L. Coffman, W. D. Johnson, and E. M. Carvalho.** 1996. Interleukin-12 restores interferon-γ production and cytotoxic responses in visceral leishmaniasis. J. Infect. Dis. **173:**1515–1516.
12. **Bacon, C. M., D. W. McVicar, J. R. Ortaldo, R. C. Rees, J. J. O'Shea, and J. A. Johnston.** 1995. Interleukin 12 (IL-12) induces tyrosine phosphorylation of JAK2 and TYK2: differential use of Janus family tyrosine kinases by IL-2 and IL-12. J. Exp. Med. **181:**399–404.
13. **Badaro, R., E. Falcoff, F. S. Badaro, E. M. Carvalho, D. Pedral-Sampaio, A. Barral, J. S. Carvalho, M. Barral-Netto, M. Brandely, L. Silva, J. C. Bina, R. Teixeira, R. Falcoff, H. Rocha, J. L. Ho, and W. D. Johnston.** 1990. Treatment of visceral leishmaniasis with pentavalent antimony and interferon gamma. N. Engl. J. Med. **322:**16–21.
14. **Balter, M.** 1995. Cytokines move from margins into the spotlight. Science **268:**203–206.
15. **Barnes, P. F., D. Chatterjee, J. S. Abrams, S. Lu, E. Wang, M. Yamamura, P. J. Brennan, and R. L. Modlin.** 1992. Cytokine production induced by *Mycobacterium tuberculosis* lipoarabinomannan. Relationship to chemical structure. J. Immunol. **149:**541–547.
16. **Barnes, P. F., S. Lu, J. S. Abrams, E. Wang, M. Yamamura, and R. L. Modlin.** 1993. Cytokine production at the site of disease in human tuberculosis. Infect. Immun. **61:**3482–3489.
17. **Barthold, S. W., D. S. Beck, G. M. Hansen, G. A. Terwilliger, and K. D. Moody.** 1990. Lyme borreliosis in selected strains and ages of laboratory rats. J. Infect. Dis. **162:**133–138.
18. **Barthold, S. W., D. H. Persing, A. L. Armstrong, and R. A. Peeples.** 1991. Kinetics of *Borrelia burgdorferi* dissemination and evolution of disease after intradermal inoculation of mice. Am. J. Pathol. **139:**263–273.
19. **Bellone, G., and G. Trinchieri.** 1994. Dual stimulatory and inhibitory effect of NK cell stimulatory factor/IL-12 on human hematopoiesis. J. Immunol. **153:**930–937.
20. **Bendelac, A., and D. T. Fearon.** 1997. Editorial overview: innate pathways that control acquired immunity. Curr. Opin. Immunol. **9:**1–3.
21. **Bermudez, L. E., M. Wu, and L. S. Young.** 1995. Interleukin-12-stimulated natural killer cells can activate human macrophages to inhibit growth of *Mycobacterium avium*. Infect. Immun. **63:**4099–4104.
22. **Bernhisel-Broadbent, J., E. E. Camargo, H. S. Jaffe, and H. M. Lederman.** 1991. Recombinant human interferon-γ as adjunct therapy for *Aspergillus* infection in a patient with chronic granulomatous disease. J. Infect. Dis. **163:**908–911.
23. **Bi, Z., P. Quandt, T. Komatsu, M. Barna, and C. S. Reiss.** 1995. IL-12 promotes enhanced recovery from vesicular stomatitis virus infection of the central nervous system. J. Immunol. **155:**5684–5689.
24. **Biron, C. A.** 1994. Cytokines in the generation of immune responses to, and resolution of, virus infection. Curr. Opin. Immunol. **6:**530–538.
25. **Biron, C. A., and R. T. Gazzinelli.** 1995. Effects of IL-12 on immune responses to microbial infections: a key mediator in regulating disease outcome. Curr. Opin. Immunol. **7:**485–496.
26. **Biron, C. A., and J. S. Orange.** 1995. IL12 in acute viral infectious disease. Res. Immunol. **146:**590–599.
27. **Blanden, R. V., M. J. Lefford, and G. B. Mackaness.** 1969. The host response to Calmette-Guérin bacillus infection in mice. J. Exp. Med. **129:** 1079–1107.
28. **Bliss, J., V. Van Cleave, K. Murray, A. Wiencis, M. Ketchum, R. Maylor, T. Haire, C. Resmini, A. K. Abbas, and S. F. Wolf.** 1996. IL-12, as an adjuvant, promotes a T helper 1 cell, but does not suppress a T helper 2 cell recall response. J. Immunol. **156:**887–894.
29. **Bodey, G. P., and E. J. Anaissie.** 1989. Chronic systemic candidiasis. Eur. J. Clin. Microbiol. Infect. Dis. **8:**855–857.
30. **Bogdan, C., A. Gessner, W. Solbach, and M. Rollinghoff.** 1996. Invasion, control and persistence of *Leishmania* parasites. Curr. Opin. Immunol. **8:**517–525.
31. **Bohn, E., and I. B. Autenrieth.** 1996. IL-12 is essential for resistance against *Yersinia enterocolitica* by triggering IFN-γ production in NK cells and $CD4^+$ T cells. J. Immunol. **156:**1458–1468.
32. **Boom, W. H., R. S. Wallis, and K. A. Chervenak.** 1991. Human *Mycobacterium tuberculosis*-reactive $CD4^+$ T-cell clones: heterogeneity in antigen recognition, cytokine production, and cytotoxicity for mononuclear phagocytes. Infect. Immun. **59:**2737–2743.
33. **Bost, K. L., and J. D. Clements.** 1995. In vivo induction of interleukin-12 mRNA expression after oral immunization with *Salmonella dublin* or the B subunit of *Escherichia coli* heat-labile enterotoxin. Infect. Immun. **63:**1076–1083.
34. **Brunda, M. J.** 1994. Interleukin-12. J. Leukocyte Biol. **55:**280–288.
35. **Brunda, M. J.** 1995. Role of IL12 as an anti-tumour agent: current status and future directions. Res. Immunol. **146:**622–627.
36. **Bullock, W. E.** 1995. *Histoplasma capsulatum*, p. 2340–2353. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practices of infectious diseases, 4th ed. Churchill-Livingstone, Inc., New York, N.Y.
37. **Capron, M., and A. Capron.** 1994. Immunoglobulin E and effector cells in schistosomiasis. Science **264:**1876–1878.
38. **Cardillo, F., J. C. Voltarelli, S. G. Reed, and J. S. Silva.** 1996. Regulation of *Trypanosoma cruzi* infection in mice by gamma interferon and interleukin-10: the role of NK cells. Infect. Immun. **64:**128–134.
39. **Carrera, L., R. T. Gazzinelli, R. Badolato, S. Hieny, W. Muller, R. Kuhn, and D. L. Sacks.** 1996. *Leishmania* promastigotes selectively inhibit interleukin 12 induction in bone marrow-derived macrophages from susceptible and resistant mice. J. Exp. Med. **183:**515–526.
40. **Carter, L. L., and R. W. Dutton.** 1996. Type 1 and type 2: a fundamental dichotomy for all T cell subsets. Curr. Opin. Immunol. **8:**336–342.
41. **Cassatella, M. A., L. Meda, S. Gasperini, S. D'Andrea, X. Ma, and G. Trinchieri.** 1995. Interleukin-12 production by human polymorphonuclear leukocytes. Eur. J. Immunol. **25:**1–5.
42. **Cassone, A., P. Chiani, I. Quinti, and A. Torosantucci.** A possible participation of polymorphonuclear cells stimulated by microbial immunomodulators in cytokine dysregulated patterns of AIDS patients. J. Leukocyte Biol., in press.
43. **Castro, A. G., R. A. Silva, and R. Appelberg.** 1995. Endogenously produced IL-12 is required for the induction of protective T cells during *Mycobacterium avium* infections in mice. J. Immunol. **155:**2013–2019.
44. **Cauwles, A., W. Fiers, and P. Brouckaert.** 1996. Murine IL-12 is involved in Calmette Guérin bacillus-induced sensitization and is by itself sufficient to sensitize mice to the lethal effects of human TNF. J. Immunol. **156:**4686–4690.
45. **Cavanaugh, V. J., L. G. Guidotti, and F. V. Chisari.** 1997. Interleukin-12 inhibits hepatitis B virus replication in transgenic mice. J. Virol. **71:**3236–3243.
46. **Cella, M., D. Scheidegger, K. Palmer-Lehmann, P. Lane, A. Lanzavecchia, and G. Alber.** 1996. Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances T cell stimulatory capacity: T-T help via APC activation. J. Exp. Med. **184:**747–752.
47. **Cellier, M., G. Govoni, S. Vidal, T. Kwan, N. Groulx, J. Liu, F. Sanchez, E. Skamene, E. Schurr, and P. Gros.** 1994. Human natural resistance-associated macrophage protein: cDNA cloning, chromosomal mapping, genomic organization, and tissue-specific expression. J. Exp. Med. **180:**1741–1752.
48. **Cellier, M., G. Prive, A. Belouchi, T. Kwan, V. Rodrigues, W. Chia, and P. Gros.** 1995. *Nramp* defines a family of membrane proteins. Proc. Natl. Acad. Sci. USA **92:**10089–10093.
49. **Cenci, E., S. Perito, K.-H. Enssle, P. Mosci, J.-P. Latgé, L. Romani, and F. Bistoni.** 1996. Th1 and Th2 cytokines in mice with invasive aspergillosis. Infect. Immun. **65:**564–570.
50. **Chan, S. H., M. Kobayashi, D. Santoli, B. Perussia, and G. Trinchieri.** 1992. Mechanisms of IFN-γ induction by natural killer cell stimulatory factor (NKSF/IL-12): role of transcription and mRNA stability in the synergistic interaction between NKSF and IL-2. J. Immunol. **148:**92–98.
51. **Chan, S. H., B. Perussia, J. W. Gupta, M. Kobayashi, M. Pospisil, H. A. Young, S. F. Wolf, D. Young, S. C. Clark, and G. Trinchieri.** 1991. Induction of IFN-γ production by NK cell stimulatory factor (NKSF): characterization of the responder cells and synergy with other inducers. J. Exp. Med. **173:**869–879.
52. **Chehimi, J., C. Paganin, I. Frank, S. Chouaib, S. Starr, and G. Trinchieri.** 1995. Interleukin-12 in the pathogenesis and therapy of HIV disease. Res. Immunol. **146:**605–614.
53. **Chehimi, J., S. Starr, I. Frank, A. D'Andrea, X. Ma, R. R. MacGregor, J. Sennelier, and G. Trinchieri.** 1994. Impaired interleukin-12 production in human immunodeficiency virus-infected patients. J. Exp. Med. **179:**1361–1366.
54. **Chehimi, J., S. Starr, I. Frank, M. Rengaraju, S. J. Jackson, C. Lanes, M. Kobayashi, B. Perussia, D. Young, E. Nickbarg, S. F. Wolf, and G. Trinchieri.** 1992. Natural killer cell stimulatory factor (NKSF) increases the cytotoxic activity of NK cells both in healthy donors and HIV-infected patients. J. Exp. Med. **175:**789–796.
55. **Chehimi, J., N. M. Valiante, A. D'Andrea, M. Rengaraju, Z. Rosado, M. Kobayashi, B. Perussia, S. Wolf, S. E. Starr, and G. Trinchieri.** 1993. Enhancing effect of natural killer cell stimulatory factor (NKSF/IL-12) on cell-mediated cytotoxicity against tumor-derived and virus-infected cells. Eur. J. Immunol. **23:**1826–1830.
56. **Chensue, S. W., J. H. Ruth, K. Warmington, P. Lincoln, and S. L. Kunkel.** 1995. In vivo regulation of macrophage IL-12 production during type 1 and type 2 cytokine-mediated granuloma formation. J. Immunol. **155:**3546–3551.
57. **Chensue, S. W., P. D. Terebuh, K. S. Warmington, S. D. Hershey, H. L. Evanoff, S. L. Kunkel, and G. I. Higashi.** 1992. Role of interleukin-4 and gamma-interferon in *Schistosoma mansoni* egg-induced hypersensitivity formation: orchestration, relative contribution and relationship to macrophage function. J. Immunol. **148:**900–910.
58. **Chizzonite, R., T. Truitt, M. Griffin, E. Nickbarg, B. Hubbard, B. B. Desai, A. S. Stern, U. Gubler, and M. Gately.** 1993. Initial characterization of the

IL-12 receptor (IL-12R) on Concanavalin-A activated mouse splenocytes. J. Cell. Biochem. **17B:**73.
59. **Chizzonite, R., T. Truitt, P. Nunes, B. B. Desai, A. O. Chua, M. K. Gately, and U. Gubler.** 1994. High and low affinity receptors for interleukin-12 (IL-12) on human T cells: evidence for a two subunit receptor by IL-12 and anti-receptor antibody binding. Cytokine **6:**A82a.
60. **Chizzonite, R., T. Truitt, F. J. Podlaski, A. G. Wolitzky, P. M. Quinn, P. Nunes, A. S. Stern, and M. Gately.** 1991. IL-12: monoclonal antibodies specific for the 40-kDa subunit block receptor binding and biologic activity on activated human lymphoblasts. J. Immunol. **147:**1548–1556.
61. **Chong, C., K. L. Bost, and J. D. Clements.** 1996. Differential production of interleukin-12 mRNA by murine macrophages in response to viable or killed *Salmonella* spp. Infect. Immun. **64:**1154–1160.
62. **Chougnet, C., M. Clerici, and G. M. Shearer.** 1995. Role of IL12 in HIV disease/AIDS. Res. Immunol. **146:**615–621.
63. **Chougnet, C., D. Margolis, A. L. Landay, H. A. Kessler, and G. M. Shearer.** 1996. Contribution of prostaglandin E_2 to the IL-12 defect in HIV-infected patients. AIDS **10:**1043–1045.
64. **Chougnet, C., T. A. Wynn, M. Clerici, A. L. Landay, H. A. Kessler, J. Rusnak, G. P. Melcher, A. Sher, and G. M. Shearer.** 1996. Molecular analysis of decreased interleukin-12 production in persons infected with human immunodeficiency virus. J. Infect. Dis. **174:**46–53.
65. **Chua, A. O., R. Chizzonite, B. B. Desai, T. P. Truitt, P. Nunes, L. J. Minetti, R. R. Warrier, D. H. Presky, S. F. Levine, M. K. Gately, and U. Gubler.** 1994. Expression cloning of a human IL-12 receptor component. A new member of the cytokine receptor superfamily with strong homology to gp130. J. Immunol. **153:**128–136.
66. **Chua, A. O., V. L. Wilkinson, D. H. Presky, and U. Gubler.** 1995. Cloning and characterization of a mouse IL-12 receptor-β component. J. Immunol. **155:**4286–4294.
67. **Clemons, K. V., E. Brummer, and D. A. Stevens.** 1994. Cytokine treatment of central nervous system infection: efficacy of interleukin-12 alone and synergy with conventional antifungal therapy in experimental cryptococcosis. Antimicrob. Agents Chemother. **38:**460–464.
68. **Clerici, M., D. R. Lucey, J. A. Berzofsky, L. A. Pinto, T. A. Wynn, S. P. Blatt, M. J. Dolan, C. W. Hendrix, S. F. Wolf, and G. M. Shearer.** 1993. Restoration of HIV-specific cell-mediated immune responses by interleukin-12 in vitro. Science **262:**1721–1724.
