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Ann. Rev. Immunol. 1989. 7:145–73
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TH1 AND TH2 CELLS: Different Patterns of Lymphokine Secretion Lead to Different Functional Properties

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Introduction

Effector functions in the immune system are carried out by a variety of cell types, and as our understanding of the complexity of the system expands, the number of recognized subdivisions of cell types also continues to increase. B lymphocytes, producing antibody, were initially distinguished from T lymphocytes, which provide help for B cells (1, 2). The T-cell population was further divided when surface markers allowed separation of helper cells from cytotoxic cells (3). Although there were persistent reports of heterogeneity in the helper T-cell compartment (reviewed below), only relatively recently were distinct types of helper T cells resolved. In this review we describe the differences between two types of cloned helper T cells, defined primarily by differences in the pattern of lymphokines synthesized, and we also discuss the different functions of the two types of cells and their lymphokines. Patterns of lymphokine synthesis are convenient and explicit markers to describe T-cell subclass differences, and evidence increases that many of the functions of helper T cells are predicted by the functions of the lymphokines that they synthesize after activation by antigen and presenting cells. The separation of many mouse helper T-cell clones into these two distinct types is now well established, but their origin in normal T-cell populations is still not clear. Further divisions of helper T cells may have to be recognized before a complete picture of helper T-cell function can be obtained.

0732–0582/89/0410–0145$02.00

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Lymphokine Activities—The Need for Monospecific Assays

During the last several years, our understanding of lymphokine structure and function has progressed enormously. Due to the availability of purified proteins, recombinant cDNA clones and monoclonal antibodies, many of the known lymphokine activities can now be unambiguously attributed to well-characterized proteins. All known lymphokines affect more than one cell type and often have diverse effects even on cells of the same lineage (reviewed in 4, 5, 6). Further complexity is added by the fact that each type of cell in the immune system responds to more than one lymphokine.

Because of this multiplicity of lymphokine action, monospecific bioassays have been difficult to establish. Monoclonal antibodies (7, 8, 9, 10, 11) have been used to improve the specificity of bioassays, and to measure lymphokines directly by ELISA assays (Table 1). For example, in the T-cell growth assay, both Interleukin 2 (IL-2) and IL-4 can cause proliferation of most T-cell lines, although the dose-response relationships are different (6, 12, 13, 14, 15, 16). Using monoclonal antibodies that neutralize the biological activities of IL-2 (6) and IL-4 (9), these bioassays can be made monospecific for either lymphokine (11).

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TH1 and TH2 Lymphokine Secretion Patterns

When stringent, apparently monospecific assays are used for evaluating lymphokine synthesis, mouse helper T-cell clones fall into two main groups. Early results showed that in a panel of clones, each clone synthesized either IL-2 and Interferon γ (IFNγ), or IL-4 (6). Using a further set of bioassays and particularly by evaluating mRNA synthesis by hybridization, the differences in lymphokine synthesis were extended to a number of lympho-

Table 1 "Monospecific" assays for lymphokines

	Bioassays[a]	ELISAs[b]
IL-2	HT2+anti-IL-4 (9)	S4B6 (7)+rabbit aIL-2
IL-4	HT2+anti-IL-2 (7)	—
IL-5		TRFK2+TRFK5 (10)
IFNγ		XMG1.2 (11)+rabbit aIFNγ
IL-3	MC/9+anti-IL-4	8F8+43D11 (8)
GM-CSF		31G6+22E9[c]

[a] Proliferation assays using the indicated target cell line, and blocking monoclonal antibodies as indicated.
[b] Two-site sandwich assays in which the first antibody is bound to the plate, and the second used in solution.
[c] J. Abrams, personal communication.

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kines and other secreted proteins (11). Table 2 lists our current knowledge of the lymphokine patterns of the two types of clone, TH1 and TH2.

TH1 clones synthesize IL-2, IFNγ, and lymphotoxin (LT), whereas these lymphokines are not detectably expressed in TH2 clones. Conversely, only TH2 clones synthesize detectable amounts of IL-4, IL-5 (11), and probably IL-6 (F. Lee, T. Mosmann, unpublished). An additional marker for TH2 clones was obtained with the discovery of the induction-specific cDNA clone P600 in cDNA libraries from an induced TH2 clone (K. D. Brown, S. M. Zurawski, T. R. Mosmann and G. Zurawski, submitted). The synthesis of IL-2, IFNγ, IL-4 and IL-5 is tightly controlled, because induced supernatants of the appropriate cell type contain at least 2,000–10,000-fold more of the lymphokine than do induced supernatants of the

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Table 2 Properties of mouse T cell clones

	TH1	CTL	TH2
Surface markers:			
LY1	+	−	+
L3T4	+	−	+
LYT2	−	+	−
Lymphokines:[a]			
Interferon γ	++	++	−
Interleukin 2	++	+/−[b]	−
Lymphotoxin	++	+	−
GM-CSF	++	++	+
Tumor necrosis factor	++	+	+
TY5	++	++	+
P500	++		+
H400	++		+
Interleukin 3	++	+	++
Met-enkephalin	+	+	++
Interleukin 4	−	−	++
Interleukin 5	−	−	++
Interleukin 6	−	−	++
P600	−		++
B cell help:			
IgM, IgG1, IgA	+		++
IgG2a	++		+
IgE	−		++
Delayed type hypersensitivity:	+	+	−
Macrophage activation:	+	+	+

[a] Lymphokine expression was evaluated by bioassays, ELISAs and RNA hybridization.
[b] Some but not all CTL clones produce IL-2.

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other cell type. Several other genes were expressed by all clones tested. These included three lymphokines, granulocyte macrophage-colony stimulating factor (GM-CSF), tumor necrosis factor (TNF) and IL-3, one neuropeptide, preproenkephalin (ppENK), and three other induction-specific genes of unknown function, TY5, P500, and H400. Careful analysis of mRNA levels revealed that TH1 cells expressed relatively more GM-CSF, TNF, TY5 (11), H400, and P500 (K. D. Brown, S. M. Zurawski, T. R. Mosmann and G. Zurawski, *J. Immunol.* In press), whereas TH2 clones expressed relatively more ppENK (11). These moderate differences (approximately five-fold in most cases) appear to be statistically significant, but we do not yet understand their biological importance.

These patterns are characteristic of the majority of long-term T-cell clones tested. Some exceptions have also been seen, e.g. expression of IFNγ by a clone that was originally a good example of a TH2. It is not yet known if these exceptions could be due to aberrations arising in tissue culture. IL-2 synthesis may be regulated independently of the synthesis of other lymphokines, since TH1 clones can often lose the ability to produce IL-2 after long periods in culture, while the synthesis of other lymphokines appears to be more stable (11). This may also account for reports of a number of T-cell clones that secrete IFNγ and LT, but not IL-2 (17). Recent evidence from clones that have been grown in culture for short periods (e.g. 4–8 weeks) suggests that there may also be other states of TH differentiation preceding the TH1 and TH2 phenotypes (T. R. Mosmann, N. Street, H. Bass and J. Schumacher, unpublished). As discussed below, the in vivo representation of TH1, TH2, and possible precursor phenotypes remains to be established.

