A large body of evidence suggests the existence of functionally polarized human T cell responses based on their profile of cytokine secretion in both the CD4+ T helper (Th) and the CD8+ T cytotoxic (Tc) cell subset. Human Th1 and Th2 cells not only produce a different set of cytokines but also exhibit distinct functional properties and the preferential expression of some activation markers, such as LAG-3 and CD30, respectively. Several factors may influence Th cell differentiation into the polarized Th1 or Th2 pathway. They include the cytokine profile of "natural immunity" evoked by different offending agents, the nature of the peptide ligand, as well as the activity of some costimulatory molecules and microenvironmentally secreted hormones, in the context of different host genetic backgrounds. Strongly polarized human Th1-type and Th2-type responses not only play different roles in protection, Th1 being effective in the defense against intracellular pathogens and Th2 against intestinal nematodes, but are also responsible for different types of immunopathological reactions. Th1-dominated responses may be involved in the pathogenesis of organ-specific autoimmune disorders, acute allograft rejection, unexplained recurrent abortions, contact dermatitis, and some chronic inflammatory disorders of unknown etiology. In contrast, Th2-type responses are responsible for Omenn's syndrome, reduced protection against some intracellular pathogens, transplantation tolerance, chronic GVHD, atopic disorders, and some systemic autoimmune diseases.

**T1- AND T2-TYPE CELLS: POLARIZED FORMS OF THE SPECIFIC IMMUNE RESPONSE**

**Definition of CD4+ Th1 and Th2 Cells**

CD4+ T helper (Th) lymphocytes can be classified into different types based on their cytokine profile. Th1 cells produce interferon-gamma (IFN-γ), interleukin (IL) 2, and tumor necrosis factor (TNF)-β and promote the production of opsonizing and complement-fixing antibodies, macrophage activation, antibody-dependent cell cytotoxicity, and delayed type hypersensitivity (DTH) (1, 2). For these reasons, Th1 cells can be considered as responsible for the phagocyte-dependent host response (3). On the other side, Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 and provide optimal help for humoral immune responses, including IgE and IgG1 isotype switching and mucosal immunity, through induction of mast cell and eosinophil growth and differentiation and facilitation to IgA synthesis. Moreover some Th2-derived cytokines, such as IL-4, IL-10, and IL-13 inhibit several macrophage functions (1, 2). Therefore, it is possible to refer to Th2 cells as responsible for the phagocyte-independent host response (3). In the absence of clear polarizing signals, CD4+ T cell subsets with a less differentiated lymphokine profile than Th1 or Th2 cells, designated Th0, usually arise that mediate intermediate effects depending upon the ratio of lymphokines produced and the nature of the responding cells (1, 2). Th0 cells probably represent a heterogeneous population of effector cells. The cytokine response of the single Th0 cell can remain mixed or further differentiate into the polarized Th1 or Th2 pathway in subjects with a particular genetic background or under the influence of strong (and/or chronic) microenvironmental signals (4) (see also below). Another possibility is that cytokine profiles are largely random at the clonal level and that the exogenous signals which appear to direct T cells to differentiate into Th1 or Th2 cells (see below) act by increasing the probability of expression of certain cytokine genes at the population level, rather than by activating the expression of a cassette of transcriptionally linked genes in the individual cell (5). Finally, we often speak of CD4+ T cells that have been differentiated to produce IL-4 but not IFN-γ as Th2 (or Th2-like) cells and those that produce IFN-γ but not IL-4 as Th1 (or Th1-like) cells, without taking into account the other set of Th1 or Th2 cytokines. With all these points in mind, the Th1/Th2 model provides a useful paradigm for the understanding of several pathophysiologic processes and possibly for the development of novel immunotherapeutic strategies.
Functional and Phenotypic Properties

There is strong evidence for the existence of human CD4+ Th cells with cytokine patterns and functions that are comparable to murine Th1 and Th2 cells (6-8), although in humans the expression of some cytokines, such as IL-2, IL-6, IL-10, and IL-13 may be less restricted (Table 1). Human Th1-like and Th2-like cells differ for their cytolytic potential, mode of help for B-cell antibody synthesis, as well as for the different ability to activate monocyctic cells (Table 1). More recently, we have shown that two activation markers, CD30 and LAG-3, are preferentially associated with activated Th2 or Th1 cells, respectively.