69. **Clerici, M., A. Sarin, R. L. Coffman, T. A. Wynn, S. P. Blatt, C. W. Hendrix, S. F. Wolf, G. M. Shearer, and P. A. Henkart.** 1994. Type 1/type 2 cytokine modulation of T-cell programmed cell death as a model for human immunodeficiency virus pathogenesis. Proc. Natl. Acad. Sci. USA **91:**11811–11815.
70. **Clerici, M., and G. M. Shearer.** 1993. A TH1→TH2 switch is a critical step in the etiology of HIV infection. Immunol. Today **14:**107–111.
71. **Clerici, M., and G. M. Shearer.** 1994. The TH1/TH2 hypothesis of HIV infection: new insights. Immunol. Today **15:**575–581.
72. **Clerici, M., T. A. Wynn, J. A. Berzofsky, S. P. Blatt, C. W. Hendrix, A. Sher, R. L. Coffman, and G. M. Shearer.** 1994. Role of interleukin-10 in T helper cell dysfunction in asymptomatic individuals infected with the human immunodeficiency virus. J. Clin. Invest. **93:**768–775.
73. **Cleveland, M. G., J. D. Gorham, T. L. Murphy, E. Tuomanen, and K. M. Murphy.** 1996. Lipoteichoic acid preparations of gram-positive bacteria induce interleukin-12 through a CD14-dependent pathway. Infect. Immun. **64:**1906–1912.
74. **Coley, W. B.** 1893. The treatment of malignant tumors by repeated inoculations of erysipelas with a report of ten original cases. Am. J. Med. Sci. **105:**483–564.
75. **Conlan, J. W., and R. J. North.** 1991. Neutrophil-mediated dissolution of infected host cells as a defense strategy against a facultative intracellular bacterium. J. Exp. Med. **174:**741–744.
76. **Conlan, J. W., A. Sjöstedt, and R. J. North.** 1994. $CD4^+$ and $CD8^+$ T-cell-dependent and independent host defense mechanisms can operate to control and resolve primary and secondary *Francisella tularensis* LVS infection in mice. Infect. Immun. **62:**5603–5607.
77. **Cooper, A. M., J. E. Callahan, J. P. Griffin, A. D. Roberts, and I. M. Orme.** 1995. Old mice are able to control low-dose aerogenic infections with *Mycobacterium tuberculosis*. Infect. Immun. **63:**3259–3265.
78. **Cooper, A. M., D. K. Dalton, T. A. Stewart, J. P. Griffin, D. G. Russell, and I. M. Orme.** 1993. Disseminated tuberculosis in interferon-γ gene-disrupted mice. J. Exp. Med. **178:**2243–2247.
79. **Cooper, A. M., A. D. Roberts, E. R. Rhoades, J. E. Callahan, D. M. Getzy, and I. M. Orme.** 1995. The role of interleukin-12 in acquired immunity to *Mycobacterium tuberculosis* infection. Immunology **84:**423–432.
80. **Cousens, L. P., J. S. Orange, H. C. Su, and C. A. Biron.** 1997. Interferon-α/β inhibition of interleukin 12 and interferon-γ production in vitro and endogenously during viral infection. Proc. Natl. Acad. Sci. USA **94:**634–639.
81. **Coutelier, J. P., J. van Broeck, and S. F. Wolf.** 1995. Interleukin-12 gene expression after viral infection in the mouse. J. Virol. **69:**1955–1958.
82. **Cox, R. A., W. Kennel, L. Boncyk, and J. W. Murphy.** 1988. Induction and expression of cell-mediated immune responses in inbred mice infected with *Coccidioides immitis*. Infect. Immun. **56:**13–17.
83. **Crutcher, J. M., M. M. Stevenson, M. Sedegah, and S. L. Hoffman.** 1995. Interleukin-12 and malaria. Res. Immunol. **146:**552–559.
84. **Daftarian, M. P., F. Diaz-Mitoma, W. D. Creery, W. Cameron, and A. Kumar.** 1995. Dysregulated production of interleukin-10 (IL-10) and IL-12 by peripheral blood lymphocytes from human immunodeficiency virus-infected individuals is associated with altered proliferative responses to recall antigens. Diagn. Lab. Immunol. **2:**712–718.
85. **Dalton, D. K., S. Pitts-Meck, S. Keshev, I. S. Figari, A. Bradley, and T. A. Stewart.** 1993. Multiple defects of immune cell function in mice with disrupted interferon-γ genes. Science **259:**1739–1742.
86. **D'Andrea, A., M. Aste-Amezaga, N. M. Valiante, X. Ma, M. Kubin, and G. Trinchieri.** 1993. Interleukin-10 inhibits human lymphocyte IFN-γ production by suppressing natural killer cell stimulatory factor/interleukin-12 synthesis in accessory cells. J. Exp. Med. **178:**1041–1048.
87. **D'Andrea, A., X. Ma, M. Aste-Amezaga, C. Paganin, and G. Trinchieri.** 1995. Stimulatory and inhibitory effects of IL-4 and IL-13 on production of cytokines by human peripheral blood mononuclear cells: priming for IL-12 and TNF-α production. J. Exp. Med. **181:**537–546.
88. **D'Andrea, A., M. Rengaraju, N. M. Valiante, J. Chehimi, M. Kubin, M. Aste-Amezaga, S. H. Chan, M. Kobayashi, D. Young, E. Nickbarg, R. Chizzonite, S. F. Wolf, and G. Trinchieri.** 1992. Production of natural killer cell stimulatory factor (NKSF/IL-12) by peripheral blood mononuclear cells. J. Exp. Med. **176:**1387–1398.
89. **Daugelat, S., and S. H. E. Kaufmann.** 1996. Role of Th1 and Th2 cells in bacterial infections. Chem. Immunol. **63:**66–97.
90. **Daugelat, S., C. H. Ladel, and S. H. E. Kaufmann.** 1995. Impact of host genetic background on bacillus Calmette-Guérin infection in naturally susceptible mice. Immunol. Lett. **48:**153–156.
91. **DeKruyff, R. H., R. S. Gieni, and D. T. Umetsu.** 1997. Antigen-driven but not lipopolysaccharide-driven IL-12 production in macrophages requires triggering of CD40. J. Immunol. **158:**359–366.
92. **Denis, M.** 1991. Involvement of cytokines in determining resistance and acquired immunity in murine tuberculosis. J. Leukocyte Biol. **50:**495–501.
93. **Denis, M.** 1991. Modulation of *Mycobacterium avium* growth in vivo by cytokines: involvement of tumour necrosis factor in resistance to atypical mycobacteria. Clin. Exp. Immunol. **83:**466–471.
94. **Denis, M.** 1994. Interleukin-12 (IL-12) augments cytolytic activity of natural killer cells toward *Mycobacterium tuberculosis* infected human monocytes. Cell. Immunol. **156:**529–536.
95. **Denis, M., and E. Ghadirian.** 1994. Dysregulation of interleukin-8, interleukin-10, and interleukin-12 release by alveolar macrophages from HIV type 1-infected subjects. AIDS Res. Hum. Retroviruses **10:**1619–1627.
96. **Derrico, C. A., and K. J. Goodrum.** 1996. Interleukin-12 and tumor necrosis factor alpha mediate innate production of gamma interferon by group B *Streptococcus*-treated splenocytes of severe combined immunodeficiency mice. Infect. Immun. **64:**1314–1320.
97. **Descoteaux, A., G. Maltashewski, and S. J. Turco.** 1992. Inhibition of macrophage protein kinase C-mediated protein phosphorylation by *Leishmania donovani* lipophosphoglycan. J. Immunol. **149:**3008–3015.
98. **Dorig, R. E., A. Marcil, A. Chopra, and C. D. Richardson.** 1993. The human CD46 molecule is a receptor for measles virus (Edmonston strain). Cell **75:**295–305.
99. **Eckmann, L., J. Fierer, and M. F. Kagnoff.** 1996. Genetically resistant (Ity^r) and susceptible (Ity^s) congenic mouse strains show similar cytokine responses following infection with *Salmonella dublin*. J. Immunol. **156:**2894–2900.
100. **Ehlers, S., M. E. A. Mielke, and H. Hahn.** 1994. Progress in TB research: Robert Koch's dilemma revisited. Immunol. Today **15:**1–4.
101. **Elkins, K. L., T. Rhinehart-Jones, C. A. Nacy, R. K. Winegar, and A. H. Fortier.** 1993. T-cell-independent resistance to infection and generation of immunity to *Francisella tularensis*. Infect. Immun. **61:**823–829.
102. **Else, K., and R. Grancis.** 1991. Cellular immune responses to the nematode parasite *Trichuris muris*. I. Differential cytokine production during acute or chronic infection. Immunology **72:**508–515.
103. **Emmerling, P., H. Finger, and J. Bockenmühl.** 1974. *Listeria monocytogenes* infection in nude mice. Infect. Immun. **12:**437–439.
104. **Emoto, M., Y. Emoto, and S. H. E. Kaufmann.** 1995. Interleukin-4-producing $CD4^+$ $NK1.1^+$ TcR $\alpha/\beta^{intermediate}$ liver lymphocytes are downregulated by *Listeria monocytogenes*. Eur. J. Immunol. **25:**3321–3325.
105. **Emoto, M., T. Naito, R. Nakamura, and Y. Yoshikai.** 1993. Different appearance of γδ T cells during salmonellosis between Ity^r and Ity^s mice. J. Immunol. **150:**3411–3420.
106. **Eng, V. M., B. D. Car, B. Schnyder, M. Lorenz, S. Lugli, M. Aguet, T. D. Anderson, B. Ryffel, and V. F. J. Quesniaux.** 1995. The stimulatory effects of interleukin (IL)-12 on hematopoiesis are antagonized by IL-12-induced interferon gamma *in vivo*. J. Exp. Med. **181:**1893–1898.
107. **Estaquier, J., T. Idziorek, W. Zou, D. Emilie, C. M. Farber, J. M. Bourez, and J. C. Ameisen.** 1995. T helper type 1/T helper type 2 cytokines and T cell death: preventive effect of interleukin 12 on activation-induced and CD95 (FAS/APO-1)-mediated apoptosis of $CD4^+$ T cells from human immunodeficiency virus-infected persons. J. Exp. Med. **182:**1759–1767.
108. **Fantuzzi, L., S. Gessani, P. Borghi, B. Varano, L. Conti, P. Puddu, and F.**

Belardelli. 1996. Induction of interleukin-12 (IL-12) by recombinant glycoprotein gp120 of human immunodeficiency virus type 1 in human monocytes/macrophages: requirement of gamma interferon for IL-12 secretion. J. Virol. **70:**4121–4124.
109. **Fearon, D. T., and R. M. Locksley.** 1996. The instructive role of innate immunity in the acquired immune response. Science **272:**50–54.
110. **Fernandes, D. M., and C. L. Baldwin.** 1995. Interleukin-10 downregulates protective immunity to *Brucella abortus*. Infect. Immun. **63:**1130–1133.
111. **Ferrieri, P.** 1990. Neonatal susceptibility and immunity to major bacterial pathogens. Rev. Infect. Dis. **12:**5394–5400.
112. **Filgueira, L., F. O. Nestlé, M. Rittig, H. I. Joller, and P. Groscurth.** 1996. Human dendritic cells phagocytose and process *Borrelia burgdorferi*. J. Immunol. **157:**2998–3005.
113. **Finkelman, F. D., K. Madden, A. Cheever, I. M. Katona, S. C. Morris, M. Gately, B. R. Hubbard, W. C. Gause, and J. Urban.** 1994. Effects of interleukin-12 on immune responses and host protection in mice infected with intestinal nematode parasites. J. Exp. Med. **179:**1563–1572.
114. **Flesch, I. E. A., J. H. Hess, S. Huang, M. Aguet, J. Rothe, H. Bluethmann, and S. H. E. Kaufmann.** 1995. Early interleukin 12 production by macrophages in response to mycobacterial infection depends on interferon γ and tumor necrosis factor α J. Exp. Med. **181:**1615–1621.
115. **Flesch, I., and S. H. E. Kaufmann.** 1987. Mycobacterial growth inhibition by interferon-γ-activated bone marrow macrophages and differential susceptibility among strains of *Mycobacterium tuberculosis*. J. Immunol. **138:**4406–4413.
116. **Flesch, I. E. A., and S. H. E. Kaufmann.** 1990. Stimulation of antibacterial macrophage activities by B-cell stimulatory factor 2 (interleukin-6). Infect. Immun. **58:**269–271.
117. **Flesch, I. E. A., and S. H. E. Kaufmann.** 1990. Activation of tuberculostatic macrophage functions by gamma interferon, interleukin-4, and tumor necrosis factor. Infect. Immun. **58:**2675–2677.
118. **Flesch, I. E. A., and S. H. E. Kaufmann.** 1995. Differential induction of IL12 synthesis by *Mycobacterium bovis* BCG and *Listeria monocytogenes*. Res. Immunol. **146:**520–525.
119. **Flynn, J. L., J. Chan, K. J. Triebold, D. K. Dalton, T. A. Stewart, and B. R. Bloom.** 1993. An essential role for interferon γ in resistance to *Mycobacterium tuberculosis* infection. J. Exp. Med. **178:**2249–2254.
120. **Flynn, J. L., M. M. Goldstein, K. J. Triebold, J. Sypek, S. Wolf, and B. R. Bloom.** 1995. IL-12 increases resistance of BALB/c mice to *Mycobacterium tuberculosis* infection. J. Immunol. **155:**2515–2524.
121. **Fortier, A. H., T. Polsinelli, S. J. Green, and C. A. Nacy.** 1992. Activation of macrophages for destruction of *Francisella tularensis*: identification of cytokines, effector cells and effector molecules. Infect. Immun. **60:**817–825.
122. **Fowell, D. J., A. E. Wakil, and R. M. Locksley.** 1995. Interleukin-12 in murine leishmaniasis—match, flame or fuel? Res. Immunol. **146:**566–574.
123. **Freund, J., J. Casals, and E. P. Hosmer.** 1937. Sensitization and antibody formation after injection of tubercle bacilli and paraffin oil. Proc. Soc. Exp. Biol. Med. **37:**509–513.
124. **Frucht, D. M., and S. M. Holland.** 1996. Defective monocyte costimulation for IFN-γ production in familial disseminated *Mycobacterium avium* complex infection: abnormal IL-12 regulation. J. Immunol. **157:**411–416.
125. **Fulton, S. A., J. M. Johnsen, S. F. Wolf, D. S. Sieburth, and W. H. Boom.** 1996. Interleukin-12 production by human monocytes infected with *Mycobacterium tuberculosis*: role of phagocytosis. Infect. Immun. **64:**2523–2531.
126. **Gately, M. K.** 1997. Interleukin-12: potential clinical applications in the treatment of chronic viral hepatitis. J. Viral Hepatol. **4**(Suppl. 1)**:**33–39.
127. **Gately, M. K., R. R. Warrier, S. Honosoge, D. M. Carvajal, D. A. Faherty, S. E. Connaughton, T. D. Anderson, U. Sarmiento, B. R. Hubbard, and M. Murphy.** 1994. Administration of recombinant IL-12 to normal mice enhances cytolytic lymphocyte activity and induces production of IFN-γ in vivo. Int. Immunol. **6:**157–167.