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Lymphokine Synthesis Patterns of Other T-Cell Types

Mouse T-cell clones of the Lyt2$^+$, cytotoxic phenotypes also express a pattern of lymphokines that corresponds closely to the TH1 pattern (18, 19; T. A. T. Fong, T. R. Mosmann, unpublished). The CTL clones that we have tested all showed good levels of IFNγ and TY5 expression, and they produced moderate amounts of GM-CSF, IL-3, LT and TNF mRNA. No IL-4 or IL-5 synthesis could be detected, and ppENK expression was detectable at low levels in some clones. These mRNA results have been confirmed by lymphokine assays for IL-3, IL-4, IL-5, GM-CSF, and IFNγ. Some clones synthesized moderate amounts of IL-2, whereas IL-2 protein or mRNA was undetectable in other clones. The variability in IL-2 synthesis has been reported previously (17) and may be physiologically relevant, or it may be an extreme manifestation of the in vitro instability of IL-2 synthesis in TH1 clones. A fourth type of T cell, the TCR1$^+$ cell, expresses the $\gamma\delta$ form of the T-cell antigen/MHC receptor and has the

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surface antigen phenotype Thy1$^+$, L3T4$^-$, Lyt2$^-$. A subset of these T cells constitutes the dendritic T cells found in the epidermis (20), and one example of a dendritic TCR1$^+$ T-cell clone expressed the TH1 pattern of lymphokines (T. R. Mosmann, R. E. Tigelaar, unpublished).

The expression of the TH1 pattern of lymphokine synthesis in three different T-cell types and the stability of the TH1 and TH2 phenotypes in culture suggest that these two patterns of lymphokine gene expression constitute two tightly controlled "cassettes" of regulation. However, there are examples of T-cell clones, especially at early times after establishment in culture, that produce a mixture of TH1 and TH2 patterns (T. R. Mosmann, N. Street, H. Bass and J. Schumacher, unpublished; A. Glasebrook, personal communication). These clones and many human clones (21) suggest that further patterns of lymphokine expression exist.

Hybrids between a TH2 clone and a CTL (expressing IFNγ) were able to produce both IL-4 and IFNγ in response to stimulation with the antigen recognized by either parent (22). This suggests that the lack of synthesis of IL-4 in a TH1, or IFNγ in a TH2 clone, is not due to a suppressive mechanism, but rather is due to the lack of positive induction. In addition, the data indicate that the phenotype for secretion of lymphokines is not linked to a particular specificity of the antigen receptor but is probably a function of the cell's state of differentiation.

Functions of TH1 and TH2 Cells and Their Lymphokines

B-CELL HELP The ability of TH clones to function as helpers for B-cell responses has been studied in vitro using two different experimental strategies. The first is the traditional hapten-carrier system used for many years to characterize normal TH populations. In this system, hapten-specific responses are measured in cultures containing primed or unprimed B cells, a carrier-specific TH clone and haptenated carrier protein (or cells) as the antigen. In such cultures, the frequency of B cells that respond specifically is low, typically 10^{-3} to 10^{-5}, although the frequency can be greatly enhanced using hapten-enriched B cells (23). The second strategy is to use TH clones specific for antigens such as Ia, Mls, or H-Y (male-specific antigen) which are expressed on most or all B cells. In this way, most B cells are, in essence, antigen-specific, antigen-presenting cells and appear to respond to cell-mediated and lymphokine-mediated signals in the same way as do antigen-specific B cells in the hapten-carrier systems. A significant refinement of this strategy is to use TH clones specific for rabbit IgG and rabbit anti-mouse IgM or IgD antibodies as the antigens (24, 25). This system depends upon a specific interaction between the antigen and Ig on the surface of the B cells, and it requires processing and Ia-restricted presentation of the rabbit IgG. A majority of splenic B cells

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can be activated and induced to proliferate and differentiate in this way (26). In this discussion, we refer to this second strategy as "polyclonal TH stimulation" and distinguish it from another form of polyclonal response, which we term "bystander stimulation" and which does not require a TH-B interaction (see below). The recent purification and gene cloning of many lymphokines and the development of neutralizing antilymphokine antibodies have made it possible at last to define which T-cell products are important in regulating B-cell growth and differentiation and to study the specific functions of each of these products.

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TH2 help for B cells It is generally agreed that murine TH2 clones can be excellent helpers, both in antigen-specific (27, 28, 29; DeKruyff, submitted) and polyclonal (25, 30, 31, 32) in vitro cultures. TH2 clones can induce growth and Ig secretion by 50–80% of B cells in limiting dilution cultures (26) and can efficiently induce responses in populations of small, resting B cells (27, 30, 32). The activation of resting B cells by TH2 clones appears to require at least three "signals." The first of these is provided by direct contact with the activated helper cell. Although a few mouse TH2 clones may secrete a soluble factor that can induce growth and differentiation of resting B cells (33, 34), in most cases, this process requires direct contact with the TH cell and cannot be achieved with TH2 supernatants (35, 36, 37). Optimum proliferation and differentiation require both IL-4 and IL-5, in addition to this cell-mediated activation. This requirement has been defined in two types of experiments. In the first, the addition of neutralizing anti-IL-5 antibodies to cultures of B cells and TH2 clones causes a substantial inhibition of Ig production (10, 30, 37). The addition of anti-IL-4 antibodies also inhibits Ig production but to a lesser and more variable extent (28, 30, 31), whereas the combination of both antibodies inhibits Ig production almost totally. Similar conclusions have been reached in experiments in which TH2 products are used to induce the differentiation of B cells polyclonally activated (but not induced to differentiate) by direct interaction with a TH1 clone. In these experiments, both IL-4 and IL-5 are required for optimal proliferation and Ig production, and no other TH2 product was active in this system (31; R. L. Coffman, J. Christiansen, B. Seymour, D. Hiraki, H. Cherwinski, R. Schreiber, M. Bond and T. Mosmann, in preparation). Thus, IL-4 and IL-5 are the major "helper factors" produced by TH2 cells, and both act to enhance the growth and differentiation of activated B cells. The important exception to this is the IgE response, for which IL-4 but not IL-5 is essential (see below).

