

# Type 1 and Type 2 Cytokine Dysregulation in Human Infectious, Neoplastic, and Inflammatory Diseases

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**INTRODUCTION**

In 1986 Mosmann and Coffman and their collaborators first reported that cloned murine helper T (Th) lymphocytes could be divided into two functional subsets on the basis of the immunoregulatory cytokines that these clones produced. Thus, Th1 clones were characterized by the production of gamma interferon (IFN- $\gamma$ ), whereas Th2 clones produced interleukin 4 (IL-4) (264, 265). Numerous reports by other laboratories as well as additional studies by Mosmann and Coffman have verified the original observations in mice. Th0 clones which could produce the cytokines of both Th1 and Th2 clones were also identified, and Thp clones which appear to serve as precursors to the other Th clones were identified (293). It was subsequently demonstrated that some of these immunoregulatory cytokines possessed cross-regulatory properties such that they not only enhanced one type of clone and its cytokine production but also suppressed the other type of clone and the cytokines that it produced. For example, IL-4 inhibited the production of IFN- $\gamma$  from Th1 clones whereas IFN- $\gamma$  inhibited the production of IL-4 from Th2 clones (266, 267, 351).

The cross-regulatory properties of Th1 and Th2 cytokines were soon linked to multiple observations, made more than 30 years ago and best summarized by Parish in 1972 (290), that an inverse relationship existed between cell-mediated immunity (CMI) and humoral immunity in response to antigenic stimuli. By the mid-1980s, murine Th1 clones were recognized to provide better helper activity for CMI whereas Th2 clones were more important for B-cell development and antibody production. There were exceptions, however; e.g., immunoglobulin G2a (IgG2a) antibody production was enhanced by Th1 clones. Although several attempts were made to generate and identify similar clones in human T lymphocytes from normal donors, it was not until the beginning of this decade that

several laboratories, led by Romagnani's group, found evidence of Th1 and Th2 clones isolated from persons with certain disease states, particularly chronic diseases (92, 93, 231, 295, 314, 315, 416, 417, 428, 429).

Although cloned T cells continue to provide important information relevant for the regulation of immune responses, such clones are by definition quite removed from the in vivo setting in which immune regulation occurs in nature. Thus, Th1 and Th2 clones are identified by the autocrine cytokines they produce. By the most stringent definition, Th1 and Th2 clones were identified by mRNA expression and production of IFN- $\gamma$  and IL-4, respectively. In a broader context, Th1 cytokines include IFN- $\gamma$ , IL-2, and tumor necrosis factor beta (TNF- $\beta$ ) (lymphotoxin) whereas Th2 cytokines include IL-4, IL-5, IL-6, IL-10, IL-13, and possibly IL-9. However, it is now realized that other cytokines not produced by Th1 or Th2 clones, such as IL-12, also make important contributions to the regulation of the immune system (384, 385). In addition, several of the Th1 and Th2 cytokines (e.g., IL-4, IL-5, IL-6, IL-10, and IFN- $\gamma$ ) are now recognized to come not only from CD4<sup>+</sup> T cells but also from multiple other leukocytes and even non-hematopoietic cells (Table 1). Moreover, many diseases and conditions that involve immune dysregulation are seldom if ever driven to the extremes that would result in isolation of Th1 and Th2 clones after in vitro culture. Hence, certain populations of cells that produce important regulatory cytokines will be selected for in the cloning process whereas others will be selected against and lost.

For the above reasons, we have suggested the terminology "type 1" or "Th1-like" instead of Th1 and "type 2" or "Th2-like" instead of Th2 in the characterization of in vivo immune-dysregulated diseases and conditions (72). The type 1 and type 2 nomenclature was originally suggested by Bloom et al. in 1992 (33), when they included CD8<sup>+</sup> T cells as well as CD4<sup>+</sup>

TABLE 1. Leukocyte sources of type 1 and type 2 cytokines

Cell source	Cytokine(s)	
	Type 1	Type 2
CD4 <sup>+</sup> T cell	IL-2, IFN- $\gamma$ , IL-12, TNF- $\beta$	IL-4, IL-5, IL-6, IL-10, IL-13
CD8 <sup>+</sup> T cell	IL-2, IFN- $\gamma$	IL-4, IL-5, IL-10
NK cell	IFN- $\gamma$ , TNF- $\beta$	IL-6, IL-10
Monocyte/macrophage	IL-12	IL-6, IL-10
B cell	IL-12, TNF- $\beta$	IL-6, IL-10
Dendritic cell	IL-12	
Neutrophil	IL-12	
Mast cell		IL-4, IL-5, IL-6
Eosinophil		IL-4, IL-5, IL-6

T cells as sources of Th1 and Th2 immunoregulatory cytokines. Our definition of type 1 and type 2 cytokines expands this concept further to include cytokines produced by non-T-cell leukocytes, such as monocytes/macrophages, natural killer (NK) cells, B cells, mast cells, and eosinophils, all of which are now known to produce cytokines originally attributed only to CD4<sup>+</sup> T cells and CD4<sup>+</sup> T-cell clones. We recognize that not all cytokines fit into the categories of type 1 and type 2. Notably, Liles and Van Voorhis (211) have recently written an excellent review of the cellular sources, activities, and nomenclature of 42 cytokines implicated in immune responses. Cytokines, including those within and those outside the type 1 and type 2 categories, form a complex interactive network. Conceptually, however, we believe that understanding the immune response from the perspective of type 1 and type 2 cytokine regulation and dysregulation is of central importance and could afford insights into the pathogenesis and therapy of multiple human diseases.

#### TYPE 1-TYPE 2 CYTOKINE NOMENCLATURE AND HUMAN DISEASES

The type 1-type 2 cytokine nomenclature emphasizes the function of a cytokine rather than the CD4<sup>+</sup> T cell as the sole source of the cytokine. In this nomenclature (72), a type 1

response is defined as a strong cellular immune response with normal or increased levels of IL-2, IFN- $\gamma$ , TNF- $\beta$ , and/or IL-12 while a type 2 response is defined as an impaired cellular response with an increase in one or more B-cell activities (e.g., hypergammaglobulinemia, autoantibody production, or hyper-IgE) and an increase in the level of IL-4, IL-5, IL-6, IL-10, and/or IL-13. This nomenclature encompasses both CD8<sup>+</sup> and CD4<sup>+</sup> T-cell as well as non-T-cell sources of these cytokines and emphasizes as the defining characteristic the functional responses that a cytokine modulates rather than its cell of origin (Table 1; Fig. 1). Importantly, in this definition the emphasis is on a relative predominance of type 1 (CMI) or type 2 (humoral immunity) cytokines and not on an absolute dichotomy (presence or absence) of either type of cytokine. Since there is a spectrum of disease severity for many human pathologic conditions, there is likely to be a spectrum of cytokine production and imbalance, or cytokine dysregulation, at different stages of diseases.

We review the rapidly expanding literature in which the concept of type 1 and type 2 cytokine dysregulation in human disease states has been studied (95, 160, 218, 219, 295, 316, 317, 359). We strongly emphasize that the purpose of this review is heuristic, i.e., to review diseases whose type 1 and type 2 cytokine responses have been analyzed, to examine therapeutic implications, and to attempt to identify human diseases in which a predominance of one or the other cytokine response profiles is likely on the basis of clinical features or by extrapolation from animal models. For example, eosinophilia, particularly when associated with increased IgE production, suggests a type 2 cytokine predominance with increased production of IL-5 (eosinophilia) and IL-4 (or IL-13) (IgE). Hypergammaglobulinemia due to increased IgG levels should also suggest a possible excess of type 2 cytokines, namely, IL-6 and IL-10. Conversely, conditions characterized by a delayed-type hypersensitivity (DTH) form of granulomatous immune response suggest a type 1 cytokine environment and increased IFN- $\gamma$  production (Fig. 1). It is possible to conceptualize novel therapeutic approaches based on restoring the balance between type 1 and type 2 cytokines in diseases in which cytokine dysregulation has resulted in either a predominant type 1 or type 2 cytokine profile.

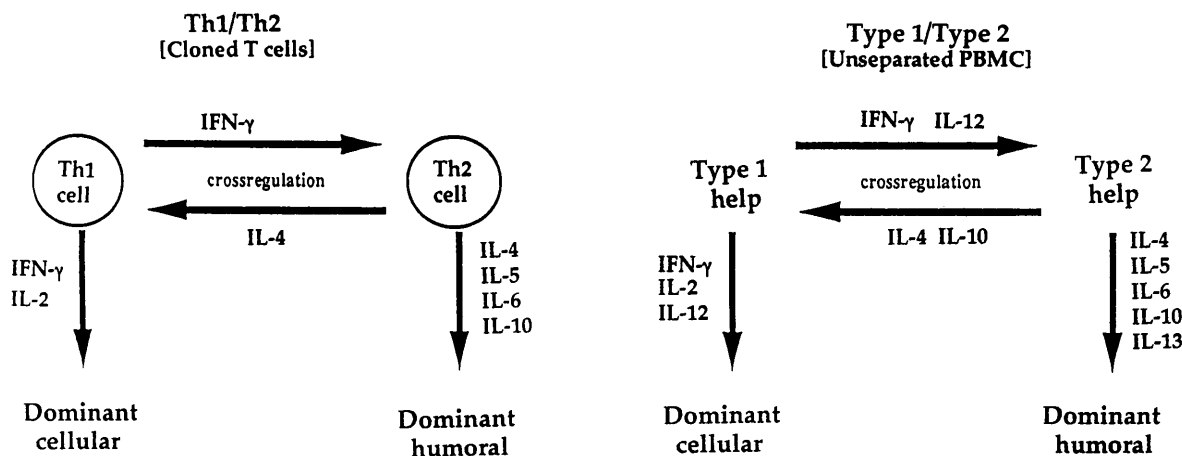


FIG. 1. Comparison of nomenclature for Th1 and Th2 cytokines produced by cloned CD4<sup>+</sup> Th cells and type 1 and type 2 cytokines produced by primary cultures of leukocytes of all types. The emphasis in the newer type 1-type 2 nomenclature is on the functional effects of the cytokines, independent of their cells of origin, and does not rely on cloned cells. Both Th1 and type 1 cytokines elicit predominantly CMI, whereas Th2 and type 2 cytokines elicit predominantly humoral immunity. At the same time, some Th1 (IFN- $\gamma$ ) and type 1 (IFN- $\gamma$ , IL-12) cytokines downregulate humoral immunity by decreasing the levels of Th2 and type 2 cytokines (horizontal arrows pointing to the right). Conversely, some Th2 (IL-4) and type 2 (IL-4, IL-10) cytokines downregulate CMI by decreasing the levels of Th1 and type 1 cytokines (horizontal arrows pointing to the left).

Much of the current work in this field is exploratory and evolving. Therefore, our discussion includes selected diseases for which, at present, an excess of only one type 1 or type 2 cytokine, rather than all the cytokines in the type 1 or type 2 profile, is apparent. Further investigation will establish whether these conditions truly represent diseases in which type 1 or type 2 cytokines are predominant, particularly if they involve a non-cross-regulatory cytokine (e.g., the role of IL-6 in multiple myeloma or Castleman's syndrome). In this review, only limited data from animal models are cited insofar as initial work in this field was performed with murine models and such work continues to point the way to potentially fruitful avenues of investigation.

Central questions in the examination of human illness from the perspective of type 1-type 2 cytokine imbalance include whether the imbalance is causal in the disease and whether restoration of type 1-type 2 cytokine balance will ameliorate the disease. Methodology can be crucial when studying cytokines in human disease (72, 219, 415); for example, how is cytokine mRNA or protein quantified, what kind of cell stimulation is used (if any), and to which body compartments do the cells under study belong? For example, does the cytokine mRNA level always reflect cytokine protein expression, is constitutive cytokine production more important than inducible cytokine production, and is cytokine production in blood a relevant indicator of cytokine production in lymphoid tissue, mucosal surfaces, spinal fluid, or other body compartments? Answers to these questions, and the ultimate test of whether the type 1-type 2 cytokine paradigm is clinically meaningful, may be determined by whether prevention and therapy of human diseases are improved by intervention strategies based on modulation of the type 1-type 2 cytokine balance.

Many of the diseases to be discussed are due to infectious agents, including viruses such as human immunodeficiency virus type 1 (HIV-1), the measles virus, and respiratory syncytial virus (RSV); mycobacteria such as *Mycobacterium leprae* and *Mycobacterium tuberculosis*; and spirochetes such as *Treponema pallidum* and *Borrelia burgdorferi*. Parasitic diseases such as leishmaniasis, filariasis, and schistosomiasis and fungal diseases such as allergic bronchopulmonary aspergillosis and several systemic mycoses are also discussed. Noninfectious processes to be discussed include neoplasia and atopic states including asthma, autoimmune diseases, and idiopathic inflammatory diseases. The type 1-type 2 cytokine model as applied to transplantation has recently been reviewed in detail (131, 277, 396) and will not be included in this review. Finally, even in some physiologic conditions, such as pregnancy, type 1-type 2 cytokine profiles may be operative, although in a compartmentalized manner. For example, in a murine model, pregnancy has been associated with a predominance of type 2 cytokines at the maternal-fetal interface but not in lymph nodes or spleen (213, 405). Progesterone may play a key role in maintaining fetal allograft survival during normal pregnancy by suppressing cellular immune responses, since this hormone can increase levels of type 2 cytokines (including the cross-regulatory cytokine IL-4) in human CD4<sup>+</sup> T-cell lines and clones (297).

#### TYPE 1 AND TYPE 2 CYTOKINE SOURCES OTHER THAN CD4<sup>+</sup> T CELLS

##### Cells That Produce Type 1 Cytokines

Leukocytes other than CD4<sup>+</sup> T cells which may produce IFN- $\gamma$  include CD8<sup>+</sup> T cells, NK cells, and possibly gamma-delta T cells (60, 122, 172). IL-2 is known to be made only by

T cells, including CD8 (172, 249, 257) and CD4 T cells. TNF- $\beta$  is primarily a T-cell product but may be made by B cells, NK cells, and lymphokine-activated killer (LAK) cells (172). IL-12 is not made by T cells but is made by monocytes, macrophages, B cells, and dendritic cells (384, 385). In addition, Cassatella et al. (54) have recently discovered that human neutrophils stimulated by lipopolysaccharide produce IL-12 and that this production can be increased by IFN- $\gamma$  and inhibited by IL-10. Cross-regulatory cytokines include type 1 cytokines such as IFN- $\gamma$  and IL-12, which can functionally decrease the production of type 2 cytokines, and type 2 cytokines such as IL-4, IL-10, and possibly IL-13, which can functionally decrease the production of type 1 cytokines (62, 71, 72, 239, 266, 293, 350) (Fig. 1; Table 1).

Although IL-15 has not been defined as a type 1 cytokine, to date its activities have been reported to be very similar to those of IL-2. Hence, IL-15 is a candidate type 1 cytokine, but further study is required before it can be included or excluded as such. Whereas IL-2 is exclusively a T-cell product, mRNA for IL-15 has not been found in T cells, although it was found in lipopolysaccharide-stimulated monocytes and in numerous tissues (144). Hence, the cellular sources of IL-2 and IL-15 appear to be different. In vitro studies of IL-15 and the probably identical novel cytokine termed interleukin-T (IL-T) were first published in 1994 (15, 48). The functional activity of IL-15 significantly overlaps that of IL-2 in terms of T-cell proliferation (144, 187), LAK cell induction (144, 227), B-cell proliferation (12, 243) and T-cell chemoattraction (418). Moreover, IL-15 binds to the IL-2 receptor beta and gamma chains but not the alpha chain. IL-15 appears to have its own alpha chain receptor subunit (81, 141, 144). IL-T was identified in the HUT-102 cell line which is infected with human T-cell leukemia virus (HTLV-1). IL-T has been postulated to play a role in adult T-cell leukemia and lymphoma (15, 48).

##### Cells That Produce Type 2 Cytokines

The classic "Th2" cytokines (IL-4, IL-5, IL-6, and IL-10) can be made by an increasingly recognized array of human leukocytes (Table 1). IL-4 can be made by CD8 T cells (347), for example, during the course of HIV-1 infection (232, 287, 349) and leprosy (259, 327). In 1992, Bloom and colleagues applied the term "type 2" to IL-4-producing CD8<sup>+</sup> T cells seen in lepromatous leprosy, discussing them in terms of "suppressor" T cells (33). IL-4 can also be made by human mast cells (37), basophils (230, 341), and eosinophils (261, 278). CD4- and CD8-double-negative gamma-delta T cells may also produce IL-4, as has been reported for murine gamma-delta T cells (122). IL-5 can be made by eosinophils (42, 100, 101), mast cells (37), and CD8<sup>+</sup> T cells (82, 232, 238, 287). IL-6 can be made by monocytes/macrophages, B cells, mast cells, and eosinophils (37, 109, 155). IL-10 is produced by monocytes/macrophages, B cells, and CD8<sup>+</sup> T cells (104, 172). Del Prete et al. have suggested that human, but not murine, type 1 as well as type 2 T-cell clones can produce IL-10 (90). IL-13, which has functional properties similar to those of IL-4 and can inhibit IL-12 and TNF- $\alpha$  production, has been reported only as a product of activated T cells (80, 86, 103, 247, 303). IL-9 is a candidate type 2 cytokine which currently is considered a T-cell product (172).