128. **Gavett, S. H., D. J. O'Hearn, X. Li, S. K. Huang, F. D. Finkelman, and M. Wills-Karp.** 1995. Interleukin 12 inhibits antigen-induced airway hyperresponsiveness, inflammation, and Th2 cytokine expression in mice. J. Exp. Med. **182:**1527–1536.
129. **Gazzinelli, R. T.** 1996. Molecular and cellular basis of interleukin 12 activity in prophylaxis and therapy against infectious diseases. Mol. Med. Today **June:**258–267.
130. **Gazzinelli, R. T., S. Bala, R. Stevens, M. Baselar, L. Wahl, J. Kovaks, and A. Sher.** 1995. HIV infection suppresses type 1 lymphokine and IL-12 responses to *Toxoplasma gondii* but fails to inhibit the synthesis of other parasite-induced monokines. J. Immunol. **155:**1565–1574.
131. **Gazzinelli, R. T., E. Y. Denkers, and A. Sher.** 1993. Host resistance to *Toxoplasma gondii*: model for studying the selective induction of cell-mediated immunity by intracellular parasites. Infect. Agents Dis. **2:**139–149.
132. **Gazzinelli, R. T., N. A. Giese, and H. C. Morse III.** 1994. In vivo treatment with interleukin 12 protects mice from immune abnormalities observed during murine acquired immunodeficiency syndrome (MAIDS). J. Exp. Med. **180:**2199–2208.
133. **Gazzinelli, R. T., S. Hieny, T. Wynn, S. Wolf, and A. Sher.** 1993. IL-12 is required for T-cell independent induction of IFN-γ by an intracellular parasite and induces resistance in T-deficient hosts. Proc. Natl. Acad. Sci. USA **90:**6115–6119.
134. **Gazzinelli, R. T., M. Makino, S. K. Chattopadhyay, C. M. Snapper, A. Sher, A. W. Hügin, and H. C. Morse III.** 1992. $CD4^+$ subset regulation in viral infection: preferential activation of Th2 cells during progression of retrovirus-induced immunodeficiency in mice. J. Immunol. **148:**182–188.
135. **Gazzinelli, R. T., M. Wysocka, S. Hayashi, E. Y. Denkers, S. Hieny, P. Caspar, G. Trinchieri, and A. Sher.** 1994. Parasite-induced IL-12 stimulates early IFN-γ synthesis and resistance during acute infection with *Toxoplasma gondii*. J. Immunol. **153:**2533–2543.
136. **Gearing, D. P., and D. Cosman.** 1991. Homology of the p40 subunit of natural killer cell stimulatory factor (NKSF) with the extracellular domain of the interleukin-6 receptor. Cell **66:**9–10.
137. **Gemmell, E., and G. J. Seymour.** 1994. Modulation of immune responses to periodontal bacteria. Curr. Opin. Periodontol. **2:**28–38.
138. **Germann, T., M. Bongartz, H. Dlugonska, H. Hess, E. Schmitt, L. Kolbe, E. Kölsch, F. J. Podlaski, M. K. Gately, and E. Rüde.** 1995. IL-12 profoundly upregulates the synthesis of antigen-specific, complement-fixing IgG2a, IgG2b and IgG3 antibody subclasses in vivo. Eur. J. Immunol. **25:**823–829.
139. **Germann, T., S. Guckes, M. Bongartz, H. Dlugonska, E. Schmitt, L. Kolbe, E. Kölsch, F. J. Podlaski, M. K. Gately, and E. Rüde.** 1995. Administration of interleukin-12 during ongoing immune responses fails to permanently suppress and can even enhance the synthesis of antigen-specific IgE. Int. Immunol. **7:**1649–1657.
140. **Germann, T., E. Rüde, F. Mattner, and M. K. Gately.** 1995. The IL-12 p40 homodimer as a specific antagonist of the IL-12 heterodimer. Immunol. Today **16:**500–501.
141. **Germann, T., E. Rüde, and E. Schmitt.** 1995. The influence of IL12 on the development of Th1 and Th2 cells and its adjuvant effect for humoral immune responses. Res. Immunol. **146:**481–485.
142. **Gerosa, F., C. Paganin, D. Peritt, F. Paiola, M. T. Scupoli, M. Aste-Amezaga, I. Frank, and G. Trinchieri.** 1996. Interleukin-12 primes human CD4 and CD8 T cell clones for high production of both interferon-γ and interleukin-10. J. Exp. Med. **183:**2559–2569.
143. **Ghalib, H. W., J. A. Whittle, M. Kubin, F. A. Hashim, A. M. el-Hassan, K. H. Grabstein, G. Trinchieri, and S. G. Reed.** 1995. IL-12 enhances Th1-type responses in human *Leishmania donovani* infections. J. Immunol. **154:**4623–4629.
144. **Giese, N. A., R. T. Gazzinelli, R. A. Morawetz, and H. C. Morse III.** 1995. Role of IL12 in MAIDS. Res. Immunol. **146:**600–604.
145. **Gillessen, S., D. Carvajal, P. Ling, F. J. Podlaski, D. L. Stremlo, P. C. Familletti, U. Gubler, D. H. Presky, A. S. Stern, and M. K. Gately.** 1995. Mouse interleukin-12 (IL-12) p40 homodimer: a potent IL-12 antagonist. Eur. J. Immunol. **25:**200–206.
146. **Golovliov, I., G. Sandström, M. Ericsson, A. Sjöstedt, and A. Tärnvik.** 1995. Cytokine expression in the liver during the early phase of murine tularemia. Infect. Immun. **63:**534–538.
147. **Greenberger, M. J., S. L. Kunkel, R. M. Strieter, N. W. Lukacs, J. Bramson, J. Gauldie, F. L. Graham, M. Hitt, J. M. Danforth, and T. J. Standiford.** 1996. IL-12 gene therapy protects mice in lethal *Klebsiella* pneumonia. J. Immunol. **157:**3006–3012.
148. **Greenberger, M. J., R. M. Strieter, S. L. Kunkel, J. M. Danforth, R. E. Goodman, and T. J. Standiford.** 1995. Neutralization of IL-10 increases survival in a murine model of *Klebsiella* pneumonia. J. Immunol. **155:**722–729.
149. **Greenberger, M. J., R. M. Strieter, S. L. Kunkel, J. M. Danforth, L. L. Laichalk, D. C. McGillicuddy, and T. J. Standiford.** 1996. Neutralization of MIP-2 attenuates neutrophil recruitment and bacterial clearance in murine *Klebsiella pneumoniae*. J. Infect. Dis. **173:**159–165.
150. **Grewall, I. S., J. Xu, and R. A. Flavell.** 1995. Impairment of antigen-specific T-cell priming in mice lacking CD40 ligand. Nature **378:**617–620.
151. **Griffin, D. E., and B. J. Ward.** 1993. Differential CD4 T cell activation in measles. J. Infect. Dis. **168:**275–281.
152. **Grzych, J. M., E. J. Pearce, A. Cheever, Z. A. Caulada, P. Caspar, S. Heiny, F. Lewis, and A. Sher.** 1991. Egg deposition is the major stimulus for the production of Th2 cytokines in murine schistosomiasis mansoni. J. Immunol. **146:**1322–1330.
153. **Gubler, U., A. O. Chua, D. S. Schoenhaut, C. M. Dwyer, W. McComas, R. Motyka, N. Nabavi, A. G. Wolitzky, P. M. Quinn, P. C. Familletti, and M. K. Gately.** 1991. Coexpression of two distinct genes is required to generate secreted, bioactive cytotoxic lymphocyte maturation factor. Proc. Natl. Acad. Sci. USA **88:**4143–4147.
154. **Gueler, M. L., J. D. Gorham, C. S. Hsieh, A. J. Mackey, R. G. Steen, W. F. Dietrich, and K. M. Murphy.** 1996. Genetic susceptibility to *Leishmania*: IL-12 responsiveness in TH1 cell development. Science **271:**912–913.
155. **Haak-Frendscho, M., J. F. Brown, Y. Ilzawa, R. D. Wagner, and C. J. Czuprynski.** 1992. Administration of anti-IL-4 antibody 11B11 increases the resistance of mice to *Listeria monocytogenes* infection. J. Immunol. **148:**3978–3985.
156. **Hahn, H., and S. H. E. Kaufmann.** 1981. The role of cell-mediated immunity in bacterial infections. Rev. Infect. Dis. **3:**1221–1250.
157. **Halpern, M. D., R. J. Kurlander, and D. S. Pisetsky.** 1996. Bacterial DNA

induces murine interferon-γ production by stimulation of interleukin-12 and tumor necrosis factor-α. Cell. Immunol. **167:**72–78.
158. **Harrison, T. S., and S. M. Levitz.** 1996. Role of IL-12 in peripheral blood mononuclear cell responses to fungi in persons with and without HIV infection. J. Immunol. **156:**4492–4497.
159. **Harrison, T. S., and S. M. Levitz.** 1997. Priming with IFN-γ restores deficient IL-12 production by peripheral blood mononuclear cells from HIV-seropositive donors. J. Immunol. **158:**459–463.
160. **Harty, T. J., L. L. Lenz, and M. J. Bevan.** 1996. Primary and secondary immune responses to *Listeria monocytogenes*. Curr. Opin. Immunol. **8:**526–530.
161. **Hayes, M. P., J. Wang, and M. A. Norcross.** 1995. Regulation of interleukin-12 expression in human monocytes: selective priming by IFN-γ of LPS-inducible p35 and p40 genes. Blood **86:**646–650.
162. **Heinzel, F. P.** 1995. Th1 and Th2 cells in the cure and pathogenesis of infectious diseases. Curr. Opin. Infect. Dis. **8:**151–155.
163. **Heinzel, F. P., F. Ahmed, A. M. Hujer, and R. M. Rerko.** 1995. Immunoregulation of murine leishmaniasis by interleukin-12. Res. Immunol. **146:**575–581.
164. **Heinzel, F. P., R. M. Rerko, F. Ahmed, and E. Pearlman.** 1995. Endogenous IL-12 is required for control of Th2 cytokine responses capable of exacerbating leishmaniasis in normally resistant mice. J. Immunol. **155:**730–739.
165. **Heinzel, F. P., D. S. Schoenhaut, R. M. Rerko, L. E. Rosser, and M. K. Gately.** 1993. Recombinant interleukin 12 cures mice infected with *Leishmania major*. J. Exp. Med. **177:**1505–1509.
166. **Hendricks, R. L., T. M. Tumpey, and A. Finnegan.** 1992. IFN-γ and IL-2 are protective in the skin but pathologic in the corneas of HSV-1 infected mice. J. Immunol. **149:**3023–3028.
167. **Hilleman, M. R.** 1994. Vaccinology, immunology, and comparative pathogenesis of measles in the quest for a preventative against AIDS. AIDS Res. Hum. Retroviruses **10:**3–12.
168. **Hoag, K. A., N. E. Street, G. B. Huffnagle, and M. F. Lipscomb.** 1995. Early cytokine production in pulmonary *Cryptococcus neoformans* infections distinguishes susceptible and resistant mice. Am. J. Respir. Cell Mol. Biol. **13:**487–495.
169. **Hoffman, S. L., J. M. Crutcher, S. K. Puri, A. A. Ansari, F. Villinger, E. D. Franke, P. P. Singh, F. Finkelman, M. K. Gately, G. P. Dutta, and M. Sedegah.** 1997. Sterile protection of monkeys against malaria after administration of interleukin-12. Nat. Med. **3:**80–83.
170. **Hoffman, S. L., D. Isenbarger, G. W. Long, M. Sedegah, A. Szarfman, L. Waters, M. R. Hollingdale, P. H. van der Meide, D. S. Finbloom, and W. R. Ballou.** 1989. Sporozite vaccine induces genetically restricted T cell elimination of malaria from hepatocytes. Science **244:**1078–1081.
171. **Hondowicz, B., and P. Scott.** 1995. The role of IL12 in modulating an established Th2 response in experimental leishmaniasis. Res. Immunol. **146:**560–565.
172. **Hsieh, C.-S., S. E. Macatonia, C. S. Tripp, S. F. Wolf, A. O'Garra, and K. M. Murphy.** 1993. Development of T_H1 $CD4^+$ T cells through IL-12 produced by *Listeria*-induced macrophages. Science **260:**547–549.
173. **Hunter, C. A., L. Bermudez, H. Beernink, W. Waegell, and J. S. Remington.** 1995. Transforming growth factor-β inhibits interleukin-12-induced production of interferon-γ by natural killer cells: a role for transforming growth factor-β in the regulation of T cell-independent resistance to *Toxoplasma gondii*. Eur. J. Immunol. **25:**994–1000.
174. **Hunter, C. A., E. Candolfi, C. Subauste, V. Van Cleave, and J. S. Remington.** 1995. Studies on the role of interleukin-12 in acute murine toxoplasmosis. Immunology **84:**16–20.
175. **Hunter, C. A., R. Chizzonite, and J. S. Remington.** 1995. IL-1β is required for IL-12 to induce production of IFN-γ by NK cells. A role for IL-1β in the T cell-independent mechanism of resistance against intracellular pathogens. J. Immunol. **155:**4347–4354.
176. **Hunter, C. A., and J. S. Remington.** 1995. The role of IL12 in toxoplasmosis. Res. Immunol. **146:**546–551.
177. **Hunter, C. A., T. Slider, and F. Araujo.** 1996. Interleukin-12-mediated resistance to *Trypanosoma cruzi* is dependent on tumor necrosis factor alpha and gamma interferon. Infect. Immun. **64:**2381–2386.
178. **Hunter, C. A., C. S. Subauste, V. H. Van Cleave, and J. S. Remington.** 1994. Production of gamma interferon by natural killer cells from *Toxoplasma gondii*-infected SCID mice: regulation by interleukin-10, interleukin-12 and tumor necrosis factor alpha. Infect. Immun. **62:**2818–2824.
179. **Huygen, K., D. Abramowicz, P. Vandenbussche, F. Jacobs, J. De Bruyn, A. Kentos, A. Drowart, J. P. van Vooren, and M. Goldman.** 1992. Spleen cell cytokine secretion in *Mycobacterium bovis* BCG-infected mice. Infect. Immun. **60:**2880–2886.
180. **Hyjek, E., H. W. Lischner, T. Hyslop, J. Bartkowiak, M. Kubin, G. Trinchieri, and D. Kozbor.** 1995. Cytokine patterns during progression to AIDS in children with perinatal HIV infection. J. Immunol. **155:**4060–4071.
181. **Izzo, A. A., and R. J. North.** 1992. Evidence for an α/β T cell-independent mechanism of resistance to mycobacteria: bacillus Calmette-Guérin causes progressive infection in severe combined immunodeficient mice, but not in nude mice or in mice depleted of $CD4^+$ and $CD8^+$ T cells. J. Exp. Med. **176:**581–586.
182. **Jackson, J. D., Y. Yan, M. J. Brunda, L. S. Kelsey, and J. E. Talmadge.** 1995. Interleukin-12 enhances peripheral hematopoiesis *in vivo*. Blood **85:**2371–2376.
183. **Jacobsen, S. E.** 1995. IL12, a direct stimulator and indirect inhibitor of haematopoiesis. Res. Immunol. **146:**506–514.
184. **Jacobson, N. G., S. J. Szabo, M. L. Güler, J. D. Gorham, and K. M. Murphy.** 1995. Regulation of interleukin-12 signal transduction during T helper phenotype development. Res. Immunol. **146:**446–456.