Large B cells, unlike resting B cells, do not require TH-B contact and can proliferate and differentiate in response to TH2 supernatants. The

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active component in these supernatants has been shown to be IL-5 (38). This response can account for much of the unlinked "bystander" response observed in TH2-stimulated cultures at high antigen concentrations (37). The response to IL-5, however, is much smaller than the response of the same large B-cell population to direct interaction with a polyclonally stimulating TH2 clone; this suggests either that IL-5 alone is a weak stimulus or that it stimulates only a subpopulation of large B cells (R. L. Coffman, unpublished). Nevertheless, this bystander response may be quite significant in some situations. For example, very young NZB/NZW F1 mice, which later in life develop a severe lupus-like autoimmune disease, appear to have a much higher proportion of IL-5–responsive B cells. Culture of these cells with IL-5 leads to substantially higher production of autoantibodies than culture of cells from nonautoimmune mice (38).

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TH1 help for B cells The helper function of TH1 cells is more uncertain since they have been shown to provide antigen-specific help in some, but not all, in vitro systems. Several groups have reported TH1 clones that can help antigen-specific secondary responses in primed B-cell populations (39; DeKruyff, submitted), and the ability of one TH1 clone to stimulate primary antihapten antibody responses in unprimed, hapten-purified B-cell populations has been characterized (29). However, Bottomly, Janeway and their colleagues have described many TH1 clones that cannot provide help for a specific primary response to the phosphorylcholine hapten, although many of these clones can induce polyclonal proliferation and differentiation of B cells at high antigen concentrations (27, 28). However, these authors have presented evidence that some of these clones produce no detectable IL-2 (17, 28), so their results may not reflect the activity of IL-2-producing TH1 clones. Similarly, Abbas and colleagues report that TH2, but not TH1, clones specific for rabbit γ-globulin can induce polyclonal proliferation and Ig production from dense, resting B cells in the presence of rabbit anti-mouse Ig antibodies (30). In our hands, most TH1 clones reactive with self- or allo-Ia or with Mls antigens, efficiently stimulate proliferation, but not Ig production, by B cells bearing the appropriate surface molecule (31). The defect in differentiation to Ig production, however, is not caused by an inherent inability of TH1 products to induce differentiation, but by insufficient production of IL-2 in vitro. Thus, addition of exogenous IL-2 to such cultures enhances Ig production. This demonstrates that helper function is possible with products of only TH1 clones and suggests that IL-2 is the most important helper factor made by TH1 cells (31). Further enhancement can often be achieved by blocking part of the IFN-γ activity with anti-IFN-γ antibodies. In other words, many TH1 clones can stimulate activation and proliferation of B

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cells in vitro and can also stimulate Ig secretion independently of the T-B contact-mediated activation signal if the levels of IL-2 and IFN-γ are optimized. It should be noted that the differentiation of TH1-activated B cells can also be induced by TH2 products, IL-4 and IL-5 (31).

TH1 cells can also suppress B-cell responses The assessment of the role of TH1 cells in B-cell responses is complicated by two things: (*a*) the fact that high concentrations of IFN-γ can be quite generally immunosuppressive (40, 41, 42), whereas low concentrations can enhance certain types of responses (42), and (*b*) by the observations that most TH1 clones are directly cytotoxic for activated B cells (43, 44). Not surprisingly, activated TH1 clones have been shown to be directly suppressive in cultures optimally stimulated by TH2 cells (45, 46, 47). The helper activity of TH1 clones in vitro appears to dominate at low antigen concentrations (suboptimal TH activation) or at low T:B ratios (<0.2) (31, 32, 39), whereas the cytotoxic activity begins to dominate at ratios exceeding 1.0 (43).

Isotype regulation by TH1 and TH2 cells One important difference between the helper function of the two TH subsets is in their ability to stimulate the production of certain Ig isotypes, most importantly IgE and IgG2a. In a panel of over 30 TH1 and TH2 clones, virtually all of the TH2 clones were capable of inducing significant IgE responses, whereas none of the TH1 clones tested could induce detectable IgE production (R. L. Coffman, B. Seymour, H. Cherwinski, J. Christiansen, D. Parker, T. R. Mosmann, manuscript in preparation, summarized in 31). IgE production stimulated by TH2 clones can be substantially or totally inhibited by either IFN-γ or anti-IL-4. These two lymphokines have been shown to have the same effects in LPS-stimulated B-cell cultures (40, 48). Furthermore, in vivo administration of either IFN-γ or anti-IL-4 can inhibit IgE responses in mice (49, 50). In fact, the induction of IgE by TH2, but not TH1, clones can be explained entirely by their differences in IL-4 and IFN-γ production. TH1 clones can induce good IgE responses if IL-4 and anti-IFN-γ antibodies are added to in vitro cultures (R. L. Coffman, B. Seymour, H. Cherwinski, J. Christiansen, D. Parker, T. R. Mosmann, in preparation). IL-4 mediates the enhancement of IgE production by increasing the frequency of isotype switching. This is shown by examination of single B cells stimulated by TH2 cells (26) and also in limiting dilution experiments with LPS-stimulated B cells (51).

The unique dependence of IgE responses on IL-4, and the ability of relatively low concentrations of IFN-γ to inhibit this activity of IL-4 (40), suggest that TH1 cells may act as isotype-specific suppressor cells for IgE, quite possibly under conditions in which they act as helpers for responses

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of other isotypes. Ovary and his colleagues have described, in SJL mice, IgE-specific suppressor cells that are Ly1$^+$, CD8$^-$, and require an antigen for activation, but which suppress IgE in an isotype-specific, antigen-nonspecific fashion (52). It is tempting to speculate that these cells are, in fact, TH1 cells.

TH1 clones, in contrast, induce substantially more IgG2a than TH2 clones (29, 31). Results for several alloreactive and rabbit IgG-specific TH1 clones show that IgG2a typically accounts for 5% to 10% of the total Ig response, whereas IgG2a usually accounts for 0.1% to 0.5% of the total response if the same B-cell population is stimulated by TH2 clones. Several lines of evidence, both in vitro and in vivo suggest that IFN-γ is important for high levels of IgG2a production, but other factors may be involved, since neither the addition of anti-IFN-γ antibody to TH1-stimulated cultures nor the addition of IFN-γ to TH2-stimulated cultures causes much change in IgG2a responses (29).

Another important observation made with TH-stimulated cultures is that IL-4 is much less important for the production of IgG1 than was predicted on the basis of its strong IgG1-enhancing activity in LPS-stimulated cultures (53). The addition of IL-4 can enhance the ability of some TH1 clones to induce an IgG1 response (29), but many other TH1 clones induce large IgG1 responses (comparable to those induced by TH2 clones) in the absence of IL-4 (31). This is consistent with observations that anti-IL-4 antibody causes little or no inhibition of IgG1 responses either in vitro (30, 31) or in vivo (48) and suggests that substantial IgG1 responses can be induced by an IL-4 independent mechanism.