CD30, a member of the TNF receptor family (9), is consistently expressed, and its soluble form (sCD30) released, by activated Th2 and Th0 clones, whereas Th1 clones usually show poor or no CD30 expression (10). Accordingly, costimulation of Th0 or Th2 clones with an agonistic anti-CD30 monoclonal antibody (M67) resulted in increase of antigen (Ag)-induced proliferation and cytokine production, whereas it had no significant effects on both proliferative response and cytokine production by Th1 clones (11). Finally, CD30 ligation induced activation of NFκB transcription factors in TH0 and TH2, but not in TH1, clones (12). A preferential association of CD30 expression with T cell responses characterized by the production of TH2 cytokines has also been demonstrated in vivo. First, a few CD4+CD30+ T cells were detected in the circulation of atopic grass pollen-sensitive donors during the seasonal exposure to grass pollens that developed into T-cell lines able to proliferate in response to grass pollen allergens and to produce IL-4 and IL-5, but not IFN-γ and TNF-β, upon polyclonal stimulation (10). Moreover, remarkable numbers of CD30+ T cells were found in the skin biopsies of patients with systemic sclerosis, a disease characterized by strong TH2-cell activation (C. Mavilia et al., manuscript in preparation), but neither in gut of patients with Crohn’s disease nor in Helicobacter pilori-induced gastric antritis, which are TH1-dominated disorders (P. Parronchi et al., submitted for publication; D’Elios et al., submitted for publication). More importantly, high numbers of CD30+ T cells were detected in lymph node and skin biopsies from three children with Omenn’s syndrome (OS; a rare congenital SCID, in which a polyclonal activation of TH2 cells has been suggested to play a pathogenic role) (13), as well as in the lymph node and peripheral blood (PB) of a fourth child with Omenn’s-like syndrome (OLS) (14) (see also below). However, no accumulation of CD30+ cells was observed in bronchial biopsies from patients with allergic asthma or in conjunctival biopsies from patients with vernal conjunctivitis, which are also considered as TH2-mediated disorders. Likewise, no difference in the accumulation of CD30+ cells between the tuberculoid (a TH1 reaction) and lepromatous form (a TH2 reaction) of leprosy was found (15). From these results, we conclude that CD30, although preferentially associated with the production of TH2 cytokines, does not represent an operational TH2 marker in vivo in all disease models. Also, because it is unlikely that in diseases sustained by Ag-specific (oligoclonal) activation of TH2 cells remarkable numbers of CD30+ cells accumulate in target organs where they usually act as effector cells without significant proliferation.

The lymphocyte activation gene-3 (LAG-3), a member of the immunoglobulin superfamily (16), showed a different TH expression in comparison with CD30. First, LAG-3 expression correlated with IFN-γ, but not IL-4, production in Ag-stimulated T cells. Moreover, LAG-3 expression was strongly up-regulated by IL-12, a powerful TH1-inducing agent (see below). Finally, most activated CD4+ T-cell clones with established TH1 profile of cytokine secretion expressed LAG-3 (but not CD30) on their surface, whereas the great majority of TH2 clones showed neither surface LAG-3 nor LAG-3 mRNA expression. TH0 clones usually showed both CD30 and LAG-3 expression (16a). So far, however, the
physiologic meaning of LAG-3, as well as the reason of its preferential expression in Th1-like cells, remain unclear.