185. **Jacobson, N. G., S. J. Szabo, R. M. Weber-Nordt, Z. Zhong, R. D. Schreiber, J. E. Darnell, and K. M. Murphy.** 1995. Interleukin 12 signalling in Th1 cells involves tyrosine phosphorylation of Stat3 and Stat4. J. Exp. Med. **181:**1755–1762.
186. **Jahiel, R. I., J. Vilcek, and R. S. Nussenzweig.** 1970. Exogenous interferon protects mice against *Plasmodium berghei* malaria. Nature **227:**1350.
187. **Jahiel, R. I., J. Vilcek, R. S. Nussenzweig, and J. Vanderberg.** 1968. Interferon inducers protect mice against *Plasmodium berghei* malaria. Science **161:**802–804.
188. **James, S. L., and D. L. Boros.** 1994. Immune effector role of macrophages in experimental *Schistosoma mansoni*. Immunol. Ser. **60:**461–466.
189. **Jankovic, D., and A. Sher.** 1996. Initiation and regulation of $CD4^+$ T-cell function in host-parasite models. Chem. Immunol. **63:**51–65.
190. **Jeannin, P., Y. Delneste, P. Life, J.-F. Gauchat, D. Kaiserlian, and J.-Y. Bonnefoy.** 1995. Interleukin-12 increases interleukin-4 production by established human Th0 and Th2-like T cell clones. Eur. J. Immunol. **25:**2247–2252.
191. **Jiang, X., and C. L. Baldwin.** 1993. Effects of cytokines on intracellular growth of *Brucella abortus*. Infect. Immun. **61:**124–129.
192. **Jones, S. M., and A. J. Winter.** 1992. Survival of virulent and attenuated strains of *Brucella abortus* in normal and gamma interferon-activated murine peritoneal macrophages. Infect. Immun. **60:**3011–3014.
193. **Kagaya, K., K. Watanabe, and Y. Fukazawa.** 1989. Capacity of recombinant gamma interferon to activate macrophages for *Salmonella*-killing activity. Infect. Immun. **57:**609–615.
194. **Kamijo, R., J. Le, D. Shapiro, E. A. Havell, S. Huang, M. Aguet, M. Bosland, and J. Vilcek.** 1993. Mice that lack the interferon-γ receptor have profoundly altered responses to infection with bacillus Calmette-Guérin and subsequent challenge with lipopolysaccharide. J. Exp. Med. **178:**1435–1440.
195. **Kanangat, S., J. Thomas, S. Gangappa, J. S. Babu, and B. T. Rouse.** 1996. Herpes simplex virus type 1-mediated up-regulation of IL-12 (p40) mRNA expression. J. Immunol. **156:**1110–1116.
196. **Kaplan, M. H., Y.-L. Sun, T. Hoey, and M. J. Grusby.** 1996. Impaired IL-12 responses and enhanced development of Th2 cells in Stat4-deficient mice. Nature **382:**174–177.
197. **Karp, C. L., M. Wysocka, L. M. Wahl, J. M. Ahearn, P. J. Cuomo, B. Sherry, G. Trinchieri, and D. E. Griffin.** 1996. Mechanism of suppression of cell-mediated immunity by measles virus. Science **273:**228–231.
198. **Karttunen, R., T. J. Karttunen, M. M. Yousfi, H. M. el-Zimaity, D. Y. Graham, and F. A. el-Zaatari.** 1997. Expression of mRNA for interferon-γ, interleukin-10, and interleukin-12 (p40) in normal gastric mucosa and in mucosa infected with *Helicobacter pylori*. Scand. J. Gastroenterol. **32:**22–27.
199. **Karttunen, R., H. M. Surcel, G. Andersson, H. P. T. Ekre, and E. Herva.** 1991. *Francisella tularenesis*-induced in vitro gamma-interferon, tumor necrosis factor α, and interleukin-2 responses appear within 2 weeks of tularemia vaccination in human beings. J. Clin. Microbiol. **29:**753–756.
200. **Kato, T., R. Hakamada, H. Yamane, and H. Nariuchi.** 1996. Induction of IL-12 p40 messenger RNA expression and IL-12 production of macrophages via CD40-CD40 ligand interaction. J. Immunol. **156:**3932–3938.
201. **Kaufmann, S. H. E.** 1993. Immunity to intracellular bacteria. Annu. Rev. Immunol. **11:**129–163.
202. **Kaufmann, S. H. E., and I. Flesch.** 1986. Function and antigen recognition pattern of $L3T4^+$ T-cell clones from *Mycobacterium tuberculosis*-immune mice. Infect. Immun. **54:**291–296.
203. **Kaufmann, S. H. E., E. Hug, and G. DeLibero.** 1986. *Listeria monocytogenes*-reactive T lymphocyte clones with cytolytic activity against infected target cells. J. Exp. Med. **164:**363–368.
204. **Kawakami, K., M. Tohyama, Q. Xie, and A. Saito.** 1996. IL-12 protects mice against pulmonary and disseminated infection caused by *Cryptococcus neoformans*. Clin. Exp. Immunol. **104:**208–214.
205. **Kawamura, I., H. Tsukada, H. Yoshikawa, M. Fujita, K. Nomoto, and M. Mitsuyama.** 1992. IFN-γ-producing ability as a possible marker for the protective T cells against *Mycobacterium bovis* BCG in mice. J. Immunol. **148:**2997–2893.
206. **Keane-Myers, A., and S. P. Nickell.** 1995. T-cell subset-dependent modulation of immunity to *Borrelia burgdorferi* in mice. J. Immunol. **154:**1770–1776.
207. **Keane-Myers, A., and S. P. Nickell.** 1995. Role of IL-4 and IFN-γ in modulation of immunity to *Borrelia burgdorferi* in mice. J. Immunol. **155:**2020–2028.
208. **Kennedy, M. K., K. S. Picha, W. C. Fanslow, K. H. Grabstein, M. R. Alderson, K. N. Clifford, W. A. Chin, and K. A. Mohler.** 1996. CD40/CD40 ligand interactions are required for T cell-dependent production of inter-

leukin-12 by mouse macrophages. Eur. J. Immunol. **26:**370–378.
209. **Khan, I. A., T. Matsuura, and L. H. Kasper.** 1994. Interleukin-12 enhances murine survival against acute toxoplasmosis. Infect. Immun. **62:**1639–1642.
210. **Kim, J. J., V. Ayyavoo, M. L. Bagarazzi, M. A. Chattergoon, K. Dang, B. Wang, J. D. Boyer, and D. B. Weiner.** 1997. In vivo engineering of a cellular immune response by coadministration of IL-12 expression vector with a DNA immunogen. J. Immunol. **158:**816–826.
211. **Kincy-Cain, T., J. D. Clements, and K. L. Bost.** 1996. Endogenous and exogenous interleukin-12 augment the protective immune response in mice orally challenged with *Salmonella dublin*. Infect. Immun. **64:**1437–1440.
212. **King, C. L., J. Hakimi, M. T. Shata, and T. Medhat.** 1995. IL-12 regulation of parasite antigen-driven IgE production in human helminth infections. J. Immunol. **155:**454–461.
213. **Kipps, T. J.** 1989. The CD5 B cell. Adv. Immunol. **47:**117–186.
214. **Klapproth, J.-M., M. S. Donnenberg, J. M. Abraham, H. L. T. Mobley, and S. P. James.** 1995. Products of enteropathogenic *Escherichia coli* inhibit lymphocyte activation and lymphokine production. Infect. Immun. **63:**2248–2254.
215. **Klinman, D. M., A. K. Yi, S. L. Beaucage, J. Conover, and A. M. Krieg.** 1996. CpG motifs present in bacteria DNA rapidly induce lymphocytes to secrete interleukin 6, interleukin 12, and interferon gamma. Proc. Natl. Acad. Sci. USA **93:**2879–2883.
216. **Kobayashi, M., L. Fitz, M. Ryan, R. M. Hewick, S. C. Clark, S. Chan, R. London, F. Sherman, B. Perussia, and G. Trinchieri.** 1989. Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biologic effects on human lymphocytes. J. Exp. Med. **170:**827–846.
217. **Kobayashi, K., T. Kasama, J. Yamazaki, M. Hosaka, T. Katsura, T. Mochizuki, K. Soejima, and R. M. Nakamura.** 1995. Protection of mice from *Mycobacterium avium* infection by recombinant interleukin-12. Antimicrob. Agents Chemother. **39:**1369–1371.
218. **Kobayashi, K., J. Yamazaki, T. Kasama, T. Katsura, K. Kasahara, S. F. Wolf, and T. Shimamura.** 1996. Interleukin (IL)-12 deficiency in susceptible mice infected with *Mycobacterium avium* and amelioration of established infection by IL-12 replacement therapy. J. Infect. Dis. **174:**564–573.
219. **Koch, F., U. Stanzl, P. Jannewein, K. Janke, C. Heufler, E. Kampgen, N. Romani, and G. Schuler.** 1996. High level IL-12 production by murine dendritic cells: upregulation via MHC class II and CD40 molecules and downregulation by IL-4 and IL-10. J. Exp. Med. **184:**741–746.
220. **Kohno, K., J. Kataoka, T. Ohtsuki, Y. Suemoto, I. Okamoto, M. Usui, M. Ikeda, and M. Kurimoto.** 1997. IFN-γ-inducing factor (IGIF) is a costimulatory factor on the activation of Th1 but not Th2 cells and exerts its effect independently of IL-12. J. Immunol. **158:**1541–1550.
221. **Kornelisse, R. F., C. E. Hack, H. F. J. Savelkoul, T. C. T. M. van der Pouw Kraan, W. C. J. Hop, G. van Mierlo, M. H. Suur, H. J. Neijens, and R. de Groot.** 1997. Intrathecal production of interleukin-12 and gamma interferon in patients with bacterial meningitis. Infect. Immun. **65:**877–881.
222. **Kozel, T. R.** 1993. Cryptococcosis, p. 277–302. *In* J. W. Murphy, H. Friedman, and M. Bendinelli (ed.), Fungal infection and immune response. Plenum Press, New York, N.Y.
223. **Kubin, M., J. M. Chow, and G. Trinchieri.** 1994. Differential regulation of interleukin-12 (IL-12), tumor necrosis factor-α, and IL-1β production in human myeloid leukemia cell lines and peripheral blood mononuclear cells. Blood **83:**1847–1855.
224. **Kubin, M., M. Kamoun, and G. Trinchieri.** 1994. Interleukin-12 synergizes with B7/CD28 interaction in inducing efficient proliferation and cytokine production of human T cells. J. Exp. Med. **180:**211–222.
225. **Kumaratilake, L. M., and A. Ferrante.** 1994. T-cell cytokines in malaria: their role in the regulation of neutrophil and macrophage-mediated killing of *Plasmodium falciparum* asexual blood forms. Res. Immunol. **145:**423–429.
226. **Kurup, V. P., V. Hari, I. Guo, P. J. Murali, A. Resnick, M. Krishnan, and I. N. Fink.** 1996. *Aspergillus fumigatus* peptides differentially express Th1 and Th2 cytokines. Peptides **17:**183–190.
227. **Kurup, V. P., B. W. P. Seymour, H. Choi, and R. L. Coffman.** 1994. Particulate *Aspergillus fumigatus* antigens elicit a Th2-response in BALB/c mice. J. Allergy Clin. Immunol. **93:**1013–1020.
228. **Ladel, C. H., J. Hess, S. Daugelat, and S. H. E. Kaufmann.** 1995. Contribution of α/β and γ/δ T lymphocytes to immunity against *Mycobacterium bovis* BCG infection: studies with T cell receptor deficient knockout mice. Eur. J. Immunol. **25:**838–846.
229. **Lagrange, P. H., and G. B. Mackaness.** 1975. A stable form of delayed-type hypersensitivity. J. Exp. Med. **141:**82–96.
230. **Lahesmaa, R., H. Yssel, S. Batsford, R. Luukkainen, T. Möttönen, L. Steinman, and G. Petz.** 1992. *Yersinia enterocolitica* activates a T helper type 1-like T cell subset in reactive arthritis. J. Immunol. **148:**3079–3085.
231. **Landay, A. L., M. Clerici, F. Hashemi, H. Kessler, J. A. Berzofsky, and G. M. Shearer.** 1996. In vitro restoration of T cell immune function in human immunodeficiency virus-positive persons: effects of interleukin (IL)-12 and anti-IL-10. J. Infect. Dis. **173:**1085–1091.
232. **Langhorne, J., S. Gillard, B. Simon, S. Slade, and K. Eichmann.** 1989. Frequencies of CD4+ T cells reactive with *Plasmodium chabaudi*: distinct response kinetics for cells with Th1 and Th2 characteristics during infection. Int. Immunol. **1:**416–424.
233. **Launois, P., T. Ohteki, K. Swihart, H. R. MacDonald, and J. A. Louis.** 1995. In susceptible mice, *Leishmania major* induce very rapid interleukin-4 production by $CD4^+$ T cells which are $N.K.1.1^-$. Eur. J. Immunol. **25:**3298–3307.
234. **Leiby, D. A., A. H. Fortier, R. M. Crawford, R. D. Schreiber, and C. A. Nacy.** 1992. In vivo modulation of the murine immune response to *Francisella tularensis* LVS by administration of anticytokine antibodies. Infect. Immun. **60:**84–89.
235. **Leiby, D. A., R. D. Schreiber, and C. A. Nacy.** 1993. IFN-γ produced in vivo during the first two days is critical for resolution of murine *Leishmania major* infections. Microb. Pathog. **14:**495–500.
236. **Lester, M. R., M. F. Hofer, M. Gately, A. Trumble, and D. Y. M. Leung.** 1995. Down-regulating effects of IL-4 and IL-10 on the IFN-γ response in atopic dermatitis. J. Immunol. **154:**6174–6181.
237. **Leung, D. Y. M., M. Gately, A. Trumble, B. Ferguson-Darnell, P. M. Schlievert, and L. J. Picker.** 1995. Bacterial superantigens induce T cell expression of the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen, via stimulation of interleukin 12 production. J. Exp. Med. **181:**747–753.
238. **Libraty, D. H., L. E. Airan, K. Uyemura, D. Jullien, B. Spellberg, T. H. Rea, and R. L. Modlin.** 1997. Interferon-γ differentially regulates interleukin-12 and interleukin-10 production in leprosy. J. Clin. Invest. **99:**336–341.
239. **Lin, Y., M. Zhang, F. M. Hofman, J. Gong, and P. F. Barnes.** 1996. Absence of a prominent Th2 cytokine response in human tuberculosis. Infect. Immun. **64:**1351–1356.
240. **Lindblad, E. B., M. J. Elhay, R. Silva, R. Appelberg, and P. Andersen.** 1997. Adjuvant modulation of immune responses to tuberculosis subunit vaccines. Infect. Immun. **65:**623–629.
241. **Liu, W., and R. J. Kurlander.** 1995. Analysis of the interrelationship between IL-12, TNF-α, and IFN-γ production during murine listeriosis. Cell. Immunol. **163:**260–267.
242. **Locksley, R. M.** 1993. Interleukin 12 in host defense against microbial pathogens. Proc. Natl. Acad. Sci. USA **90:**5879–5880.
243. **Locksley, R. M.** 1994. Th2 cells: help for helminths. J. Exp. Med. **179:**1405–1407.