HELP FOR CYTOTOXIC T CELLS The generation of mature cytotoxic T cells can be enhanced by helper T cells, although it is not yet clear whether TH1 and TH2 cells are equally efficient. Several years ago IL-2 was recognized as a major helper factor (54), and recent evidence has shown that IFNγ (55), IL-4 (56) and IL-5 (57) are also able to enhance the generation of CTLs. Thus TH1 and TH2 clones each produce two lymphokines that induce CTLs, and so both can probably function as helpers. Since these four lymphokines are effective in subtly different ways, their helper functions for CTLs may be operative in different situations, or result in CTL populations with different functional properties.

DELAYED TYPE HYPERSENSITIVITY Delayed type hypersensitivity (DTH) is an inflammatory reaction mediated by the products of T cells, mainly of the Ly1$^+$ helper phenotype (58). When the distinction between TH1 and TH2 clones was discovered, it became important to ask whether DTH was a function of one or both subsets. In an experimental system in which T cells and antigen were injected directly into mouse footpads, only TH1

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clones were able to elicit antigen-specific swelling (59). In some experimental systems, $Lyt2^+$ cells account for substantial DTH (60), which is consistent with the production of similar patterns of lymphokines by TH1 cells and CTLs.

Although the induction of the effector phase of the DTH reaction by TH1 but not TH2 clones appears to be clearcut, the DTH reaction is complex, and why TH2 clones are unable to induce DTH is not known. In particular, it has not been proven that the TH2 clones were activated in the footpad environment, which is especially important since TH1 clones with dual specificity for antigen/MHC or Mls only induce DTH in response to antigen/MHC stimulation (59). Thus, it is possible that TH2 clones cannot induce DTH, because they do not produce essential mediators for the DTH reaction or because they are not activated by antigen-presenting cells in the footpad. Some support for the first possibility comes from recent evidence (T. A. T. Fong, T. R. Mosmann, unpublished) that IFNγ is responsible for part but not all of the swelling reaction in response to TH1 clone activation, and also from evidence that IFNγ is chemotactic for at least some of the cells that migrate into the inflammatory site during a DTH reaction (61).

A normal DTH reaction may involve two phases (62); an initial activation signal results in recruitment of effector T cells into the site, after which these T cells are activated to recruit the monocytes and granulocytes that mediate subsequent stages of the reaction. TH1 clones can clearly mimic the effector phase of the reaction, but the T cell responsible for the early phase is not yet identified.

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Differentiation of TH1 and TH2 Cells

ARE RESTING T CELLS COMMITTED TO TH1/2 LYMPHOKINE PATTERNS? Although the TH1 and TH2 patterns are distinct when long-term mouse T-cell clones are examined, we do not yet know if normal resting mouse lymphocytes are already committed to these patterns. Another important question is whether other lymphokine secretion patterns are exhibited by precursor stages in the development of the mature TH1 and TH2 phenotypes. The latter may be final differentiation states analogous to the plasma cells producing different isotypes of antibody in the B cell lineage. If mixed spleen cell populations are polyclonally stimulated, they produce large amounts of IL-2, and low amounts of IFNγ, IL-4, and IL-5 (N. Street, T. R. Mosmann, unpublished results). This pattern cannot be explained simply by some mixture of TH1, TH2, and CTLs. Either there are cells with other lymphokine secretion phenotypes, or else differential regulation of lymphokine synthesis must occur in the mixed population. Preliminary evidence suggests that such differential regulation occurs, but it does not

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explain the lymphokine differences between clones and normal lymphocytes (N. Street, T. R. Mosmann, unpublished).

Recently we examined the lymphokine profiles of helper clones soon (e.g. 2 to 6 weeks) after establishment in culture. In some experiments, the patterns are not recognizably TH1 or TH2 at early times, but they sometimes change into clearcut TH1 or TH2 phenotypes on continued growth in culture (T. R. Mosmann, H. Bass, N. F. Street, J. Schumacher, unpublished results). Similar results have been obtained in another laboratory (A. Glasebrook, personal communication), except that the time needed to change phenotype could be several months. These results may also explain the puzzling observation that human helper clones do not fall cleanly into TH1 and TH2 patterns. Although human TH1 and TH2 phenotypes have been reported (63), there are also many examples of clones that secrete a mixture of the two patterns (21, 63). These results can be reconciled with the data from mice if it is assumed that in culture human cells tend to persist as the mixed phenotype, whereas clones from mice tend to differentiate more rapidly into TH1 and TH2.

These experiments, and the lymphokine patterns of total spleen cells, suggest that there are precursor stages in the development of the TH1 and TH2 differentiation states. Figure 1 shows two possible models for the derivation of TH1 and TH2: In model A, a single precursor, the TH0 cell, can give rise to either TH1 or TH2 cells depending on the antigen-presenting cell. Model B proposes that the precursors of TH1 and TH2 (TH1P and TH2P) are already committed to their final lymphokine secretion phenotype before antigen stimulation and that they have different activation requirements. In both models, we propose that the precursor cells synthesize a set of lymphokines that fits neither TH1 nor TH2 patterns. From the results of stimulation of normal spleen lymphocytes, the precursors may secrete IL-2, but little or no IFNγ, IL-4 and IL-5. This is consistent with the results of Budd and coworkers (64), who found that memory T cells, identified by the Pgp1 cell surface marker, synthesized similar amounts of IL-2 but larger amounts of IFNγ when compared to unprimed T cells. These results have also been extended to IL-3 and IL-4, which are also synthesized at higher levels by Pgp1^{+} cells (R. C. Budd, J. H. Schumacher, T. R. Mosmann, unpublished).

RELATIONSHIP OF TH1 AND TH2 TO PREVIOUSLY DESCRIBED T-CELL SUBTYPES Bottomly and coworkers described the division of a panel of CD4^{+} T-cell clones into four groups, based on the patterns of help provided to B cells (27). These groups were later assessed for lymphokine production, and two of the groups appear to fit with the TH1 and TH2 lymphokine classification (84). Groups 1 and 2 were equivalent to TH2 clones and

