*Immunologic Research* 1999;20:147–161

# The Paradigm of Th1 and Th2 Cytokines

## *Its Relevance to Autoimmunity and Allergy*

*V. K. Singh*[1]
*S. Mehrotra*[1]
*S. S. Agarwal*[2]

[1]Department of Immunology
[2]Medical Genetics, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, 226 014, INDIA

## Abstract

In the past few years, considerable evidence has accumulated to suggest the existence of functionally polarized responses by the $CD4^+$ T helper (Th)—and the $CD8^+$ T cytotoxic (Tc)—cell subsets that depend on the cytokines they produce. The Th1 and Th2 cellular immune response provide a useful model for explaining not only the different types of protection, but also the pathogenic mechanisms of several immunopathological disorders. The factors responsible for the polarization of specific immune response into a predominant Th1 or Th2 profile have been extensively investigated in mice and humans. Evidence has accumulated from animal models to suggest that Th1-type lymphokines are involved in the genesis of organ-specific autoimmune diseases, such as experimental autoimmune uveitis, experimental allergic encephalomyelitis, or insulin-dependent diabetes mellitus. Accordingly, data so far available in human diseases favor a prevalent Th1 lymphokine profile in target organs of patients with organ-specific autoimmunity. By contrast, Th2-cell predominance was found in the skin of patients with chronic graft-versus host disease, progressive systemic sclerosis, systemic lupus erythematosus, and allergic diseases. The Th1/Th2 concept suggests that modulation of relative contribution of Th1- or Th2-type cytokines regulate the balance between protection and immunopathology, as well as the development and/or the severity of some immunologic disorders. In this review, we have discussed the paradigm of Th1 and Th2 cytokines in relation to autoimmunity and allergy.

## Key Words

Allergy
Autoimmunity
Th1 and Th2 Cytokines

## Introduction

It is now well established that both the initiation and maintenance of immune response is regulated by cytokines. More importantly, the cytokines select the type of immune response and effector mechanism that elimi-

Dr. V.K. Singh
Lab. Mol. Immunol.
Dept. Immunol.
Sanjay Gandhi Post-Graduate Inst. Med. Sci.
Lucknow – 226 014, INDIA
Email: vksingh@sgpgi.ac.in


0257–277X/99/
20:2:147–161/$13.75

nates the offending antigen. Some cytokines, particularly when produced in excess, could be pathogenic *(1)*. In 1986, Mosmann and colleagues *(2)* revolutionized immunology by dividing T helper (Th) cells into two distinct populations with contrasting and cross-regulating cytokine profiles. Studies on Leishmania infection in mice were instrumental in establishing functional relevance of these two Th subsets. Th1 cells produce interferon γ (IFN-γ), interleukin 2 (IL-2), IL-12, IL-18, and tumor necrosis factor β (TNF-β); promote production of opsonizing and complement-fixing antibodies, macrophage activation, antibody-dependent cell cytotoxicity, and delayed type hypersensitivity (DTH) reactions (Table 1). By contrast, Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13; provide help for humoral immune response, including IgE–IgG1 isotype switching and mucosal immunity through facilitation of IgA synthesis *(3,4)*. Further Th1 cells are considered to be phagocyte-dependent and Th2 cells phagocyte-independent host response *(5)*.

Last decade has been an exciting time for the proponents of Th1 and Th2 paradigm. From mice the concept has been extended to rat *(6)* and human *(7)*, and has been applied to infectious disease, cancer, transplantation, neonatal tolerance, immunodeficiency, autoimmunity, allergy, virology, and more *(8)*. Th1 responses predominate in organ-specific autoimmune disorders, acute allograft rejection, unexplained recurrent abortions, and some chronic inflammatory disorders of unknown etiology. In contrast, Th2 responses predominate in transplantation tolerance, chronic graft vs host disease, and systemic sclerosis. Allergen-reactive Th2 cells are involved in triggering of atopic disorders. The concept of Th1 and Th2 cells not only allows one to explain different types of protective immune responses but also provides the basis for pathogenesis of several immunological diseases.

## Polarizing Signals for Th1 and Th2 Responses

Factors that could be responsible for polarization of specific immune response into Th1- and Th2-type have been extensively investigated in mice and humans. It has been found that Th1 and Th2 cells are not derived from distinct lineages; they rather develop from the same precursor (Fig. 1). The differentiation into Th1 or Th2 type of response depends on dose of antigen, nature of immunogen, adjuvant, route of antigen exposure, and other undefined factors including genetic background of the individual. These factors influence Th1/Th2 differentiation mainly by determining the predominance of a given cytokine in the microenvironment of the responding Th cells *(9)*. Presence of IL-4 is a potent stimulus for Th2 differentiation, whereas IL-12 and IFNs favor Th1 development *(10,11)*. The mechanism responsible for initial IL-4 production remains unclear. Recently, it has been shown that IL-6 derived from antigen presenting cells may induce IL-4 production *(12)*. Prostaglandin E2 has also been suggested to favor development of Th2 response by inhibiting production of IL-12 by dendritic cells and IFN-γ by T cells *(13)*. It is not only the dose of priming peptide but also its affinity to MHC molecules and T cell receptor (TCR) which may influence the type of the response *(14)*. In general, Th2-type cytokines are induced by weak TCR signals.

Molecular mechanisms by which IL-4 and IL-12 promote development of naïve Th cells into Th2 or Th1-type of effectors are also not well defined. Binding of cytokines to their receptors results in rapid phosphorylation of signal transducers and activators of transcription (STATs). STAT4 appears to be selectively activated by IL-12. Targeting of the STAT4 gene results in inhibition of Th1 response *(15,16)*. On the other hand, signaling by IL-4 occurs through activation of STAT6. STAT6 gene knockout animals have deficient Th2 responses *(17,18)*.