Murine CD8<sup>+</sup> cytotoxic T cells (CTLs) are capable of becoming CD8 and CD4 double negative and secreting IL-4, IL-5, IL-6, and IL-10, particularly after being cultured in a type 2-dominant environment (i.e., with IL-4) (117, 347). These CTLs then lose their cytolytic activity (117). In related work, Actor and et al. (1, 2) demonstrated that mice infected with

schistosomes have impairment of virus-specific CTLs (i.e., recombinant vaccinia virus expressing HIV-1 gp160 envelope protein), decreased levels of type 1 cytokines, and decreased virus clearance compared with controls not infected with schistosomes. Recently, Coyle et al. (82) demonstrated that murine CD8<sup>+</sup> T cells specific for viral peptides from a respiratory pathogen could shift from type 1 cytokine production to IL-5 production and induce pulmonary eosinophilia after a type 2 cytokine (IL-4) milieu was induced by immunization with ovalbumin and alum adjuvant. The authors propose that a similar mechanism occurs in humans to explain the clinical observation that exacerbations of asthma (eosinophil-predominant airway inflammation and bronchospasm) can occur during viral respiratory infections. Whether this process of CD8<sup>+</sup> T-cell switching to type 2 cytokine production frequently occurs in humans is not yet established, but it has recently been demonstrated in patients with HIV infection with and without the hyper-IgE syndrome (232, 287, 349). A similar event may also occur in leprosy, in which CD8<sup>+</sup> T cells producing IL-4 are also found (33, 259, 260, 327).

#### POTENTIAL FLOW CYTOMETRY MARKERS FOR TYPE 1 AND TYPE 2 CYTOKINE PRODUCTION

The identification of a specific cell surface marker for type 1 or type 2 cytokine-producing cells or the ability to stain for such cytokines intracellularly would greatly facilitate the study of these cells and their role in human diseases. Currently, there are no well-established markers which distinguish type 1 and type 2 cells. Several candidate markers, amenable to study by flow cytometry, have been reported. These markers are primarily for type 2 cells or for Th0/Th2 cells, i.e., cells that produce primarily type 2 cytokines but may produce smaller amounts of type 1 cytokines as well. These putative cell surface markers include CD4<sup>+</sup> CD27<sup>-</sup>, CD4<sup>+</sup> CD7<sup>-</sup>, CD4<sup>+</sup> CD30<sup>+</sup>, and CD8<sup>+</sup> CD30<sup>+</sup>. In addition, direct intracellular detection of cytokines by flow cytometry has been accomplished, in some cases in combination with cell surface marker expression (114). CD ("cluster of differentiation") antigen nomenclature and methods for the detection of CD antigens on cell surfaces have recently been thoroughly reviewed (338).

#### CD27 Negativity

CD27 is a member of the TNF-nerve growth factor receptor superfamily, which includes CD30, CD40, and Fas antigen. Approximately 90% of peripheral blood T cells express CD27. De Jong et al. (87) reported that populations of CD27<sup>-</sup> memory CD4<sup>+</sup> T cells from atopic and nonatopic individuals contained a disproportionately large number of IL-4-secreting cells. However, both CD27<sup>-</sup> and CD27<sup>+</sup> CD4<sup>+</sup> memory T cells produced IFN- $\gamma$ , suggesting that CD27 negativity was not exclusively a specific marker for type 2 CD4<sup>+</sup> T cells. Elson et al. (115) studied CD27 expression on CD4<sup>+</sup> T cells in 21 persons with active helminthic infections, eosinophilia, and increased IgE levels. CD4<sup>+</sup> CD27<sup>-</sup> T cells produced more IL-4 and IL-5 than did CD4<sup>+</sup> CD27<sup>+</sup> T cells, although both phenotypes produced similar amounts of IFN- $\gamma$ . These authors then went on to separate CD4<sup>+</sup> T cells isolated from normal controls and helminth-infected patients into CD27<sup>+</sup> and CD27<sup>-</sup> populations and to use three-color flow cytometry to stain intracellularly for IFN- $\gamma$ , IL-4, and IL-5 after mitogen stimulation. Importantly, they were able to define cells within the CD27<sup>-</sup> population which were Th2, Th1, and Th0 cells (114). Thus, CD27 expression did not differentiate Th1 and Th2 T cells per se, but the majority of cytokine-producing

CD4<sup>+</sup> T cells were in the CD27<sup>-</sup> subgroup. Of interest, they found almost no cells producing both IL-5 and IFN- $\gamma$ , although a small number produced both IL-4 and IFN- $\gamma$ . They suggested that expression of type 2 cytokines might impair the ability of the host to respond with type 1 cytokine expression, a concept consistent with the findings of other investigators (1, 2, 33, 82, 117, 232, 349).

#### CD7 Negativity

CD7 is the earliest T-cell differentiation antigen and in normal controls is absent from approximately 10% of CD4<sup>+</sup> T cells. Autran et al. (14) have reported that human CD4<sup>+</sup> T cells that are CD7<sup>-</sup> have a Th0/Th2-like cytokine profile. Stimulated CD4<sup>+</sup> CD7<sup>-</sup> T cells from both normal controls and HIV-seropositive persons produced more IL-4 and IL-10 and less IL-2 than did CD4<sup>+</sup> CD7<sup>+</sup> T cells. The authors addressed whether their CD4<sup>+</sup> CD7<sup>-</sup> cells were also CD4<sup>+</sup> CD27<sup>-</sup> and found that most were not. The cytokine profile of the CD4<sup>+</sup> CD7<sup>-</sup> cells was also the same for CD4<sup>+</sup> CD7<sup>-</sup> clones. These investigators had previously found that the population of CD4<sup>+</sup> CD7<sup>-</sup> cells was expanded during HIV-1 infection, suggesting that they may play a role in type 1-type 2 cytokine imbalance.

#### CD30 Positivity

Like CD27, CD30 is a member of the TNF-nerve growth factor receptor superfamily (120). The CD30 ligand is homologous to TNF- $\alpha$ , TNF- $\beta$ , and the CD40 ligand (364). CD30 was originally termed the Ki-1 antigen when it was first described on the Reed-Sternberg cells of Hodgkin's disease (HD) (342). CD30 is a cellular activation marker that is inducible on human T and B cells (112, 368). Cell membrane expression of CD30 and soluble CD30 (sCD30) in serum has recently been proposed by Romagnani and colleagues to be a potential marker for Th2 cells (89, 94, 238). They have reported preferential type 2 cytokine production by both CD4<sup>+</sup> and CD8<sup>+</sup> human T cells as well as increases in sCD30 levels in conditions associated with type 2 cytokine predominance.

Del Prete et al. (89) studied human CD4<sup>+</sup> Th1, Th2, and Th0 clones, as well as T cells activated by antigens in vitro, and demonstrated that CD30 expression is highest on Th2 clones and antigen-stimulated T cells expressing only type 2 cytokines. Th1 clones and antigen-stimulated T cells expressing only type 1 cytokines expressed minimal or no CD30, and Th0 clones expressed an intermediate level of CD30. In addition, a small subpopulation of allergen-reactive type 2 T cells expressing CD30 could be demonstrated in the peripheral blood of patients with allergic symptoms. CD30 expression by human CD8<sup>+</sup> T-cell clones that produce increased levels of IL-4 and IL-5 and decreased or absent levels of IFN- $\gamma$  has also been reported by Manetti et al. in persons with HIV-1 infection (238). CD8<sup>+</sup> T-cell clones from normal controls did not express CD30 and produced IFN- $\gamma$  but no IL-4.

Increased levels of sCD30 in serum correlate with the prognosis in untreated patients with Hodgkin's disease and are a predictor of progression in HIV-mediated disease (301). In addition, Del Prete et al. discuss preliminary evidence for increases in sCD30 levels in a variety of diseases that may be associated with type 2 cytokine predominance, e.g., HIV-1 infection, measles, atopy, systemic lupus erythematosus (SLE), and Ommen's syndrome (94).

At the same time, Alzona et al. have reported that CD30<sup>+</sup> T cells are activated by IL-12 to produce the type 1 cytokine IFN- $\gamma$  (7). They reported that CD30<sup>+</sup> human T cells can produce both IFN- $\gamma$  and IL-5, as well as preferentially increase

B-cell activity (6). One further consideration is that Yssel et al. have recently shown that IL-12 can stimulate IFN- $\gamma$  production even from human Th2 clones, although this production is not maintained in the absence of IL-12 (427). Therefore, whether CD30 is a strict marker for type 2 cytokine-expressing cells requires further investigation. In summary, continued efforts toward defining surface markers for type 1 and type 2 cells, as well as validating the novel techniques of intracellular cytokine staining discussed above and those of Andersson and colleagues (11, 114), are required.

### MONOCYTES/MACROPHAGES IN THE TYPE 1-TYPE 2 CYTOKINE MODEL

The role of the monocyte/macrophage within the conceptual framework of type 1-type 2 cytokine imbalance is being increasingly appreciated (55, 202, 219, 339, 345). Monocytes/macrophages, as a source of immunoregulatory cytokines, were excluded from the original murine Th1-Th2 cytokine nomenclature in terms of being cellular sources of Th1 and Th2 cytokines. However, they were included in the initial Th1-Th2 paradigm as critical effector cells for DTH reactions and CMI. The Th1 cytokine IFN- $\gamma$  is recognized to activate monocytes/macrophages for CMI responses against pathogens. Monocytes/macrophages are sources of diverse cytokines, can often be infected (and possibly subverted) by pathogens that are associated with type 1-type 2 cytokine dysregulation, and may act via their function as antigen-presenting cells (APCs) to preferentially direct type 1 or type 2 cytokine production.

#### Source of Type 1 and Type 2 Cytokines

Monocytes/macrophages produce some of the cytokines associated with type 2 Th cells, such as IL-6 and IL-10. In response to IFN- $\gamma$ , they release proinflammatory cytokines such as TNF- $\alpha$  and IL-1, which interact with type 1 and type 2 cytokines as part of the complex interregulatory cytokine networks (163, 403). For example, monocyte TNF- $\alpha$  can stimulate IL-10, which in turn downregulates TNF- $\alpha$  production (403). Macrophages also produce IL-12, which is not made by T cells but which is associated with stimulation of IFN- $\gamma$  production and development of type 1 Th cells (60, 61, 68, 216, 384, 385). Furthermore, monocyte production of IL-10 and IL-12 can have opposite and cross-regulatory effects on each other and on type 1 and type 2 Th-cell populations.

#### Target for Intracellular Pathogens and Effector for Granuloma Formation

Many of the infectious-disease organisms that are intracellular pathogens can infect monocytes/macrophages, e.g., HIV-1, measles virus, mycobacteria, and *Leishmania*, *Brucella*, *Listeria*, and *Histoplasma* spp. Monocyte/macrophage cytokine production and effector function can be altered by such infections and by monocyte/macrophage interactions with T cells. Monocytes may influence the development of type 1 or type 2 T-cell responses (e.g., via IL-12 or IL-10, respectively), and, in turn, monocyte effector function may be influenced by these Th-cell subsets (e.g., via IFN- $\gamma$ , IL-4, IL-10, or IL-13).

The macrophage is a critical cell in the granulomatous immune response. Granulomas form in response to infectious and noninfectious processes, under conditions in which both type 1 and type 2 cytokines predominate. For example, granuloma formation occurs with mycobacterial infections, fungal infections, syphilis, brucellosis, cat scratch disease, Whipple's disease, sarcoidosis, berylliosis, giant cell (temporal) arteritis, Wegener's granulomatosis, lymphomatoid granulomatosis,

inflammatory bowel disease (Crohn's disease and ulcerative colitis), schistosomiasis, Hodgkin's disease, and many other conditions. Most of the above conditions have clinical or pathological features that could warrant investigation from the perspective of type 1-type 2 cytokine dysregulation, highlighting the importance of the monocyte/macrophage in this cytokine model of disease pathogenesis.

### Antigen-Presenting Cell and Source of Costimulatory Molecules

In some animal models, monocytes/macrophages have been reported to act preferentially as APCs for distinct Th-cell populations (usually favoring type 1 responses) (55, 127, 339, 345). Secrist et al. (345) have shown that allergens presented by B cells elicit more IL-4 from CD4<sup>+</sup> T cells of patients with atopic conditions than do monocytes. Notably, low concentrations of these allergens also elicited higher levels of IL-4 than did high concentrations. The role of costimulatory molecules in the determination of type 1 or type 2 cytokine responses to APC-T-cell interactions in humans has begun to be studied and may provide insight into whether specific APCs (monocytes/macrophages, B cells, dendritic cells, eosinophils) preferentially direct the immune response toward type 1 or type 2 cytokine responses.

For example, using animal models, Kuchroo et al. (202) studied the effect of the potent family of APC costimulatory molecules (B7-1 [CD80] and B7-2 [CD86]) on the development of type 1 or type 2 cytokine-producing T cells from their undifferentiated precursor Th cell (Thp). They found that B7-1 acted as a costimulatory molecule for the generation of T cells producing type 1 cytokines and that antibodies against B7-1 resulted in inhibition of such type 1 T cells. The converse occurred with B7-2 and T cells producing type 2 cytokines. The authors provided evidence that manipulation of the interaction between B7-1 and B7-2 on APCs with their shared counterreceptors on T cells (CD28 and CTLA-4) could be used in the treatment of autoimmune diseases (202).

### Source of Nitric Oxide or Analogous Effector Molecules for Type 1 Cytokine-Driven Immune Responses

Murine macrophages are recognized to produce nitric oxide (NO) in response to type 1 cytokines (IFN- $\gamma$  and/or IL-12) and thereby use NO as an effector molecule to destroy or control certain infectious agents. For example, NO is a potent cytotoxic monocyte/macrophage effector molecule, e.g., for *Leishmania* spp. and schistosome parasites (118, 148). NO appears to mediate the Th1 protection against rodent malaria (346, 377), to be stimulated by IFN- $\gamma$  in order to inhibit replication of several murine viruses (180), and to be inhibited by IL-10 and stimulated by IFN- $\gamma$  in a parasite model (136). Taylor-Robinson et al. have reported that although murine macrophages produce NO in response to IFN- $\gamma$ , murine CD4<sup>+</sup> type 1 T cells alone can produce NO in response to antigenic or mitogenic stimuli (377).

In humans, however, production of NO from monocytes or other leukocytes has been difficult to detect (270, 340), although it has been reported in selected circumstances (98, 176, 241, 406). The level of NO is increased in the serum of patients receiving IL-2, a type 1 cytokine, as therapy for cancer (164, 279). The cellular source of this NO, however, is unknown. In response to NO, human peripheral blood mononuclear cells (PBMCs) are activated and TNF- $\alpha$  production is increased (206). Recently, macrophage expression and ligation of the low-affinity IgE receptor (CD23) have been implicated in the production of NO by mature monocytes/macrophages (108).

Other work has unsuccessfully attempted to explain the apparent lack of monocyte/macrophage NO as being due to insufficient tetrahydrobiopterin or excessive transforming growth factor  $\beta$  (273, 406). Even neopterin, a nonspecific marker of macrophage activation with no definite biologic function (223, 400, 407), has been implicated in the enigma of human monocyte/macrophage NO production (273).

Ongoing studies will further clarify the conditions under which human monocytes/macrophages make NO. However, patients with conditions in which excess IFN- $\gamma$  is found (e.g., temporal arteritis, multiple sclerosis, sarcoidosis, Graves' disease, Hashimoto's thyroiditis) may be the most fruitful to examine for cytokine-inducible macrophage NO. Alternatively, if NO is a macrophage effector molecule modulated by the type 1-type 2 cytokine network in mice but not in humans, a critical question is which molecule in humans serves the function of murine macrophage NO.

### EOSINOPHILIA AND INCREASED IgE LEVELS SUGGEST A TYPE 2 CYTOKINE-DOMINANT STATE

Clinical conditions that are characterized by increased IgE levels (suggesting an increased ratio of IL-4 or IL-13 to IFN- $\gamma$ ) and blood or tissue eosinophilia (suggesting increased levels of IL-5) are likely candidates for type 2 cytokine-predominant states. Examples of these conditions include Ommen's syndrome, the hypereosinophilic syndrome (HES), Kimura's disease, Job's syndrome, Wells' syndrome, atopic conditions, helminthic parasite infections, and other illnesses associated with tissue or blood eosinophilia. Diseases in which either the IgE level or eosinophilia is increased also suggest increased levels of either IL-4 or IL-5 (respectively), while the presence of both of these type 2 cytokines is more consistent with the classically defined Th2 profile of cloned CD4<sup>+</sup> T cells since they produce both cytokines. IL-4 is a cross-regulatory cytokine, whereas IL-5 is not; therefore, in disease conditions with high IgE levels and eosinophilia, patients may be more likely to have decreased levels of type 1 cytokines such as IFN- $\gamma$ .

Increased IgE levels in serum and blood or tissue eosinophilia occur in helminthic parasite infections and atopic conditions, as well as in a large number of more unusual diseases. Some of these conditions are idiopathic, and no effective therapy is available, or therapy is limited to steroid administration, with its associated side effects. Consideration of these diseases as ones in which type 2 cytokines predominate may lead to novel methods of therapy or immunization based on optimizing cytokine production and balance.

#### Ommen's Syndrome

Ommen's syndrome is a congenital immunodeficiency syndrome characterized by elevated IgE levels, hypereosinophilia, impaired T-cell proliferation response to soluble antigens and mitogens, frequent infections, erythroderma, and failure to thrive. Schandene et al. (333) reported a child with Ommen's syndrome whose CD4<sup>+</sup> CD45 RO (memory) T cells produced high levels of IL-4 and IL-5 but minimal levels of IFN- $\gamma$  upon stimulation with ionophore and phorbol 12-myristate 13-acetate (PMA). These cells also produced high levels of IL-5 constitutively. Moreover, mRNA for IL-4, IL-5, and IL-10 but not IL-2 or IFN- $\gamma$  was present in PBMCs. Administration of exogenous IFN- $\gamma$  resolved the eosinophilia, and mRNA for IL-5 and IL-10 disappeared from PBMCs. The IgE levels in serum and mRNA for IL-4 did not change, although the patient's overall clinical status improved. Definition of the ge-

netic basis for Ommen's syndrome might offer insights into the mechanism of development of CD4<sup>+</sup> Th2-like T cells.