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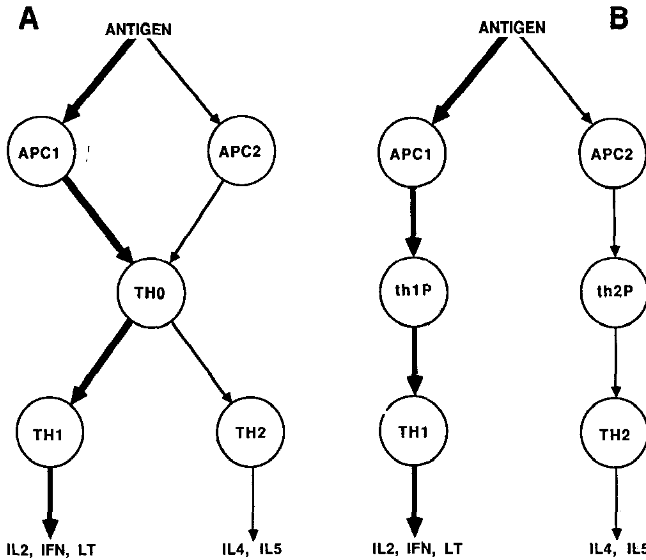

Figure 1 Possible TH1 and TH2 differentiation pathways. Two possible pathways of differentiation are shown. Heavy arrows show the predominant effects that occur when a TH1-preferential antigen is used. Both models show two different APCs with different preferential stimulation effects on TH1 and TH2. The models could also be drawn with a single APC which is able to deliver different signals, depending on the physical nature of antigen.

differed from each other in their ability to provide help for the T15 idiotype (84). This may have reflected a difference in specificity rather than phenotype. Group 3 included TH1 clones, and group 4 was another set of TH2 clones specific for self-antigens (27). Bottomly (84) has suggested that TH1 cells should be called inflammatory T cells because of their role in inflammatory processes, and that TH2 cells be called T helper cells because they have stronger helper functions for B cells. Since TH1 clones can also provide help for B cells, and probably T cells, we prefer the TH1/TH2 nomenclature at present.

Another division between T cells is the separation of helper T cells in vivo into the T1 and T2 sets (65, 66, 67, 68, 69, 70). T1 cells are short-lived (rapidly lost after adult thymectomy), relatively resistant to in vivo administration of anti-lymphocyte serum (ALS), probably not recirculating, and able to provide B-cell help, but with relatively slow kinetics. T2 cells are long-lived, sensitive to ALS, probably recirculating, able to provide B-cell help with rapid kinetics, and probably include the memory T-cell population. Recent results from Swain and colleagues (71) have shown that freshly isolated lymphocytes express IL-2 and IFNγ, but not

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IL-4 or IL-5. After in vitro culture under defined conditions of stimulation, IL-4 and IL-5 can be synthesized. Adult thymectomy abrogates the ability of surviving T cells to produce IL-2, and after stimulation in culture, the resulting cells develop the ability to synthesize both IL-2 and IL-4. Based on these results, Swain et al (71) suggested that T1 cells are equivalent to TH2, and T2 (long-lived) cells are the TH1 population. A second group has also reported that IL-2 but not IL-4 can be detected in supernatants from stimulated normal lymphocytes, either in bulk culture or in limiting dilution experiments (72). However, results from our laboratory and others show that IL-4 and IL-5 can be readily detected in stimulated normal spleen cell supernatants, suggesting that patterns of lymphokine synthesis may vary from one animal colony to another. The T1 compartment can contain precursors of B helper cells, DTH effectors (66, 67) and cells producing IL-2 and IL-4 (71). The T2 compartment can contain active helper cells (66, 67) and IL-2-producing cells (71), and T2 cells can be derived from the T1 compartment (68). From these observations, it appears unlikely that T1 and T2 are equivalent to the TH2 and TH1 subsets. Instead, it is much more likely that the short-lived T1 population includes the precursors of both TH1 and TH2 cells (either TH0 or TH1P and TH2P, see Figure 1), and that the long-lived T2 population includes mature TH1 and TH2 cells (Figure 2). Depending on the background immunity or the antigenic stimulus used, the T2 population might preferentially contain TH1 or TH2 cells. This possibility may explain why some laboratories produce mainly or entirely TH1 clones, whereas others produce only TH2. In our own laboratory, we find that in different experiments, apparently identical methods and strain combinations can lead to drastically different ratios of TH1 and TH2 clones. If the immune system of the mouse is in a constantly changing state of balance between the two types of response, this could explain both individual variation between experiments, and more systematic variations between investigators using different mouse colonies with, presumably, different ongoing immune responses. By this argument, the balance is more important than the degree of response, i.e. a mouse colony with a large number of infectious agents could be biased in either direction, as could a "clean" or specific pathogen-free colony.

Other types of helper T cell diversity have been described. In a series of papers, Kappler, Marrack and colleagues showed that one type of helper could help in a linked manner, whereas another could only help bystander B cells (73). This heterogeneity may be related to the TH1 and TH2 subsets, but the connection is not yet clear. Helper T cells were also heterogenous for expression of a determinant(s) recognized by an anti-I region allo-antiserum (74). Waldmann & Lefkovits (75) also showed evidence for

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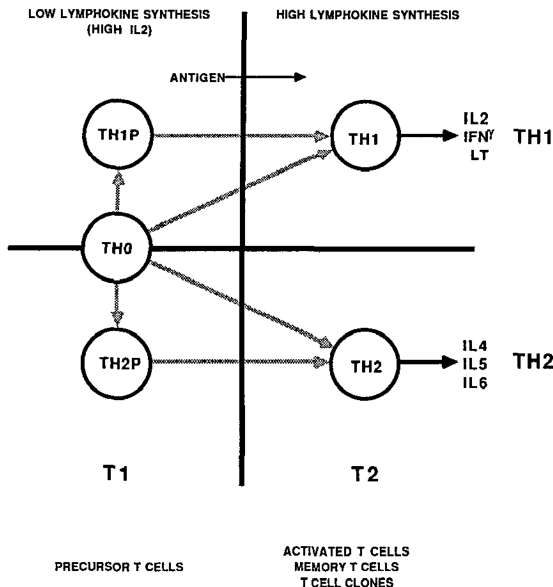

Figure 2 Possible relationships of TH1/TH2 and T1/T2 subsets. Stippled arrows show possible alternative pathways for the generation of mature TH1 and TH2 cells from precursor(s).

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different helper cells by limiting dilution experiments, and Tada and colleagues (76) showed that T cells with surface "Ia" determinants could be separated by nylon wool columns and were functionally distinguishable from Ia^- T helper cells. Janeway and colleagues described another type of diversity with the discovery of T helper cells that appeared to be specific for the B-cell idiotype, rather than for the antigen (77). This second type of helper could synergize with conventional helpers for optimal responses (78). The relationship of each of these kinds of heterogeneity to each other and to the current TH1 and TH2 types is still not clear. At the risk of accusations of avoiding the question, we suggest that these kinds of heterogeneity might not all be equivalent to the TH1/TH2 separation but could represent additional diversity within the helper T cell compartment.

