Editorial

The study of lymphokines and cytokines has contributed greatly over 25 years to understanding regulatory and effector functions of cell-mediated immunity in molecular terms. There has been a continuing hope that lymphokines, available in potentially unlimited quantities, albeit at considerable expense, would have a major impact on treatment of infectious, neoplastic, and autoimmune diseases. However, with some notable exceptions, e.g., GM-CSF, lymphokine therapy has not been terribly successful. There are many reasons: most cytokines have very short biological half-lives, they are difficult to target and maintain at the sites where they are most needed, and systemic administration in large amounts led to unanticipated toxicities. The premise that single lymphokines or cytokines could carry out the desired important functions directly, probably requires revising, since the analysis of the dynamics of lymphokines produced in lesions indicates that it is the mix of lymphokines that probably determines the protective and pathogenetic outcomes.

In mice functional CD4 cells were found to comprise mutually exclusive subsets that produce predominantly either IL-2 and IFN-γ (Th1 or type 1 cells), or IL-4, IL-5, and IL-10 (Th2 or type 2 cells). A third subset of memory cells can produce all the lymphokines in low levels (Th0 cells). The existence of functional T cell subsets in humans that could be distinguished by their lymphokine patterns has been much more problematic until recently. Results from several laboratories studying individuals whose immune systems are actively engaged by antigen, for example by infection or allergy, suggest that defined functional subsets of both CD4 and CD8 T cells do exist in humans, although the differences in lymphokine patterns are quantitative rather than qualitative (1–3). Increasing evidence indicates that these functional subsets are mutually antagonistic, i.e., type 2 cells inhibit type 1 T cell function, and vice versa, such that the decision of which subset predominates within an infection may determine its outcome.

Two human tropical infectious diseases have provided unique insights into the dynamics of T cell function where the action is, in the lesions. Both leprosy and leishmaniasis are infectious diseases whose lesions are readily accessible for study and which produce a spectrum of clinical manifestations. These diseases also exhibit a spectrum of immune responses ranging from heightened cell-mediated immunity associated with restriction of the parasite dissemination but resulting in tissue damage, to a state of selective immunological unresponsiveness to all the antigens of the parasite. Insight into the selective inability to respond effectively to the leishmanial parasite is provided by two papers in this issue of *The Journal.* Both use molecular technology to amplify mRNAs for a variety of lymphokines from human biopsies that had previously been effective in distinguishing lymphokine patterns in healing or relative progressing lesions of leprosy (4). Karp et al. (5) report that in patients with active visceral leishmaniasis whose cell-mediated immunity is suppressed, differential expression of IL-10 and IFN-γ mRNAs was seen in bone marrow biopsies. Since IL-10 is known, in the presence of macrophages, to suppress type 1 CD4 cell function, they implicate IL-10 in the suppression of cell-mediated immunity in these patients. In studies on skin lesions of localized American cutaneous leishmaniasis, Pirmez et al. (6) observe a predominance of IL-4 mRNA also with an increased level of IL-10 mRNA in patients with chronic and destructive mucocutaneous forms of the disease. Other studies in leishmaniasis indicated that while IFN-γ levels were comparable, IL-4 was found to be elevated in the serum of patients with visceral leishmaniasis (7) and IL-4 and IL-10 are found differentially expressed in lesions of immunologically unresponsive diffuse cutaneous leishmaniasis patients (8). Together these studies suggest that the failure to mount a protective immune response in patients with visceral or cutaneous leishmaniasis is due to the relatively higher levels of two cytokines known to antagonize the proliferation and function of Th1 cells.

Cytokine therapy for human diseases has most often been thought about in positive terms for intervening with lymphokines or their agonists directly. Clearly one long-term hope of the present work is that IL-4 and IL-10 might be harnessed to permit useful immunosuppressive interventions in autoimmune diseases. But perhaps we should think more negatively in the sense of seeking to neutralize molecules such as IL-10 or IL-4 that suppress protective immune responses or which are responsible for tissue damage. It is noteworthy that in a mouse model of leishmaniasis in which a protective type 1 T cell response was inhibited by type 2 T cells, administration of IFN-γ, known to be critical to protection, was not able to induce cure. Administration of neutralizing monoclonal antibody to IL-4, however, was able to bring about resolution of the infection (9). In the present papers, IFN-γ was found in most lesions, yet healing did not occur. Since the suppressive activities of lymphokines appear to be epistatic or dominant (10), the present studies suggest that it may be time to consider carefully the potential of antilymphokine and anticytokine therapy. Treatment could include specific neutralizing monoclonal antibodies, or lymphokine receptor antagonists. By analogy with the successful therapy of susceptible mice with anti-IL-4 treatment, one could contemplate treating patients unable to develop an appropriate protective response against leishmaniasis with anti-IL-4 or anti-IL-10 antibodies, or possibly, a combination of these antibodies, to block the factors responsible for inhibiting development of protective cell-mediated responses. One could ascertain whether after short-term anticytokine therapy, the balance between type 1 and type 2 responses would be restored to a protective response. Alternatively under cover of the anticytokine therapy, the efficacy of therapeutic vaccines against leishmaniasis (11) could well be significantly improved and the duration of treatment shortened. Specific anticytokine treatment in infectious, allergic, and autoimmune diseases represents a therapeutic strategy that could be clinically effective and provide new insights into immunoregulation in humans.

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J. Clin. Invest.
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0021-9738/93/04/1265/02 $2.00
Volume 91, April 1993, 1265–1266

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