**Table 1.** Major differences in Th1 and Th2 subsets

| Properties | Th1 | Th2 | References |
|---|---|---|---|
| Cytokine secretion profile | IL-2, IL-12, IL-18, IFN-γ, TNF-β | IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 | *3,4* |
| Prime cytokines for subset development | IL-12 and IFN-γ direct Th1 development | IL-4 directs Th2 development | *2,10,11* |
| Type of immune response | Cell mediated immune response | Predominantly helps humoral response | *4* |
| Effect on inflammatory response | Proinflammatory | Anti-inflammatory | *1* |
| Macrophage activity | Activates macrophage activity | Inhibits macrophage activity | *3,6* |
| Phagocytic activity | Phagocyte dependent | Phagocyte independent | *5* |
| Effect on parasites | Protects against intracellular pathogens | Protects against extracellular pathogens | *3,4* |
| Effect on antibody isotype | Switch to IgG2a type (IgG2c in IgG2a deleted mice) | Switch to IgG1 type | *25–27* |
| Membrane molecules | (i) Does not express CD30 | Expresses CD30 | *10* |
| | (ii) Fas and OX40 present on 10-20% cells | Fas and OX40 present on 20–40% cells | *7* |
| | (iii) Express LAG-3 | Does not express LAG-3 | *10* |
| Autoimmunity | Pathogenic for organ-specific autoimmune diseases | Usually pathogenic in systemic autoimmune diseases | *29–31* |
| Allergy | Does not play important role in allergy | Implicated in allergic responses (switch to IgE) | *6,8,78–79* |

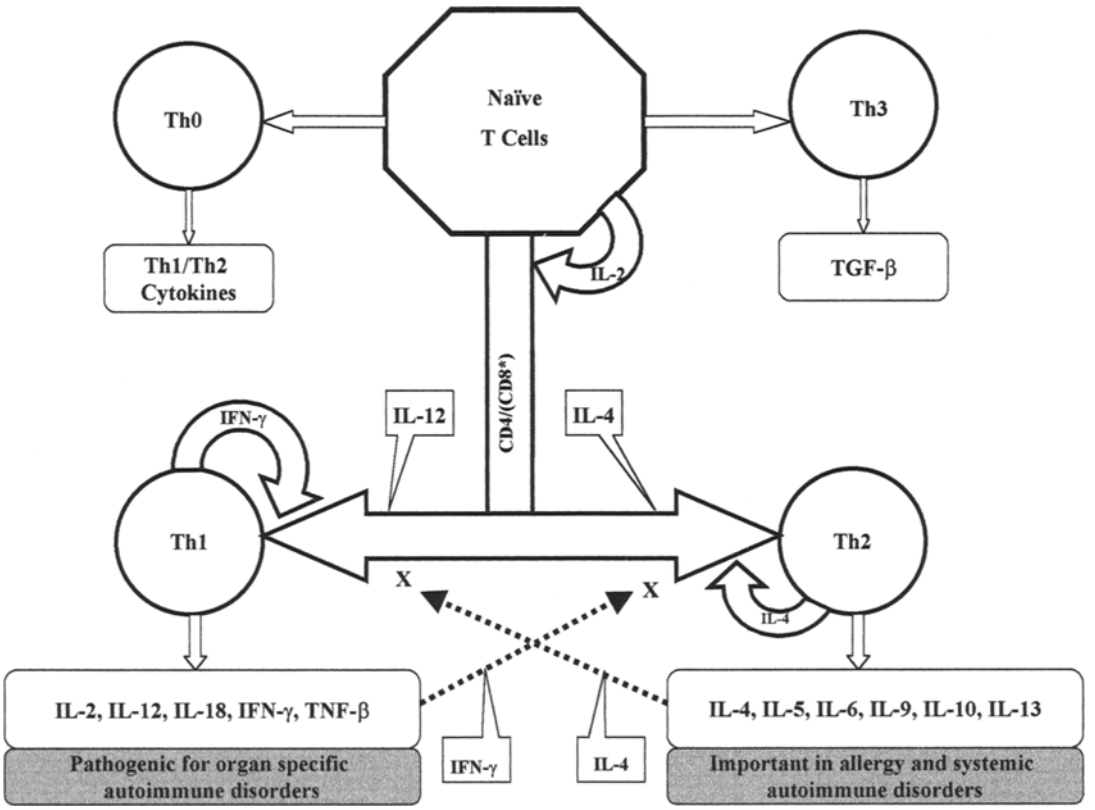


Fig. 1. Diagrammatic representation of Th1.Th2 cytokines: induction, polarization, and their role. * = Two types of CD8 cells are also called Tc1 and Tc2, X = inhibition.

Lane et al. *(19)* have provided evidence that $CD8^+$ lymphocytes provide signal to $CD4^+$ T cells to develop into Th1 cells whereas B cells stimulate Th2-type of response. The OX40L, which is expressed by both CD40-activated B cells and dendritic cells, is a molecular switch, which programs IL-4 secretion and follicular migration of naïve $CD4^+$ T cells. The $CD8^+$ T cells by secreting IFN-γ could act on dendritic cells to induce IL-12 expression, thereby determining that $CD4^+$ T cells switch to a Th1 phenotype.

Role of costimulatory molecules B7.1 and B7.2 has also been demonstrated in Th1 and Th2 development. Anti-B7.1 reduces the incidence of experimental allergic encephalomyelitis whereas anti-B7.2 increases disease severity *(20)*. Neither antibody affects overall T cell function, but they alter cytokine profile. Administration of anti-B7.1 at the time of immunization results in predominant generation of Th2 clones.

## New Th Subclasses

Th1- and Th2-types of responses are not the only cytokine patterns seen. In the absence of clear cut polarizing signal, the $CD4^+$ T cells express cytokines of both the patterns. This type of response is designated as Th0-type of cytokine response. It is possible that in such situations both the Th1 and Th2 subsets may be present separately *(21)*. Additional patterns have been identified among long-term clones. These include Tr1 (characterized by IL-10

production) and Th3 (characterized by TGF-β production) type of responses.