POSSIBLE CELL SURFACE ANTIGEN DIFFERENCES The leukocyte common antigen (LCA), expressed on the surface of most hemopoietic cells, has an unusual genetic structure in which different exons are expressed near the N-terminus in various cell lineages and differentiation states (79, 80). Monoclonal antibodies have been produced against a particular determinant of the mouse, rat, and human versions of this antigen, and the subsets of cells expressing this determinant appear to be related to the

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TH1 and TH2 subsets. In rat T cells, $OX22^+$ cells produce the majority of IL-2, whereas $OX22^-$ cells mediate the majority of helper activity for B cells (81). Human helper T cells can also be divided into subsets by anti-LCA antibodies (82, 83), and recently antibodies have been identified that perform a similar function for mouse helper T cells (84; E. Pure, personal communication). The lymphokines secreted by the two separated mouse populations correlate to some extent with those produced by the TH1 and TH2 subsets, but unfortunately, in all three species, the expression patterns are more complex, so that the LCA determinants may be both lineage- and activation-specific markers (85; K. Bottomly, personal communication). The existence of antigenically distinct populations of normal T cells that produce particular lymphokine patterns is difficult to reconcile with cloning experiments that suggest that the TH1 and TH2 lymphokine patterns sometimes do not emerge until several weeks have elapsed. Limiting dilution experiments (72) were able to demonstrate only IL-2-producing clones unless the cells were taken through an in vitro cycle of antigen stimulation. These various results are difficult to fit into a simple model consisting of only TH1 and TH2 cells, and so it is likely that further differentiation states of helper T cells exist and that the number of T cells in each differentiation state can vary widely between different laboratories and protocols.

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Interregulation of TH1 and TH2 Responses

WHAT DETERMINES THE SELECTIVE ACTIVATION OR DIFFERENTIATION OF TH1 OR TH2 CELLS? The ratio of TH1 to TH2 cells produced in various immune responses appears to be tightly controlled, as assessed both by the types of clones generated in tissue culture, and by the characteristic responses elicited by particular antigens or modes of immunization. Whether or not the responding T cells are already precommitted to the TH1 or TH2 patterns, mechanisms must exist for selectively activating, expanding, or differentiating precursor T cells into TH1 or TH2 cells. The antigen-presenting cell (APC) is a good candidate for the cell influencing the TH1/TH2 ratio, and it has been proposed that TH1 cells may be selectively activated and expanded by B cells, whereas macrophages (producing IL-1) cause clonal expansion of TH2 cells (44). On the other hand, TH1 cells are probably more effective at activating macrophages, whereas TH2 cells are probably the major B-cell helper population, leading to the proposal that the most important interactions of TH1 and TH2 cells are with macrophages and B cells respectively (30). These two divergent views could represent a real dichotomy between the most advantageous T-cell-APC interaction for T-cell proliferation, as distinct from the optimal interaction for activation of the non–T cell partner. Alternatively, both views may be partially correct, since B cells can enhance antigen presentation to

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proliferating T cells (probably TH1) by direct presentation as well as by producing antibody that enhances the ability of non-B cells (probably macrophages) to present antigen (86). Conversely, TH2 activation can be mediated by macrophages, and by B cells if IL-1 is added to the culture or supplied by bystander macrophages (87). A single APC type might also influence the TH1/2 ratio by providing different accessory signals to TH cells, depending on the physical nature of the antigen encountered. For example, Janeway has suggested that TH1 cells can only be activated by high antigen density on the surface of APC (44).

TH1 AND TH2 HAVE DIFFERENT GROWTH RESPONSES *Autocrine or paracrine growth responses?* Both types of T helper cell produce a T-cell growth factor, either IL-2 or IL-4. This has led to suggestions that the growth of these T cells is regulated by an autocrine pathway (12, 88, 89). However, the production of lymphokines occurs for only a few hours after stimulation in vitro, while proliferation occurs for several days provided that IL-2 or IL-4 is present. If this pattern occurs in vivo, then the rapid clearance of lymphokines in vivo (e.g. 90) would mean that both TH1 and TH2 cells would normally proliferate in response to lymphokines (either IL-2 or IL-4), produced by other T cells. Although both TH1 and TH2 clones respond to IL-2 and IL-4, some complexities exist in their growth requirements.

The TH1 growth response After activation by antigen and antigen-presenting cells, TH1 clones respond strongly to IL-2, and weakly to IL-4 (89). Several days after antigen stimulation, the IL-2 response is somewhat lower, but the IL-4 response has disappeared (88, 89, 91), although IL-4 will still synergize with suboptimal amounts of IL-2 (88). The TH1 response to IL-4 cannot be enhanced by IL-1 which is consistent with the lack of IL-1 receptors on TH1 clones (88, 91). IFNγ does not have an effect on the growth response of TH1 clones to either IL-2 or IL-4 (89), as would be expected for a cell that produces high levels of IFNγ. An unknown TH2 product inhibits the growth of at least TH1 cells (92), raising the possibility that each TH type can reciprocally inhibit the growth of the other type.

The TH2 growth response Antigen-stimulated TH2 cells also proliferate strongly in response to IL-2 and weakly in the presence of IL-4 (88, 89, 91). The response to IL-4 is maintained for a longer period than in TH1 clones, and so TH2 cells remain responsive to both lymphokines. The response to IL-4 after lectin stimulation requires the presence of IL-1, and this correlates with the presence of IL-1 receptors on TH2 cells (88, 91). IFNγ inhibits the proliferative response of TH2 clones to either IL-2 or IL-4 (89, 93).

RECIPROCAL REGULATION OF TH1 AND TH2 Because of the growth properties

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of TH1 and TH2 clones summarized above, the T-cell type that is stimulated more strongly during the initial stages of an immune response would be expected to encourage similar responses and inhibit the other type of response. These effects may explain the dominance of responses in certain parasite-infected mice where both the parasite and bystander responses are biased towards IgE and may also explain the reciprocal nature of DTH and antibody responses against the same antigen (94, 95). Strong immune responses of a particular type against certain adjuvants could predispose the immune response against accompanying antigens in the same direction as the adjuvant response, e.g. towards IgE in the case of alum and/or *Bordetella pertussis* immunizations.

This mutually inhibitory regulation of the two T-cell types could account for the bias in immune responses caused by strong antigens, but it raises the question as to how the system returns to a state of balance after an infection has been cured. Antibody could be the signal that tends to reverse the trend late in an immune response, since IgG2a antibodies (enhanced by IFNγ and hence TH1s) are inhibitory for DTH reactions and enhancing for antibody reactions, whereas IgG1 antibodies (enhanced by IL-4 and hence TH2s) have the opposite effect (96, 96a, 97, 97a). The nature of the link between antibody subclass and T-cell regulation is unknown. The lymphokine cross-inhibitory effects would be expected to take effect early in the immune response, since lymphokines are secreted in the first few hours after T-cell activation, whereas antibody effects would be expected to reach a peak a few days later, when serum titers have built up. The combination of these two mechanisms would then account for a transient bias of the general immune system in the same direction as that induced by a major immunizing antigen, followed by a resetting of the system towards a state of balance (Figure 3).