**CD8+ Tc1 and Tc2 Cells**

Although the great majority of CD8+ T cells produce IFN-γ, but no IL-4, CD8+ T cell clones producing IL-4 upon restimulation can be obtained by stimulation of murine CD8+ T cells in the presence of IL-4 (17). More importantly, CD8+ T cell clones that produce IL-4 have been generated from the skin of immunologically unresponsive individuals with leprosy (18), as well as from PB of HIV-infected patients (19). Based on these findings, the names Tc1 and Tc2 for cytotoxic CD8+ T cells secreting Th1-like and Th2-like cytokines have been proposed (20). While the functional role of CD8+ Tc1 cells is well established, the in vivo functional meaning of CD8+ Tc2 cells is still unclear. One possible explanation is that CD8+ Tc2 cells act as suppressor or anti-inflammatory cells through the production of “helper” cytokines (21).

**NATURE OF POLARIZING SIGNALS**

**Murine Th Cells**

Although theoretically Th1 and Th2 cells might arise from distinct precursors, most experiments favor the possibility that a single precursor can differentiate to either a Th1 or Th2 phenotype (22, 23). Both genetic and environmental factors are responsible for the Th1 or Th2 differentiation (Table 2), although the mechanisms by which the genetic background controls the type of Th cell differentiation still remain elusive. With regard to the environmental factors, a role for the site of Ag presentation, the physical form of immunogen, the type of adjuvant, and the dose of Ag has been demonstrated. Parenteral immunization can induce either a Th1 or a Th2 response, whereas inhaled or ingested Ag more easily promotes Th2 responses. Soluble Ag may evoke both Th1 and Th2 responses, while corpuscolate Ag preferentially promotes the development of Th1 cells. Likewise, CFA usually promotes Th1 cells, while alum and Bordetella pertussis toxin mainly promote Th2 responses. It was initially suggested that low doses of Ag induce DTH because they evoke Th1-dominated responses, whereas high Ag doses mainly stimulate humoral immunity by promoting prevalent Th2 responses (24). More recently, however, by using CD4+ naive T cells from T cell receptor (TCR)-transgenic mice, it was found that high Ag leads to Th1 responses, whereas a low dose of the same peptide induced T cells with the same TCR to differentiate into Th2 cells (25). In another model of TCR-transgenic mice, low-medium doses of Ag resulted in Th1 activation, whereas increasing the dose of Ag resulted in the disappearance of IFN-γ and the development of IL-4-producing cells. However, at extremely low doses of Ag, IL-4 production was also dominant over IFN-γ (26). A role for peptide density and peptide binding affinity in influencing the profile of cytokine response has also been suggested. Although the usage of the same TCR by both Th1 and Th2 cells is clearly proved (27), it appears that certain epitopes can preferentially induce one of the two subsets of Th cells. More importantly, varying either the antigenic peptide (changes as little as those concerning a single amino acid residue are sufficient) or the MHC class II molecules can determine whether Th1-like or Th2-like responses are obtained (28). Likewise, by using a set of ligands with various class binding affinities but unchanged T-cell specificity, it has been shown that stimulation with the highest affinity ligand resulted in IFN-γ production, whereas ligands with relatively lower MHC class II binding induced only IL-4 secretion.

**TABLE 2**

Factors Involved in the Differentiation of CD4+ T Cells into the Th1 or Th2 Phenotype

<table>
<thead>
<tr>
<th>Factors</th>
<th>Th1</th>
<th>Th2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-12 + IFN-γ (or IFN-α)</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>TGF-β</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>IL-4</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>IL-10</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Androgen steroids</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>25(OH)D3</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Progesteron</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Relaxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional APC (macrophages, dendritic cells, B cells)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Keratinocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFA</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Alum</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>B. pertussis toxin</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Costimulatory molecules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B7.1</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>B7.2</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>CD30L</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Physical form of the immunogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpuscolate</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Saluble</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Dose of antigen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Medium-low</td>
<td>+</td>
<td></td>
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<tr>
<td>Very low</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Peptide density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Peptide affinity to MHC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>+</td>
<td></td>
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</tbody>
</table>
Attention has also been focused on the possibility that the type of response is dependent upon the nature of antigen presenting cell (APC). However, no independent relationship between types of APC (macrophage, dendritic cell, B cell) has been definitely established (30). Costimulatory molecules present on APC have also received considerable attention. The possibility that B7.1 and B7.2 can deliver different costimulatory signals, B7.1 favoring both Th1 and Th2 responses and B7.2 preferentially favoring Th2 responses, has also been suggested (31), but not definitely proved.