244. **Locksley, R. M., and P. Scott.** 1991. Helper T-cell subsets in mouse leishmaniasis: induction, expansion and effector function. Immunol. Today **12:**A58–A61.
245. **Locksley, R. M., and C. B. Wilson.** 1995. Cell-mediated immunity and its role in host defense, p. 102–149. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Basic principles in the diagnosis and management of infectious diseases, 4th ed. Churchill Livingstone, Inc., New York, N.Y.
246. **Lucey, D. R., M. Clerici, and G. M. Shearer.** 1996. Type 1 and type 2 cytokine dysregulation in human infectious, neoplastic, and inflammatory diseases. Clin. Microbiol. Rev. **9:**532–562.
247. **Lucey, D. R., and J. H. Maguire.** 1993. Schistosomiasis. Infect. Dis. Clin. North Am. **7:**635–655.
248. **Ma, X., J. M. Chow, G. Gri, G. Carra, F. Gerosa, S. F. Wolf, R. Dzialo, and G. Trinchieri.** 1996. The interleukin 12 p40 gene promoter is primed by IFN-γ in monocytic cells. J. Exp. Med. **183:**147–157.
249. **Ma, X., A. D'Andrea, M. Kubin, M. Aste-Amezaga, A. Sartori, J. Monteiro, L. Showe, M. Wysocka, and G. Trinchieri.** 1995. Production of interleukin-12. Res. Immunol. **146:**432–438.
250. **Ma, Y., K. P. Seiler, K.-F. Tai, L. Yang, and M. Woods.** 1994. Outer surface lipoproteins of *Borrelia burgdorferi* stimulate nitric oxide production by the cytokine-inducible pathway. Infect. Immun. **62:**3663–3671.
251. **Macatonia, S. E., N. A. Hosken, M. Litton, P. Vieira, C. Hsieh, J. A. Culpepper, M. Wysocka, G. Trinchieri, K. M. Murphy, and A. O'Garra.** 1995. Dendritic cells produce IL-12 and direct the development of Th1 cells from naive $CD4^+$ T cells. J. Immunol. **154:**5071–5079.
252. **Mackaness, G. B., and W. C. Hill.** 1969. The effect of anti-lymphocyte globulin on cell-mediated resistance to infection. J. Exp. Med. **129:**993–1012.
253. **Magee, D. M., and R. A. Cox.** 1995. Roles of gamma interferon and interleukin-4 in genetically determined resistance to *Coccidioides immitis*. Infect. Immun. **63:**3514–3519.
254. **Magee, D. M., and R. A. Cox.** 1996. Interleukin-12 regulation of host defenses against *Coccidioides immitis*. Infect. Immun. **64:**3609–3613.
255. **Maggi, E., M. Mazzetti, A. Ravina, F. Annunziato, M. De Carli, M. P. Piccinni, R. Manetti, M. Carbonari, A. M. Pesce, G. Del Prete, and S. Romagnani.** 1994. Ability of HIV to promote a Th1 to Th0 shift and to replicate preferentially in Th2 and Th0 cells. Science **265:**244–248.
256. **Magram, J., S. E. Connaughton, R. R. Warrier, D. M. Carvajal, C. Y. Wu, J. Ferrante, C. Stewart, U. Sarmiento, D. A. Faherty, and M. K. Gately.** 1996. IL-12-deficient mice are defective in IFN-γ production and type 1 cytokine responses. Immunity **4:**471–481.
257. **Mahon, B. P., M. S. Ryan, F. Griffin, and K. H. Mills.** 1996. Interleukin-12 is produced by macrophages in response to live or killed *Bordetella pertussis* and enhances the efficacy of an acellular pertussis vaccine by promoting induction of Th1. Infect. Immun. **64:**5295–5301.

258. **Manetti, R., F. Annunziato, V. Giannò, L. Tomasévic, L. Beloni, C. Mavilia, and E. Maggi.** 1996. Th1 and Th2 cells in HIV infection. Chem. Immunol. **63:**138–157.
259. **Manetti, R., F. Gerosa, M.-G. Giudizi, R. Biagiotti, P. Parronchi, M.-P. Piccinni, S. Sampognaro, E. Maggi, S. Romagnani, and G. Trinchieri.** 1994. Interleukin-12 induces stable priming for interferon-γ (IFN-γ) production during differentiation of human T helper (Th) cells and transient IFN-γ production in established Th2 cell clones. J. Exp. Med. **179:**1273–1283.
260. **Manetti, R., P. Parronchi, M. G. Giudizi, R. Biagiotti, M.-P. Piccinni, E. Maggi, G. Trinchieri, and S. Romagnani.** 1993. Natural killer cell stimulatory factor (NKSF/IL-12) induces Th1-type specific immune responses and inhibits the development of IL-4 producing Th cells. J. Exp. Med. **177:**1199–1204.
261. **Maruyama, T., A. McLachlan, S. Iino, K. Koike, K. Kurokawa, and D. R. Milich.** 1993. The serology of chronic hepatitis B infection revisited. J. Clin. Invest. **91:**2586–2595.
262. **Mastroeni, P., J. A. Harrison, J. A. Chabalgoity, and C. E. Hormaeche.** 1996. Effect of interleukin 12 neutralization on host resistance and gamma interferon production in mouse typhoid. Infect. Immun. **64:**189–196.
263. **Matsuo, R., M. Kobayashi, D. N. Herndon, R. B. Pollard, and F. Suzuki.** 1996. Interleukin-12 protects thermally injured mice from herpes simplex virus type 1 infection. J. Leukocyte Biol. **59:**623–630.
264. **Mattner, F., S. Fischer, S. Guckes, S. Jin, H. Kaulen, E. Schmitt, E. Rüde, and T. Germann.** 1993. The interleukin-12 subunit p40 specifically inhibits effects of the interleukin-12 heterodimer. Eur. J. Immunol. **23:**2202–2208.
265. **Mattner, F., J. Magram, J. Ferrante, P. Launois, K. Di Padova, R. Behin, M. K. Gately, J. A. Louis, and G. Alber.** 1996. Genetically resistant mice lacking interleukin-12 are susceptible to infection with *Leishmania major* and mount a polarized Th2 cell response. Eur. J. Immunol. **26:**1553–1559.
266. **Matyniak, J. E., and S. L. Reiner.** 1995. T helper phenotype and genetic susceptibility in experimental Lyme disease. J. Exp. Med. **181:**1251–1254.
267. **McDyer, J. F., M. N. Hackley, T. E. Walsh, J. L. Cook, and R. A. Seder.** 1997. Patients with multidrug-resistant tuberculosis with low $CD4^+$ T cell counts have impaired Th1 responses. J. Immunol. **158:**492–500.
268. **Mencacci, A., R. Spaccapelo, G. Del Sero, K.-H. Enssle, A. Cassone, F. Bistoni, and L. Romani.** 1996. $CD4^+$ T-helper-cell responses in mice with low-level *Candida albicans* infection. Infect. Immun. **64:**4907–4914.
269. **Merberg, D. M., S. F. Wolf, and S. C. Clark.** 1992. Sequence similarity between NKSF and the IL-6/G-CSF family. Immunol. Today **13:**77–78.
270. **Metzger, D. W., R. Raeder, V. H. van Cleave, and M. D. Boyle.** 1995. Protection of mice from group A streptococcal skin infection by interleukin-12. J. Infect. Dis. **171:**1643–1645.
271. **Metzger, D. W., L. A. Vogel, V. H. van Cleave, T. L. Lester, and J. M. Buchanan.** 1995. The effects of IL12 on B-cell subset function. Res. Immunol. **146:**499–505.
272. **Meyaard, L., E. Hovenkamp, N. Pakker, T. C. van der Pouw Kraan, and F. Miedema.** 1997. Interleukin-12 (IL-12) production in whole blood cultures from human immunodeficiency virus-infected individuals studied in relation to IL-10 and prostaglandin E_2 production. Blood **89:**570–576.
273. **Mielke, M. E. A.** 1991. T cell subsets in granulomatous inflammation and immunity to *L. monocytogenes* and *B. abortus*. Behring Inst. Mitt. **88:**99–111.
274. **Milich, D. R., S. F. Wolf, J. L. Hughes, and J. E. Jones.** 1995. Interleukin 12 suppresses autoantibody production by reversing helper T-cell phenotype in hepatitis B antigen transgenic mice. Proc. Natl. Acad. Sci. USA **92:**6847–6851.
275. **Miller, M. A., M. J. Skeen, and H. K. Ziegler.** 1995. Nonviable bacterial antigens administered with IL-12 generate antigen-specific T cell responses and protective immunity against *Listeria monocytogenes*. J. Immunol. **155:**4817–4828.
276. **Modlin, R. L.** 1994. Th1-Th2 paradigm: insights from leprosy. J. Invest. Dermatol. **102:**828–832.
277. **Modlin, R. L., and P. F. Barnes.** 1995. IL12 and the human immune response to mycobacteria. Res. Immunol. **146:**526–531.
278. **Moore, K. J., S. Lebrecque, and G. Matlashewski.** 1993. Alteration of *Leishmania donovani* infection levels by selective impairment of macrophage signal transduction. J. Immunol. **150:**4457–4465.
279. **Morris, S. C., K. B. Madden, J. J. Adamovicz, W. C. Gause, B. R. Hubbard, M. K. Gately, and F. D. Finkelman.** 1994. Effects of IL-12 on in vivo cytokine gene expression and Ig isotype selection. J. Immunol. **152:**1047–1056.
280. **Morrissey, P. J., and K. Charrier.** 1990. GM-CSF administration augments the survival of *Ity*-resistant A/J mice, but not *Ity*-susceptible C57BL/6 mice, to a lethal challenge with *Salmonella typhimurium*. J. Immunol. **144:**557–561.
281. **Morrissey, P. J., and K. Charrier.** 1994. Treatment of mice with IL-1 before infection increases resistance to a lethal challenge with *Salmonella typhimurium*: the effect correlates with the resistance allele at the *Ity* locus. J. Immunol. **153:**212–219.
282. **Mosmann, T. R., H. Cherwinski, M. W. Bond, M. A. Giedlin, and R. L. Coffman.** 1986. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J. Immunol. **136:**2348–2357.
283. **Mosmann, T. R., and R. L. Coffman.** 1989. Th1 and Th2 cells: different patterns of lymphokine secretion lead to different functional properties. Annu. Rev. Immunol. **7:**145–173.
284. **Mougneau, E., F. Altare, A. E. Wakil, S. Zheng, T. Coppolla, Z.-E. Wang, R. Waldmann, R. M. Locksley, and N. Glaichenhaus.** 1995. Expression cloning of a protective *Leishmania* antigen. Science **268:**563–566.
285. **Mountford, A. P., S. Anderson, and R. A. Wilson.** 1996. Induction of Th1 cell-mediated protective immunity to *Schistosoma mansoni* by coadministration of larval antigens and IL-12 as an adjuvant. J. Immunol. **156:**4739–4745.
286. **Muller, G., J. Saloga, T. Germann, I. Bellinghausen, and M. Mohamadzadeh.** 1994. Identification and induction of human keratinocyte-derived IL-12. J. Clin. Invest. **94:**1799–1805.
287. **Munk, M. E., and M. Emoto.** 1995. Functions of T-cell subsets and cytokines in mycobacterial infections. Eur. Respir. J. **20**(Suppl. P)**:**668–675s.
288. **Munk, M. E., P. Mayer, P. Anding, K. Feldmann, and S. H. E. Kaufmann.** 1996. Increased numbers of interleukin-12-producing cells in human tuberculosis. Infect. Immun. **64:**1078–1080.
289. **Muotiala, A., and P. H. Makela.** 1990. The role of IFN-γ in murine *Salmonella typhimurium* infection. Microb. Pathog. **8:**135–141.
290. **Murphy, T. L., M. G. Cleveland, P. Kulesza, J. Magram, and K. M. Murphy.** 1995. Regulation of interleukin 12 p40 expression through an NF-κB half-site. Mol. Cell. Biol. **15:**5258–5267.
291. **Murphy, E. E., G. Terres, S. E. Macatonia, C. Hsieh, J. Mattson, L. Lanier, M. Wysocka, G. Trinchieri, K. Murphy, and A. O'Garra.** 1994. B7 and IL-12 cooperate for proliferation and IFN-γ production by mouse T helper clones that are unresponsive to B7 costimulation. J. Exp. Med. **180:**223–231.
292. **Murray, H. W., and J. Hariprashad.** 1995. Interleukin 12 is effective treatment for an established systemic intracellular infection: experimental visceral leishmaniasis. J. Exp. Med. **181:**387–391.
293. **Murray, H. W., J. Hariprashad, D. F. McDermott, and M. Y. Stoeckle.** 1996. Multiple host defense defects in failure of C57BL/6 *ep/ep* (pale ear) mice to resolve visceral *Leishmania donovani* infection. Infect. Immun. **64:**161–166.
294. **Nabors, G. S., L. C. C. Afonso, J. P. Farrell, and P. Scott.** 1995. Switch from a type 2 to type 1 T helper cell response and cure of established *Leishmania major* infection in mice is induced by combined therapy with interleukin 12 and Pentostam. Proc. Natl. Acad. Sci. USA **92:**3142–3146.
295. **Nagai, H., J. Guo, H. Choi, and V. P. Kurup.** 1995. Interferon-γ and tumor necrosis factor-α protect mice from invasive aspergillosis. J. Infect. Dis. **172:**1554–1560.
296. **Nakano, Y., K. Onozuka, Y. Terada, H. Shinomiya, and M. Nakano.** 1990. Protective effect of recombinant tumor necrosis factor-α in murine salmonellosis. J. Immunol. **144:**1935–1941.
297. **Nauciel, C.** 1990. Role of $CD4^+$ T cells and T-independent mechanisms in acquired resistance to *Salmonella typhimurium* infection. J. Immunol. **145:**1265–1269.
298. **Nauciel, C., and F. Espinasse-Maes.** 1992. Role of γ interferon and tumor necrosis factor α in resistance to *Salmonella typhimurium* infection. Infect. Immun. **60:**450–454.
299. **Neta, R., S. M. Stiefel, F. Finkelman, S. Herrmann, and N. Ali.** 1994. IL-12 protects bone marrow from and sensitizes intestinal tract to ionizing radiation. J. Immunol. **153:**4230–4238.
300. **Newman, G. W., J. R. Guarnaccia, E. A. Vance III, J. Y. Wu, H. G. Remold, and P. H. Kazanjian, Jr.** 1994. Interleukin-12 enhances antigen-specific proliferation of peripheral blood mononuclear cells from HIV-positive and negative donors in response to *Mycobacterium avium*. AIDS **8:**1413–1419.
301. **Noll, A., and I. B. Autenrieth.** 1996. Immunity against *Yersinia enterocolitica* by vaccination with *Yersinia* HSP60 immunostimulating complexes or *Yersinia* HSP60 plus interleukin-12. Infect. Immun. **64:**2955–2961.
302. **O'Garra, A., and K. Murphy.** 1994. Role of cytokines in determining T-lymphocyte function. Curr. Opin. Immunol. **6:**458–466.
303. **O'Garra, A., and K. Murphy.** 1995. T-cell subsets in autoimmunity. Curr. Opin. Immunol. **5:**880–886.
304. **Olivier, M., R. W. Brownsey, and N. E. Reiner.** 1992. Defective stimulus-response coupling in human monocytes infected with *Leishmania donovani* is associated with altered activation and translocation of protein kinase C. Proc. Natl. Acad. Sci. USA **89:**7481–7485.