Because CTLs synthesize a pattern of lymphokines very similar to that of TH1 cells, activation of CTLs might also be expected to shift the balance of helper cells in favor of TH1 cells. Since viral infections would be expected to result in greater CTL activation than immunization with protein antigens, it is possible that viral infections would result mainly in TH1 activation (Figure 4). This would be consistent with the findings of van Snick and colleagues (98) that viral infections resulted in higher IgG2a/IgG1 ratios than protein immunization, which could be explained by the preferential enhancement of IgG2a synthesis by the TH1 product IFNγ.

Expected Roles of TH1 and TH2 Cells in Normal Responses

THE TH1 RESPONSE A predominantly TH1 response is expected to result in enhancement of several cytotoxic mechanisms (Figure 5). IFNγ and LT activate macrophages, resulting in increased killing of intracellular para-

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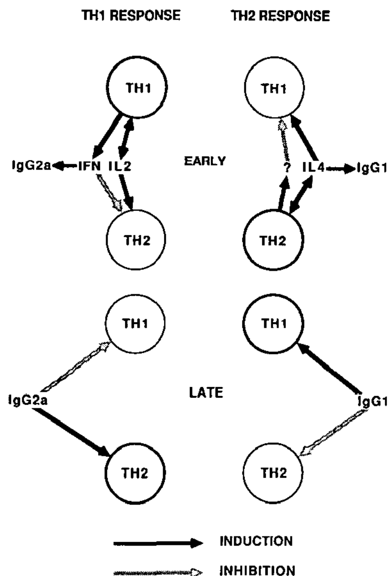

Figure 3 Inter-regulation of TH1 and TH2. Heavy arrows show the predominant effects expected during the early and late phases of responses dominated by either TH1 or TH2 responses. The lymphokine designated by "?" is possibly the TH2-derived inhibitor described by Horowitz et al (92).

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sites and tumor cells (99, 100), and increased expression of Fc receptors for IgG2a antibodies (101). These receptors could then bind the increased IgG2a levels produced in response to IFNγ (42), leading to increased antibody-dependent macrophage cytotoxicity. Lymphotoxin and IFNγ synergize in the killing of target cells (102), and IgG2a can kill target cells by complement lysis. TH1 clones also cause effective DTH reactions. All of these effector mechanisms are appropriate for dealing with intracellular (viral and parasite) infections. In general, a strong TH1 response in the absence of any TH2 response might be expected to result in DTH but little or no antibody.

THE TH2 RESPONSE Preferential activation of TH2 cells should lead to high general antibody levels. IL-4 should cause increased IgE production, as well as increased levels of IgE Fcε receptor on B cells (103) and Ia antigens on macrophages (104). IL-3 and IL-4 would be expected to result in mucosal mast cell proliferation (6), and IL-5 would cause proliferation of eosinophils (105). Thus, several features of an allergic response are increased by TH2 activation (Figure 6). In contrast, TH1 clones inhibit the pathway by decreasing TH2 growth and inhibiting IgE production by B cells.

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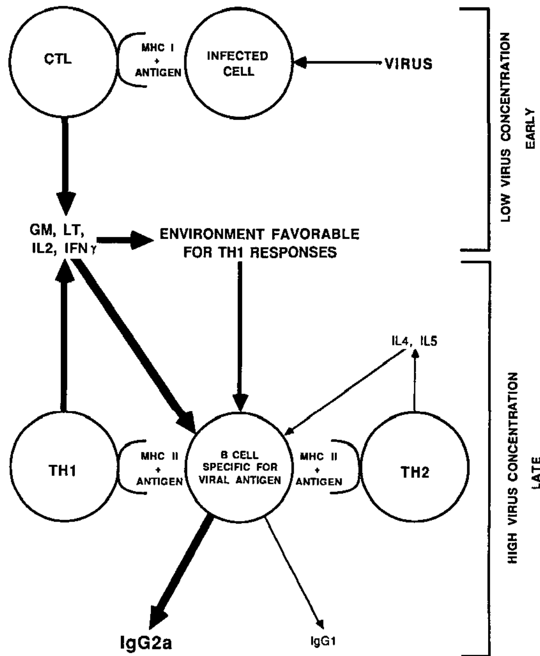

Figure 4 Immune responses against viral antigens. Some of the expected features of the immune response during a viral infection are shown. Compared to a response against a protein antigen, the anti-viral response should produce more IFNγ and LT because of the activation of CTLs. This should then lead to an enhancement of the TH1-like side of the response, resulting in a bias towards IgG2a production.

MIXED TH1 AND TH2 RESPONSES Although strongly biased TH1 or TH2 responses would be expected to result in clearly distinguishable immune responses, as described above, many normal responses may involve a mixture of the two types of cell, especially in cases where the response is neither strong nor prolonged. Under these conditions, we might expect that IgE would not be produced due to the dominant suppression by IFNγ, and a DTH response might also not occur because of possible inhibition of DTH by a TH2 response (94; T. A. T. Fong, T. R. Mosmann, unpublished). Since both TH types can activate B cells, which are then responsive to lymphokines produced by either TH type, antibody responses would be strongly supported in a mixed TH1 and TH2 response. The isotype patterns may depend on the ratio of TH1 and TH2 activation, with a TH1 bias giving preferentially IgG2a, and a TH2 preference resulting in more IgG1. These expected properties of a mixed TH1 and TH2 response are clearly compatible with the majority of immune responses, i.e. variable IgG isotype responses, without significant IgE or DTH reactions. The

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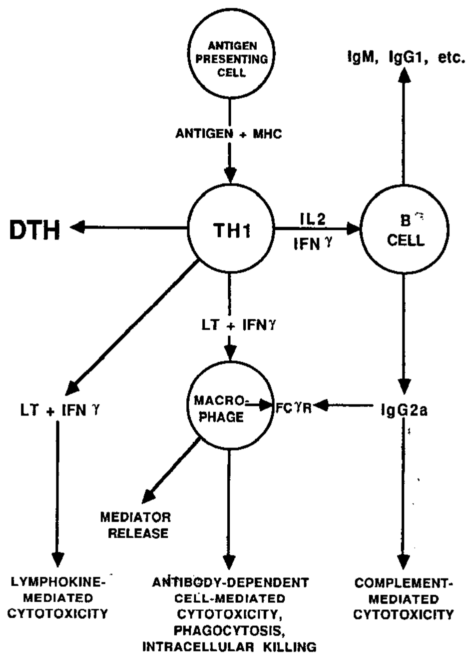

Figure 5 TH1-mediated effector functions.

patterns of normal immune responses could be even more complex when it is realized that TH1-biased or TH2-biased responses could theoretically occur simultaneously in different anatomical locations, provided that the responses were not strong enough to provoke systemic regulatory effects.