#### Hypereosinophilic Syndrome

Some cases of HES may be due to a clonal proliferation of CD4<sup>+</sup> type 2 T cells and may be amenable to cytokine therapy (75, 184). Cogan et al. reported on a patient with HES and increased IgE levels who had clonal proliferation of CD4<sup>+</sup> CD2<sup>+</sup> CD3<sup>-</sup> T cells which produced excess IL-4 and IL-5 but reduced levels of IFN- $\gamma$  and IL-2 (75). Treatment with IFN- $\alpha$  resulted in a decline in eosinophilia and CD4<sup>+</sup> CD3<sup>-</sup> cells but no change in the IgE level in serum. Preliminary data by Simon and Blaser (362) on another patient with HES suggest that CD4<sup>-</sup> CD8<sup>-</sup> CD3<sup>+</sup> T cells can also overproduce IL-4, IL-5, and IL-6. The recent review on HES by Weller and Bubley (410) emphasizes that HES is a clinically heterogeneous condition. Some patients have increased IgE levels, while others do not. Therapy usually consists of either steroids or cytotoxic agents (e.g., hydroxyurea), while IFN- $\alpha$  has been tried with success in some patients. IFN- $\alpha$  has been reported to inhibit the IL-4-mediated induction of IgE in vitro and to increase IFN- $\gamma$  production from CD4<sup>+</sup> T cells, thereby increasing the ratio of type 1 to type 2 cytokines (40, 296). Further investigation will determine the frequency of clonally expanded type 2 T cells in patients with HES.

#### Kimura's Disease

Kimura's disease is an idiopathic disease characterized by eosinophilia, increased IgE levels, and usually localized subcutaneous nodules and lymphadenopathy (268). Enokihara et al. (116) reported that peripheral blood lymphocytes express mRNA for IL-5. High levels of eosinophil proteins in serum have also been found in patients with this disease (263). Tabata et al. (373) reported a patient with Kimura's disease who had markedly increased levels of CD4<sup>+</sup> HLA-DR<sup>+</sup> T cells in the blood and lymph nodes. To our knowledge, further study of Kimura's disease from the perspective of a type 2 cytokine-predominant state has not been published. We postulate that Kimura's disease is a prime candidate for consideration as a disease characterized by excessive IL-4 and IL-5 levels and impaired IFN- $\gamma$ , IL-2, and/or IL-12 production and has the potential for therapeutic intervention with one or more of these type 1 cytokines or with IFN- $\alpha$ .

#### Job's Syndrome

Job's syndrome, or hyper-IgE syndrome with recurrent infections, is characterized by high levels of IgE (>2,000 IU/ml), eosinophilia, eczema, and sinopulmonary infections. Investigations of hyper-IgE syndrome have shown defects in IFN- $\gamma$  production and possible clinical benefit with IFN- $\gamma$  therapy (97, 189, 287, 288). While Job's syndrome can occur in infancy and childhood, it has recently also been recognized in patients with HIV-1 infection and AIDS. Maggi et al. (232) derived T-cell clones from blood and skin of HIV-seropositive patients with Job's syndrome which were either CD8<sup>+</sup> CD3<sup>+</sup> or CD4<sup>-</sup> CD8<sup>-</sup> CD3<sup>+</sup>. Most cells produced IL-4 and IL-5 but not IFN- $\gamma$ . In addition, they provided B-cell help for IgE synthesis and had diminished cytolytic activity. Paganelli et al. (287) studied three patients with AIDS, hyper-IgE syndrome, and hypereosinophilia. They found that CD8<sup>+</sup> T-cell clones derived from peripheral blood T cells could produce type 2 cytokines (IL-4, IL-5, and IL-6), which probably accounted for the patients' hyper-IgE and eosinophilia. This phenotypic and functional profile is reminiscent of murine CD8<sup>+</sup> T cells which

developed into CD4<sup>-</sup> CD8<sup>-</sup> cells, became noncytolytic, and produced IL-4, IL-5, and IL-10 but not IFN- $\gamma$  when stimulated with mitogens or alloantigens in the presence of IL-4 (117). Earlier, Seder et al. (347) had found that when naive CD8<sup>+</sup> T cells were stimulated by anti-CD3 antibody in the presence of IL-4, the CD8<sup>+</sup> T cells produced IL-4 after restimulation (347). Thus, in diseases characterized by high levels of IgE and/or eosinophilia, not only CD4<sup>+</sup> T cells but also CD8<sup>+</sup> T cells and CD4<sup>-</sup> CD8<sup>-</sup> T cells may be responsible for elevated production of IL-4 and/or IL-5.

### Wells' Syndrome

Wells' syndrome is an idiopathic disorder characterized by eosinophilic cellulitis with "flame figure" granulomas and increased levels of IgE in serum (289). From these observations, we postulate that increased levels of IL-4 and IL-5 contribute to the abnormalities seen in this disease. Cytokine-based novel therapeutic approaches would be directed toward lowering the levels of type 2 cytokines and/or increasing the levels of type 1 cytokines. To our knowledge, however, cytokine profiles have not been studied in these patients. As with many of the idiopathic, eosinophilic diseases, treatment is primarily symptomatic and may include the use of systemic steroids.

### Other Conditions Associated with Eosinophilia and/or Increased IgE Levels

Field et al. (123) extensively studied a patient with increased IgE and IgG4 levels, eosinophilia, chronic allergic symptoms, and seropositive rheumatoid arthritis and found evidence for an expansion of the number of CD4<sup>+</sup> Th2 memory T cells in peripheral blood. By PCR, mRNA levels for IL-4 and IL-5 were found to be increased, as was production of IL-4 by stimulated lymphocytes. In the memory CD4<sup>+</sup> T-cell population more than twice as many cells were transcribing IL-4 as were transcribing IFN- $\gamma$ . The authors concluded that human Th2 CD4<sup>+</sup> T cells do occur in vivo, with the expected clinical manifestations.

Cytokine data from other conditions in which increased IgE levels and eosinophilia occur, including the broad categories of helminthic parasite infections and allergic states including the atopic form of asthma, will be discussed below. Other diseases characterized by eosinophilia and/or increased IgE levels, such as the 1981 toxic oil syndrome in Spain (134, 378), the 1989 eosinophilia-myalgia syndrome in the United States (285), and the panoply of organ- and tissue-specific eosinophil disorders (e.g., eosinophilic fasciitis, vasculitis, gastroenteritis, pneumonia/pneumonitis, and Churg-Strauss vasculitis with asthma and eosinophilia), are also a priori candidates for type 2 cytokine-predominant states and candidates for cytokine-based therapies.

### EOSINOPHILS AS CONTRIBUTORS TO A TYPE 2 CYTOKINE-DOMINANT STATE

Unlike monocytes, eosinophils are not known to make any type 1 cytokines, to be infected by any infectious agents, or to function as APCs in vivo. However, they have the capacity to produce type 2 cytokines (IL-4, IL-5, and IL-6) (100, 101, 155, 278) and TNF- $\alpha$  (126). Lucey et al. originally found that mature eosinophils can express class II major histocompatibility complex (MHC) molecules (226), and subsequently these cells have been shown to function as APCs in vitro (88, 157, 244, 412). Interestingly, type 2 cytokines have been proposed to play a role in the development and maintenance of eosinophil states by inhibition of eosinophil programmed cell death. Si-

mon and Blaser (362) have recently discussed this hypothesis, specifically with regard to HES and atopic diseases, including asthma. Type 2 cytokines may inhibit programmed cell death signals within eosinophils (162, 369).

### Eosinophils as a Source of Type 2 but Not Type 1 Cytokines

Since eosinophils have the capacity to produce IL-4, IL-5, and IL-6 but are not known to produce IL-2, IFN- $\gamma$ , or IL-12, they may contribute directly to a type 2 cytokine milieu in blood or tissues as well as serve as a marker for such an environment. By contributing directly to the creation and maintenance of a type 2 cytokine milieu, eosinophils might also be responsible for conversion of CD8<sup>+</sup> cytolytic (type 1 cytokine-dominant) T cells into noncytolytic T cells producing IL-4 or IL-5, as described for Job's syndrome and HIV-1 infection, as well as in several animal models of disease (1, 2, 82, 117). A shift from the normally type 1 cytokine-producing CD8<sup>+</sup> CTLs to noncytolytic type 2 cytokine-producing T cells may impair the ability to control infections that require a type 1 cytokine response and/or CTLs. An inverse relationship between cytolytic activity and the ability to provide help for Ig synthesis by Th1-like T cells has been previously established (93).

### Eosinophils as Antigen-Presenting Cells Eliciting Type 2 Cytokine Responses

Eosinophils might further contribute to a type 2 cytokine milieu if they function in vivo as APCs for antigens that preferentially elicit type 2 cytokine responses. Candidate antigens for such a hypothesis might include allergens, parasite antigens, and some viral and fungal antigens. Mature human eosinophils are known to express class II MHC in vitro (157, 226) and in vivo, particularly in a compartmentalized or organ-specific manner (23, 156, 310). For example, Beninati et al. demonstrated that eosinophils obtained by bronchoalveolar lavage from a person with chronic eosinophilic pneumonia expressed HLA-DR although peripheral blood eosinophils did not express HLA-DR (23). Several laboratories have now demonstrated that eosinophils can function as APCs for conventional antigens (88, 157, 244, 412). In addition, Mawhorter et al. have demonstrated that eosinophils expressing class II MHC antigens can interact with superantigens, thereby causing CD4<sup>+</sup> T-cell proliferation (244). If eosinophils function as APCs in vivo, we hypothesize that they can function preferentially to elicit a type 2 cytokine response.

In contrast to monocytes/macrophages, there are no known intracellular pathogens that infect eosinophils. Eosinophil bone marrow precursors cultured in IL-5 express CD4 and can be infected with some strains of HIV-1 (132). A subpopulation of eosinophils has been reported to express, or be induced to express, low levels of CD4 (220, 307, 309, 313, 409) and thereby bind the HIV-1 gp120 envelope protein (220). Such eosinophils can be infected with a laboratory-adapted strain of HIV-1 in vitro (411). HIV-1 field isolates have not been tested for infectivity in vitro, nor have HIV-1 subtypes ("clades") from areas of the world where eosinophilia due to helminthic parasites is common and where the ability of HIV-1 to infect eosinophils may be more likely. The clinical relevance of these in vitro infection studies is unclear, however, since only one report has suggested that eosinophils from HIV-seropositive patients are infected in vivo with the virus (77). However, if eosinophils can express CD4 in vivo but not be infected with HIV-1, they are unique among CD4<sup>+</sup> leukocytes. Defining the mechanism of such resistance to in vivo infection could provide insight into viral entry, HIV-1 replication, and/or anti-HIV-1 effects of eosinophil proteins.

TABLE 2. Infectious agents associated with a predominance of type 1 or type 2 cytokines

Agent	Examples
Viruses .....	Measles virus, RSV, HIV-1, hepatitis B virus (CAH)
Bacteria.....	<i>Mycobacterium leprae</i> , <i>Mycobacterium tuberculosis</i> , <i>Mycobacterium avium</i> complex, <i>Brucella abortus</i> , <i>Listeria monocytogenes</i> , <i>Legionella pneumophila</i> , <i>Yersinia enterocolitica</i> (synovitis), <i>Chlamydia trachomatis</i> (synovitis), <i>Borrelia burgdorferi</i> (synovitis), <i>Treponema pallidum</i>
Parasites.....	<i>Leishmania braziliensis</i> , <i>Leishmania donovani</i> , <i>Onchocerca volvulus</i> , <i>Loa loa</i> , <i>Wuchereria bancrofti</i> , <i>Brugia malayi</i> , <i>Schistosoma mansoni</i> , <i>Toxocara canis</i>
Fungi .....	<i>Aspergillus fumigatus</i> (allergic bronchopulmonary form), <i>Candida albicans</i> , <i>Cryptococcus neoformans</i> , <i>Blastomyces dermatitidis</i> , <i>Paracoccidioides brasiliensis</i> , <i>Coccidioides immitis</i> , <i>Histoplasma capsulatum</i>

No information is available on whether tissue-dwelling eosinophils (only 1% of eosinophils reside in the blood; the remainder are in the tissues) are infected by HIV-1 or whether patients with advanced AIDS and eosinophilia are more likely to have HIV-infected eosinophils. Finally, since eosinophils may be able to express low levels of CD4, bind HIV-1 gp120, and possibly be infected by HIV-1, they may also serve as APCs for gp120 or other HIV-1 antigens. If such APC activity resulted in type 2 cytokine (e.g., IL-4) production, the production of type 1 cytokines by CD8<sup>+</sup> CTLs could be impaired, as suggested in other experimental systems (1, 2, 82, 117).

## INFECTIOUS DISEASES

### Viral Diseases

Human infectious diseases, including those caused by selected viruses, mycobacteria, bacteria, parasites, and fungi, will be viewed from the perspective of type 1-type 2 cytokine balance (Table 2). Recent information from studies of four viral infections will be discussed: HIV-1 infection, measles, RSV infection, and chronic active hepatitis (CAH) caused by hepatitis B virus.

**Human immunodeficiency virus infection and AIDS.** HIV-1 has been studied recently from the perspective of type 1 and type 2 cytokine profiles. One of the first suggestions that the immune system of patients with AIDS might involve immune dysregulation rather than immune deficiency was the study of Mildvan et al. in 1982, in which the B-cell compartment of AIDS patients appeared to be relatively intact compared with T-cell function (253). It is noteworthy that these investigators suggested that the immune defect of AIDS patients might reside in a subpopulation of helper cells involved mainly in cellular responses and that this suggestion was made in an AIDS study 4 years before Mosmann and Coffman (266, 267) published their Th1-Th2 model, based on murine CD4<sup>+</sup> T-cell clones. Subsequently, Romagnani's laboratory (314) demonstrated that Th1 and Th2 clones that produce IFN- $\gamma$  and IL-4, respectively, could be isolated from human peripheral blood. The same laboratory reported in 1987 that cloned PBMC from patients with AIDS exhibit reduced IL-2 and IFN- $\gamma$  production but enhanced helper activity for IgG synthesis (233).

A number of investigators have noted hypergammaglobulinemia and abnormalities in B-cell activity as part of HIV infection and AIDS (207, 221, 305). In 1983, Lane et al. (207) were one of the first groups to report aberrant B-cell activation

in patients with advanced HIV infection or AIDS (207). In a later study of 853 HIV-seropositive patients representing all stages of HIV-1 disease, Lucey et al. found that the total IgG level in serum increased beginning in the early stage of HIV disease whereas increases in total IgA levels in serum occurred at a later stage of disease and levels of IgM in serum did not significantly increase (221). In a related study of 622 HIV-seropositive patients, total IgE levels in serum also increased primarily at a late stage, similarly to the pattern for IgA levels in serum (229).

Concurrently, other laboratories observed that Th-cell function, assessed by proliferation or IL-2 production in response to recall antigens (including HIV synthetic peptides), anti-CD3 monoclonal antibody, HLA alloantigens, and T-cell mitogens was deficient, even in asymptomatic HIV-seropositive individuals with near-normal CD4 counts (73, 74, 140, 250, 252, 355).

On the basis of the above findings, early data showing an increase in mitogen-stimulated IL-4 (67) and IL-10 (65) production concomitant with loss of proliferative and IL-2 responses to recall antigens, and the Th1-Th2 model noted above, it was suggested that cytokine imbalance contributed significantly to AIDS progression and was associated with a switch or shift from a dominant Th1-like to a dominant Th2-like cytokine profile (71, 72, 298, 328, 356). This hypothesis has led to increased interest, experimentation, and controversy concerning the role of immunoregulatory cytokines in HIV infection and AIDS progression. The controversy stems from discordant findings from different laboratories concerning the expression of Th1 and Th2 cytokine mRNA and protein production. Thus, the laboratories of Fauci and Romagnani concluded that there was no switch or shift from a dominant-Th1 (IFN- $\gamma$ ) to a dominant-Th2 (IL-4) cytokine profile (147, 234) whereas the data from other laboratories favor a Th1-to-Th2 shift (16, 251, 275).

Subsequent studies have suggested that helper cells of the Th0 phenotype, producing both IFN- $\gamma$  and IL-4 but with overproduction of IL-4, are detected in HIV-infected individuals (234, 318, 398, 399). Other immunoregulatory cytokines also appear to play a role in progression to AIDS, as IL-12 production (produced by monocytes/macrophages) was decreased in HIV-positive patients (59) and addition of exogenous IL-12 to cultures of PBMC from HIV-positive individuals restored Th responses to recall antigens in approximately 70% of the patients tested (68). These complexities of immunoregulatory cytokine production by multiple cell types led to a modification of the Th1-Th2 AIDS hypothesis to the type 1-type 2 model of resistance and susceptibility to HIV infection and AIDS progression (72). This model is not limited to CD4<sup>+</sup> T-cell clones but includes cytokines produced by various cell types and the effects of these cytokines on Th-cell function which modulate cellular and humoral immunity (72, 357). Thus, type 1 cytokines, including IFN- $\gamma$ , IL-2, IL-12, and possibly IL-15, augment mainly cellular immune effector responses, whereas IL-4, IL-5, IL-6, IL-10, and possibly IL-13 enhance mainly antibody responses.