305. **Orange, J. S., and C. Biron.** 1996. An absolute and restricted requirement for interleukin-12 in natural killer (NK) cell interferon-γ production and antiviral defense: studies of NK and T-cell responses in contrasting viral infections. J. Immunol. **156:**1138–1142.
306. **Orange, J. S., and C. Biron.** 1996. Characterization of early IL-12, IFN-αβ, and TNF effects on antiviral state and NK cell responses during murine cytomegalovirus infection. J. Immunol. **156:**4746–4756.
307. **Orange, J. S., T. P. Salazar-Mather, S. M. Opal, R. L. Spencer, A. H. Miller, B. S. McEwen, and C. A. Biron.** 1995. Mechanism of interleukin 12-mediated toxicities during experimental viral infections: role of tumor necrosis factor and glucocorticoids. J. Exp. Med. **181:**901–914.
308. **Orange, J. S., B. Wang, C. Terhorst, and C. A. Biron.** 1995. Requirement for natural killer (NK) cell-produced interferon γ in defense against murine cytomegalovirus infection and enhancement of this defense pathway by

interleukin 12 administration. J. Exp. Med. **182:**1045–1056.
309. **Orange, J. S., S. F. Wolf, and C. A. Biron.** 1994. Effects of IL-12 on the response and susceptibility to experimental viral infections. J. Immunol. **152:**1253–1264.
310. **Orme, I. M., E. S. Miller, A. D. Roberts, S. K. Furney, J. P. Griffin, K. M. Dobos, D. Chi, B. Rivoire, and P. J. Brennan.** 1992. T lymphocytes mediating protection and cellular cytolysis during the course of *Mycobacterium tuberculosis* infection. J. Immunol. **148:**189–196.
311. **Orme, I. M., A. D. Roberts, J. P. Griffin, and J. S. Abrams.** 1993. Cytokine secretion by CD4 T lymphocytes acquired in response to *Mycobacterium tuberculosis* infection. J. Immunol. **151:**518–525.
312. **Oswald, I. P., I. Eltoum, T. A. Wynn, B. Schwartz, P. Caspar, D. Paulin, A. Sher, and S. L. James.** 1994. Endothelial cells are activated by cytokine treatment to kill an intravascular parasite, *Schistosoma mansoni*, through the production of nitric oxide. Proc. Natl. Acad. Sci. USA **91:**999–1003.
313. **Ozmen, L., M. Aguet, G. Trinchieri, and G. Garotta.** 1995. The in vivo antiviral activity of interleukin-12 is mediated by gamma interferon. J. Virol. **69:**8147–8150.
314. **Ozmen, L., M. Pericin, J. Hakimi, R. A. Chizzonite, M. Wysocka, G. Trinchieri, M. Gately, and G. Garotta.** 1994. IL-12, IFN-γ, and TNF-α are the key cytokines of the generalized Shwartzmann reaction. J. Exp. Med. **180:**907–916.
315. **Paganin, C., I. Frank, and G. Trinchieri.** 1995. Priming for high interferon-γ production induced by interleukin-12 in both $CD4^+$ and $CD8^+$ T cell clones from HIV-infected patients. J. Clin. Invest. **96:**1677–1682.
316. **Parish, C. R.** 1972. The relationship between humoral and cell-mediated immunity. Transplant. Rev. **13:**35–66.
317. **Paul, W. E., and R. A. Seder.** 1994. Lymphocyte responses and cytokines. Cell **76:**241–251.
318. **Pearlman, E., F. P. Heinzel, F. E. Hazlett, Jr., and J. W. Kazura.** 1995. IL-12 modulation of T helper responses to the filarial helminth, *Brugia malayi*. J. Immunol. **154:**4658–4664.
319. **Perales, M. A., P. R. Skolnik, and J. Lieberman.** 1996. Effect of interleukin 12 on in vitro HIV type 1 replication depends on clinical stage. AIDS Res. Hum. Retroviruses **12:**659–668.
320. **Perez, V. L., J. A. Lederer, E. Carniel, A. Lichtman, and A. K. Abbas.** 1995. The role of IL12 in helper T-cell differentiation. Res. Immunol. **146:**477–480.
321. **Perez, V. L., J. A. Lederer, A. H. Lichtman, and A. K. Abbas.** 1995. Stability of Th1 and Th2 populations. Int. Immunol. **7:**869–875.
322. **Perussia, B., S. Chan, A. D'Andrea, K. Tsuji, D. Santoli, M. Pospisil, D. Young, S. Wolf, and G. Trinchieri.** 1992. Natural killer cell stimulatory factor or IL-12 has different effects on the proliferation of $TCR\alpha\beta^+$ T lymphocytes and NK cells. J. Immunol. **149:**3495–3502.
323. **Podlaski, F. J., V. B. Nanduri, J. D. Hulmes, Y.-C. E. Pan, W. Levin, W. Danho, R. Chizzonite, M. K. Gately, and A. S. Stern.** 1992. Molecular characterization of interleukin 12. Arch. Biochem. Biophys. **294:**230–237.
324. **Powrie, F., and R. L. Coffman.** 1993. Cytokine regulation of T-cell function: potential for therapeutic intervention. Immunol. Today **14:**270–274.
325. **Presky, D. H., U. Gubler, R. A. Chizzonite, and M. K. Gately.** 1995. IL12 receptors and receptor antagonists. Res. Immunol. **146:**439–445.
326. **Presky, D. H., H. Yang, L. J. Minetti, A. O. Chua, N. Nabavi, C. Y. Wu, M. K. Gately, and U. Gubler.** 1996. A functional interleukin 12 receptor complex is composed of two β-type cytokine receptor subunits. Proc. Natl. Acad. Sci. USA **93:**14002–14007.
327. **Puccetti, P., L. Romani, and F. Bistoni.** 1995. A T_H1/T_H2-like switch in candidiasis: new perspectives for therapy. Trends Microbiol. **3:**237–240.
328. **Radolf, J. D., L. L. Arndt, D. R. Akins, L. L. Curetty, M. E. Levi, Y. Shen, L. S. Davis, and M. V. Norgard.** 1995. *Treponema pallidum* and *Borrelia burgdorferi* lipoproteins and synthetic lipopeptides activate monocytes/macrophages. J. Immunol. **154:**2866–2877.
329. **Reed, S. G.** 1988. *In vivo* administration of recombinant IFN-γ induces macrophage activation, and prevents acute disease, immune suppression, and death in experimental *Trypanosoma cruzi* infection. J. Immunol. **140:**4342–4347.
330. **Reiner, S. L., and R. M. Locksley.** 1995. The regulation of immunity to *Leishmania major*. Annu. Rev. Immunol. **13:**151–177.
331. **Reiner, S. L., S. Zheng, Z.-E. Wang, L. Stowring, and R. M. Locksley.** 1994. *Leishmania* promastigotes evade interleukin-12 (IL-12) induction by macrophages and stimulate a broad range of cytokines from $CD4^+$ T cells during initiation of infection. J. Exp. Med. **179:**447–456.
332. **Remington, J. S., R. McLeod, and G. Desmonts.** 1994. Toxoplasmosis, p. 140–267. *In* J. S. Remington, and J. O. Klein (ed.), Infectious diseases of the fetus and newborn infant, 4th ed. The W. B. Saunders Co., Philadelphia, Pa.
333. **Rex, J. H., J. E. Bennett, J. I. Gallin, H. L. Malech, E. S. DeCarlo, and D. A. Melnick.** 1991. In vivo interferon-γ therapy augments the in vitro ability of chronic granulomatous disease neutrophils to damage *Aspergillus* hyphae. J. Infect. Dis. **163:**849–852.
334. **Robinson, D. S., S. Ying, I. K. Taylor, A. Wangoo, D. M. Mitchell, A. B. Kay, Q. Hamid, and R. J. Shaw.** 1994. Evidence for a Th1-like bronchoalveolar T-cell subset and predominance of interferon-gamma gene activation in pulmonary tuberculosis. Am. J. Respir. Crit. Care Med. **149:**989–993.
335. **Rogers, H. W., K. C. F. Sheehan, L. M. Brunt, S. K. Dower, E. R. Unanue, and R. D. Schrieber.** 1992. Interleukin-1 participates in the development of anti-*Listeria* responses in both normal and SCID mice. Proc. Natl. Acad. Sci. USA **89:**1011–1015.
336. **Rogge, L., L. Barberis-Maino, M. Biffi, N. Passini, D. H. Presky, U. Gubler, and F. Sinigaglia.** 1997. Selective expression of an interleukin-12 receptor component by human T helper 1 cells. J. Exp. Med. **185:**825–831.
337. **Romagnani, S.** 1991. Human T_H1 and T_H2 subsets: doubt no more. Immunol. Today **12:**256–257.
338. **Romagnani, S.** 1992. Induction of Th1 and Th2 responses: a key role for the "natural" immune response? Immunol. Today **13:**379–383.
339. **Romagnani, S.** 1994. Regulation of the development of type 2 T helper cells in allergy. Curr. Opin. Immunol. **6:**838–846.
340. **Romani, L., F. Bistoni, A. Mencacci, E. Cenci, R. Spaccapelo, and P. Puccetti.** 1995. IL12 in *Candida albicans* infections. Res. Immunol. **146:**532–538.
341. **Romani, L., F. Bistoni, and P. Puccetti.** Initiation of T helper cell immunity to *Candida albicans* by IL-12: the role of neutrophils. Chem. Immunol., in press.
342. **Romani, L., E. Cenci, A. Mencacci, F. Bistoni, and P. Puccetti.** 1995. T helper cell dichotomy to *Candida albicans*: implications for pathology, therapy, and vaccine design. Immunol. Res. **14:**148–162.
343. **Romani, L., E. Cenci, A. Mencacci, R. Spaccapelo, U. Grohmann, P. Puccetti, and F. Bistoni.** 1992. Gamma interferon modifies $CD4^+$ subset expression in murine candidiasis. Infect. Immun. **60:**4950–4952.
344. **Romani, L., and D. H. Howard.** 1995. Mechanisms of resistance to fungal infections. Curr. Opin. Immunol. **7:**517–523.
345. **Romani, L., A. Mencacci, E. Cenci, G. Del Sero, F. Bistoni, and P. Puccetti.** 1997. An immunoregulatory role for neutrophils in $CD4^+$ T helper subset selection in mice with candidiasis. J. Immunol. **158:**2356–2362.
346. **Romani, L., A. Mencacci, E. Cenci, P. Puccetti, and F. Bistoni.** 1997. Neutrophils and the adaptive immune response to *Candida albicans*. Res. Immunol. **147:**512–518.
347. **Romani, L., A. Mencacci, E. Cenci, R. Spaccapelo, G. Del Sero, I. Nicoletti, G. Trinchieri, F. Bistoni, and P. Puccetti.** 1997. Neutrophil production of IL-12 and IL-10 in candidiasis and efficacy of IL-12 therapy in neutropenic mice. J. Immunol. **158:**5349–5356.
348. **Romani, L., A. Mencacci, E. Cenci, R. Spaccapelo, C. Toniatti, P. Puccetti, F. Bistoni, and V. Poli.** 1996. Impaired neutrophil response and $CD4^+$ T helper cell 1 development in interleukin-6-deficient mice infected with *Candida albicans*. J. Exp. Med. **183:**1345–1355.
349. **Romani, L., A. Mencacci, L. Tonnetti, R. Spaccapelo, E. Cenci, P. Puccetti, S. F. Wolf, and F. Bistoni.** 1994. IL-12 is both required and prognostic in vivo for T helper type 1 differentiation in murine candidiasis. J. Immunol. **152:**5167–5175.
350. **Romani, L., A. Mencacci, L. Tonnetti, R. Spaccapelo, E. Cenci, S. Wolf, P. Puccetti, and F. Bistoni.** 1994. Interleukin-12 but not interferon-γ production correlates with induction of T helper type-1 phenotype in murine candidiasis. Eur. J. Immunol. **24:**909–915.
351. **Romani, L., P. Puccetti, and F. Bistoni.** 1996. Biological role of Th cell subsets in candidiasis. Chem. Immunol. **63:**115–137.
352. **Rothe, H., B. Hartmann, P. Geerlings, and H. Kolb.** 1996. Interleukin-12 gene expression of macrophages is regulated by nitric oxide. Biochem. Biophys. Res. Commun. **224:**159–163.
353. **Rudin, W., H. P. Eugster, G. Bordmann, J. Bonato, M. Muller, M. Yamage, and B. Ryffel.** 1997. Resistance to cerebral malaria in tumor necrosis factor α/β-deficient mice is associated with a reduction of intercellular adhesion molecule-1 up-regulation and T helper type 1 response. Am. J. Pathol. **150:**257–266.
354. **Ryffel, B.** 1997. Interleukin-12: role of interferon-γ in IL-12 adverse effects. Clin. Immunol. Immunopathol. **83:**18–20.
355. **Salgame, P., J. S. Abrams, C. Clayberger, H. Goldstein, J. Convit, R. L. Modlin, and B. R. Bloom.** 1991. Differing lymphokine profiles of functional subsets of human CD4 and CD8 T cell clones. Science **245:**279–282.
356. **Saunders, B. M., Y. Zhan, and C. Cheers.** 1995. Endogenous interleukin-12 is involved in resistance of mice to *Mycobacterium avium* complex infection. Infect. Immun. **63:**4011–4015.
357. **Scharton, T. M., and P. Scott.** 1993. Natural killer cells are a source of interferon-gamma that drives differentiation of $CD4^+$ T cell subsets and induces early resistance to *Leishmania major* in mice. J. Exp. Med. **178:**567–577.
358. **Scharton-Kersten, T., L. C. C. Afonso, M. Wysocka, G. Trinchieri, and P. Scott.** 1995. IL-12 is required for natural killer cell activation and subsequent T helper 1 cell development in experimental leishmaniasis. J. Immunol. **154:**5320–5330.
359. **Scharton-Kersten, T. M., E. Y. Denkers, R. T. Gazzinelli, and A. Sher.** 1995. Role of IL12 in induction of cell-mediated immunity to *Toxoplasma gondii*. Res. Immunol. **146:**539–545.
360. **Scharton-Kersten, T. M., and P. Scott.** 1995. The role of the innate immune response in Th1 cell development following *Leishmania major* infection. J. Leukocyte Biol. **57:**515–522.
361. **Scharton-Kersten, T. M., T. A. Wynn, E. Y. Denkers, S. Bala, E. Grunvald,**

S. Heiny, R. T. Gazzinelli, and A. Sher. 1996. In the absence of endogenous IFN-γ, mice develop unimpaired IL-12 responses to *Toxoplasma gondii* while failing to control acute infection. J. Immunol. **157:**4045–4054.
362. **Schijns, V. E. C. J., B. L. Haagmans, and M. C. Horzinek.** 1995. IL-12 stimulates an antiviral type 1 cytokine response but lacks adjuvant activity in IFN-γ-receptor-deficient mice. J. Immunol. **155:**2525–2532.
363. **Schijns, V. E. C. J., B. L. Haagmans, E. O. Rijke, S. Huang, M. Aguet, and M. C. Horzinek.** 1994. Interferon-γ receptor-deficient mice generate antiviral Th1-characteristic cytokine profiles but altered antibody responses. J. Immunol. **153:**2029–2037.