Recently $CD8^+$ T cells have also been segregated into two groups based on the type of the cytokine profile of these cells. Although majority of $CD8^+$ T cells produce IFN-γ, IL-4 producing $CD8^+$ T cells may also be obtained in presence of IL-4 *(22)*. $CD8^+$ T cell clones that produce IL-4 have been generated from the skin of immunologically unresponsive individuals with leprosy, and also from peripheral blood lymphocytes of HIV-infected patients. Based on these findings, the designation of Tc1 and Tc2 for cytotoxic $CD8^+$ T cells secreting Th1-like and Th2-like cytokines has been proposed. Although the functional role of $CD8^+$ Tc1 T lymphocytes is well established, the in vivo functional role of $CD8^+$ Tc2 cells is unclear. One possible explanation is that $CD8^+$ Tc2 cells act as suppressor or anti-inflammatory cells through production of helper cytokines.

## Th1/Th2 Cytokines and Antibody Isotypes

Antibody production generally requires help from $CD4^+$ T cells. With this help the antibodies may be detected in lymph nodes draining the site of immunization by $4^{th}$ or $5^{th}$ day after immunization *(23)*. The switch from IgM to IgG is also facilitated by T cell help *(24)*, but the IgG isotype response depends upon the type of Th cell response. In mice, it has been shown that Th1 response is associated with switch to IgG2a, while Th2 activity is linked with switching to IgG1 production *(25,26)*. Some antigens evoke an early IgG1 response, e.g. alum precipitated proteins, e.g., chicken γ globulin, while viral/bacterial proteins tend to induce IgG2a response.

The IFN-γ induced expression of IgG2a isotype, a characteristic of Th1-type immune response *(27)*, needs a word of caution. In mouse strains with *Igh1*-b allele, such as C57BL/6, C57BL/10, SJL, and nonobese diabetic (NOD) mice, the gene for IgG2a is deleted. These mouse strains express a different subclass of IgG, viz., isotype IgG2c in response to Th1 type of response *(28)*. Its estimation is possible only with specific polyclonal anti-IgG2c or monoclonal antibodies specific for *Igh1*-b allotype. The existence of IgG2c isotype has not become a common knowledge. Studies in mouse strains lacking the IgG2a gene may produce misleading data unless the precaution is taken to measure the IgG2c levels.

## Th1/Th2 Cytokines in Autoimmunity

The discovery of dichotomy between Th1 and Th2 helper cells represents one of the most important advances in immunology. Sufficient evidence has now accumulated that demonstrates the role of Th1 and Th2 cells in induction and control of several experimental autoimmune diseases *(29)*. In chronic inflammatory organ-specific autoimmune diseases such as insulin dependent diabetes mellitus (IDDM), multiple sclerosis (MS), rheumatoid arthritis (RA) and uveitis, Th1 cells have been found to be pathogenic whereas Th2 cells are protective. A switch from Th1 to Th2-dominated immune response could benefit individuals suffering from these diseases. However, the distinction is not always clear cut *(30)*. Under certain circumstances, Th2 cells can be pathogenic as well *(21)*. Furthermore, in systemic autoimmune diseases such as systemic lupus erythematosus and Sjogren's syndrome, both the Th1 and Th2 responses may be pathogenic.

### Experimental Allergic Encephalomyelitis (EAE)

EAE is considered to be an experimental model of MS, which is a putative autoimmune demyelinating disease. Immunization of susceptible strains of rats and mice with heterologous myelin basic protein (MBP) in complete Freund's adjuvant (CFA) results in paralysis that usually appears after 2 wk and spontaneously resolves after

another week *(31)*. Several findings show that induction of EAE is mediated by Th1 cells:

a) Inflammatory lesion in the central nervous system (CNS) resembles DTH reaction.
b) In a majority of cases there is a strong correlation between occurrence of EAE and development of cutaneous DTH response to myelin antigens.
c) IL-2, TNF-β, and IFN-γ are detected in CNS at the acme of the disease.
d) The disease can be transferred passively by Th1 cell reactive to the encephalitogenic peptide but not by Th2 cell lines.
e) Treatment with antilymphotoxin, anti-TNF-α, and anti-IL-12 monoclonal antibodies ameliorates the EAE.

While induction of EAE is clearly due to Th1 cells, several experiments suggest that regulatory phase is under control of Th2 cells. The remission is associated with predominance of IL-4, IL-10, and TGF-β in CNS. It has been possible to prevent development of EAE by altering the Th1 response to Th2 response in the following ways:

a) Administration of IL-4, IL-10, or IL-13 has beneficial effect.
b) Treatment with pentoxifylline enhances cAMP, which in turn inhibits IL-2 production.
c) Targeting of autoantigen to B cells favors Th2 response that results in protection.
d) Autoantigen administered orally inhibits induction of EAE. It is associated with appearance of $CD4^+$ and $CD8^+$ suppressor cells, which produce IL-4 and/or TGF-β, the Th2 cytokines.
e) Treatment of mice with monoclonal antibody against the costimulatory molecule B7.1 also converts the Th1 response to Th2 response *(20)*.

Modulation of antigen presenting cells interferes with development of Th1 response. It has been observed that injection of proteolipid specific Th2 clone not only prevents occurrence of EAE but also cures established disease. However, the mechanism of action is not yet elucidated. IL-10 deficient (knock out) mice are more susceptible and develop more severe EAE. On the other hand IL-10 transgenic mice are completely resistant to disease, suggesting that IL-10 may play a critical role in regulation of EAE by regulating autopathogenic Th1 responses (32).