So far, the clearest examples of factors affecting the differentiation pathways of Th cells appear to be cytokines released by APC and/or other cell types at the triad (Ag/APC/Th cell) recognition level. There is a general consensus that the presence of IL-12 or IL-4 at the time of Ag presentation is critical in determining the development of the naive Th cell into the Th1 or Th2 pathway, respectively (4). IL-12, a cytokine produced by the cells of the "natural immunity" (macrophages and dendritic cells) of the dominant factor in inducing CD4 T cells to develop into Th2 cells (32), as well as in IL-12 p40 knock out mice (33). In spite of some controversies, IL-12-driven development of murine Th1 cells from naive Th cells appears to be dependent on IFN-γ, whose requirement can be replaced by IFN-α (34).

Other cytokines, such as TNF-α and TGF-β may also play some favoring role in development of Th1 cells (34). Even more critical appears to be the role of IL-4 in determining the development of Th2 cells (35), inasmuch as the presence of IL-4 during primary stimulation of naive Th cells usually overcomes the Th1-promoting effect of IL-12 (4). The Th2-promoting role of IL-4 has been demonstrated in TCR transgenic mice (36), in mice infected with L. major (37), and in IL-4 knock out mice (38).

The source of IL-4 which is required for priming naive T cells to develop into Th2 cells is still unclear. Four major candidates have been suggested. They include Fcε receptor 1-positive (FcεR1+) non-T cells, the CD45RBlowCD62Llow memory CD4+ T cell subset, the CD4+NK1+ subset, and the CD45RhighCD62Lhigh naive CD4+ T cells themselves. FcεR1+ non-T cells able to release IL-4 include non-T, non-B cells belonging to the mast cell lineage that expand dramatically in Nippostrongylus brasiliensis infection and in association with anti-IgD antibody injection (39). These cells may represent the "natural immunity" analogue for the development of Th2 cells. However, it is unlikely that parasites or allergens would be able to crosslink their receptors to a specific immune response that had produced parasite-specific IgG and/or IgE antibodies. On the other hand, mast cell-deficient mice develop normal Th2 responses (40). Finally, in IL-4 knock out mice only those mice which are reconstituted with IL-4-producing T (but not with IL-4-producing non-T) cells produce antigen-specific IgE (41). Thus, IL-4 production by FcεR1+ non-T cells triggered by antigen-IgE antibody immune complexes can play a role in amplifying secondary Th2 responses to parasites, but unlikely account for the Th2 development in primary responses. CD4+ memory T cells, which have been shown to secrete significant amounts of IL-4 upon primary stimulation in vitro, may also provide the IL-4 required by naive T cells (42). However, in order to explain how memory T cells can be activated by any primary antigen challenge, the existence of many cross-reactivities to previously encountered antigens should be hypothesized. The CD4+NK1+ T cell subset is a specialized population of T cells showing both T-cell and NK-cell surface receptors, highly restricted TCR repertoire (a single invariant TCR β chain, paired with one of three β chains) and CD1 restriction (43). Several findings suggest that CD4+NK1+ T cells may represent an important source for IL-4 required by naive CD4+ T cells to develop into Th2 cells: (i) CD4+NK1+ T cells are able to produce high IL-4 amounts (43); (ii) spleen CD4+NK1+ T cells are the first cell type that produce IL-4 after in vivo injection of anti-CD3 antibody (44); (iii) β2-microglobulin-deficient mice (which are also deficient in CD1 expression) do not produce IL-4 nor IgE after injection of anti-IgD antibody (45); (iv) SJL mice that are unable to produce IgE, neither possess CD4+NK1+ T cells nor express IL-4 following in vivo injection of anti-CD3 antibody (46).