364. **Schijns, V. E. C. J., C. M. H. Wierda, M. von Hoeji, and M. C. Horzinek.** 1996. Exacerbated viral hepatitis in IFN-γ receptor-deficient mice is not suppressed by IL-12. J. Immunol. **157:**815–821.
365. **Schlaak, J., E. Hermann, M. Ringhoffer, P. Probst, H. Gallati, K. H. Meyer zum Büschenfelde, and B. Fleischer.** 1992. Predominance of Th1-type T cells in synovial fluid with *Yersinia*-induced reactive arthritis. Eur. J. Immunol. **22:**2771–2776.
366. **Schmitt, E., P. Hoehn, T. Germann, and E. Rüde.** 1994. Differential effects of IL12 on the development of naive mouse $CD4^+$ T cells. Eur. J. Immunol. **24:**343–347.
367. **Schoenhaut, D. S., A. O. Chua, A. G. Wolitzky, P. M. Quinn, C. M. Dwyer, W. McComas, P. C. Familletti, M. K. Gately, and U. Gubler.** 1992. Cloning and expression of murine IL-12. J. Immunol. **148:**3433–3440.
368. **Scott, B., R. Liblau, S. Degermann, L. A. Marconi, L. Ogata, A. J. Canton, H. O. McDevitt, and D. Lo.** 1994. A role for non-MHC genetic polymorphism in susceptibility to spontaneous autoimmunity. Immunity **1:**73–83.
369. **Scott, P.** 1993. IL-12: initiation cytokine for cell-mediated immunity. Science **260:**496–497.
370. **Scott, P.** 1996. Th cell development and regulation in experimental cutaneous leishmaniasis. Chem. Immunol. **63:**98–114.
371. **Scott, P., and S. H. E. Kaufmann.** 1991. The role of T-cell subsets and cytokines in the regulation of infection. Immunol. Today **12:**346–348.
372. **Sedegah, M., F. Finkelman, and S. L. Hoffman.** 1994. Interleukin 12 induction of interferon γ-dependent protection against malaria. Proc. Natl. Acad. Sci. USA **91:**10700–10702.
373. **Seder, R. A., R. Gazzinelli, A. Sher, and W. E. Paul.** 1993. Interleukin 12 acts directly on $CD4^+$ T cells to enhance priming for interferon γ production and diminishes interleukin 4 inhibition of such priming. Proc. Natl. Acad. Sci. USA **90:**10188–10192.
374. **Seder, R. A., B. L. Kelsall, and D. Janovic.** 1996. Differential roles for IL-12 in the maintenance of immune responses in infectious versus autoimmune disease. J. Immunol. **157:**2745–2748.
375. **Seder, R. A., and W. E. Paul.** 1994. Acquisition of lymphokine-producing phenotype by $CD4^+$ T cells. Annu. Rev. Immunol. **12:**635–673.
376. **Seder, R. A., W. E. Paul, M. M. Davis, and B. Fazekas de St. Groth.** 1992. The presence of interleukin 4 during in vitro priming determines the lymphocyte-producing potential of $CD4^+$ T cells from T cell receptor transgenic mice. J. Exp. Med. **176:**1091–1098.
377. **Seiler, K. P., and J. J. Weiss.** 1996. Immunity to Lyme disease: protection, pathology, and persistence. Curr. Opin. Immunol. **8:**503–509.
378. **Sher, A., and R. L. Coffman.** 1992. Regulation of immunity to parasites by T cells and T cell-derived cytokines. Annu. Rev. Immunol. **10:**385–409.
379. **Sher, A., R. L. Coffman, S. Heiny, and A. W. Cheever.** 1990. Ablation of eosinophil and IgE responses with anti-IL-5 or anti-IL-4 antibodies fail to affect immunity against *Schistosoma mansoni* in the mouse. J. Immunol. **145:**3911–3920.
380. **Sher, A., R. T. Gazzinelli, I. P. Oswald, M. Clerici, M. Kullberg, E. J. Pearce, J. A. Berzofsky, T. R. Mosmann, S. L. James, H. C. Morse, and G. M. Shearer.** 1992. Role of T-cell derived cytokines in the down-regulation of immune responses in parasitic and retroviral infection. Immunol. Rev. **127:**183–204.
381. **Sher, A., I. P. Oswald, S. Heiny, and R. T. Gazzinelli.** 1993. *Toxoplasma gondii* induces a T-independent IFN-γ response in NK cells which requires both adherent accessory cells and TNF-α. J. Immunol. **150:**3982–3989.
382. **Sieburth, D., E. W. Jabs, J. A. Warrington, X. Li, J. Lasota, S. LaForgia, K. Kelleher, K. Huebner, J. J. Wasmuth, and S. F. Wolf.** 1992. Assignment of genes encoding a unique cytokine (IL12) composed of two unrelated subunits to chromosomes 3 and 5. Genomics **14:**59–62.
383. **Sieling, P. A., X.-H. Wang, M. K. Gately, J. L. Oliveros, T. McHugh, P. F. Barnes, S. F. Wolf, L. Golkar, M. Yamamura, Y. Yogi, K. Uyemura, T. H. Rea, and R. L. Modlin.** 1994. IL-12 regulates T helper type 1 cytokine responses in human infectious disease. J. Immunol. **153:**3639–3647.
384. **Silva, J. S., P. J. Morrissey, K. H. Grabstein, K. M. Mohler, D. Anderson, and S. G. Reed.** 1992. Interleukin 10 and IFN-γ regulation of experimental *Trypanosoma cruzi* infection. J. Exp. Med. **175:**169–174.
385. **Silva, J. S., D. Twardzik, and S. G. Reed.** 1991. Regulation of *Trypanosoma cruzi* infections in vitro and in vivo by transforming growth factor-beta. J. Exp. Med. **174:**539–545.
386. **Sirianni, M. C., I. J. Ansotegui, F. Aiuti, and H. Wigzell.** 1995. Natural killer cell stimulatory (NKSF)/IL-12 and cytolytic activities of PBL/NK cells from human immunodeficiency virus type-1 infected patients. Scand. J. Immunol. **40:**83–86.
387. **Sjöstedt, A., M. Eriksson, G. Sandström, and A. Tärnvik.** 1992. Various membrane proteins of *Francisella tularensis* induce interferon-γ production on both $CD4^+$ and $CD8^+$ T cells of primed humans. Immunology **76:**584–592.
388. **Skamene, E., P. Gros, A. Forget, P. A. L. Kongshavn, C. St. Charles, and B. A. Taylor.** 1982. Genetic regulation of resistance to intracellular pathogens. Nature **297:**506–509.
389. **Skeen, M. J., M. A. Miller, T. M. Shinnick, and H. K. Ziegler.** 1996. Regulation of murine macrophage IL-12 production. Activation of macrophages in vivo, restimulation in vitro, and modulation by other cytokines. J. Immunol. **156:**1196–1206.
390. **Skeen, M. J., and H. K. Ziegler.** 1995. Activation of γδ T cells for production of IFN-γ is mediated by bacteria via macrophage-derived cytokines IL-1 and IL-12. J. Immunol. **154:**5832–5841.
391. **Skeiky, Y. A. W., J. A. Guderian, D. R. Benson, O. Bacelar, E. M. Carvalho, M. Kubin, R. Badaro, G. Trinchieri, and S. G. Reed.** 1995. A recombinant *Leishmania* antigen that stimulates human peripheral blood mononuclear cells to express a Th1-type cytokine profile and to produce interleukin 12. J. Exp. Med. **181:**1527–1537.
392. **Smith, T. J., L. A. Ducharme, and J. H. Weis.** 1994. Preferential expression of interleukin-12 or interleukin-4 by murine bone marrow mast cells derived in mast cell growth factor or interleukin-3. Eur. J. Immunol. **24:**822–826.
393. **Smythies, L. E., P. S. Coulson, and R. A. Wilson.** 1992. Monoclonal antibody to IFN-γ modifies pulmonary inflammatory responses and abrogates immunity to *Schistosoma mansoni* in mice vaccinated with attenuated cercariae. J. Immunol. **149:**3654–3658.
394. **Snidjers, A., C. M. Hilkens, T. C. van der Pouw Kraan, M. Engel, L. A. Aarden, and M. L. Kapsenberg.** 1996. Regulation of bioactive IL-12 production in lipopolysaccharide-stimulated human monocytes is determined by the expression of the p35 subunit. J. Immunol. **156:**1207–1212.
395. **Song, F., G. Matsuzaki, M. Mitsuyama, and K. Nomoto.** 1996. Differential effects of viable and killed bacteria on IL-12 expression of macrophages. J. Immunol. **156:**2979–2984.
396. **Spaccapelo, R., L. Romani, L. Tonnetti, E. Cenci, A. Mencacci, G. Del Sero, R. Tognellini, S. Reed, P. Puccetti, and F. Bistoni.** 1995. TGF-β is important in determining the in vivo patterns of susceptibility or resistance in mice infected with *Candida albicans*. J. Immunol. **155:**1349–1360.
397. **Stahl, N., and G. D. Yancopoulos.** 1993. The alphas, betas and kinases of cytokine receptor complexes. Cell **74:**587–590.
398. **Stern, A. S., F. J. Podlaski, J. D. Hulmes, Y. E. Pan, P. M. Quinn, A. G. Wolitzky, P. C. Familletti, D. L. Stremio, T. Truitt, R. Chizzonite, and M. K. Gately.** 1990. Purification to homogeneity and partial characterization of cytotoxic lymphocyte maturation factor from human B-lymphoblastoid cells. Proc. Natl. Acad. Sci. USA **87:**6808–6812.
399. **Stevens, D. A.** 1995. *Coccidioides immitis*, p. 2365–2375. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practice of infectious disease, 4th ed. Churchill Livingstone, Inc., New York, N.Y.
400. **Stevens, M. G., G. W. Pugh, and L. B. Tabatabai.** 1992. Effects of gamma interferon and indomethacin in preventing *Brucella abortus* infections in mice. Infect. Immun. **60:**4407–4409.
401. **Stevenson, M. M., M. F. Tam, S. F. Wolf, and A. Sher.** 1995. IL-12-induced protection against blood-stage *Plasmodium chabaudi* AS requires IFN-γ and TNF-α and occurs via a nitric oxide-dependent mechanism. J. Immunol. **155:**2545–2556.
402. **Svetic, A., Y. C. Jian, P. Lu, F. D. Finkelman, and W. C. Gause.** 1993. *Brucella abortus* induces a novel cytokine expression pattern characterized by elevated IL-10 and IFN-γ in $CD4^+$ T cells. Int. Immunol. **8:**877–883.
403. **Swain, S. L.** 1993. IL-4 dictates T-cell differentiation. Res. Immunol. **144:**567–651.
404. **Swain, S. L., L. M. Bradley, M. Croft, S. Tonkonogy, G. Atkins, A. D. Weinberg, D. D. Duncan, S. M. Hedrick, R. W. Dutton, and G. Huston.** 1991. Helper T-cell subsets: phenotype, function and the role of lymphokines in regulating their development. Immunol. Rev. **123:**115–144.
405. **Sypek, J. P., C. L. Chung, S. E. H. Mayor, J. M. Subramanyam, S. J. Goldman, D. S. Sieburth, S. F. Wolf, and R. G. Schaub.** 1993. Resolution of cutaneous leishmaniasis. Interleukin 12 initiates a protective Th1 immune response. J. Exp. Med. **177:**1797–1802.
406. **Szabo, S. J., A. S. Dighe, U. Gubler, and K. M. Murphy.** 1997. Regulation of the interleukin (IL)-12R β2 subunit expression in developing T helper 1 (Th1) and Th2 cells. J. Exp. Med. **185:**817–824.
407. **Szabo, S. J., N. G. Jacobson, A. S. Dighe, U. Gubler, and K. M. Murphy.** 1995. Developmental commitment to the Th2 lineage by extinction of IL-12 signaling. Immunity **2:**665–675.
408. **Takenaka, H., S. Maruo, N. Yamamoto, M. Wysocka, S. Ono, M. Kobayashi, H. Yagita, K. Okumura, T. Hamaoka, G. Trinchieri, and H. Fujiwara.** 1997. Regulation of T cell-dependent and -independent IL-12 production by the three Th2-type cytokines IL-10, IL-6, and IL-4. J. Leukocyte Biol. **61:**80–87.
409. **Tang, Y. W., and B. S. Graham.** 1995. Interleukin-12 treatment during immunization elicits a T helper cell type 1-like immune response in mice challenged with respiratory syncytial virus and improves vaccine immuno-

genicity. J. Infect. Dis. **172:**734–738.
410. **Taoufik, Y., O. Lantz, C. Wallon, A. Charles, E. Dussaix, and J. F. Delfraissy.** 1997. Human immunodeficiency virus gp120 inhibits interleukin-12 secretion by human monocytes: an indirect interleukin-10-mediated effect. Blood **89:**2842–2848.
411. **Taylor, A. P., and H. W. Murray.** 1997. Intracellular antimicrobial activity in the absence of interferon-γ: effect of interleukin-12 in experimental visceral leishmaniasis in interferon-γ gene-disrupted mice. J. Exp. Med. **185:**1231–1239.
412. **Teixeira, H. C., M. E. Munk, and S. H. E. Kaufmann.** 1995. Frequencies of IFN-γ and IL-4 producing cells during *Mycobacterium bovis* BCG infection in two genetically susceptible mouse strains: role of α/β T cells and NK1.1 cells. Immunol. Lett. **46:**15–19.
413. **Thierfelder, W. E., J. M. van Deursen, K. Yamamoto, R. A. Tripp, S. R. Sarawar, R. T. Carson, M. Y. Sangster, D. A. Vignali, P. C. Doherty, G. C. Grosveld, and J. N. Ihle.** 1996. Requirement for Stat4 in interleukin 12-mediated responses of natural killer and T cells. Nature **382:**171–174.
414. **Tite, J. P., G. Dougan, and S. N. Chatfield.** 1991. The involvement of tumor necrosis factor in immunity to *Salmonella* infection. J. Immunol. **147:**3161–3164.
415. **Tone, Y., S. A. Thompson, J. M. Babik, K. F. Nolan, M. Tone, C. Raven, and H. Waldmann.** 1996. Structure and chromosomal location of the mouse interleukin-12 p35 and p40 subunit genes. Eur. J. Immunol. **26:**1222–1227.
416. **Trinchieri, G.** 1993. Interleukin-12 and its role in the generation of T_H1 cells. Immunol. Today **14:**335–338.
417. **Trinchieri, G.** 1995. Interleukin-12: a pro-inflammatory cytokine with immunoregulatory functions that bridges innate resistance and antigen-specific adaptive immunity. Annu. Rev. Immunol. **13:**252–276.
418. **Trinchieri, G.** 1996. Role of interleukin-12 in human Th1 response. Chem. Immunol. **63:**14–29.
419. **Trinchieri, G.** 1997. Function and clinical use of interleukin-12. Curr. Opin. Hematol. **4:**59–66.
420. **Trinchieri, G., and F. Gerosa.** 1996. Immunoregulation of interleukin-12. J. Leukocyte Biol. **59:**505–511.
421. **Trinchieri, G., and P. Scott.** 1994. The role of interleukin 12 in the immune response, disease and therapy. Immunol. Today **15:**460–463.
422. **Trinchieri, G., and P. Scott.** 1995. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions. Res. Immunol. **146:**423–431.