Contrary to the aforementioned, there is a report that MBP specific Th2 cells cause EAE in immunodeficient mice rather than protecting them *(33)*. In addition, it has been shown that IL-4 is not necessary for spontaneous remission of the disease or for prevention of relapse *(34)*. Furthermore, IL-10 may not only be insufficient to reverse the effector response; it may even enhance the cascade of events leading to EAE *(35)*.

## Experimental Autoimmune Uveitis (EAU)

EAU, an animal model for human posterior uveitis, is a prototypic organ-specific, T cell-mediated disease. It is elicited in rodents and nonhuman primates by immunization with retinal antigens or their fragments that lead to destruction of neural retina and related tissues. The pathogenesis of EAU is mediated through Th1 response *(36)*. The susceptibility to EAU is characterized by conversion of early Th0/Th2-like response to Th1-type response, whereas resistance is associated with Th2-type response. Mercuric chloride triggers IL-4 production in LEW X BN hybrids and protects the treated rats against development of EAU *(37)*. Pathogenic T cell populations produce large amounts of IFN-γ *(38)*. Recent results suggest that endogenous IL-10 production limits expression of EAU. It may play an important role in natural resolution of the disease *(39)*. Exogenous IL-10 has been found to be useful for therapeutic control of EAU. While IL-10 is sufficient to suppress Th1 response, concomitant administration of IL-4 is required to shift the immune response to non-pathogenic Th2 pathway *(39)*.

IL-12-deficient mice (knock out) failed to develop EAU and their antigen-specific response was Th2-like. These mice were able to develop EAU when infused with their own

primed cells that had been incubated with antigen in the presence of IL-12 *(40)*. Thus one can conclude that endogenous IL-12 is required for EAU development and IL-12 deficient mice fail to develop Th1 response.

In apparent contradiction to above findings, mice deficient in IFN-γ are susceptible to EAU and develop disease inspite of Th2-type cytokine profile *(41)*. Thus, IFN-γ plays a protective role against EAU in mice *(42)*. Further, administration of IL-12 to EAU susceptible mice immunized with retinal antigens in CFA results in abrogation of the disease development *(43)*. These results suggest that whereas a Th1 response is required for susceptibility, resistance is not dependent on a Th2 response. Regulatory influences other than skewing the response toward the Th2 pathway may be equally effective at conferring resistance to EAU *(44)*.

## Autoimmune Diabetes

IDDM is a chronic autoimmune disease that spontaneously develops in NOD mice and also in man. The disease in the NOD mice is Th1 mediated. The antigen likely to be related to causation of the disease is glutamic acid decarboxylase (GAD). Th1 clones have been obtained which proliferate in presence of islets or GAD, produce Th1 cytokines and are able to transfer the disease passively or accelerate its appearance *(31)*. IL-12, a cytokine that favors Th1-type of response has a worsening effect; while anti-IL-2 receptor (monoclonal), anti-IFN-γ(monoclonal), and IL-4 have a beneficial effect *(30)*. Liblau et al. (31) have recently developed a model of spontaneous diabetes in double transgenic mice that express αβ TCR for haemagglutinin on T cells and haemagglutinin as an autoantigen on pancreatic β islets. The induction of diabetes in these mice depends upon their genetic background and the profile of cytokines produced by them. A Th1 pattern of cytokine response is associated with development of the disease while Th2-type of response confers protection.

However, there is no clear indication that a primary imbalance between protective Th2 and deleterious Th1 cells at early stages can trigger the autoimmune process. Protective $CD4^+$ cells detected in nondiabetic young nonobese diabetic mice have not been shown to work through Th2 cytokines *(45)*. There is also report that same Th2 cells that produce a harmless insulitis in neonatal NOD mice produce intense and generalized pancreatitis and insulitis associated with islet cell necrosis, abscess formation, and subsequent diabetes when transferred into immunocompromised NOD SCID (severe combined immunodeficient) mice *(46)*. Th2-mediated destruction of islet cells was mediated by local IL-10 production and not by IL-4. These findings suggest that under certain conditions immunocompromised Th2 cells may not produce a benign or protective insulitis but rather acute pathology and disease *(46)*. This questions the feasibility of Th2-based therapy in type I diabetes.

Conflicting results have been reported concerning the effect of IL-10 in NOD mice. Administration of recombinant IL-10 ameliorates the disease while β cells from NOD mice that express IL-10 transgene are destroyed more rapidly *(47,48)*. The deleterious effect could be due to high levels of the cytokine produced locally. Expression of IL-10 on α pancreatic islet cells is also associated with a severe insulitis. Adjuvant therapy in the form of BCG vaccination prevents the occurrence of diabetes in NOD mice and also seems to have a beneficial effect in diabetic patients. Its effect is probably mediated through IL-4 production *(49,50)*.

## Collagen Induced Arthritis

Immunization of susceptible mice ($H\text{-}2^q$ or $H\text{-}2^r$) with collagen II, emulsified in CFA, produces arthritis which is comparable to RA. The inflammatory features of collagen induced arthritis (CIA) are mediated through Th1 cytokines. The

Th2 cytokines are known to down-regulate the disease. For example, the disease is attenuated in DBA/1 mice treated with anti-IFN-γ antibodies, IL-4 or IL-13. Anti-TNF-α antibody also has a beneficial effect *(51,52)*. It has been shown that the anti-inflammatory effect of IL-4 in CIA is mediated by down regulation of Th1 response rather than up regulation of Th2 response.

On the other hand, Th2 preeminence may be associated with development of CIA in susceptible Biozzi mice. Two Biozzi mouse lines (H I and H II, both expressing $H\text{-}2^q$ haplotype) differ in their ability to develop the disease. H II mice are resistant whereas H I mice are susceptible. It has been shown that H II mice mount a preferential Th1 response upon immunization with collagen II and do not develop arthritis whereas H I mice display high titers of anticollagen II IgG1 and IgE antibodies and develop arthritis *(53)*. It has been shown that IFN-γ exacerbates CIA by enhancing the levels of type II collagen-specific IgG antibodies rather than by creating an imbalance in Th1/Th2 cells *(54)*.