Part of the controversy about cytokine regulation of immune responses in HIV infection can be attributed to the issue of Th1-Th2 versus type 1-type 2. IL-4, the cytokine that defines Th2 clones, appears to exhibit transient rather than prolonged production in HIV-infected individuals (67, 71). In contrast, IL-10, a type 2 cytokine that downregulates CMI, is produced for an extended period during AIDS progression. Thus, assessment of only IL-4 expression or production at a single point in the progression to AIDS could lead to the conclusion that there is no switch or shift to Th2 with HIV disease progression. It is possible that a transient increase in IL-4 production pre-

cedes a more extensive increase in IL-10 production. We believe that two of the major immunoregulatory cytokines that control the progression to AIDS will turn out to be IL-12 and IL-10 (72). In this context, it is noteworthy that PBMC from HIV-infected individuals exhibit reduced expression and production of IL-12 concomitant with increased expression and production of IL-10 (63). Therefore, we favor the use of the type 1-type 2 model and terminology in describing the dynamics of immune modulation in HIV infection and AIDS. A similar cytokine regulation profile involving IL-12 versus IL-10, rather than IFN- $\gamma$  versus IL-4 (the classic Th1 and Th2 cytokines), may accompany other diseases and conditions in which immune dysfunction is a characteristic.

Are the changes in T-cell function and cytokine profiles noted above predictive of clinically relevant events? We demonstrated that loss of the ability to respond to recall antigens (as well as other stimuli) was predictive of a significant decline in the CD4 count during the subsequent 1 to 2 years (225). It was subsequently found by several groups that loss of T-cell function was predictive of the time to AIDS diagnosis (105, 323, 335).

Are there clinical parameters that support this type-1-to-type-2 shift in progression to AIDS? The loss of delayed-type skin reactivity has been found to be a marker for progression (29, 242). On the other side of immune regulation, several laboratories have reported hyper-IgE associated with progression toward AIDS (177, 229, 393, 394, 419). Furthermore, a surprisingly high frequency of atopic conditions and allergic drug reactions have been observed during progression to AIDS (150, 291, 363). Eosinophilia, suggesting increased production of IL-5, has also been reported (107, 365) and levels of eosinophil cationic proteins in serum increase as disease progresses (286). Thus, clinical parameters such as loss of skin DTH and increases in IgE levels and eosinophilia have been observed that are consistent with a type-1-to-type-2 cytokine shift.

Are there virologic and immunologic parameters that can be accounted for by protective cellular immunity and a dominant type 1 cytokine profile? During the acute phase of HIV infection, the dramatic decline in levels of HIV in plasma is paralleled by a strong cellular immune response, exemplified by potent HIV-specific CTL responses that kill virus-infected CD4<sup>+</sup> T cells, thereby destroying the source of HIV production (35, 199, 200, 325). HIV-specific neutralizing antibodies do not usually appear in appreciable titers until several weeks after the decrease in the high levels of HIV-1 in plasma seen with acute infection (199, 200). These kinetic studies are most compatible with the view that the cellular arm of the immune system is primarily responsible for clearing virus from the circulation.

Furthermore, recent studies of HIV-positive children who are nonprogressors (no decline in CD4 count) or whose disease is progressing rapidly (declining CD4 counts) indicate that phytohemagglutinin (PHA)-stimulated PBMCs from the nonprogressor patient population do not produce IL-4 or IL-10, whereas PBMCs from more rapid progressors produce both of these type 2 cytokines (394).

Some of the cytokines that are affected by HIV infection not only modulate immune function but also may affect HIV production (354). Thus, IL-4, IL-10, and IL-12 (130, 357, 408) have been shown *in vitro* to have several effects on HIV replication. For example, Weissman et al. have demonstrated that the effect of IL-10 on HIV-1 production is complex and may increase or decrease depending on the presence or absence of other cytokines (408). We have found that IL-15 stimulates HIV-1 production from PBMCs *in vitro* (227). Therefore, attempts to normalize the immune dysregulation of HIV-in-

ected patients by cytokine-based interventions (348) will need to include concomitant anti-HIV drug therapy, as was done by Kovacs et al. in the trials of IL-2 therapy (201).

Of particular interest is the finding reported now by at least two laboratories that human Th0 and Th2 clones are readily infected with HIV but Th1 clones are not (58, 234, 318). Could this mean, as recently suggested (72, 318), that the Th1-to-Th2 shift in AIDS progression is tempered by the selective infection-induced loss of Th2 cells and, further, that the potential pool of uncommitted Th0 cells is also compromised? On the other side of this immunologic fulcrum are the Th cells that mainly enhance cellular effector responses. This population of helpers has been suggested to be susceptible to mitogen- or antigen-induced T-cell death when stimulated in a type 2 cytokine environment (72). In fact, type 1 cytokines protect against such death whereas type 2 cytokines do not and can enhance this form of apoptotic death (70). Furthermore, only the CD4<sup>+</sup> subset is affected when specific antigens are used for stimulation of T-cell death (69). Thus, we now have potential mechanisms for the selective destruction of Th-1-like CD4<sup>+</sup> T cells (antigen-induced apoptotic death) and of Th2-like CD4<sup>+</sup> T cells (HIV infection). Susceptibility to T-cell death may depend on T-cell activation via an aberrant T-cell signal and would therefore not be dependent on the susceptible CD4<sup>+</sup> T cell being either infected or HIV specific. Such a "bystander" mechanism (124) could permit the destruction of large numbers of CD4<sup>+</sup> T cells as seen in AIDS progression (72).

An inconsistency with the findings *in vitro* that Th responses of HIV-positive individuals (noted above) are impaired is the report suggesting that the T cells of patients are in an activated state. This dichotomy can be accounted for if one considers that the interaction between CD4<sup>+</sup> T cells and HIV or an HIV product can result in an aberrant T-cell signal that primes, sensitizes or activates the T cells for T-cell apoptotic death upon restimulation by antigen. Such T cells, primed for T-cell death, could express activation markers (such as MHC class II or CD38) and release  $\beta_2$ -microglobulin (119, 224).

An important aspect of the Th1-Th2 concept (both for HIV infection and AIDS and for other immune-dysregulated diseases) would be the development of surface markers that could distinguish between "Th-1-like" and "Th2-like" cells. Such a development should permit the efficient screening of blood samples by flow-cytometric methods to determine their cytokine expression and production profiles. One such method would be to use labelled reagents that would detect the cytokines themselves on cell surfaces or intracellularly. Developmental efforts are in progress to achieve this objective. Another approach would be to look at more traditional cell surface markers (e.g., CD30) to determine whether any of them correlate with Th1- and Th2-like function, as previously discussed.

**Measles.** Another human viral infection, measles, has been reported by Griffin and Ward (151) to lead to a predominant type 2 cytokine profile with increased antibody responses and decreased CMI responses. In particular, they found an increase in IL-4 levels in plasma after resolution of the measles rash whereas IL-2 levels in plasma were increased during and immediately after the rash. Thus, the point in time at which cytokines are measured during the natural history of a disease can influence the reported relative balance of type 1 and type 2 cytokines, a critical consideration in the study of human diseases and cytokines. After clearance of the measles rash, anti-CD3 stimulation of T cells from patients resulted in increased IL-4 and IL-6 levels but decreased IFN- $\gamma$  production.

Previous work has demonstrated that measles infection is associated with impaired type 1-mediated immunologic param-

eters, such as skin DTH, T-cell proliferation, and NK cell activity, and increases in type 2 cytokine parameters, such as elevated IgE levels in plasma. Clinically, persons with measles are at increased risk of developing tuberculosis (TB) (13, 374). In this regard, measles virus is similar to HIV-1 infection, which impairs CMI and increases the risk of TB as well as other opportunistic infections normally controlled by CMI.

In preliminary work, increased sCD30 levels have also been found during measles infection, which could suggest a type 2 cytokine-predominant state (94). Distinguishing between sCD30 as a generalized lymphocyte activation marker, and sCD30 as a specific type 2 T-cell cytokine marker is still required. On the basis of both immunologic and virologic comparisons between measles virus and HIV-1, Hilleman has proposed the study of measles pathogenesis to gain insight into the pathogenesis and control of HIV-1 infection (166).

Ward and Griffin also demonstrated that vaccination with live attenuated measles vaccine induces a type 2 cytokine state (404). After measles immunization, production of IL-4 by unstimulated PBMCs (>72 h in culture) and by PHA-stimulated PBMCs increases. No differences in IL-4 levels in plasma were found. The authors noted that after administration of live, but not killed, measles virus vaccine, there is impairment of the skin test DTH responses and of antigen- and mitogen-induced lymphocyte proliferation. There is also an increase in spontaneous proliferation of PBMCs after live measles virus immunization and an increase in the production of neopterin, a marker of macrophage activation.

**Respiratory syncytial virus infection.** RSV was reported in 1994 to induce a Th1 (type 1) memory T-cell response after naturally acquired infection (10). PCR was used to measure the levels of cytokine mRNA in PBMCs of children and adults with and without previous RSV infection. The authors postulated that induction of type 1 memory T cells is likely to be a beneficial property of an RSV vaccine and suggested that cytokine responses should be included in the evaluation of candidate RSV vaccines (9, 10). A safe and effective RSV vaccine has not been developed. In the 1960s, administration of a formalin-inactivated RSV vaccine (FI-RSV) resulted in more severe disease when recipients were naturally infected with RSV. The pathogenesis of this enhanced disease phenomenon has not been definitively established. Live attenuated RSV vaccines have not resulted in enhanced disease but have been associated with other difficulties such as inadequate attenuation, low levels of immunogenicity, and excessive reversion to wild-type RSV (9, 10, 153).

Graham et al. (145, 146) found that in animal models of RSV, mice immunized with inactivated RSV or with the fusion (F) subunit glycoprotein yielded a type 2 cytokine pattern when challenged with live RSV. In contrast, mice immunized with live RSV produced a type 1 cytokine pattern when given live RSV. Subsequently, these investigators found that mice given antibody to IL-4 (anti-IL-4) at the time of immunization with inactivated RSV had less clinical disease, increased CD8<sup>+</sup> CTL counts, and a type 1 cytokine response (increased IFN- $\gamma$  with respect to IL-4 mRNA and increased titers of RSV-specific IgG2a) (375). When the anti-IL-4 antibody was given at the time of RSV challenge rather than at the time of RSV vaccination, none of these clinical or immunological differences occurred. Thus, the cytokine response associated with RSV immunization may influence the clinical and immunologic response upon subsequent natural virus infection. Tang and Graham have also found that mice given IL-12 at the time of immunization with FI-RSV had reduced RSV replication in the lungs upon challenge and an increased ratio of IFN- $\gamma$  to IL-4 mRNA in the lungs (376). Unlike the experiments in

which anti-IL-4 was given at the time of immunization, however, IL-12 did not change the CTL activity or clinical outcome of the mice after RSV challenge.

In related work, Connors et al. (76) reported on the effect of type 1 and type 2 cytokine modulation on RSV infection and immunization. They had demonstrated that lung abnormalities induced by live RSV challenge after FI-RSV vaccination of BALB/c mice could be blocked by removing CD4<sup>+</sup> T cells. They then studied the effects of antibodies against IL-4, IL-10, IL-2, and IFN- $\gamma$  on the enhanced lung disease seen in their experimental model (i.e., BALB/c mice immunized with FI-RSV and then challenged with live RSV). Depletion of IL-2 and/or IFN- $\gamma$  did not change the pulmonary histopathologic findings, whereas the abnormalities were prevented by the combination of antibodies to IL-4 and IL-10. Of interest, anti-IL-4 alone decreased bronchiolar but not perivascular histopathologic abnormalities whereas anti-IL-10 alone did not alter them (76).

**Chronic active hepatitis B.** CAH infection has been associated with type 1 cytokine-producing T cells, although the role of these T cells in the pathogenesis of CAH is uncertain. In 1987, Ferrari et al. (121) reported that CD8<sup>+</sup> as well as CD4<sup>+</sup> T-cell lines expressing type 1 cytokines could be isolated from the liver of CAH patients. These T-cell lines specifically recognized the hepatitis B virus nucleoprotein. Barnaba et al. isolated CD4<sup>+</sup> T cells from liver biopsy specimens of patients with CAH due to hepatitis B virus (17). In addition to CD4, a proportion (25 to 40%) of these cells expressed CD56 and were CTLs. Interestingly, these CD4<sup>+</sup> CD56<sup>+</sup> T cells were not found in the blood at the time they were found in the liver, suggesting an immunologic compartmentalization. When T-cell clones specific for hepatitis B envelope antigen were derived from these CD4<sup>+</sup> CD56<sup>+</sup> cells, they had a type 1 profile (secreting IFN- $\gamma$  but not IL-4 or IL-5).

Using a different population, Tsutsui et al. (387) studied CD4<sup>+</sup> T-cell clones specific for hepatitis B surface antigen (HBsAg) derived from two patients who were hepatitis B surface antibody positive but HBsAg negative. They concluded that no distinct Th1-Th2 cytokine dichotomy was evident in these clones. On the other hand, Benvenuto et al. studied T-cell clones from patients with CAH (hepatitis B surface antigen positive) and found a type 1 cytokine profile (25).

Vingerhoets et al. (395) have analyzed the *in vitro* responses of PBMCs to recombinant HBsAg from persons who were either nonresponders or responders to hepatitis B vaccination. The PBMCs of vaccine nonresponders, defined as not demonstrating antibody to HBsAg after vaccination, did not produce cytokine in response to HBsAg. In contrast, the PBMCs of persons who had a strong response to vaccination demonstrated *in vitro* production of IFN- $\gamma$  and IL-2 but not IL-4 or IL-5 after stimulation with HBsAg. This observation suggests that hepatitis vaccine responsiveness is associated with induction of a type 1 cytokine response to HBsAg, whereas failure to elicit this cytokine response is associated with vaccine unresponsiveness.

### Mycobacterial and Other Bacterial Diseases

**Leprosy.** Of the human bacterial infections in which type 1 and type 2 cytokine changes have been studied, the mycobacterial diseases leprosy and tuberculosis have been among the most extensively analyzed. In the lepromatous form of leprosy, in which CMI is highly impaired and mycobacterial organisms are most numerous, a type 2 cytokine profile is dominant in skin lesions. Conversely, a type 1 Th cell response is characteristic of the tuberculoid form of leprosy, in which patients

have strong CMI and few organisms (259, 327, 422). CD8<sup>+</sup> T cells predominate in lepromatous skin lesions, whereas CD4<sup>+</sup> T cells predominate in tuberculoid leprosy. These CD8<sup>+</sup> T cells produce type 2 cytokines including IL-4, IL-10, and possibly IL-13 and express predominantly HLA-DQ rather than HLA-DR molecules. These cytokines can "suppress" the function of macrophages and their ability to kill *Mycobacterium leprae* (259). A type 1 cytokine pattern has also been found in CD4<sup>+</sup> T-cell clones, derived from peripheral blood T cells of patients with tuberculoid leprosy, which were reactive with *M. leprae* (152).

Several additional points concerning leprosy and cytokine profiles deserve emphasis. First, both the polarized type 1 cytokine-predominant tuberculoid and the type 2 cytokine-predominant lepromatous forms of leprosy are still disease states; i.e., the presence of a type 1 predominance does not always confer complete protection against the disease. Second, these two clinically and immunologically polarized forms of leprosy (tuberculoid and lepromatous) are not the only manifestations of the disease; instead, they are the two polar extremes of the clinical spectrum of leprosy. In 1966, a classification scheme which recognized at least five distinct clinical forms of leprosy as part of a clinical spectrum was defined (308). Patients may move along this spectrum as part of the natural history of their disease or in response to therapeutic interventions.

Third, the clinical and immunologic changes that occur along the spectrum of leprosy are worth considering in light of postulated analogies between leprosy and HIV-1 infection or other human disease reflective of a skewing of the type 1-type 2 cytokine balance. For example, Sampaio et al. (332) found that patients with lepromatous leprosy treated with IFN- $\gamma$  might develop an immune complex-type reaction, termed erythema nodosum leprosum, with clinical worsening of their disease. Interestingly, one therapy for erythema nodosum leprosum is thalidomide, a drug that not only decreases monocyte TNF- $\alpha$  production but also induces a type-1-to-type-2 switch (with decreased IFN- $\gamma$  production) in PBMCs stimulated by either antigens or mitogens (246). Thus, cytokine-based therapy of leprosy, HIV-1 infection, or other diseases with apparent type 1-type 2 cytokine dysregulation could have immunologically mediated toxicities.

Another clinical and immunologic change that can occur along the spectrum of leprosy is an apparently spontaneous upgrading of the CMI/DTH immune response, particularly in patients with the lepromatous or borderline form of leprosy. Such "reversal reactions" have been shown (423) to involve an upregulation of type 1 cytokines. A type 1 cytokine predominance has also been demonstrated by Yamamura et al. (423) during the DTH skin test (lepromin or Mitsuda) reaction. Interestingly, Salgame et al. (327) also reported that a dominant type 1 cytokine profile was found in *M. leprae*-specific CD4<sup>+</sup> T-cell clones derived from the blood of an asymptomatic relative of a person with leprosy. This is possible evidence for a situation analogous to that in which in vitro T-cell proliferation and/or CTLs specific for HIV-1 antigens are found in patients who have no serologic or clinical evidence of HIV infection but have been exposed to the virus (64, 298, 356).

Sieling et al. (360) have studied the role of IL-12 in leprosy. They reported IL-12 p40 mRNA and IL-12 p70 protein levels to be 10 times higher in tuberculoid than lepromatous lesions. In vitro, IL-12 stimulated the proliferation of CD4<sup>+</sup> Th1-like clones from tuberculoid lesions but not CD8<sup>+</sup> Th2-like clones from lepromatous lesions. Furthermore, anti-IL-12 antibody inhibited the T-cell proliferation in response to *M. leprae* in tuberculoid leprosy patients. Taken together, these studies sug-

gest a role for IL-12 in this mycobacterial disease and perhaps other human infectious diseases.