Therefore, it is possible that immunogens having associated superantigens that could interact with a sufficiently large fraction of these cells may promote a pulse of IL-4 being available at the time of naive CD4+ T cells were responding to antigen for the first time. It is unlikely, however, that all antigens able to promote the differentiation of naive Th cells into the Th2 pathway would necessarily activate CD4+NK1+, CD1-restricted, T cells. Thus, a more likely possibility is that the source of IL-4 in the primary response is the naive CD4+ T cells themselves. First, low intensity signalling of TCR, such as that mediated by low peptide doses or by mutant peptides, led to secretion of low levels of IL-4 by murine naive T cells (47). Naive T cells, recently activated in the presence of costimulatory molecules-expressing fibroblasts (i.e., in the absence of outside influences from other cells), required two or more stimulation events to produce IL-4 and IL-5. However, this induction of Th2-type cytokine secretion was blocked by inhibiting IL-4 action, suggesting it was due to endogenous IL-4 produced by the naive T cells themselves (48).

**Human Th Cells**

Interestingly, data obtained in humans by using in vitro models also suggest a critical regulatory role of cytokines, including those produced by cells of the 'natu-
ral immunity," in determining the development of Th cells into one or another cytokine profile (49). Before the Th1-promoting role of IL-12 was discovered, we demonstrated that the addition in PBMC bulk culture before cloning of IFN-γ plus anti-IL-4 antibody, IFN-α, TGF-β, or polyinosinic-polycytidylic acid (Poly I-Poly C) promoted the differentiation of TES- or allergen-specific T cells into Th0/Th1 instead of Th2 clones (49–51). Then, we found that IL-12 addition in bulk culture shifted the development of allergen-specific T cells from the Th0/Th2 to the Th1 profile, whereas the neutralization in bulk culture of endogenously produced IL-12 by an anti-IL-12 antibody shifted the differentiation of PPD-specific T cells from the Th1 to the Th0/Th2 phenotype (49, 52). Taken together, these data suggest that IL-12 and even IFN-γ, IFN-α, and TGF-β (probably in the presence of small amounts of endogenously produced IL-12), favor the development of Th1 cells. We subsequently showed that IL-12 directly affects at single cell level the differentiation of both CD4+ and CD8+ human T cells, by inducing a stable priming effect for high IFN-γ production and is also able to promote transient IFN-γ mRNA expression and small but detectable IFN-γ production by already established Th2 clones (53). Moreover, the Th1-promoting effect of Poly I-Poly C could recently be ascribed to the combined activity of IL-12 and IFN-α released by macrophages (54). Therefore, it is reasonable to suggest that, given the capacity of intracellular bacteria and some viruses to stimulate macrophages to the production of IL-12 and IFN-α (that in turn induce IFN-γ production by both T cells and NK cells), human Th cells responding to these pathogens may be simultaneously presented with processed antigen plus cytokines that induce them to differentiate toward a Th1 phenotype (3, 49).

With regard to the development of human Th2 cells, a promoting role of IL-4 similar to that already described in the mouse (35–38) was suggested by the demonstration that addition of recombinant IL-4 in bulk cultures before cloning shifted the differentiation of PPD-specific T cells from the Th1 to the Th0, or even to the Th2 phenotype (50). More recently, we showed that the interaction between CD30L and CD30 may also play some role in the development of human Th2 cells. In fact, the addition in bulk culture before cloning of an agonistic anti-CD30 antibody favored the development of tetanus toxoid-specific T cells into Th2-like clones, whereas early blocking in bulk culture of CD30L–CD30 interaction by an anti-CD30L antibody or a soluble CD30-Ig fusion protein promoted the preferential development of Th1-like T-cell clones (11). However, whether CD30L–CD30 interaction acts by favoring early IL-4 production by some cell type present in bulk culture or via a different mechanism is unclear.