## Experimental Autoimmune Thyroiditis (EAT)

EAT is induced by immunization of susceptible mice with thyroglobulin in Freund's adjuvant. It is also considered to be a Th1 mediated disease. Autoreactive T cell clones transfer disease very similar to the disease induced by immunization with thyroglobulin *(55)*. On the other hand, T cells cultured in the presence of anti-IFN-γ or anti-IL-2R induce another histological form of thyroiditis *(56)*. In the latter case, it is hypothesized that Th2 cells are activated which induces a distinct form of autoimmunity.

## Experimental Lupus Erythematosus (SLE)

SLE is characterized by T cell-dependent B cell hyperactivity with production of various autoantibodies and multiple organ lesions including nephropathies. Studies in lupus-prone mice suggest that both Th1 and Th2 cytokines may be pathogenic. The murine SLE evolves in two stages; first associated with Th1 cytokines, followed by Th2 cytokines. The disease may be attenuated by anti-IFN-γ antibodies in (NZB X NZW)F1 mice *(57)*. It has also been shown that soluble IFN-γ receptor inhibits the onset of glomerulonephritis in (NZB X NZW) mice *(58)*. The role of IFN-γ in the glomerulonephritis of MRL lpr/lpr mice has also been observed. The autoreactive T-cell lines from MRL lpr/lpr mice produce both IL-4 and IFN-γ. This nephritis is accelerated by IL-6 administration and inhibited by anti-IL-10 *(59,60)*. It is possible that either both Th1 and Th2 subsets or Th0 cells are involved. IFN-γ production is associated with particularly bad prognosis. A T cell line has been derived from the MRL lpr/lpr mice and is called MRL lpr/lpr l/l (where l/l stands for long lived) which produces IL-4 and IgG1 antibodies compared to IgG3 antibodies and IFN-γ by the classical MRL lpr/lpr mice.

It is important to note that in experimental animal models, a number of diseases can be prevented by switching the immune response from Th1 to Th2 or from Th2 to Th1-type. Also the Th1/Th2 concept provides guidelines for the use of cytokines and monoclonals for the modification of immunopathology observed in the particular models *(11)*. However, the pattern appears to vary from model to model.

## Human Autoimmune Diseases

Studies on patients with MS have shown that the disease is Th1 mediated. The Th2 response contributes to recovery from the disease *(61)*. Much higher levels of IL-12 have been reported in MS patients compared to individuals with various allergic disorders. This is considered to enhance Th1 cytokine synthesis and reduce production of Th2 cytokines *(62)*. It has been demonstrated that antigen specific cytokine secretion from MS patients and normal controls can be shifted to Th1 or Th2-type depending upon culture con-

ditions, indicating that phenotype of MBP reactive T cells can be altered even in longstanding chronic progressive cases of MS. There was no difference in the cytokine pattern secreted by MBP reactive T cells in patients with MS as compared to normal individuals *(63)*. Higher levels of TNF-α and IFN-γmRNA have been reported in HLA-DR$^+$ clones as compared to HLA-DR$^-$ MBP specific cells of MS patients *(64)*. In another study significantly higher serum levels of IFN-γ, TNF-α, and IL-4 in patients with MS suggest simultaneous activation of both Th1 and Th2 cells during the acute stage (65). Others have reported upregulation of IFN-γ, TNF-α, and β, IL-6, IL-12 and downregulation of TGF-β and IL-10 *(66)*. Moreover, IFN-γ therapy has been found to be associated with disease aggravation *(67)*. Taken together, the studies described above from patients with MS emphasize the need for caution in use of Th1/Th2 concept derived from EAE studies *(68)*.

Th1 cells play an important role in the pathogenesis of RA. Their activity predominates in joints of patients with RA *(69)*. The cells obtained from synovia of RA patients produce Th0/Th1-type cytokines. Synovial tissue from these patients produces high amounts of IL-1 and TNF-α. Th1 cells infiltrate into the synovium and cause pathogenic immune responses in the tissues, and also induce migration and activation of Tc2-type cells into the active site of inflammation. Tc2 cells appear to down-regulate the activity of Th1 cells and modulate the excess immune response.

Anti-TNF-α therapy is very effective in RA patients *(70)*. Treatment with anti-TNF-α also restores cell-mediated immune responses that are impaired in RA patients *(71)*. Verhoef and associates *(72)* have found that the prevalence of hay fever (Th2 mediated disease) in RA patients is low compared to non-RA controls. Further, RA patients with hay fever show a lower disease activity than RA patients without hay fever.

Raziuddin et al. *(73)* have determined that in children with systemic onset juvenile rheumatoid arthritis (JRA), PBMC constitutively and after stimulation with various antigens in vitro induced higher secretion of IL-4 and IL-10 with a characteristic deficiency of IL-2 and IFN-γ. The CD3/CD28 costimulatory molecule was found to be a potent inducer of IL-4 and IL-10 secretion. Augmented IL-10 secretion was inhibited by exogenous Th1 cytokines (IL-2, IL-12, IFN-γ). Although IL-10 inhibits proinflammatory cytokines IL-1α and IFN-α, it had no effect on IL-6 production. The finding of a distinctly enhanced mixed Th1/Th2 response in JRA provides a framework for developing strategies for immunologic intervention in this rheumatic disorder in children.