**Tuberculosis.** Del Prete and colleagues have reported that purified protein derivative of *Mycobacterium tuberculosis* preferentially increases the number of type 1 CD4<sup>+</sup> T cells whereas parasitic antigens from *Toxocara canis* increase the number of type 2 CD4<sup>+</sup> T cells after in vitro stimulation (92). There is also in situ evidence for a predominant type 1 Th cell response in the tuberculin (purified protein derivative) skin reaction (386), as noted above for the lepromin skin test reaction (423).

Human TB is considered a prime example of a disease controlled by CMI and not by humoral immunity. Although humans infected with *M. tuberculosis* make abundant antimycobacterial antibodies, these have not been shown to play a protective role against the development of TB (57, 99). Using a guinea pig model, Chase first demonstrated in 1945 that tuberculin hypersensitivity could be transferred by cells and thereby implicated CMI in playing a critical role against *M. tuberculosis* infection (57).

On the other hand, CMI responses against TB may be responsible for tissue damage to the host as well as being responsible for eradication of the infection. Dannenberg (83, 84) has distinguished between a DTH immune response, which controls the growth of mycobacteria by killing quiescent macrophages laden with mycobacteria but at the same time can cause tissue necrosis, and a CMI response, which activates macrophages via cytokines such as IFN- $\gamma$  to kill the intracellular mycobacteria without inducing extensive tissue damage. Thus, the potential for cytokine-based therapy of TB to have immunologically based side effects should be kept in mind. Insights into strategies to optimize vaccines for TB and/or leprosy have been recently discussed by Bloom and Fine (32) and Bretscher (38), emphasizing the role of cellular immunity against these mycobacteria. Again, the potential for antimycobacterial CMI to cause tissue damage must be considered in vaccine design.

Whether strict type 1 and type 2 cytokine profiles are critical in the pathogenesis of human tuberculosis is still under investigation (18, 19, 260, 262, 334, 402). Schaaf et al. have found that HIV-seronegative persons with pulmonary TB have a 10-fold decrease in the number of IL-2 responsive cells in their peripheral blood (334). Since most of their patients had IL-4 mRNA in their unstimulated PBMCs but none had IL-2 mRNA, the authors questioned whether IL-4 was inhibiting the normal proliferative effects of IL-2 on T cells and NK cells. They proposed that the immunodepressive effect of IL-4 in these patients could provide a rationale for the use of IL-2 as part of the therapeutic regimen against TB. Surcel et al. also provided evidence for a type 2 cytokine predominance in active tuberculosis. In response to stimulation with mycobacterial antigens, they found an increase in the number of IL-4-secreting PBMCs in persons with active TB (372).

As with HIV-1 infection and other systemic conditions, cytokine profiles in mycobacterial disease may vary within different body compartments (e.g., skin, lungs, blood, lymph nodes, and nervous system) depending on the degree of involvement within an anatomical site. In addition, monocyte production of cytokines (e.g., TNF- $\alpha$ , IL-1, IL-6, IL-8, IL-10, IL-12, and possibly IL-15) may have particular significance in mycobacterial infections such as TB. In this regard, Barnes et al. found that the lipoarabinomannan component of *M. tuberculosis* can induce TNF- $\alpha$  and IL-10 production whereas another mycobacterial component, the protein-peptidoglycan complex, induces IFN- $\gamma$  production (18, 19). Zhang et al. (430) found a decrease in the level of type 1 cytokines and an increase in the level of IL-10 in persons with TB and HIV-1 infection, two

diseases linked by compromised CMI. TB is more common in persons with HIV-1 infection and is more likely to be extrapulmonary and multidrug resistant than in immunocompetent individuals.

In murine models, IFN- $\gamma$  is critical for an effective immune response against TB, probably via induction of nitric oxide (78, 129). Recent reviews of cytokines and human TB (163, 262, 402) have emphasized the importance of IFN- $\gamma$  and TNF- $\alpha$  in the immune response to TB. Whether nitric oxide is operative in human macrophages and whether it serves as a cytokine (e.g., IFN- $\gamma$ )-induced effector molecule against mycobacteria are unknown. Hernandez-Pando and Rook have suggested that TNF- $\alpha$  can play either a beneficial or a detrimental role in TB depending on the relative type 1-type 2 cytokine balance. In a type 1 cytokine milieu, TNF- $\alpha$  is beneficial to the host by enhancing macrophage activation and antimycobacterial function. In a type 2 cytokine or mixed-cytokine milieu, TNF- $\alpha$  functions more to damage tissues than to help eradicate the mycobacteria (163).

**Mycobacterium avium complex infection.** *M. avium* is a common opportunistic pathogen in persons with HIV infection or AIDS and very low CD4<sup>+</sup> T-cell counts (<100/ $\mu$ l). Newman et al. (276) demonstrated that IL-12 increased PBMC proliferation in response to *M. avium* in vitro in 24 HIV-positive donors, most of whom had peripheral blood CD4<sup>+</sup> T-cell counts of  $\leq$ 100/ $\mu$ l. Holland et al. (169) studied seven HIV-seronegative patients with atypical mycobacterial infections who had received maximum conventional medical therapy. In vitro production of IFN- $\gamma$  in response to PHA, but not PMA and ionomycin together, was decreased relative to controls. Therapy with subcutaneous IFN- $\gamma$  led to marked clinical improvement within 2 months. In a murine model, *M. avium* infection elicited IL-10 production. Moreover, antibody against IL-10 markedly decreased the number of viable *M. avium* organisms (27).

**Intracellular bacterial infections.** Human bacterial diseases, other than leprosy and TB, have not been intensively analyzed in terms of type 1 and type 2 cytokine profiles, although heat-inactivated *Brucella abortus* has been reported to stimulate human T cells to produce IFN- $\gamma$  but not IL-4 (30). This bacterium may serve as an adjuvant for vaccines by stimulating a Th1-like immune response, a strategy discussed by Golding et al. (143).

Kitsukawa et al. found that mRNA for IFN- $\gamma$  but not IL-4 was produced by in vitro stimulation of human PBMCs with live or formalin-killed *Legionella pneumophila* (195). CD4<sup>+</sup> T-cell clones specific for *L. pneumophila* also expressed mRNA for IFN- $\gamma$  but not IL-4. On the other hand, both IFN- $\gamma$  and IL-4 mRNAs were found in PBMCs stimulated with *Legionella* culture supernatant, suggesting that either Th1 or Th0 cytokine responses may be elicited by this intracellular pathogen. Whether similar events occur in vivo with *Legionella* infection awaits further investigation.

Infection of mice with *Listeria monocytogenes* has been used extensively as a model for the study of type 1 cytokines, including IFN- $\gamma$  and IL-12, in controlling an intracellular infection (122, 173, 344). In addition, Ferrick et al. (122) used a murine model to demonstrate anti-*Listeria* activity which was mediated by IFN- $\gamma$  produced by CD4<sup>-</sup> CD8<sup>-</sup> gamma-delta T cells prior to the expected IFN- $\gamma$  production by CD4<sup>+</sup> T cells. This example of cytokine production by non-CD4<sup>+</sup> T cells, which has a critical effect on disease outcome, again emphasizes the rationale for the use of the function-based type 1-type 2 cytokine nomenclature.

High levels of IL-10 are found in the spinal fluid of mice with *Listeria meningitis*. This IL-10 inhibits the anti-*Listeria* func-

tion of macrophages infected with this pathogen (133). *Listeria meningitis* is uncommon in humans, and cytokine studies comparable to those with mice are lacking. In general, there is little literature addressing the study of type 1 and type 2 cytokines within the central nervous system. From studies with a murine model of acute Sindbis virus encephalitis and studies of chronic HIV-1 encephalopathy, Wesselingh and Griffin (412a) have proposed that a type 2 cytokine profile with local antibody production and minimal cytotoxicity would be preferable to a type 1 response.

***Yersinia enterocolitica* and *Chlamydia trachomatis* synovitis-reactive arthritis.** Simon et al. have studied the cytokine profile of synovial T-cell clones from two individuals with arthritis due to *Chlamydia trachomatis*, another intracellular pathogen (361). They found that both CD4 and CD8 chlamydia-reactive synovial T-cell clones were primarily of a type 1 cytokine profile, producing IFN- $\gamma$  without IL-4. This cytokine response would be appropriate for control of this intracellular pathogen. On the other hand, this type 1 cytokine immune response might also cause a reactive arthritis in some patients. As discussed above with regard to TB and leprosy, a CMI response may have both beneficial effects against an infecting pathogen and detrimental effect in terms of host tissue damage.

*Yersinia enterocolitica* has also been reported by two groups of investigators to stimulate a type 1 cytokine response from T cells, which may in turn cause a reactive arthritis. Type 1 T cells have been found in synovial fluid of joints of persons with a reactive arthritis due to *Y. enterocolitica* (204, 302). Probst et al. reviewed information on the bacteria associated with reactive arthritis and propose a T-cell-mediated model of DTH in the pathogenesis of reactive arthritis due to chlamydiae or enteric bacteria such as *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* spp. (302).

**Lyme disease and syphilis.** Spirochetal diseases such as Lyme disease and syphilis have been studied in terms of their Th cell cytokine profile. CD4<sup>+</sup> T-cell clones derived from the blood and synovial fluid of persons with chronic Lyme arthritis due to *Borrelia burgdorferi* infection have been shown by Yssel et al. to exhibit the type 1 cytokine profile (428, 429). They suggested that the spirochete-induced IFN- $\gamma$  and IL-2 (as well as TNF- $\alpha$ ) contributed to the synovitis and arthritis of Lyme disease.

Fitzgerald has noted that resolution of acute infection with *Treponema pallidum*, the spirochetal agent of syphilis, occurs via a type 1 cytokine response whereas chronic infection is associated with a switch to a type 2 response (128). Van Voorhis and colleagues have recently reported evidence for type 1 cytokine elicitation in response to both primary and secondary lesions of syphilis (390).

Sell and Hsu (352) have compared the clinical and immunologic spectrum of syphilis with that of leprosy. In this comparison, tertiary syphilis is analogous to lepromatous leprosy in terms of a weak DTH/CMI response and the presence of persistent organisms. Latent and secondary syphilis are immunologically similar to the borderline forms of leprosy. Resolution of syphilis by a strong DTH/CMI response is viewed as being analogous to tuberculoid leprosy, in which there are few persisting organisms. From this analogy between syphilis and leprosy, the authors predict that an effective vaccine against syphilis would require the induction of a strong anti-treponemal DTH response (352).

### Parasitic Diseases

Both protozoan and helminthic (worm) parasitic infections of humans have been analyzed in terms of type 1-type 2 cyto-

kine dysregulation. Sher et al. (359) have called attention to immunologic similarities between the cytokine-modulated immunologic response to parasitic infections and HIV-1 infection. Maizels et al. (237) reviewed the complexities of the interaction of helminthic parasites with the human immune response within a global epidemiologic context. They emphasized the importance of continuing to define the role of T-cell subsets and T-cell cytokines in human helminthic infections for the purpose of improving treatments and developing vaccines. They leave open the question whether Th1 and Th2 T cells are uniformly beneficial or detrimental for a given parasitic disease and whether the murine Th1-Th2 model applies to human helminthic infections. In this regard, Locksley has proposed that Th2 T cells provide "help for helminths" (217). For example, type 2 cytokines help control and expel intestinal helminths from the gut in several animal models. In one murine model, the type 1 cytokine IL-12 appears to inhibit the clearance of intestinal helminths (125).

Various forms of leishmaniasis in mice and in humans have been extensively studied in terms of their cytokine responses. *Leishmania major* infection in mice is one of the classic examples of Th1-Th2 cytokine predominance associated with resistance (Th1) and susceptibility (Th2). Bretscher et al. (39) found that the number of *L. major* parasites can also influence the clinical outcome. They found that BALB/c mice, known to be susceptible to leishmaniasis, develop CMI when infected with small numbers of parasites and are protected against subsequent challenge with higher doses of parasites. Cytokine production, however, was not reported in their study.

**Protozoan parasite infections: cutaneous and visceral leishmaniasis.** Cytokine studies of human visceral leishmaniasis (VL) and cutaneous leishmaniasis have been summarized by Bloom (31). In his view, elevated levels of type 2 T-cell cytokines (IL-4 and IL-10), which inhibit type 1 T cells, may be responsible for the lack of protection against these parasitic diseases. Carvalho et al. (53) initially demonstrated that PBMCs from persons with active VL showed no IFN- $\gamma$  or IL-2 production after stimulation in vitro with *Leishmania* antigen. These responses were restored after therapy (53). Later, high levels of mRNA for IL-4 and IL-10 in PBMCs of patients with VL were also demonstrated. Anti-IL-10 antibody restored in vitro production of IFN- $\gamma$  and T-cell proliferation to *Leishmania* antigens (52). A synergistic effect of anti-IL-4 antibody and anti-IL-10 antibody on lymphocyte proliferation was similarly observed.

Ghalib et al. (138) found increased IL-10 mRNA levels in lymph nodes and IL-10 production from PBMCs after in vitro stimulation with *Leishmania* lysate in persons with acute VL. These findings were no longer present after successful drug therapy for VL. Zwingenberger et al. found increases in IL-4 levels in the sera of persons with VL (431). Kemp et al. (186) studied CD4<sup>+</sup> T-cell clones from persons who had recovered from visceral leishmaniasis due to *Leishmania donovani*. They found a majority of Th1-like clones (producing IFN- $\gamma$  without IL-4), although some Th2-like and Th0 clones were present.

Patients with localized cutaneous leishmaniasis have a predominance of type 1 cytokine mRNA by PCR. With more extensive mucocutaneous leishmaniasis due to *Leishmania brasiliensis*, however, increases in IL-4 mRNA levels and a mixed cytokine pattern were found. A type 1 cytokine profile has also been found in response to the DTH of the intradermal *Leishmania* (Montenegro) skin test (299), as noted above for the lepromin and purified protein derivative skin tests.

Notably, different cytokine profiles may be found in persons with a given disease, depending on which compartment of the body is analyzed. For example, Karp et al. found that patients

with VL had increased levels of mRNA for both IL-10 and IFN- $\gamma$  in bone marrow aspirates whereas PBMCs failed to produce IFN- $\gamma$  when cultured with *Leishmania* parasite antigen in vitro (179). Hence, the cytokine profiles in peripheral blood may differ from those in tissues involved in an infectious disease process.

Murray and Hariprashad (269) have suggested that IL-12 may have benefit even in established VL infection. IL-12 has shown promise as an adjuvant for vaccination against *Leishmania* infection as demonstrated in an animal model by Afonso et al. (3). Similarly, IL-12 combined with a pentavalent antimony compound (Pentostam) cured mice with a chronic type 2 cytokine-dominant state due to infection with *L. major* (271). In an important clinical trial combining immune system-based therapy and drug therapy, Sundar et al. (371) demonstrated that addition of IFN- $\gamma$  to antimony chemotherapy of VL in Indian patients can result in cure when antimony therapy alone fails.

**Helminthic diseases. (i) Filariasis.** Mahanty et al. found that persons with helminthic (worm) parasitic infections, such as lymphatic filariasis, had an increased number of peripheral blood Th type 2 cells in response to parasite-specific antigens (236). They provided important evidence documenting a linkage of IL-4 and IL-5 production by T cells during human helminth infections, finding that levels of both cytokines were increased in persons with high IgE levels in serum and eosinophilia (235). Limaye et al. also demonstrated that the eosinophilia associated with parasitic worm infections was linked to increases in IL-5 levels (212). King et al. (191, 192) studied 15 patients with filarial (*Loa loa* and *Onchocerca volvulus*) infections. They found that filarial antigen-stimulated IgE production was mediated by IL-4 and inhibited by IFN- $\gamma$ . They also studied B-cell precursor frequencies in patients with helminth infections and, using a filter spot enzyme-linked immunosorbent assay (ELISA) (193), demonstrated a link between IgE and IgG4 production, in that both are stimulated by IL-4 and inhibited by IFN- $\gamma$  (173). King et al. demonstrated that filarial-antigen-specific IgE production from PBMCs is inhibited by IL-12, in part via inhibition of IL-4 and stimulation of IFN- $\gamma$  (190).

Elson et al. (113) compared the immune response to *O. volvulus* in persons who appeared to be immune to this filarial parasite with that of persons in the same geographic area who had active onchocerciasis. The "putatively immune" (PI) persons were long-term residents ( $\geq 17$  years) of an *O. volvulus*-hyperendemic area of Ecuador. They were negative for *O. volvulus* infection by PCR, as well as by parasitologic and clinical examination. Overall, PBMCs of the PI persons had a type 1 (increased IFN- $\gamma$ ) response to *O. volvulus* antigens compared with patients with onchocerciasis. Cytokine heterogeneity in the PI group, in terms of IFN- $\gamma$  and IL-2 production, was clearly evident. Interestingly, spontaneous production of IL-10 was higher in the patients with active disease, as was IL-5 production in response to mitogen (PMA and ionomycin) and nonparasite antigens. There was no antigen-induced PBMC production of IL-4 in either group, however (113). PI persons also had less parasite-specific IgG (IgG1 and IgG4). The authors concluded that a protective immune response to *O. volvulus* appears to be at least partially due to a parasite antigen-specific Th1-type response.

In a similar study comparing a PI group of persons with onchocerciasis patients in Guatemala, Steel and Nutman found that IL-2 is needed for the increased CD4<sup>+</sup> T-cell production of IL-5 which occurs during infection with *O. volvulus*. A possible protective role for IL-5, a type 2 cytokine, in onchocerciasis was suggested by this study (367). Taken together,

these two studies from Ecuador and Guatemala again emphasize the complexities of interpreting type 1 and type 2 cytokine profiles, even in human helminthic infections (237).