The source of IL-4 required by human T cells to develop into Th2 cells has also been investigated. It has been shown that IL-4 can be released by human bone marrow non-T, non-B cells belonging to the mast cell/ basophil lineage (55), mast cells (56), basophils (57), and eosinophils (58); however, for the reasons discussed above, it is unlikely that these cells are responsible for the development of Th2 cells. On the other hand, human CD45RA+ (naive) adult peripheral blood T cells, as well as human neonatal T cells, have been found to develop into IL-4-producing cells in the absence of any preexisting source of IL-4 and in spite of the presence of anti-IL-4 antibodies (59, 60). In addition, high proportions of T-cell clones showing a clear-cut Th2 profile of cytokine production could be generated from single thymus-derived CD4+ T cells, which required exogenous IL-12 (IFN-γ was not effective) to be primed to IFN-γ production (60a). Thus, evidence is accumulating to suggest that the maturation of naive human T cells into the Th2 pathway is the basic type of specific effector response, which mainly depends on the levels and the kinetics of autocrine IL-4 production at priming. This Th2 maturation can occur without exposure to IL-4 from accessory cells and may likely be determined by (i) the genetic background of the individual; (ii) the nature and the intensity of TCR signaling by the peptide ligand. Priming of naive T cells to IFN-γ production probably results from the stimulation of "natural immunity" and consequent release of IL-12 and IFNs (γ and α) by different pathogens.

Since the majority of studies performed with human Th cells reflect in vitro secondary responses, their meaning was initially questioned, the dogma derived from mouse studies being that only primary, but not secondary immune responses, can be influenced by exogenous cytokines. Recently, however, it has been demonstrated that even murine memory CD4+ T cells, regardless to prior commitment, may retain the capacity to be further influenced by IL-4, IFN-γ, or IL-12 during effector cell development to become subsets that are at least temporarily polarized to have a particular pattern of cytokine secretion (61, 62).

### POLARIZED CYTOKINE PRODUCTION AND DISEASE STATES

#### Infectious Diseases

Studies in animal models have revealed that the ability of a host to effectively eradicate an invading organism depends on the class of effector-specific immune response that is generated. In general, the proper opponent of bacterial toxins is the Th2 cell which produces cytokines that favor B-cell maturation and production of appropriate antibody isotypes. In contrast, Th1 cells are more suitable for protection against intracellular parasites because of their production of cytokines which activate macrophage and cytolytic T cells.
Primary Immunodeficiencies

Selective defects or imbalances of lymphokine production have been reported in some primary immunodeficiencies. A clonal analysis revealed that patients with hyper-IgE syndrome had markedly lower proportions of circulating T cells able to produce IFN-γ and TNF-α in comparison with controls (69). OS is a rare and severe combined immunodeficiency, characterized by hypereosinophilia and increased serum IgE levels. Defective production of IFN-γ and IL-2 and increased production of IL-4, IL-5, and IL-10 have been described in a 17-month-old girl suffering from this disease, who could be transiently cured by injection of IFN-γ (13). More recently, in three patients with OS and in one patient with OLS, we found high numbers of CD4+CD30+ T cells in both lymph nodes and skin, as well as high levels of soluble CD30 (sCD30) in their serum. The great majority of T-cell clones generated from CD4+CD30+ T cells present in the circulation of the patient with OLS showed a clear-cut Th2 profile, whereas most clones generated from the CD4+CD30− cells were Th1 (14).

Acquired Immune Deficiency Syndrome (AIDS)

It has been suggested that during human immunodeficiency virus (HIV) infection there is a bias toward Th2-like responses and hence Th1 inhibition, which may contribute to the loss of control of the immune system over HIV infection, resulting in progression to AIDS (70). In recent studies, we have been unable to support the concept of a general massive alteration to a Th2 pattern in HIV-infected individuals (71). However, large numbers of CD8+ T-cell clones showing a clear-cut Th2-like cytokine profile were generated from both PB and skin biopsies of subjects in advanced phases
of HIV infection (19); moreover, we found that HIV replicates preferentially in Th2 and Th0 rather than Th1 T-cell clones infected in vitro with HIV (70). Finally, elevated levels of sCD30 have been found in the serum of HIV-infected individuals, suggesting high turnover of CD30 in the course of HIV infection (72), and we (73) and others (74) have recently shown that CD30 triggering on HIV-infected CD4+ T cells might play an important role in HIV replication.