CD30 is preferentially expressed on cells producing Th2-type cytokines *(29)*. Elevated levels of soluble CD30 have been found in patients with SLE. In addition, the titer of soluble CD30 correlates with the clinical activity of the disease. It suggests the involvement of Th2 cells in vivo *(74)*. It has also been found that peripheral blood lymphocytes from newly diagnosed, untreated SLE patients produce large amounts of IL-6 and IL-10 *(75)*. The IL-10 producing cells are monocytes and, to a lesser extent, B cells. Transfer of peripheral blood lymphocytes into SCID mice induces production of total IgG anti-ds-DNA antibodies in these mice, which gets abrogated by administration of anti-IL-10 antibody *(75)*.

IDDM results from destruction of pancreatic-insulin secreting β islet cells. It is a T cell mediated autoimmune disease. In humans, there is little evidence that IDDM results from a Th1 response *(45)*. Indeed, efficient experimental systems are lacking in human to study the regulation of autoimmune response in vitro. Interestingly several immunotherapy strategies have aimed at inducing a Th2 response. However, recent trials in humans using oral administration of insulin to prevent

diabetes are based on a protective mechanism that seems to depend on TGF-β. This cytokine is not dependent on Th1/Th2 dichotomy. Thus, although several attempts have been made to induce a Th1/Th2 switch to obtain a protective effect, a different and more complex mechanism probably (and paradoxically) accounts for the oral protection actually tested in humans.

## Th1/Th2 Cytokines in Allergy

The allergic immune response is characterized by a number of cellular and molecular interactions. The allergens entering the body through respiratory or digestive tract or skin are taken by B cells or macrophages. After phagocytosis and processing of the exogenous antigens, the fragments of allergens are presented to allergen-specific T cells *(76)*. The allergen-reactive T cells are predominantly of the Th2 type, which secrete IL-4, IL-5, and IL-10 cytokines *(7,77)*. Recently, it has been shown that allergen-reactive Th2 cytokines play a triggering role in the activation and/or recruitment of IgE antibody-producing B cells, mast cells, and eosinophils *(78)*. Direct contact of Th2 cells with B cells results in activation of B cells. The Th2 cytokines IL-4 and IL-13 instruct B cells to switch from IgM to IgE antibody production *(79)*. These cytokines appear to act via common receptor *(80)*. A second signal is required for production of IgE. This can be provided by CD40/CD40L interaction at the cell surface of B cells with T cells or mast cells and basophils. The Th2 cytokines IL-5 and IL-6 enhance IgE production, whereas IL-8, IL-12, TGF-β, IFN-γ, and α are inhibitory *(81)*.

IgE antibodies play a central role in induction of allergic disease. These antibodies are taken up by basophils and mast cells by virtue of high-affinity receptors for IgE on these cells. Allergen confrontation leads to activation of such IgE-sensitized cells, which in turn release various mediators such as histamine, leukotrienes, and prostaglandins; together they induce the clinical manifestations of allergic reactions. The upregulation of genes controlling IL-4 expression and/or abnormalities of regulatory mechanisms of Th2 development and/or function may be responsible for Th2 responses against common environmental allergens in atopic people. IL-5 generated by allergen-reactive Th2 cells attract and activate eosinophils, which are responsible for tissue destruction in allergic asthma.

## Atopic Dermatitis and Asthma

It has been suggested that imbalance in number and activity of Th1/Th2 cells may be responsible for abnormal pattern of cytokine production in atopic dermatitis *(82)*. Acute atopic dermatitis is associated with increased expression of IL-13 (Th2) mRNA. In contrast, there is relative increase in IL-12 mRNA in chronic atopic dermatitis patients suggesting a role for Th1 cells *(83,84)*.

Analysis of Th subsets at different intervals after allergen challenge showed that Th2 cells play an important role in initial phase of inflammatory reactions whereas in later stages Th1 cells can be detected in greater numbers *(85)*.

Cry j 1, the major allergen of Japanese cedar pollen, produces both Th1 and Th2-types of response, while Cry j 2 (another allergen of Cedar pollen) plays a minor role *(86)*. Phl p 1 is a major allergen of timothy grass. Specific T cell clones from patients with pollinosis show Th2-like pattern which changes to Th1-type due to decrease in IL-4 production on specific immunotherapy *(87)*. Activation of both Th1 (IFN-γ) and Th2 (IL-4) cytokines has been observed in patients allergic to house-dust mite *(88)*. Recently it has been demonstrated that release of Th1/Th2 cytokines by cells from pollinosis patients depends on environmental exposure to sensitizing pollens *(89)*. Nickel is able to induce Th2 cells in nickel induced contact dermatitis and may

contribute to immunopathogenesis of contact dermatitis *(90)*. Single sensitizing allergen can deplete peripheral blood of Th2 cells specific for all sensitizing allergens, but not of Th1 cells. These Th2 cells may be migrating to target organs *(91)*.

### Immunotherapy

For many years immunotherapy with specific allergen injection has been used in the treatment of atopic allergic disease *(92)*. Recent studies with standardized, purified allergen extracts confirm that this treatment can be effective *(93)*. In vitro studies of allergen-specific T cells show that these can be inactivated with allergen peptide in vitro and in animal models. Secrist et al. *(94)* demonstrated that allergen induced proliferation of peripheral blood mononuclear cells was reduced after successful immunotherapy in atopic subjects, and that production of IL-4 by allergen-specific $CD4^+$ T cells was reduced after immunotherapy to levels observed in nonatopic individuals. This suggests that immunotherapy may alter cytokine production by established Th2 memory T cells. Recently, examination of skin biopsies from allergen-challenged sites of patients who had undergone successful grass pollen immunotherapy showed increased expression of IL-12 mRNA when compared to diluent-injected sites *(95)*. These changes were not seen in grass-pollen-sensitive atopics who had not received immunotherapy. It is possible that immunotherapy alters allergen responsiveness and antigen presentation to an IL-12 producing cell which may thus favor a Th1 response *(96)*. The cellular and clonal basis for the effects of current immunotherapy protocols remains to be clarified.