Immune Responses in Which TH1 and TH2 Ratios May Be Important

Several antigens, particularly with certain adjuvants, characteristically induce particular classes of immune response, e.g. alum adjuvant, especially with *Bordetella pertussis*, provokes good IgE responses, whereas complete Freund's adjuvant gives high antibody levels but not IgE. Several other biased immune responses suggest selective activation of the TH1 or TH2 pathways (reviewed in reference 44). A notable example is the immune response to collagen type IV, which produces an apparent TH1 response in $H2^s$ mice and a TH2 response in other mice (106). Several infectious agents may also induce biased responses, such as the antiviral response discussed above, and a number of protozoan and metazoan parasites.

NIPPOSTRONGYLUS BRASILIENSIS Most helminth parasite infestations induce significant IgE responses, often accompanied by substantial production of

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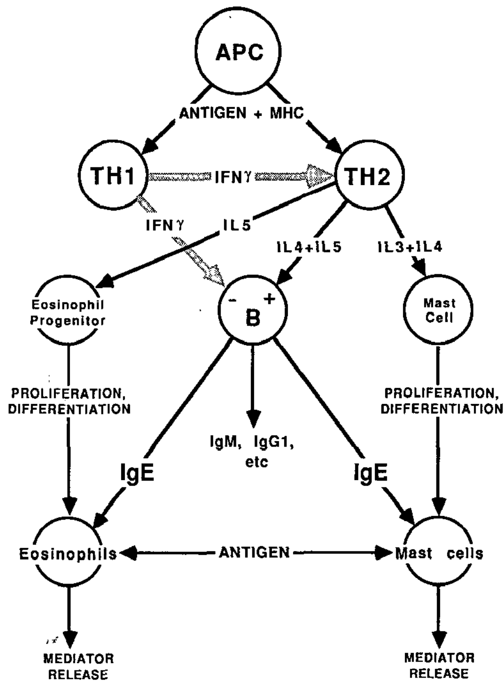

Figure 6 TH1 and TH2 regulation of IgE. Stippled arrows indicate inhibitory effects, and solid arrows show stimulatory effects.

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polyclonal IgE. In addition to the high IgE levels, these infestations are often associated with eosinophilia and intestinal mast cell hyperplasia. A well-studied example is *Nippostrongylus brasiliensis* (Nb, 107, 108, 109), in which these effects can be explained by the preferential activation of TH2 cells (Table 3). The high IgE levels can be inhibited by in vivo administration of anti-IL-4 antibody (110), and the eosinophilia can be inhibited by anti-IL-5 antibody (R. L. Coffman, D. M. Rennick, unpublished). Since the T-cell response (possibly involving mast cells) has been implicated in expulsion of worms from the gut (111), the TH2 response can be considered appropriate for this parasite. We have recently studied the lymphokine patterns synthesized by spleen and lymph node cells from Nb-infected mice, and we find that IL-2 and IFNγ levels are suppressed below normal levels and that IL-4 and IL-5 levels are greatly elevated. This is probably due both to selective amplification of TH2 cells, and regulation of activation of TH1 and TH2 (N. Street, T. R. Mosmann, unpublished).

LEISHMANIA Infection of mice by *Leishmania major* (Lm) results in one

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Table 3 Immune responses against parasites

Nippostrongylus brasiliensis		
High IgE levels (polyclonal)		
Eosinophilia		
Mast cell hyperplasia		
High IL-4 levels		
High IL-5 levels		
Low IL-2 levels		
Low IFNγ levels		
Leishmania major in mice		
Balb/c	High IL-4 Low IFNγ High IgE levels High antibody No DTH	Progressive, fatal disease
C57Bl/6	Low IL-4 High IFNγ Low IgE Low antibody Strong DTH	Limited disease, cure

Nippostrongylus elimination is associated with a TH2-like pattern.
Leishmania elimination is associated with a TH1 response.

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of two responses (Table 3). In susceptible strains, such as Balb/c, the response has the features expected of TH2 activation, such as high antibody levels (including IgE; M. Sadick, R. L. Coffman, unpublished), high IL-4 and low IFNγ expression, and no DTH. The Balb/c mice develop a severe and progressive disease and die (112). In contrast, resistant strains such as C57Bl/6, develop strong DTH, low antibody levels with no elevation of serum IgE, high IFNγ, and low IL-4 expression, and the infection is local and ultimately is cured (112). These results and others suggest that a TH1 response is effective in eliminating this parasite (an intracellular parasite in macrophages), possibly because of the ability of IFNγ to activate macrophages. The most direct evidence for the TH1 requirement has recently been obtained by Scott et al (113), who have prepared TH1 and TH2 cell lines and clones specific for Lm antigens. When these cells are injected back into Lm-infected mice, the TH1 line completely cures the infection, whereas the TH2 line actually exacerbates the course of the disease. Thus for Lm infection, the TH1 response is the appropriate response that leads to elimination of the parasite. The Lm system in mice is particularly interesting since *Leishmania donovani* infection in humans also produces two alternative forms of the immune response, either DTH leading to local containment of the infection and elimination of the

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parasite, or the Kala-Azar response in which high antibody levels are associated with low DTH reactions and a severe, disseminated disease (114). It remains to be seen whether these responses are linked to TH1 and TH2 responses in humans.

Concluding Remarks

Although we still lack conclusive proof that TH1 and TH2 cells exist in vivo in the mouse, and especially in humans, the weight of evidence now suggests that, at least in the mouse, these two types of helper cell exist, and because of their profoundly different functions, they are important regulators of the class of immune response. Several major immune responses, especially against parasites, show a remarkably good fit with the features expected of either TH1 or TH2 responses. Because the appropriate response (i.e. the response that eliminates the infection) can be either TH1 or TH2, depending on the infectious agent, it is obviously important to consider the interregulation of these types of cell when inducing therapeutic immune responses.

In closing, some of the outstanding questions in this area are these: Are TH1 and TH2 cells found in vivo? What are the precursors of TH1 and TH2 cells? What are the lymphokine secretion patterns of the precursors? Is the commitment to one of the two lymphokine secretion patterns made before or after exposure to antigen? Do human $CD4^+$ cells have a similar dichotomy of lymphokine synthesis and function? Which cell regulates the preferential activation of TH1 or TH2 by certain antigens, and how is this achieved? How is the regulation of TH1 and TH2 activation connected to the ongoing pattern of response? Since excellent tools are now available to explore these possibilities further, we look forward to answers for many of these questions in the next few years.

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