**Allergic Disorders**

Several findings support the concept that atopic diseases (hay fever, bronchial asthma, atopic dermatitis) reflect Th2-dominated responses to single or multiple common environmental allergens: (i) allergens preferentially expand Th cells showing a Th2-like profile in atopic donors, whereas allergen-specific T cells in nonatopic donors are prevalently Th1-like; (ii) Th2-like cells accumulate in the target organs of allergic patients; (iii) allergen-challenge results in the local activation and recruitment of allergen-specific Th2-like cells; (iv) successful specific immunotherapy associates with changes in the cytokine profile of allergen-reactive Th cells; (v) allergen-reactive CD30+ Th2 cells are present in the circulation of allergic patients during seasonal allergen exposure (reviewed in 75). The demonstration that allergen-specific Th2-like cells play a triggering role in the pathogenesis of atopic disorders suggests that atopic individuals may have alterations in the development and/or the functional capability of their Th cells. Accordingly, we have recently shown that CD4+ T-cell clones generated from umbilical cord blood lymphocytes of newborns with atopic parents produce higher IL-4 concentrations than neonatal lymphocytes of newborns with nonatopic parents (M-P. Piccinni et al., manuscript in preparation). This finding, together with the evidence for a linkage of overall IgE to markers in chromosome 5q31.1, especially to the IL-4 gene (76), suggests that atopic subjects may have an altered regulation at level of the IL-4 gene. However, numerous genes map within 5q31.1, including IL-13, which can also promote IgE production (77). Other possible candidates are IFN-regulatory factor 1 (IRF1), whose gene product up-regulates IFN-α, which in turn can down-regulate IgE production and inhibit Th1 cell development, and IL12B, which encodes the β chain of IL-12. Thus, either alterations of molecular mechanisms directly involved in the regulation of IL-4 gene expression, or deficient regulatory activity of cytokines responsible for inhibition of Th2-cell development (such as IFN-α/γ and IL-12), or both, may account for the preferential Th2-type response toward environmental allergens in atopic people.

**Autoimmune and Other Immune-Mediated Disorders**

Evidence is accumulating in animal models to suggest that Th1-type lymphokines are involved in the genesis of organ-specific autoimmune diseases, as such experimental autoimmune uveoretinitis, experimental allergic encephalomyelitis, or insulin-dependent diabetes mellitus (78, 79). In contrast, a less clear-cut lymphokine pattern is emerging from studies on systemic autoimmune diseases, even if the possible pathogenic role of Th2-type cells in systemic autoimmune induced by allogeneic interactions or chemicals is proved (78). Accordingly, data so far available in human diseases are in favor of a prevalent Th1 lymphokine profile in target organs of patients with organ-specific autoimmunity, such as autoimmune thyroid diseases (80) and multiple sclerosis (MS) (81) (Table 3). Studies performed some years ago in my laboratory showed that the majority of CD4+ T cell clones isolated from lymphocytic thyroid infiltrates of patients with Hashimoto's thyroiditis or Graves' disease had a clear-cut Th1 lymphokine profile with production of high TNF-α and IFN-γ concentrations and exhibited cytolytic potential (80). More recently, a quite homogenous Th1 profile was also observed in CD4+ T cell clones derived from retroorbital infiltrates of patients with Graves' ophthalmopathy (82). Most clones derived from both PB and cerebrospinal fluid (CSF) of patients with multiple sclerosis (MS) show a Th1 profile (81). Accordingly, using immunocytochemistry both TNF-α, TNF-β and IL-12 were identified in acute and chronic active MS lesions (83, 84). Determination of TNF-α in both plasma and CSF was shown to be a possible predictor of relapse in MS patients (85), and high levels of soluble LAG-3 (sLAG-3), but not of sCD30 (see above), were found in the serum of patients with relapsing MS (16a). In contrast, high levels of sCD30 have been detected in the serum of patients with active systemic lupus erythematosus (SLE) (86) or systemic sclerosis (SS) (Mavilia et al., submitted for publication), whereas sLAG-3 was present in the serum of a few patients with SLE and in none of patients with SS (R. Manetti, unpublished results).