## Conclusion and Future Direction

The Th1/Th2 concept has proved quite useful. It is likely to continue to be so as it describes a clearly observable phenotype of cytokines *(7,77)*. Th1/Th2 paradigm has been able to explain the pathogenesis of autoimmunity and allergy *(21)*. Th1-driven autoimmune disease may be the "price one has to pay" for having a broad T cell based immune response that eliminates viral and other infections via Th1-cells. By contrast, allergic diseases such as asthma may be the "price for strong Th2-type responses" necessary to fight parasitic diseases. Several findings indicate that it would be more appropriate to define the combination of cytokines and types of effector cells required for successful immune response rather than to classify protective immunity as Th1-type or Th2-type. In many infectious diseases, both Th1 and Th2-type responses are required for a favorable outcome.

The new insights in the pathophysiology of T cell responses in atopic diseases provide exciting opportunities for the development of novel immunotherapeutic strategies *(97)*. They include the induction of nonresponsiveness in allergen-specific Th2 cells by allergen peptides or redirection of allergen-specific Th2 responses by Th1 inducing cytokines. In severe atopic patients, the possibility of nonallergen-specific immunotherapeutic regimens designed to target Th2 dependent effector molecules such as specific IL-4 transcription factors, IL-4, IL-5, and IgE may be suggested.

There are lots of questions still unanswered. One needs to know whether these cytokines specifically block and alter disease, e.g., aerosolized soluble IL-4R reduces asthma. What are the relative contributions of the immunogen and the genetic background in evoking Th1-or Th2 dominated responses? What is the role of Th1-Th2 balance in recognition of self-antigens and how are these polarized response states maintained? How is it possible to change the cytokine profile of established or ongoing Th1 and Th2 responses? The protective role of Th2 cytokines also needs to be explored in depth. An important question is whether T

cells, once differentiated into Th1/Th2 cells, can change their Th1/Th2 polarization. If aforementioned questions are solved, not only could the Th1/Th2 paradigm represent a useful model for understanding the pathogenesis of several pathological conditions, but it could also provide the basis for the development of novel immunotherapeutic strategies.


## Acknowledgments

Authors are thankful to Dr. Amita Aggarwal for her valuable suggestions. Financial assistance from Council of Scientific and Industrial Research, and Indian Council of Medical Research is acknowledged. SM is supported by CSIR as junior research fellow. The laboratory infrastructure was provided by JICA grant-in-aid to SGPGI project.


## References


1 Fresno M, Kopf M, Rivas L: Cytokines and infectious diseases. Immunol Today 1997;18:56–58.

2 Mosmann TR, Cherwinski II, Bond MW, Giedlin MA, CoffmanRI: Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 1986;136:2348–2357.

3 Romagnani S: The Th1/Th2 paradigm. Immunol Today 1997;18:263–266.

4 Rook GA, Stanford JL: Give us this day our daily germs. Immunol Today 1998;19:113–116.

5 Cohen IR: The Th1/Th2 Dichotomy, hsp60 autoimmunity,and type I diabetes. Clin Immunol Immunopathol 1997;84:103–106.

6 Fowell D, McKnight AJ, Powrie F, Dyke R, Mason D: Subsets of $CD4^+$ T cells and their role in the induction and prevention of autoimmunity. Immunol Rev 1991;123:37–64.

7 Romagnani S: Human Th1 and Th2: Doubt on more. Immunol Today 1991;12:256–257.

8 Allen JE, Maizels RM: Th1–Th2: Reliable paradigm or dangerous Fig. 1. Diagrammatic representation of Th1.Th2 cytokines: Induction, Polarization and their role. * = Two types of CD8 cells are also called Tc1 and Tc2, X = inhibition.dogma? Immunol Today 1997;18:387–392.

9 Constant SL, Bottomly K: Induction of Th1 & Th2 $CD4^+$ T cell responses: The alternative approach. Annu Rev Immunol 1997;15:297–322.

10 Seder RA, Paul WE: Acquisition of lymphokine producing phenotype by $CD4^+$ T cells. Annu Rev Immunol 1994;12:635–674.

11 Del Prete G: The concept of type–1 and type–2 helper T cells and their cytokines in humans. Int Rev Immunol 1998;16:427–455.

12 Rincon M, Anguita J, Nakamura T, Fikriz, E, Fravell RA: Interleukin–6 (IL–6) direct the differentiation of IL–4 producing $CD4^+$ T cells. J Exp Med 1997;185:461–469.

13 Hilkens C, Snijders A, Vermeulen H, Vander Meide P, Wierenga E, Kapsenberg M: Accessory cell–derived interleukin–12 and prostaglandin E2 determine the level of interferon gamma produced by activated human $CD4^+$ cells. Ann New York Acad Sci 1996;759:349–350.

14 Martin R, Ruddle NH, Reingold S, Hafler DA: T helper cell differentiation in multiple sclerosis and autoimmunity. Immunol Today 1998;19:495–498.

15 Jacobson NG, Szabo SJ, Weber–Nordt RM, Zhang Z, Schoeiber RD, Parnell JE, Jr., Murphy KM: Interleukin 12 signaling in T helper cell type I (Th1) cells involves tyrosine phosphorylation of signal transducer and activator of transcription (Stat) 3 and 4. J Exp Med 1995;181:1755–1762.

16 Kaplan MH, Sum YL, Hoey T, Grusby MJ: Impaired IL–12 responses and enhanced development of Th2 cells in Stat 4 deficient mice. Nature 1996;382:174–177.

17 Hou J, Schindler U, Henzel WJ, HO TG, Brasseur M, MacKnight SL: An interleukin–4 induced transcription factor:– IL–4 Stat. Science 1994;265:1701–1706.

18 Takeda K, Tanaku T, Shi W, Matsumoto M, Minami M, Kashiwamura S, Yoshida N, Kishimoto T, Akira S: Essential role of stat 6 in IL–4 signaling. Nature 1996;380:627–630.