423. **Tripp, C. S., M. K. Gately, J. Hakimi, P. Ling, and E. R. Unanue.** 1994. Neutralization of IL-12 decreases resistance to *Listeria* in SCID and C.B-17 mice. Reversal by IFN-γ. J. Immunol. **152:**1883–1887.
424. **Tripp, C. S., O. Kanagawa, and E. R. Unanue.** 1995. Secondary response to *Listeria* infection requires IFN-γ but is partially independent of IL-12. J. Immunol. **155:**3427–3432.
425. **Tripp, C. S., and E. R. Unanue.** 1995. Macrophage production of IL12 is a critical link between the innate and specific immune responses to *Listeria*. Res. Immunol. **146:**515–519.
426. **Tripp, C. S., S. F. Wolf, and E. R. Unanue.** 1993. Interleukin 12 and tumor necrosis factor α are costimulators of interferon γ production by natural killer cells in severe combined immunodeficiency with listeriosis and interleukin 10 is a physiologic antagonist. Proc. Natl. Acad. Sci. USA **90:**3725–3729.
427. **Uehara, S., Y. Hitoshi, F. Numata, M. Makino, M. Howard, T. Mizuochi, and K. Takatsu.** 1994. An IFN-γ-dependent pathway plays a critical role in the pathogenesis of murine immunodeficiency syndrome induced by LP-BM5 murine leukemia virus. Int. Immunol. **6:**1937–1947.
428. **Uherova, P., E. Connick, S. MaWhinney, R. Schlichtemeier, R. T. Schooley, and D. R. Kuritzkes.** 1996. In vitro effect of interleukin-12 on antigen-specific lymphocyte proliferative responses from persons infected with human immunodeficiency virus type 1. J. Infect. Dis. **174:**483–489.
429. **Ungar, B. L. P., J. A. Burris, C. A. Quinn, and F. D. Finkelman.** 1990. New mouse models for chronic *Cryptosporidium* infection in immunodeficient hosts. Infect. Immun. **58:**961–969.
430. **Ungar, B. L. P., T. C. Kao, J. A. Burris, and F. D. Finkelman.** 1991. *Cryptosporidium* infection in an adult mouse model: independent roles for IFN-γ and CD4 T lymphocytes in protective immunity. J. Immunol. **147:**1014–1022.
431. **Urban, J., K. Madden, A. Svetic, A. Cheever, P. Trotta, W. Gause, I. Katona, and F. Finkelman.** 1992. The importance of Th2 cytokines in protective immunity to nematodes. Immunol. Rev. **127:**205–210.
432. **Urban, J. F., Jr., R. Fayer, S.-J. Chen, W. C. Gause, M. K. Gately, and F. D. Finkelman.** 1996. IL-12 protects immunocompetent and immunodeficient neonatal mice against infection with *Cryptosporidium parvum*. J. Immunol. **156:**263–268.
433. **van der Pouw Kraan, T. C. T. M., L. C. M. Boeije, R. J. T. Smeenk, J. Wijdenes, and L. A. Aarden.** 1995. Prostaglandin-E_2 is a potent inhibitor of human interleukin 12 production. J. Exp. Med. **181:**775–779.
434. **Vezzio, N., M. Sarfati, L. P. Yang, C. E. Demeure, and G. Delespesse.** 1996. Human Th2-like cell clones induce IL-12 production by dendritic cells and may express several cytokine profiles. Int. Immunol. **8:**1963–1970.
435. **Vieira, L. Q., B. D. Hondowicz, L. C. C. Afonso, M. Wysocka, G. Trinchieri, and P. Scott.** 1994. Infection with *Leishmania major* induces interleukin-12 production in vivo. Immunol. Lett. **40:**157–161.
436. **Voest, E. E., B. M. Kenyon, G. A. Truitt, M. S. O'Reilly, R. J. D'Amato, and J. Folkman.** 1995. Interleukin 12 inhibits angiogenesis in vivo. J. Natl. Cancer Inst. **87:**581–586.
437. **Vogel, L. A., L. C. Showe, T. L. Lester, R. M. McNutt, V. H. Van Cleave, and D. W. Metzger.** 1996. Direct binding of IL-12 to human and murine B lymphocytes. Int. Immunol. **8:**1955–1962.
438. **Wagner, R. D., H. Steinberg, H. Brown, and C. J. Czuprynski.** 1994. Recombinant interleukin-12 enhances resistance of mice to *Listeria monocytogenes* infection. Microb. Pathog. **17:**175–186.
439. **Walsh, T. J., J. Hiemenz, and P. A. Pizzo.** 1994. Evolving risk factors for invasive fungal infections: All neutropenic patients are not the same. Clin. Infect. Dis. **18:**793–798.
440. **Wang, B., C. Biron, J. She, K. Higgins, M.-J. Sunshine, E. Lacy, N. Lonberg, and C. Terhorst.** 1994. A block in both early T lymphocyte and natural killer cell development in transgenic mice with high-copy numbers of the human CD3ε gene. Proc. Natl. Acad. Sci. USA **91:**9402–9406.
441. **Wang, Z.-E., S. L. Reiner, S. Zheng, D. K. Dalton, and R. M. Locksley.** 1994. $CD4^+$ effector cells default to the Th2 pathway in interferon-γ-deficient mice infected with *Leishmania major*. J. Exp. Med. **179:**1367–1371.
442. **Wang, Z.-E., S. Zheng, D. B. Corry, D. K. Dalton, R. A. Seder, S. L. Reiner, and R. M. Locksley.** 1994. Interferon γ-independent effects of interleukin 12 administered during acute or established infection due to *Leishmania major*. Proc. Natl. Acad. Sci. USA **91:**12932–12936.
443. **Wolf, S. F., J. Bliss, K. Stokes, and J. Sypek.** 1995. Activity of IL12 as adjuvant in promoting Th1 and Th2 recall responses. Res. Immunol. **146:**486–493.
444. **Wolf, S. F., P. A. Temple, M. Kobayashi, D. Young, M. Dicig, L. Lowe, R. Dzialo, L. Fitz, C. Ferenz, R. M. Hewick, K. Kelleher, S. Hermann, S. C. Clark, L. Azzoni, S. H. Chan, G. Trinchieri, and B. Perussia.** 1991. Cloning of cDNA for natural killer cell stimulatory factor, a heterodimeric cytokine with multiple biologic effects on T and natural killer cells. J. Immunol. **146:**3074–3081.
445. **Wu, C.-Y., C. E. Demeure, M. Gately, F. Podlaski, H. Yssel, M. Kiniwa, and G. Delespesse.** 1994. In vitro maturation of human neonatal CD4 T lymphocytes. J. Immunol. **152:**1141–1153.
446. **Wu, C.-Y., R. R. Warrier, D. M. Carvajal, A. O. Chua, L. J. Minetti, R. Chizzonite, P. K. A. Mongini, A. S. Stern, U. Gubler, D. H. Presky, and M. K. Gately.** 1996. Biological function and distribution of human interleukin-12 receptor β chain. Eur. J. Immunol. **26:**345–350.
447. **Wu, C. Y., R. R. Warrier, X. Wang, D. H. Presky, and M. K. Gately.** 1997. Regulation of interleukin-12 receptor β1 chain expression and interleukin-12 binding by human peripheral blood mononuclear cells. Eur. J. Immunol. **27:**147–154.
448. **Wu-Hsieh, B. A., and D. H. Howard.** 1987. Inhibition of the intracellular growth of *Histoplasma capsulatum* by recombinant murine gamma interferon. Infect. Immun. **55:**1014–1016.
449. **Wynn, T. A., A. W. Cheever, D. Jankovic, R. W. Poindexter, P. Caspar, F. A. Lewis, and A. Sher.** 1995. An IL-12-based vaccination method for preventing fibrosis induced by schistosome infection. Nature (London) **376:**594–597.
450. **Wynn, T. A., I. Eltoum, I. P. Oswald, A. W. Cheever, and A. Sher.** 1994. Endogenous interleukin 12 (IL-12) regulates granuloma formation induced by eggs of *Schistosoma mansoni* and exogenous IL-12 both inhibits and prophylactically immunizes against egg pathology. J. Exp. Med. **179:**1551–1561.
451. **Wynn, T. A., D. Jankovic, S. Hieny, A. W. Cheever, and A. Sher.** 1995. IL-12 enhances vaccine-induced immunity to *Schistosoma mansoni* in mice and decreases T helper 2 cytokine expression, IgE production, and tissue eosinophilia. J. Immunol. **154:**4701–4709.
452. **Wynn, T. A., D. Jankovic, S. Hieny, K. Zioncheck, P. Jardieu, A. W. Cheever, and A. Sher.** 1995. IL-12 exacerbates rather than suppresses T helper 2-dependent pathology in the absence of endogenous IFN-γ. J. Immunol. **154:**3999–4009.
453. **Wynn, T. A., A. Reynolds, S. James, A. W. Cheever, P. Caspar, S. Heiny, D. Jankovic, M. Strand, and A. Sher.** 1996. IL-12 enhances vaccine-induced immunity to schistosomes augmenting both humoral and cell-mediated immune responses against the parasite. J. Immunol. **157:**4068–4078.
454. **Wynn, T. A., and A. Sher.** 1995. IL12 as an adjuvant for vaccines designed to prevent infection and immunopathology by schistosomes. Res. Immunol. **146:**582–589.
455. **Wysocka, M., M. Kubin, L. Q. Vieira, L. Ozmen, G. Garotta, P. Scott, and G. Trinchieri.** 1995. Interleukin-12 is required for interferon-γ production and lethality in lipopolysaccharide-induced shock in mice. Eur. J. Immunol. **25:**672–676.
456. **Yamashita, T., and D. L. Boros.** 1992. IL-4 influences IL-2 production and granulomatous inflammation in murine *Schistosoma mansoni*. J. Immunol. **149:**3659–3664.
457. **Yang, D. M., N. Fairweather, L. L. Button, W. R. McMaster, L. P. Kahl, and F. Y. Liew.** 1990. Oral *Salmonella typhimurium* (AroA−) vaccine expressing a major leishmanial surface protein (gp63) preferentially induces T helper

1 cells and protective immunity against leishmaniasis. J. Immunol. **145:** 2281–2285.
458. **Yang, L., J. H. Weis, E. Eichwald, C. P. Kolbert, D. H. Persing, and J. J. Weis.** 1994. Heritable susceptibility to severe *Borrelia burgdorferi*-induced arthritis is dominant and is associated with persistence of large numbers of spirochetes in tissues. Infect. Immun. **62:**492–500.
459. **Yang, Y., G. Trinchieri, and J. M. Wilson.** 1995. Recombinant IL-12 prevents formation of blocking IgA antibodies to recombinant adenovirus and allows repeated gene therapy to mouse lung. Nat. Med. **1:**890–893.
460. **Yap, G. S., P. Jacobs, and M. M. Stevenson.** 1994. Th cell regulation of host resistance to blood-stage *Plasmodium chabaudi* AS. Res. Immunol. **145:** 419–422.
461. **Yoshida, A., Y. Koide, M. Uchijima, and T. O. Yoshida.** 1995. Dissection of strain difference in acquired protective immunity against *Mycobacterium bovis* Calmette-Guérin bacillus (BCG). Macrophages regulate the susceptibility through cytokine network and the induction of nitric oxide synthase. J. Immunol. **155:**2057–2066.
462. **Yoshimoto, T., and W. E. Paul.** 1994. $CD4^{pos}$, $N.K.1.1^{pos}$ T cells promptly produce interleukin 4 in response to in vivo challenge with anti-CD3. J. Exp. Med. **179:**1285–1295.
463. **Yssel, H., M.-C. Shanafelt, C. Soderberg, P. V. Schneider, J. Anzola, and G. Peltz.** 1991. *Borrelia burgdorferi* activates a T helper type 1-like T cell subset in Lyme arthritis. J. Exp. Med. **174:**593–601.
464. **Zaitseva, M., H. Golding, M. Betts, A. Yamauchi, E. T. Bloom, L. E. Butler, L. Steven, and B. Golding.** 1995. Human peripheral blood $CD4^+$ and $CD8^+$ T cells express Th1-like cytokine mRNA and protein following in vitro stimulation with heat-inactivated *Brucella abortus*. Infect. Immun. **63:**2720–2728.
465. **Zaitseva, M., H. Golding, J. Manischewitz, D. Webb, and B. Golding.** 1996. *Brucella abortus* as a potential vaccine candidate: induction of interleukin-12 secretion and enhanced B7.1 and B7.2 and intracellular adhesion molecule 1 surface expression in elutriated human monocytes stimulated by heat-inactivated *B. abortus*. Infect. Immun. **64:**3109–3117.
466. **Zhan, Y., and C. Cheers.** 1993. Endogenous gamma interferon mediates resistance to *Brucella abortus* infection. Infect. Immun. **61:**4899–4901.
467. **Zhan, Y., and C. Cheers.** 1995. Endogenous interleukin-12 is involved in resistance to *Brucella abortus* infection. Infect. Immun. **63:**1387–1390.
468. **Zhan, Y., Z. Liu, and C. Cheers.** 1996. Tumor necrosis factor alpha and interleukin-12 contribute to resistance to the intracellular bacterium *Brucella abortus* by different mechanisms. Infect. Immun. **64:**2782–2786.
469. **Zhang, M., M. K. Gately, E. Wang, S. F. Wolf, S. Lu, R. L. Modlin, and P. F. Barnes.** 1994. Interleukin-12 at the site of disease in tuberculosis. J. Clin. Invest. **93:**1733–1739.
470. **Zhang, M., J. Gong, D. V. Iyer, B. E. Jones, R. L. Modlin, and P. F. Barnes.** 1994. T-cell cytokine responses in persons with tuberculosis and human immunodeficiency virus infection. J. Clin. Invest. **94:**2435–2442.
471. **Zhang, M., Y. Lin, D. V. Iyer, J. Gong, J. S. Abrams, and P. F. Barnes.** 1995. T-cell cytokine responses in human infection with *Mycobacterium tuberculosis*. Infect. Immun. **63:**3231–3234.
472. **Zhou, P., M. C. Sieve, J. Bennett, K. J. Kwon-Chung, R. P. Tewari, R. T. Gazzinelli, A. Sher, and R. A. Seder.** 1995. IL-12 prevents mortality in mice infected with *Histoplasma capsulatum* through induction of IFN-γ. J. Immunol. **155:**785–795.
473. **Zhou, P., M. C. Sieve, R. P. Tewari, and R. A. Seder.** 1997. Interleukin-12 modulates the protective immune response in SCID mice infected with *Histoplasma capsulatum*. Infect. Immun. **65:**936–942.
474. **Zitvogel, L., and M. T. Lotze.** 1995. Role of interleukin-12 (IL12) as an anti-tumour agent: experimental biology and clinical application. Res. Immunol. **146:**628–638.
475. **Zou, J., D. H. Presky, C. Y. Wu, and U. Gubler.** 1997. Differential associations between the cytoplasmic regions of the interleukin-12 receptor subunits β1 and β2 and JAK kinases. J. Biol. Chem. **272:**6073–6077.
476. **Zou, J. J., D. S. Schoenhaut, D. M. Carvajal, R. R. Warrier, D. H. Presky, M. K. Gately, and U. Gubler.** 1995. Structure-function analysis of the p35 subunit of mouse interleukin 12. J. Biol. Chem. **270:**5864–5871.