The role of T cells and T cell-derived lymphokines in the pathogenesis of intestinal lesions in patients with chronic inflammatory bowel diseases has also been actively investigated. High numbers of CD4+ T-cell clones producing IFN-γ, but no IL-4, were generated from coloscopic mucosal biopsies of patients with Crohn's disease, thus revealing a clear-cut Th1 lymphokine profile, whereas Th0-like clones predominated in control guts (P. Parronchi et al., submitted for publication). Likewise, Th1-like cells were enriched in the liver of patients with hepatitis C virus (HCV) infection, whereas in chronic HBV infection the majority of liver-infiltrating T cells were Th0, able to produce Th2 cytokines and lower levels of IFN-γ (Bartoletti et al., submitted). These results suggest different pathogenic mechanisms operating in HBV and HCV infections, having HBV and HCV probably evolved different strat-
Allograft Rejection and Fetal Transplantation

It appears that Th1-dependent effector mechanisms, such as delayed-type-hypersensitivity and cytotoxic T lymphocyte (CTL) activity, play a central role in acute allograft rejection (87). Proteins and/or transcripts for intragraft IL-2, IFN-γ, and the CTL-specific marker, granzyme B, have consistently been detected in rejecting allografts (84). Accordingly, CD4+ T cell clones generated from kidney allografts during the acute phase of rejection showed a clear-cut Th1 profile (G-F. Del Prete et al., unpublished results). On the other hand, the production of Th2-type cytokines may be central to the induction and maintenance of allograft tolerance (87). Several in vivo studies that examined the pattern of cytokine expression during tolerance induction have consistently shown a dramatic decrease in the expression of IL-2 and IFN-γ, while increased levels of IL-4 and IL-10 transcripts are manifest (87). Thus, although its validity is not yet proved, the Th1/Th2 paradigm may represent the basis for understanding the mechanisms of rejection and tolerance in transplantation (87).

Embryos, because of the presence of paternal MHC antigens, are alike to an allograft which, however, is not rejected by the maternal immune system until the time of delivery. In order to explain this apparent paradox, it has recently been suggested that a Th2 switch at the level of materno-fetal interface may allow fetal survival by inhibiting Th1 responses which promote allograft rejection (88). We, therefore, compared the cytokine profile of CD4+ and CD8+ T cell clones established from both decidua and PB of women with unexplained recurrent abortion (URA) or voluntary abortion (normal gestation). Although the majority of T cell clones showed a Th0-like profile, significantly higher numbers of Th1-like T cell clones were generated from the decidua of women suffering from URA, whereas no differences in the cytokine profile of PB-derived T-cell clones were observed (M-P. Piccinni et al., unpublished data). These results suggest that local production of IL-4 may be important for the maintenance of pregnancy, whereas its reduced production can compromise pregnancy. Of note is that progesterone (PG), at concentrations comparable to those present at the materno-fetal interface, favors the development of human T cells producing Th2-type cytokines (i.e., IL-4 and IL-5) (89). It is also of interest that PG is able to inhibit production of both IFN-γ and TNF-α by PBMC from women with URA stimulated with trophoblast antigens (K. Polgar, personal communication). Thus, the high levels of PG present at the materno-fetal interface during gestation may contribute, at least in part, to the development of prevalent Th2-type profile which allows successful pregnancy. More recently, we examined the effects of another corpus lutem-derived hormone, relaxin (RLX), on the in vitro differentiation of human CD4+ T cells. Preliminary results indicate that RLX, at the physiologic concentrations found during pregnancy, favors the development of T cells producing Th1-type cytokines (90). These data provide an excellent frame of reference to test additional hypotheses on the physiology of the immune system, as well as on its relationship with the endocrine system.

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TH1 AND TH2 CELLS IN HUMAN DISEASES


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