Some patients infected with the lymphatic system-dwelling *Wuchereria bancrofti* or *Brugia malayi* develop a syndrome termed tropical pulmonary eosinophilia (TPE), characterized by wheezing, cough, very high IgE concentrations in serum, and marked eosinophilia (>3,000 cells per  $\mu$ l). These characteristics of TPE are similar to those of allergic bronchopulmonary aspergillosis (ABPA), and the name "allergic bronchopulmonary helminthiasis" has been applied to TPE and related helminthic syndromes. The majority of the IgE appears to be filaria specific (284). Extensive cytokine studies have yet to be reported for TPE, but given the marked elevations in IgE level and eosinophilia, increased IL-4 and IL-5 levels would be expected.

(ii) **Schistosomiasis.** Other human parasitic diseases such as schistosomiasis have also been studied from the perspective of type 1 and type 2 cytokine profiles. Schistosome eggs elicit an eosinophil and macrophage granulomatous immune response, which can in turn cause tissue damage in nearly every organ of the human host (222). Hence, the disease caused by this trematode parasite is largely immune system mediated.

Capron and Dessaint (49) and Capron and Capron (50) have reviewed the controversy concerning whether the rat or the mouse model of schistosomiasis is most relevant to human schistosomiasis. In humans and in the rat model, the primary anti-schistosome larva immune response appears to be antibody-dependent cell-mediated cytotoxicity, whereas in the murine model, activated macrophages are critical (50). Using the murine model, Oswald et al. (283) found that IL-12 can block the normal type 2 cytokine responses induced by *Schistosoma mansoni* infection. Subsequently, Wynn et al. demonstrated in the murine model that vaccination with IL-12 and *S. mansoni* markedly decreased the hepatic granulomas and fibrosis seen after challenge with *S. mansoni* larvae, although overall egg production was unchanged (420).

Mice with severe combined immunodeficiency (SCID mice) have also served as a model to demonstrate an apparent subversion of the immune system by schistosome parasites. In these animals, TNF- $\alpha$  stimulated both granuloma formation (the host immune response) and schistosome egg laying (the parasite's response that enhances its potential for transmission) (8).

An oligosaccharide associated with schistosome eggs has been shown to stimulate IL-10 production from murine leukocytes (391). A parallel with TB may be drawn because IL-10 can be induced by the lipoarabinomannan component of the mycobacteria (18). Cross-regulation between IL-10 and TNF- $\alpha$  may occur in schistosomiasis and in TB, given that IL-10 inhibits TNF- $\alpha$  production by human monocytes and that TNF- $\alpha$  itself stimulates IL-10 production by monocytes (403). A feedback loop between IL-10 and TNF- $\alpha$  would be predicted in other diseases, such as HIV-1 infection, in which high levels of IL-10 or TNF- $\alpha$  have been found.

Patients with schistosomiasis who do not clear their infection after treatment have been reported to have lower ratios of IFN- $\gamma$  to IL-4 than do uninfected controls or patients who do clear their infection after therapy (432). Capron and Capron (50) have reviewed recent findings on the role of IgE in schistosomiasis and the role of type 1 and type 2 responses. They conclude that in human schistosomiasis, protective immunity is linked more with Th2 cytokine responses than with Th1 responses. Thus, IgE antibodies against schistosomes may be associated with immunity and elevated IL-5 levels may be associated with a lower risk of reinfection with schistosomes.

## Fungal Diseases

Fungal infections being studied from the perspective of type 1-type 2 cytokine dysregulation include ABPA, candidiasis, coccidioidomycosis, paracoccidioidomycosis, cryptococcosis, and histoplasmosis. Only limited data from human studies of these fungal infections are currently available. Information from animal models, however, suggests that clinically progressive forms of several fungal diseases may be associated with a type 2 cytokine predominance. Conversely, prevention or resolution of these infections would be favored by a type 1 cytokine profile.

**Allergic bronchopulmonary aspergillosis.** ABPA is characterized by very high levels of IgE in serum, eosinophilia, and bronchospasm in association with pulmonary colonization by *Aspergillus fumigatus*. Walker et al. found that concentrated bronchoalveolar lavage fluid from persons with ABPA contained increased levels of IL-4 and IL-5 but no increase in the level of IFN- $\gamma$  and only a modest increase in the level of IL-2 (401). Knutsen et al. established CD4<sup>+</sup> T-cell lines against *Aspergillus* antigens from peripheral blood of patients with ABPA and showed that these cells had a Th2 pattern (198). Specifically, they produced IL-4 but not IFN- $\gamma$  or IL-2. Proliferation of these T-cell lines could be blocked by anti-IL-4 but not anti-IL-2 antibody. In a murine model (BALB/c), particulate *A. fumigatus* antigens induce a pulmonary Th2-predominant state with increased IL-4 and IL-5 production (203).

**Candidiasis.** Extensive work by Romani et al. with murine models of candidiasis has demonstrated that type 1 cytokine responses are linked to disease resistance against *Candida albicans*. These authors have elucidated a critical role for IFN- $\gamma$  and IL-12 in this immune response (319–321). However, little work has been published to date on type 1 and type 2 cytokine profiles in human candidiasis, either visceral or mucocutaneous.

**Cryptococcosis.** Cryptococcal fungal infection is considered to be primarily controlled by CMI, suggesting a predominantly type 1 cytokine response. Data from a murine model of pulmonary *Cryptococcus neoformans* infection demonstrated that immune mice have increased levels of IL-2 but not type 2 cytokines (IL-4, IL-5, and IL-10) in pulmonary lymph nodes and lung cell cultures (168). Susceptible mice had decreased IL-2 levels and increased IL-5 levels. However, they did not have increased IL-4 or IL-10 levels, suggesting that susceptibility to cryptococcal infection was not dependent on these type 2 cytokines.

Surprisingly, Clemons et al. reported that IL-12 alone had a beneficial effect on the outcome of cryptococcal meningitis in a murine model. Systemic IL-12 also enhanced the effect of fluconazole in this meningitis model (64). Cryptococcal meningitis and brain abscesses are difficult to treat in humans, particularly in the setting of AIDS. Therefore, investigational studies of IL-12 as adjunctive therapy for the treatment of central nervous system cryptococcal infection may be considered in the future.

**Paracoccidioidomycosis.** Hostetler and colleagues (171) studied paracoccidioidomycosis in a murine model and found a type 2 cytokine predominance, with increased IgE levels in serum during acute, progressive infection. Anti-IL-4 antibody treatment decreased the IgE levels. Antifungal chemotherapy decreased both the IgE levels and the number of fungal organisms, effects which were enhanced by IFN- $\gamma$ . CMI appears to be more important than antibody in human paracoccidioidomycosis, although definitive cytokine studies from the perspective of the type 1-type 2 paradigm have not been reported (43). Acute infection is associated with a decreased CD4/CD8

T-cell ratio, as a result of a decrease in the number of CD4<sup>+</sup> T cells and/or an increase in the number of CD8<sup>+</sup> T cells. Reversal of anergy to the *Paracoccidioides* DTH skin test with drug treatment, implying an improvement in CMI against the fungus, is considered a good clinical prognostic marker (43).

**Blastomycosis.** In human blastomycosis, CMI rather than antibody is considered to confer protection against infection and disease progression. Type 1-type 2 cytokine studies in humans with blastomycosis have not been reported. However, Brummer et al. have studied pulmonary blastomycosis in a murine model (44). They found a switch from a type 1 (IFN- $\gamma$  and IL-2) to a type 2 (IL-4 and increased IgE levels in serum) profile in the setting of progressive disease, a pattern predicted for other progressive systemic mycoses as well.

**Coccidioidomycosis.** Stevens has postulated that an effective immune response to *Coccidioides immitis* infection may be mediated by a type 1 cytokine profile. He has noted that progressive disease is associated with increased IgE levels, impaired T-cell responses, and high levels of anticoccidioidal antibody (370). Tissue and blood eosinophilia can also be seen with coccidioidomycosis. Beaman has found that IFN- $\gamma$  increases the antifungal activity of human blood monocytes against *C. immitis* endospores in vitro (21). Dooley et al. (106) have demonstrated increases in IL-1, IL-6, and TNF- $\alpha$  levels after in vitro *Coccidioides*-specific stimulation of human mononuclear cells. Whether this finding relates to the type 1-type 2 cytokine balance (e.g., increased IFN- $\gamma$  production), however, awaits further investigation.

**Histoplasmosis.** Similarly to several other systemic mycoses, an effective immune response to infection with *Histoplasma capsulatum* is thought to be predominantly cell mediated (46). A clinical similarity among TB, coccidioidomycosis, and histoplasmosis is that all three infections are seen with increased frequency and severity in persons with impaired CMI as a result of HIV-1 infection. Moreover, the clinical and immunologic spectrum of progressive disseminated histoplasmosis consists of polar extremes connected by a continuum (46). This clinical spectrum of progressive disseminated histoplasmosis is reminiscent of leprosy, HIV infection and AIDS, and possibly syphilis (33, 72, 259, 352), in which at one polar extreme CMI is only mildly diminished and the number of infectious organisms is small whereas at the other extreme CMI is absent and the number of organisms is large.

As with TB and coccidioidomycosis, DTH skin testing has been extensively performed as a test for exposure to *H. capsulatum*. Edwards et al. tested over 670,000 U.S. Navy recruits with histoplasmin and two mycobacterial skin tests. Using this information, they created an epidemiologic atlas of the country in terms of prior exposure to *H. capsulatum*, *M. tuberculosis*, and atypical mycobacteria (111).

On the basis of skin-testing data with antigens from *H. capsulatum*, *C. immitis*, *M. tuberculosis*, and *M. leprae*, we would argue that DTH skin tests could be developed for other diseases in which CMI appears to be predominantly responsible for disease prevention. For example, DTH skin testing with HIV-1 and HIV-2 antigen(s) should be feasible and allow epidemiologic studies like those with *H. capsulatum* to be performed in both developed and less-developed nations. HIV skin tests may also afford a way to identify HIV-exposed but seronegative persons. In the event that such an immune profile (DTH in the absence of antibody) confers protection against either infection or disease (AIDS), identification of such persons prior to enrollment in prophylactic HIV vaccine studies would be important to the interpretation of vaccine efficacy data.

## NEOPLASTIC DISEASES

### Cutaneous Basal Cell and Squamous Cell Carcinomas

Human neoplastic conditions have also begun to be studied in terms of type 1 and type 2 cytokine profiles. Yamamura et al. (421) reported that basal cell carcinoma exhibits a type 2 Th-cell pattern of local cytokine production whereas the benign skin condition seborrheic keratosis exhibits a type 1 pattern of local cytokine production. By observing that UV-irradiated Langerhans cell APCs preferentially stimulate type 2 CD4<sup>+</sup> T cells, they suggested that UV light may contribute to the pathogenesis of cutaneous malignancy by causing APCs to preferentially stimulate type 2 Th-cell responses.

Similarly, Kim et al. suggested that the type 2 cytokine IL-10 may allow immune system evasion by cutaneous basal cell and squamous cell carcinomas. They found increased expression of IL-10 mRNA in both carcinomas. IL-4 mRNA levels were also increased in basal cell carcinoma compared with matched PBMCs. Treatment of basal cell carcinoma with intralesional IFN- $\alpha$  resulted in downregulation of IL-10 mRNA, upregulation of IL-2 mRNA in the lesions, and a partial remission of tumor size (188).

### Sézary Syndrome

At least three laboratories, using different experimental conditions, have reported that Sézary syndrome, the leukemic stage of cutaneous CD4<sup>+</sup> T-cell lymphoma, is characterized by a type 2 cytokine profile (324, 379, 397). Immunologic abnormalities in Sézary syndrome include increased IgE levels, eosinophilia, and impaired T-cell, NK, and LAK cell responses. Vowels et al. (397) demonstrated that PHA-stimulated PBMCs from patients with Sézary syndrome had more IL-4, less IFN- $\gamma$ , and less IL-2 than did cells from normal controls. Saed et al. (324) used PCR to demonstrate a predominance of mRNA for IL-4, IL-5, and IL-10 in both skin and PBMCs of patients with Sézary syndrome. In contrast, a type 1 cytokine profile was found in the skin of patients with mycosis fungoides T-cell lymphoma and the skin of patients with psoriasis.

Tendler et al. (379) purified leukemic T cells, rather than whole PBMCs, from patients with Sézary syndrome and HTLV-1 adult T-cell leukemia (ATL). They found increased IL-4 mRNA and IL-4 protein levels in PHA- or PMA-stimulated Sézary leukemic cells compared with those in cells from ATL patients and normal controls. IFN- $\gamma$ , IL-2, and IL-5 mRNA and protein levels were decreased in Sézary syndrome and ATL compared with controls. Thus, a discordance between IL-4 and IL-5 was found in the leukemic Sézary cells. CD4<sup>+</sup> cells from patients with HTLV-1 ATL showed decreases in both type 1 and type 2 cytokine levels but high levels of transforming growth factor  $\beta$ , which was postulated to contribute to the cutaneous anergy and opportunistic infections (414) seen in persons with ATL.

Rook et al. (322) showed that PBMCs from persons with Sézary syndrome had decreased LPS- and *Staphylococcus aureus*-stimulated IL-12 p40 homodimer and p70 heterodimer production. These cells also exhibited decreased PHA-stimulated IFN- $\gamma$  levels and increased IL-4 production. Addition of exogenous IL-12 in vitro, with or without IFN- $\alpha$ , could increase IFN- $\gamma$  levels, decrease IL-4 levels, and increase NK cell killing of K-562 target cells. From these findings, and the poor prognosis associated with Sézary syndrome, the authors suggested that IL-12 be tested against this malignancy in controlled clinical trials.

Evidence from animal tumor models has suggested that IL-12 has a potent effect against a variety of tumors, including

both lymphomas and carcinomas, and that its activity is mediated at least in part by IFN- $\gamma$  (45). Conversely, in other murine models of selected malignancies, the type 2 cytokine IL-4 has been reported to have an antitumor effect, which is mediated in part by eosinophils (167, 380).

### Lymphomas

**EBV-associated B-cell non-Hodgkin's lymphoma.** The herpes family virus Epstein-Barr virus (EBV) produces a protein termed BCRF1, which is homologous to IL-10. This protein has many of the same functional properties as IL-10 and has been referred to as viral IL-10 (104, 258). EBV B-cell lines from patients with American Burkitt's lymphoma and AIDS-mediated B-cell lymphomas are reported to produce very high levels of IL-10 (24). EBV-transformed human B cells are induced to produce IL-10 (47). Thus, either EBV-produced viral IL-10 or leukocyte IL-10 (from T cells, monocytes, or B cells) may play a role in some B-cell lymphomas, including those seen in patients with AIDS.

**Hodgkin's disease.** The Reed-Sternberg (RS) malignant cells of HD have recently been postulated to be Th2-like cells (300) and to contain IgE (330). HD is characterized clinically by increased concentrations of IgE in serum, mild eosinophilia, and cutaneous anergy, all consistent with a Th2-like predominant state. Furthermore, Clerici et al. have recently observed that the *in vitro* Th-cell response patterns of patients with HD are very similar to those reported for HIV-infected patients, in terms of a spectrum of impaired IL-2 responses to recall antigens, alloantigens, and mitogens (66). The RS cell is known to express IL-5 mRNA, and this cytokine has been implicated in the eosinophilia associated with HD (331). Eosinophils are reported to be the primary source of the transforming growth factor  $\beta$  in the nodular sclerosis form of HD. Since TGF- $\beta$  has been specifically implicated in the pathogenesis of this common form of HD, eosinophils may play a multifactorial role in the etiology of this lymphoma (178).

Haluska et al. (154) reviewed the biology of the RS cell and cytokines in HD. They concluded that since HD tissues and cell lines can produce IL-4, IL-5, IL-6, and IL-9 (a putative type 2 cytokine), RS cells are probably of lymphocyte origin. IL-2 has not been found in HD tissue or cell lines, and IFN- $\gamma$  has been reported only from one HD cell line. Expression of CD30, a possible type 2 cytokine marker, was originally described on RS cells staining with the Ki-1 antibody (345). Elevated levels of soluble CD30 in serum are a prognostic marker in untreated patients with HD (272).

**Large cell anaplastic (CD30<sup>+</sup>) lymphoma.** While only the RS cells, a minority of the cellular infiltrate in HD lesions, express CD30, in large cell anaplastic lymphoma (LCAL) there is uniform expression of CD30 by most cells forming the tumor; hence its designation as CD30 (Ki-1)-positive large cell lymphoma (4). Thus, if CD30 is truly a type 2 cytokine marker, LCAL is a prime candidate for a type 2 cytokine-predominant malignancy, and soluble CD30 levels may also have prognostic significance in this disease. LCAL has also been reported to produce IL-9, like HD but unlike several other lymphomas (248). Orscheshek et al. (282) have suggested a common pathogenesis between LCAL and HD on the basis of a chromosomal translocation which results in the expression of a tyrosine kinase gene belonging to the insulin receptor kinase family. Expression of this tyrosine kinase may be linked to type 2 cytokine production and CD30 expression if both HD and LCAL are in fact malignancies characterized by type 2 cytokine excess (228).

### Multiple Myeloma and Castleman's Syndrome

Multiple myeloma has been linked with excess production of the type 2 cytokine IL-6 (183). High levels of IL-6 in serum are associated with worse disease prognosis and more frequent bone lesions (294). Klein et al. (196) recently reviewed the emerging linkage between IL-6 and multiple myeloma. They noted that IL-6 appears to be a paracrine myeloma cell growth factor, derived from monocytic and myeloid cells as well as bone marrow stromal cells, although it may also come from immature tumor cells (preplasma cells) (159). The crucial step in the proliferation of myeloma cells is activation of the gp130 subunit of the IL-6 receptor, which is shared by IL-6, IL-11, leukemia inhibitory factor, oncostatin M, and ciliary neurotrophic factor, all of which are growth factors for malignant plasmablastic cells *in vitro*. Thus, novel therapies for myeloma could include blocking the IL-6 receptor, including the gp130 signal transduction subunit, and blocking IL-6 itself. Few patients with myeloma have received anti-IL-6 antibody as a potential therapy (196). Multiple myeloma has not been associated with elevations of the levels of other type 2 cytokines, of T-cell or non-T-cell origin, and is not characterized by increased IgE levels or eosinophilia.

Castleman's syndrome is a lymphoproliferative disorder which, like multiple myeloma, is associated with high levels of IL-6 and which has been treated with anti-IL-6 antibody (22). Hypergammaglobulinemia and marked but localized lymph node hyperplasia are characteristic of this disease. Interestingly, the lymph node appears to be critical to the pathologic findings of this disease for at least two reasons. First, the increased IL-6 production appears to originate in the B cells of the germinal centers, in large transformed lymphoid cells, and in immunoblasts of the mantle layer and interfollicular zones of the involved lymph nodes. T cells do not appear to be the source of the IL-6. Secondly, resection of the enlarged, localized lymph nodes can result in complete remission of the disease (22, 426). Again, as with multiple myeloma, there is no known elevation of the concentration of other type 2 cytokines in Castleman's disease.

### Kaposi's Sarcoma

The pathogenesis of Kaposi's sarcoma (KS) has also been linked with cytokines, including IL-6 and oncostatin M, two ligands of the gp130 IL-6 common receptor subunit discussed above (139, 254, 424). The pathogenesis of KS has not been directly linked to an imbalance of type 1 and type 2 cytokines. In a preliminary report, however, Romagnani has noted CD8<sup>+</sup> T cells with "an unusual Th2-like phenotype" in KS lesions of persons with HIV-1 infection (316, 317). How these findings integrate with the recent discovery (56) of a novel herpes family virus as an apparent infectious etiology of KS is unclear. As discussed above, at least one example is known of a human virus encoding a type 2 cytokine, namely, the EBV herpes family virus encoding a "viral IL-10" which has functional activity indistinguishable from the biologic IL-10 produced by human leukocytes (104). Hence, if a type 2 cytokine were produced by this putative KS-causing herpes family virus, it would not be without precedent, although its role in the pathogenesis of KS would remain to be defined.

Most of the above-mentioned malignancies are thought to involve increases in the levels of one or more type 2 cytokines. One must ask what clinical conditions would be expected in a malignancy overproducing type 1 cytokines (IL-12, IFN- $\gamma$ , TNF- $\beta$ , or IL-2)? Are there any such recognized cancers? Of the type 1 cytokines, only IL-2 excess has been implicated in a

malignancy, i.e., HTLV-1 ATL. IL-2 is often scarce or absent, however, during the full-blown leukemic manifestations of the disease, even though the alpha chain of the IL-2 receptor is still upregulated. A role for "interleukin-T" (probably identical to IL-15) in ATL has been suggested (15, 48). Malignancies associated with overproduction of type 1 cytokines (IL-2, IL-12, and possibly IL-15) would be predicted to show excessive T-cell or NK cell proliferation (possibly leukemic growth). Alternatively, malignancies associated with excessive IFN- $\gamma$  or IL-12 levels would be predicted to exhibit diffuse inflammatory and granulomatous lesions. Patients with such malignancies would be unlikely to have eosinophilia, hypergammaglobulinemia, or increased IgE levels.

## ATOPIC CONDITIONS

### Cutaneous Atopy

Much of the initial work demonstrating an imbalance in type 1 and type 2 cytokines in humans involved the study of atopic conditions. Many of these studies focused on atopic skin conditions, including house dust mite allergic dermatitis (326, 417), grass pollen immediate-type cutaneous hypersensitivity (292), and atopic eczema (36, 149). In 1990 and 1991, Wierenga et al. (416, 417) demonstrated that the allergen-specific T-cell clones of atopic persons have a high frequency of a type 2 cytokine profile (producing IL-4 but not IFN- $\gamma$ ). Kay et al. demonstrated a predominant type 2 cytokine mRNA pattern in allergen-induced late-phase cutaneous reactions (185). In 1991, Romagnani summarized the evidence for human Th type 1 and type 2 expression, emphasizing that patients with atopy afforded convincing evidence of type 2 cytokine-predominant states (314).

### Atopic Asthma

Persons with atopic asthma have bronchial and bronchoalveolar T cells displaying type 2-predominant cytokine profiles. Robinson et al. (312) reported in 1992 that persons with atopic asthma had leukocytes (mainly T cells and fewer eosinophils and mast cells) in their bronchoalveolar lavage fluid that expressed a predominance of IL-4 and IL-5 mRNA, with little IFN- $\gamma$  mRNA. This classic cytokine pattern was modified, however, by modest increases in IL-2 mRNA levels. Similarly, Del Prete et al. found that grass pollen allergen challenge can activate type 2 cytokine production. They derived T-cell clones from bronchial and nasal airway mucosa of persons with atopic asthma and allergic rhinitis (91). More recently, increased IL-13 mRNA and protein levels have been found in the bronchoalveolar lavage fluid of allergen-challenged asthmatic patients, suggesting that this type 2 cytokine may contribute to the allergen-induced inflammatory response of asthma (174).

Corrigan and Kay (79) proposed a model for the pathogenesis of atopic asthma in which predominantly type 2 cytokine (IL-4 and IL-5) production by T cells in response to allergens or virus antigens leads to bronchospasm and bronchial inflammation. Eosinophils are the primary inflammatory effector cells in this model, in conjunction with mast cells. We would propose that these eosinophils contribute to the type 2 cytokine state by the production of IL-4 and IL-5. As noted above, in a type 2 cytokine (IL-4) milieu, CD8<sup>+</sup> T cells responding to a respiratory viral infection may switch from production of IFN- $\gamma$  to production of IL-5, thereby inducing the pulmonary eosinophilic inflammation characteristic of atopic asthma (82).

In 1994, Kline and Hunninghake reviewed the role of T cells and cytokines in asthma (197). They emphasized the inflam-

matory nature of the disease and the predominant involvement of IL-4 and IL-5 in atopic asthma. A potential role for type 1 cytokines in the etiology of a minority of cases of asthma, however, was proposed (197). Barnes and Liew have expanded the model of type 1 and type 2 cytokines and asthma to include nitric oxide. They propose that NO from airway epithelial cells inhibits IFN- $\gamma$ . This decrease in IFN- $\gamma$  levels results in increased IL-4 and IL-5 levels, which in turn lead to increased IgE levels and recruitment of eosinophils into the lung (20). Holt has actually proposed the development of a vaccine against asthma based on modulation of the type 1 and type 2 cytokine profile (170).

Glucocorticoids are one form of therapy for asthma; however, why some patients do not respond to steroids is not well understood. Leung et al. (209) compared patients with steroid-sensitive or steroid-resistant asthma before and after 1 week of prednisone therapy. The steroid-sensitive group had a decrease in the number of bronchoalveolar lavage fluid-derived cells expressing IL-4 and IL-5 mRNA by *in situ* hybridization and an increase in the number of cells expressing IFN- $\gamma$  mRNA. In contrast, the steroid-resistant patients had no decrease in the number of cells expressing IL-4 or IL-5 mRNA but did have a decrease in the number of cells expressing IFN- $\gamma$  mRNA. A pathophysiologic mechanism for steroid-resistant asthma was postulated to involve a combination of type 1 and type 2 cytokine dysregulation with impairment of glucocorticoid binding to T cells.

### Vernal Conjunctivitis

Maggi et al. derived T-cell clones from mitogen-activated conjunctival T cells and PBMCs of three persons with seasonal (vernal) conjunctivitis, an atopic condition associated with increased IgE levels (231). The conjunctival T-cell clones were predominantly CD4<sup>+</sup>. After PHA stimulation, the majority of the conjunctival T-cell clones produced IL-4 while few produced IFN- $\gamma$ . In contrast, the majority of peripheral blood-derived clones produced IFN- $\gamma$ . Culture supernatants from these conjunctival clones could induce IgE production by normal B cells. Interestingly, compared with PHA stimulation, PMA and anti-CD3 stimulation yielded a higher proportion of conjunctival T-cell clones producing IFN- $\gamma$ , although the majority still produced IL-4. In addition, the proportion of conjunctival clones producing IL-2 was intermediate between those producing IL-4 and those producing IFN- $\gamma$ , a pattern also reported in asthma (312). This example reemphasizes the importance of noting the specific *in vitro* stimuli used when interpreting type 1 and type 2 cytokine data.

Conjunctival lesions similar to those seen with vernal conjunctivitis have been found in a transgenic-mouse model with overexpression of IL-4 by Tepper et al. (381). An eosinophilic infiltrate was also noted in this model. Subsequently, this model was used to demonstrate localized mast cell degranulation and release of histamine, which may contribute to the eyelid inflammation (110).

## INFLAMMATORY AND AUTOIMMUNE DISEASES

### Giant Cell (Temporal) Arteritis

In 1994, Weyand et al. (413) presented evidence of type 1 cytokine excess in giant cell (temporal) arteritis (GCA). They studied *in vivo* cytokine mRNAs by PCR, using temporal artery biopsy specimens from patients with GCA and with polymyalgia rheumatica (PMR), two conditions that may share a clinical spectrum of disease (137). A predominance of IFN- $\gamma$ ,

as well as IL-2, was found in the biopsy specimens from the persons with GCA, but little or no IFN- $\gamma$  was found in the specimens from the persons with PMR or controls without lesions suggestive of GCA or PMR. Interestingly, these authors also found evidence of macrophage activation in GCA but not PMR, consistent with the finding of IFN- $\gamma$  in the former but not the latter.

On the basis of these cytokine findings, the authors postulated that pharmacologic agents that selectively impair IFN- $\gamma$  production, for example via increases in cyclic AMP levels, may represent a feasible, novel therapy for GCA. Several investigators have shown that certain prostaglandins, such as prostaglandin E<sub>2</sub> inhibit the production of IFN- $\gamma$  and IL-2 but not IL-4 or IL-5, resulting in a relative type 2 cytokine predominance (28, 142, 165, 181). Moreover, Gold et al. (142) have reported that the prostaglandin E<sub>1</sub> analog misoprostol also inhibits type 1 but not type 2 cytokines.

### Systemic Lupus Erythematosus

Studies of SLE by Via et al. revealed a spectrum of APC and T-cell defects which could be consistent with loss of a type 1 Th cytokine profile (392). In a study of 150 patients with SLE, Bermas et al. (26) found that diminished T-cell function correlated with increased clinical disease activity. T-cell function was assessed by IL-2 production after stimulation with recall antigens, alloantigens, or PHA. In this study, 50% of patients responded to all three types of stimulation, 42% did not respond to recall antigens but did respond to alloantigens and PHA, and 8% responded only to PHA. Llorente et al. reported that elevated levels of IL-10 are produced by monocytes and B cells, but not T cells, in persons with SLE (214, 215). IL-10 may contribute more than IL-6 to the B-cell hyperactivity and hypergammaglobulinemia seen with SLE. SCID mice given PBMCs from persons with SLE produced autoantibodies, whose level was reduced by anti-IL-10 antibody but not anti-IL-6 antibody. Furthermore, the in vitro spontaneous Ig production by PBMCs from SLE patients was decreased by antibody to IL-10 (214, 215).

### Rheumatoid Arthritis

Miltenberg et al. (256) found a type 1 cytokine predominance (IFN- $\gamma$  without IL-4) in T-cell clones derived from the synovial membrane of patients with rheumatoid arthritis (RA). Most of these T-cell clones were CD8<sup>+</sup>. Quayle et al. (304) derived CD4<sup>+</sup> T-cell clones that also were predominantly type 1 (producing IFN- $\gamma$  without IL-4) from blood, synovial fluid, and synovial membranes of patients with RA. However, a minority of clones also produced type 2 cytokines, including IL-10. Conversely, Gold et al. (142) proposed that RA is dominated by type 2 Th cells on the basis of their observations of synovial fluid T cells producing primarily IL-4 and of the hypergammaglobulinemia associated with RA.

Katsikas et al. (182) found IL-10 protein and IL-10 mRNA in the joints of persons with RA. Both T cells and monocytes appeared to be sources of this IL-10, which was constitutively produced by these cells in vitro. Addition of anti-IL-10 antibody to the synovial membrane cultures increased the production of TNF- $\alpha$  and IL-1 $\beta$ , whereas addition of exogenous IL-10 had the opposite effect. Thus, IL-10 may play a role in both RA and SLE (214), although neither disease is likely to be associated purely with a type 1 or type 2 cytokine profile.

### Autoimmune Thyroid Diseases

Romagnani (314) found that the thyroid tissue of persons with autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis contains CD4<sup>+</sup> T cells which can be mitogen stimulated in vitro to develop into T-cell clones producing IFN- $\gamma$  but not IL-4. Moreover, from retroorbital T-cell infiltrates of persons undergoing orbital decompression for Graves' disease ophthalmopathy, De Carli et al. (85) derived a high proportion of cytolytic CD4<sup>+</sup> and CD8<sup>+</sup> T cells which could secrete type 1 cytokines (IFN- $\gamma$  and IL-2) but not type 2 cytokines (IL-4 and IL-5). A similar pattern of type 1 T-cell excess was not found in the peripheral blood of these patients, again emphasizing that compartmentalization of cytokine dysregulation does occur in vivo.

Earlier studies of T-cell clones derived from thyroid T-cell infiltrates of persons with Graves' disease and Hashimoto's thyroiditis by these investigators revealed similar findings in terms of the type 1 cytokine profile. Maggi et al. studied T-cell clones derived from intrathyroidal T cells from three patients with Graves' disease who underwent partial thyroidectomy (231). After PHA stimulation, 84% produced IFN- $\gamma$  and only 5% produced IL-4 (231). De Carli and coworkers suggested that the retroorbital and thyroid infiltrates in Graves' disease and thyroid infiltrates in Hashimoto's thyroiditis may be the result of an autoimmune disease characterized by excessive production of IFN- $\gamma$  (85, 96).

### Sarcoidosis

In 1992, Devergne et al. (102) reported increased expression of IFN- $\gamma$  and IL-1 as determined by in situ hybridization in lymph nodes containing sarcoid granulomas. A lower level of expression of the IL-2 and TNF- $\alpha$  genes was found. The finding of high levels of IFN- $\gamma$  and IL-1 inside granulomas may serve as a general marker for DTH-type granulomatous diseases, since sarcoidosis exemplifies a DTH reaction. Earlier studies on sarcoidosis demonstrated compartmentalized increases in IFN- $\gamma$  and IL-2 levels in the lungs but not the peripheral blood. Overproduction of these cytokines within the lungs was attributed to activated (HLA-DR<sup>+</sup>) CD4<sup>+</sup> T cells (311, 329). For at least some diseases with increased IFN- $\gamma$ , such as sarcoidosis, GCA, Hashimoto's thyroiditis, Graves' disease, psoriasis, and multiple sclerosis, we would predict that levels of IL-12 and/or IL-12 biologic activities are increased, leading to a state of IFN- $\gamma$  excess.

### Psoriasis

Psoriasis may represent an autoimmune disease involving a pathologic interaction between CD4<sup>+</sup> T cells and keratinocytes. Several laboratories studying psoriasis have reported a type 1 cytokine predominance (324, 337). These studies have involved PCR for cytokine mRNA in involved skin (337), as well as cytokine production by T-cell clones derived from epidermal lesions. Increased IFN- $\gamma$  mRNA production has also been found in chronic eczematous skin lesions, although type 2 cytokines predominate in the early phase of this condition (149).

Mononuclear cells from the synovial fluid of patients with psoriatic arthritis show evidence of a type 1 cytokine profile (IFN- $\gamma$  but no IL-4) (337). Thus, evidence for a type 1 cytokine predominance in synovial fluid from a small number of patients with any one of five different diseases has been reported: *Yersinia*- and *Chlamydia*-reactive arthritis, RA, *B. burgdorferi* (Lyme) chronic arthritis, and psoriatic arthritis (204, 256, 302, 304, 336, 337, 361, 428, 429).

### IgA Nephropathy

IgA nephropathy, a common cause of glomerulonephritis, is associated with increased serum IgA levels and increased numbers of activated CD4<sup>+</sup> T cells. Increases in IFN- $\gamma$  levels in serum have been found in association with increases of disease activity (425). Lai et al., however, analyzed mRNA for IL-2, IL-4, IL-5, and IFN- $\gamma$  from CD4<sup>+</sup> T cells by reverse transcription-PCR from 25 patients with IgA nephropathy; they found no evidence of an imbalance in type 1 or type 2 cytokine mRNA (205).

### Multiple Sclerosis

Brod et al. (41) cloned T cells from the cerebrospinal fluid (CSF) and blood of three persons with multiple sclerosis (MS). Compared with clones from three controls without meningitis, they found induction by PMA or ionomycin of mRNA for IFN- $\gamma$  and IL-2 but not IL-4 or IL-5 in the CSF of two of three MS patients and none of three controls. All three MS patients but none of the controls had such type 1 cytokine-producing cells. Most of the clones derived from both groups of donors had mRNA of both type 1 and type 2 cytokines.

Benvenuto et al. (25) obtained CSF lymphocytes from two patients with active MS and established CD4<sup>+</sup> and CD8<sup>+</sup> T-cell clones. They found production of IFN- $\gamma$  and IL-2 but not IL-4 after PHA stimulation. Of note, they also found high levels of TNF- $\alpha$ , reminiscent of the cytokine profile found in the orbital tissue of patients with Graves' disease (85). As controls, they used T-cell clones from patients with CAH. These clones produced much less TNF- $\alpha$  than did the CSF-derived clones but otherwise also had a type 1 profile.

Tomioka et al. (383) studied 20 patients with MS and measured IL-2 levels in CSF and serum by ELISA. Compared with healthy controls and persons with noninflammatory neurologic diseases, patients with MS had statistically significantly higher levels of IL-2 in both CSF and serum. In addition to IL-2, IFN- $\gamma$ , and TNF- $\alpha$ , another type 1 cytokine, TNF- $\beta$  (lymphotoxin) has been linked to MS lesions (353). T cells appear to be the source of the TNF- $\beta$ .

The murine model for MS is experimental allergic encephalomyelitis (EAE) (255). Liblau et al. (210) have reviewed the concept that EAE is a model for autoimmune disease mediated by type 1 cytokine-producing T cells specific for myelin basic protein. Racke et al. (306) have tested this hypothesis by giving IL-4 to animals with EAE. As predicted, IL-4-treated animals had less clinical disease and had induction of Th2-like cells specific for myelin basic protein.

Leonard et al. have demonstrated that murine IL-12 enhances EAE and antibody to murine IL-12 inhibits EAE (208). If a similar role for IL-12 is demonstrated for MS, the full array of type 1 cytokines (IL-2, IFN- $\gamma$ , TNF- $\beta$ , and IL-12) may be implicated in the pathogenesis of MS. A novel therapy for MS may consist of inducing a shift from a type 1 to type 2 cytokine profile by use of type 2 cytokines and/or antibodies to type 1 cytokines.

### BENCH TO BEDSIDE AND CLINIC: IMPLICATIONS OF THE TYPE 1-TYPE 2 CYTOKINE MODEL FOR DISEASE PREVENTION AND THERAPY

Multiple therapeutic strategies for human diseases can be designed to optimize the type 1-type 2 cytokine balance. Examples of these strategies include type 1 and type 2 cytokines themselves, antibodies against these cytokines, antibodies against cytokine receptors, soluble cytokine receptors, and drugs (e.g., thalidomide) or other cytokines (e.g., IFN- $\alpha$ ) that

modulate the type 1-type 2 cytokine balance. Immune system-based therapy, combined with drug therapy, in this era of "emerging" and multidrug-resistant infectious diseases and malignancies may become essential over the next decade for the optimal control and cure of a growing array of human diseases. The rational design and testing of new vaccines and adjuvants against diseases such as AIDS, TB, leprosy, RSV infection, and parasitic diseases may become possible with an understanding of the optimal vaccine-induced type 1 (cellular) and type 2 (antibody) cytokine responses.

In this review multiple examples of the therapeutic uses of cytokines have been discussed. Most of these examples have involved type 1 cytokines. For example, IFN- $\gamma$  has been used for lepromatous leprosy, hyper-IgE syndrome, Ommen's syndrome, HIV-1 infection, chronic *M. avium* pneumonia, chronic granulomatous disease, and, in combination with antimony therapy, VL (135, 169, 274, 332, 333, 371); IL-2 has been used in conjunction with zidovudine for HIV-1 infection (201) and certain malignancies; and IL-12 has entered clinical trials for HIV-1 and malignancies. In addition, IL-2 has been proposed for the treatment of tuberculosis (201, 334). Given the emerging epidemic of multidrug-resistant TB and the encouraging results of Holland and colleagues using IFN- $\gamma$  to treat *M. avium* pulmonary infection (169), IFN- $\gamma$  or IL-12 could also be studied in conjunction with chemotherapy against multidrug-resistant TB.

On the basis of animal studies with fungal infections such as candidiasis (320, 321) and cryptococcal meningitis (64), IL-12 may also play a role in the treatment of these and other systemic mycoses which appear to rely on CMI for their control, i.e., blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and histoplasmosis. Again, optimal therapy may be achieved by combining antifungal drug therapy (e.g., fluconazole, amphotericin B, itraconazole, or ketoconazole) with cytokine therapy. Since IL-12 acts partially through stimulation of IFN- $\gamma$ , IFN- $\gamma$  should also be considered in the treatment of fungal diseases (171). Given the poor prognosis of fungal (particularly *Aspergillus*) endocarditis, hepatosplenic candidiasis, and disseminated mycoses in general, cytokine therapy in conjunction with antifungal drug therapy should be considered in these conditions.

Surprisingly, even systemic administration of IL-12 appears to have activity against cryptococcal meningitis in a murine model. If a similar effect of IL-12 could be demonstrated in humans for cryptococcal and other forms of fungal meningitis (e.g., due to *Coccidioides*, *Histoplasma*, and *Candida* spp.), the currently problematic management of these diseases could be significantly improved.

Important variables in the use of cytokines as therapy include the route and schedule of administration, duration of effect, toxicities, interactions with other parts of the cytokine network, body compartment(s) of the disease, stage of disease, and cytokine environment of the disease process. Organ-specific cytokine delivery systems may become feasible, e.g., aerosolized cytokine therapy (IFN- $\gamma$ , IL-12, others) for pulmonary disease (mycobacterial, fungal, parasitic, or asthmatic) or intestinal delivery systems for small-bowel or colonic diseases (such as inflammatory bowel diseases). Such site-directed therapy for compartmentalized disease processes should minimize the systemic toxicities of cytokine therapy.

Multiple hazards of therapy with cytokines have already been documented in human and animal studies. For example, Orange et al. (281) studied IL-12 in murine lymphocytic choriomeningitis virus infection and found that lower doses of IL-12 enhanced cellular immunity and decreased viral replication. At higher doses, however, IL-12 impaired CMI, and virus

replication increased. The mechanism of this higher-dose IL-12 toxicity appeared to be associated with induction of TNF- $\alpha$  and corticosteroids in vivo. Interestingly, the authors speculated that dengue virus hemorrhagic shock syndrome could be related to viral induction of an IL-12-like cytokine with acute overproduction of TNF- $\alpha$  (280). IL-2 therapy has often been associated with diverse metabolic, vascular, hematologic, and severe "flu-like" side effects (280, 343, 382). These effects can vary with dose and treatment schedules. IFN- $\gamma$  therapy also has side effects, including development of erythema nodosum leprosum in persons being treated for lepromatous leprosy (332).

Cytokine therapy may also be complicated by the development of anticytokine antibodies or binding of the administered cytokine to endogenous anticytokine antibodies. For example, Turano and colleagues (51, 388) found endogenous antibodies against IFN- $\gamma$  at low levels in healthy individuals and at increased levels in persons with certain disease states, including HIV-1 infection. They note that endogenous antibodies against other cytokines such as IFN- $\alpha$  and TNF- $\alpha$  have also been found in the sera of normal donors. Extrapolating from the observation that anti-IFN- $\gamma$  antibodies appear to protect NZB mice against autoimmune disease, they suggested that anti-IFN- $\gamma$  antibodies could be therapeutic candidates for clinical trials against SLE, RA, MS, or any condition with excessive cellular immune activity. Similarly, Hansen et al. (158) emphasized that endogenous IgG antibody to IL-6 occurs in healthy individuals, in disease states, and possibly in response to exogenous IL-6. Anti-IL-6 antibody has been given to a limited number of patients with multiple myeloma and Castleman's syndrome, with variable results (22, 196).

Additional potential cytokine-based therapeutic strategies involve the administration of exogenous antibodies against type 1 or type 2 cytokines or against cytokine receptors (e.g., anti-IL-2 receptor antibody therapy for HTLV-1 ATL/lymphoma). Similarly, soluble cytokine receptors may prove effective in decreasing free cytokine levels. Bloom has advocated the use of antibodies against type 2 cytokines for certain disease states (e.g., leishmaniasis) in which CMI is impaired (31). Anti-IL-4 may play a role in treating fungal (171) and parasitic infections and other conditions associated with increased IgE levels. Conversely, antibody against IL-12 or therapy with IL-4 itself (306) may be of value in some autoimmune conditions, such as MS, by decreasing the ratio of type 1 to type 2 cytokines (208).

Certain drugs have recently been recognized to modulate the type 1-type 2 cytokine balance. For example, thalidomide has been reported to effect a type-1 (decrease in IFN- $\gamma$ )-to-type-2 cytokine switch in PBMCs after stimulation with recall antigen or PHA mitogen. Thalidomide also decreases TNF- $\alpha$  production by monocytes (246). This decrease in TNF- $\alpha$  production could be related to deactivation of monocytes by the decreased IFN- $\gamma$  production from T cells and/or NK cells. Prostaglandins such as prostaglandin E<sub>2</sub> and E<sub>1</sub> analogs (e.g., misoprostol) have been reported to inhibit type 1 cytokine production and switch Th0-like cells to type 2 cytokine production (142). Weyand et al. have suggested that such agents might be used in diseases such as GCA in which excess IFN- $\gamma$  may play a pathogenic role (413). Conversely, anti-inflammatory drugs which inhibit these prostaglandins might enhance type 1 cytokine responses and be of potential value in treating type 2 cytokine-predominant diseases (142).

Corticosteroids are a commonly used therapy for many diseases, some of which may be conceptualized as type 1 cytokine predominant (e.g., GCA, sarcoidosis, and MS) and some of which may be type 2 predominant (e.g., asthma, HES, and ABPA). Steroids may act to decrease the dominant cytokine

profile, whether type 1 or type 2. As discussed for asthma (209), the development of resistance to steroid therapy may be associated with a loss of the ability to control the dominant cytokine profile, through alteration of steroid binding to T cells or through other mechanisms. Given the spectrum of side effects associated with steroid therapy, a more specific, immune system-based therapy directed at restoring the particular cytokine imbalance of a given disease warrants study. For example, trials of type 1 cytokines such as IFN- $\gamma$  or IL-12 for the management of asthma, HES, or ABPA could be undertaken. Similarly, type 2 cytokines such as IL-4 or IL-10, prostaglandins (prostaglandin E<sub>2</sub>), or antibody to IFN- $\gamma$  or to IL-12 could be studied as therapy for GCA, sarcoidosis, or MS.

Cytokines such as IFN- $\alpha$  can also modulate the type 1-type 2 balance. IFN- $\alpha$  can increase IFN- $\gamma$  levels and decrease IL-4-mediated IgE production (40, 296). This may contribute to the effects of IFN- $\alpha$  in its current role as a therapy for HES, KS, hepatitis C virus infection, HIV-1 infection, basal cell carcinoma, and certain forms of leukemia. Thus, diverse medical interventions including drugs, prostaglandins and prostaglandin inhibitors, non-type 1 or type 2 cytokines, and even blood transfusions (161, 194) can modulate the type 1-type 2 cytokine balance.

More generally, understanding the mechanisms whereby the cytokine profile is skewed toward type 1 or type 2 predominance will open new approaches to therapy and prevention. For example, a better understanding of the complexities of the APC-T-cell interaction in terms of the type of APC, the concentration of antigen, the expression of costimulatory molecules, and the cytokine environment in which the interaction occurs would allow manipulation away from pathologic cytokine dysregulation. Therapeutic intervention could be directed specifically at the primary APC, whether macrophage, B cell, dendritic cell, or eosinophil, or at the APC-T-cell interaction.

Preventive vaccines are also being examined from the perspective of type 1 and type 2 cytokines, i.e., CMI as well as humoral immunity. Such vaccines and candidate vaccines include those for measles (404), RSV infection (76, 145, 146, 375, 376), leishmaniasis (3), TB (32, 38), leprosy (38), syphilis (352), and HIV-1 infection (34, 240, 366). Strategies for vaccination to prevent not only infectious diseases but also atopic diseases, including asthma (170), have been proposed on the basis of the type 1-type 2 cytokine paradigm.

Cytokines are also under investigation as adjuvants for vaccines in animal models (e.g., IL-12 for vaccines against leishmaniasis, RSV infection, and schistosomiasis (3, 335, 420), as are antibodies to cytokines (e.g., anti-IL-4 and/or anti-IL-10 for a vaccine against RSV infection [76, 145, 146, 375]). Other potential adjuvants which induce a type 1 or type 2 cytokine bias (e.g., *Brucella abortus* induction of IFN- $\gamma$ ) are also under study (5, 30, 143). Hughes and Babiuk have recently reviewed the immunologic effects of conventional and novel vaccine adjuvants, within the context of cytokine production (175). In addition to adjuvants, vaccine dose (low dose versus high dose) may be critical in the optimization of cellular and humoral immune responses against certain diseases, with low-dose antigen usually considered to elicit more CMI than humoral immunity (38, 39, 328).

Finally, the rapidly emerging field of DNA vaccines (389) is closely linked to the concept that a strong CMI response may be at least as critical to the efficacy of a prophylactic or therapeutic vaccine as is a strong humoral immune response. DNA vaccines stimulate strong CD8<sup>+</sup> CTL responses, since the DNA enters the MHC class I pathway, whereas conventional vaccine antigens are proteins which enter primarily the MHC class II system and optimize antibody responses (245). Animal

model studies are already under way with DNA vaccines against influenza, hepatitis B and C, HIV-1 infection, malaria, schistosomiasis, and TB, among others. An integral part of the immunologic evaluation of these first-generation DNA vaccines is assessment of type 1 and type 2 cytokine induction and the relation of these cytokines to CMI and antibody induction. Thus, DNA vaccines afford one means of testing the clinical relevance of the type 1-type 2 cytokine model and the immunologic relevance of the model for understanding disease pathogenesis as well as for understanding human CMI and humoral immune responses.

## CONCLUSIONS

The focus of this review has been on the heuristic value of looking at the pathogenesis and therapy of human diseases from the immunologic perspective of the type 1-type 2 cytokine model. During the past decade since the landmark discovery of Th1 and Th2 clones, an expanding array of cells (including CD8 T cells and non-T-cell leukocytes) which make type 1 and type 2 cytokines have been recognized and a growing number of these cytokines (e.g., IL-5, IL-6, IL-10, IL-12, and IL-13) have been described. Emphasis has shifted from the CD4<sup>+</sup> T cell as the source of "Th1 and Th2" cytokines to the functional effect of the type 1 and type 2 cytokines regardless of their cell of origin. Moreover, the critical role of the monocyte/macrophage in this cytokine model has been increasingly recognized. The eosinophil may play a crucial role as well, being both a marker of and a contributor to type 2 cytokine-dominant states.

In addition, our understanding about how type 1 and type 2 cytokines interact with other cytokines (e.g., TNF- $\alpha$  and IL-10; IFN- $\alpha$  and IFN- $\gamma$ ) and how they cross-regulate each other (e.g., type 1 [IFN- $\gamma$  and IL-12] versus type 2 [IL-4 and IL-10]) has increased. Appreciation of the complex interactions of CMI responses (favored by type 1 cytokines) and humoral immune responses (favored by type 2 cytokines) has continued to evolve since the time of Metchnikoff and Ehrlich a century ago. Their productive debates about the relationship between cellular and humoral immunity can be seen continuing into the 1960s and 1970s (reviewed by Parish [290]), then into the mid-1980s with the discovery by Mosman and Coffman of murine Th1 and Th2 cytokines and their relationship to cellular and humoral immune responses, and finally into the 1990s with the study of type 1 and type 2 cytokines in humans and their relationship to disease pathogenesis, immunology, therapy, and vaccinology.

How can the clinician apply the type 1-type 2 cytokine model to the practice of medicine in the 1990s? From a clinical diagnostic perspective, a type 2 cytokine-predominant state is more readily suggested from a patient's history and clinical laboratory information than is a type 1 cytokine-dominant response. For example, a history of atopy and elevated IgE levels in serum suggest increased IL-4 (or possibly IL-13) levels, atopy or eosinophilia suggests increased IL-5 levels, and hypergammaglobulinemia (IgG) suggests increased IL-6 and/or IL-10 levels. Absence of skin test reactivity (DTH) may indirectly suggest a type 2 cytokine-dominant state due to impaired CMI. The probability that several of these type 2 cytokines are elevated at the same time is higher when more than one of the above abnormalities (atopy, high IgE or IgG levels, eosinophilia, anergy) are present simultaneously. Other clinical clues to type 2 cytokine-dominant conditions include helminthic and some protozoan parasitic infections, atopic asthma, mycobacterial infections, and systemic fungal infections, particularly

when chronic or progressive, implying an inadequate CMI response.

Type 1 cytokine-predominant responses are less readily apparent from serum tests or the differential on the complete blood count. In general, however, type 1 cytokine-predominant conditions should be considered in infections with intracellular pathogens (mycobacteria and selected bacteria, viruses, and fungi), as well as in certain granulomatous or inflammatory diseases (e.g., GCA, sarcoidosis, MS, Graves' disease and Hashimoto's thyroiditis, reactive arthritis-synovitis, and Lyme arthritis).

From a therapeutic perspective, immune system-based therapy combined with drug therapy will probably prove essential in the arriving age of multidrug-resistant and "emerging" disease (infectious and noninfectious) epidemics. Currently available medications, as well as investigational drugs and prostaglandins, are being examined in terms of their effect on type 1-type 2 cytokine regulation, as are preventive vaccines and their adjuvants, blood transfusions, and administration of non-type 1 or type 2 cytokines.

The nomenclature of the type 1-type 2 cytokine model and the experimental methodology testing this model continue to evolve and to stimulate controversy. Evidence of the heuristic value of the type 1-type 2 cytokine model in the study of human diseases and their treatment and prevention is provided by the rapidly increasing literature in this field since 1990. If the type 1-type 2 cytokine model can provide insight into human disease pathogenesis, it should afford novel therapies and vaccines against these diseases as proof of the clinical value of the model.

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