19 Lane P, Flynn S, Walker L, Raykundalia C, Broker T, Gulbrason–Judge A: CD4 cytokine differentiation who and what decides? Immunologist 1988;6:182–185.

20 Kuchroo VK, Das MP, Brown JA, Ranger AM, Zamvil SS, Sobel RA, Weiner HL, Nabavi N, Glimcher LH: B7–1 and B7–2 costimulatory molecules activate differentially the Th1/Th2 development pathways: Application to autoimmune disease therapy. Cell 1995;80:707–718.

21 Romagnani S: Th1 and Th2 in human diseases. Clin Immunol Immunopathol 1996;80:225–235.

22 Seder RA, Boulay JL, Finkelman F, Barbier S, Ben–Sasson SL, Le Gros GG, Paul WE: $CD8^+$ T cells can be primed *in vitro* to produce IL–4. J Immunol 1992;148:1652–1656.

23 Caton AJ, Swartzentruber JR, Kuhl AL, Cading SR, Stark SE: Activation and negative selection of functionally distinct subset of antibody secreting cells by Influenza haemagglutinin as a viral and a neo-self antigen. J Exp Med 1996;183:13–26.
24 Luther SA, Gulbranson-Judge A, Acha-Orbea H, Mac Lennan ICM: Viral superantigen drives extrafollicular and follicular B cell differentiation leading to virus-specific antibody production. J Exp Med 1997;185:551–562.
25 Esser C, Radbrunch A: Immunoglobulin class switching: Molecular and cellular analysis. Annu. Rev Immunol 1990;8:717–735.
26 Martin RM, Lew AM: Is IgG2a a good Th1 marker in mice? Immunol Today 1998;19:49.
27 Snapper CM, Paul WE: Interferon gamma and B cell stimulatory factor-1 reciprocally regulate Ig isotype production. Science 1987;236:944–947.
28 Martin RM, Silva A, Lew AM: The Igh-1 sequence of the nonobese diabetic (NOD) mouse assigns it to the IgG2c isotype. Immunogenetics 1997;46:167–168.
29 Duret P, Sheela R, Pelletier L: Th1 and Th2 cells in autoimmunity. Clin Exp Immunol 1995;101(S):9–12.
30 O'Garra A, Steinman L, Gijbels K: $CD4^+$ T cell subsets in autoimmunity. Curr Opin Immunol 1997;9:872–873.
31 Liblau RS, Singer SM, McDevitt HO: Th1 and Th2 $CD4^+$ T cells in the pathogenesis of organ specific autoimmune diseases. Immunol Today 1995;16:34–38.
32 Battelli E, Das MP, Howard ED, Weiner HL, Sobel RA, Kuchroo VK: IL-10 is critical in the regulation of autoimmune encephalomyelitis as demonstrated by studies of IL-10 and IL-4 deficient and transgenic mice. J Immunol 1998:161:3299–3306.
33 Lafaille JJ, Keere FV, Hsu Al, Baron JL, Haas W, Raine CS, Tonegawa S: Myelin basic protein-specific T helper2 (Th2) cells cause experimental autoimmune encephalomyelitis in immunodeficient hosts rather than protect them from the disease. J Exp Med 1997;186:307–312
34 Liblau R, Steinman L, Brocke S: Experimental autoimmune encephalomyelitis in IL-4-deficient mice. Int Immunol 1997;9:799–803.
35 Cannela B, Gao YL, Brosnan C, Raine CS: IL-10 fails to abrogate experimental autoimmune encephalomyelitis. J Neurosci 1996;45:735–746.
36 Xu H, Rizzo H, Silver PB, Caspi RR: Uveitogenicity is associated with a Th1-like lymphokine profile: Cytokine dependent modulation of early and committed effector T cells in experimental autoimmune uveitis. Cell Immunol 1997;178:69–78.
37 Saoudi A, Kuhn J, Huygen K, de-Kozak Y, Velu T, Goldman M, Duret P, Bellon B: Th2 activated cells prevent experimental autoimmune uveoretinitis, a Th1 dependent autoimmune disease. Eur J Immunol 1993;23:3096–3103.
38 Caspi RR, Silver PB, Chan CC, Sun B, Agarwal RK, Wells J, Oddo S, Fujino Y, Najafian F, Wilder RL: Genetic susceptibility to experimental autoimmune uveoretinitis in the rats associated with an elevated Th1 response. J Immunol 1996;157:-2668–2675.
39 Rizzo LV, XU H, Chan CC, Wiggert B, Caspi RR: IL-10 has a protective role in experimental autoimmune uveoretinitis. Int Immunol 1998;-10:807–814.
40 Tarrant TK, Silver PB, Chan CC, Wiggert B, Caspi RR: Endogenous IL-12 is required for induction and expression of experimental autoimmune uveitis. J Immunol 1998;161:122–127.
41 Jones LS, Rizzo LV, Agarwal RK, Tarrant TK, Chan CC, Wiggert B, Caspi RR: Interferon gamma-deficient mice develop experimental autoimmune uveitis in the context of a deviant effector response. J Immunol 1997;158:5997–6005.
42 Caspi RR, Chan CC, Grubbs BG, Silver PB, Wiggert B, Parsa CF, Bahmanyar S, Billiau A, Herremans H: Endogenous systemic IFN-γ has a protective effect against ocular autoimmunity in mice. J Immunol 1994;52:890–899.
43 Caspi RR, Silver PB, Agarwal RK, Rizzo LV, Chan CC, Tarrant TK: Systemic administration of IL-12 protects mice from experimental autoimmune uveitis through a mechanism involving IFN-γ. J Allergy Clin Immunol 1997;-99:S368.
44 Sun B, Rizzo LV, Sun SH, Chan CC, Wiggert B, Wilder RL, Caspi RR: Genetic susceptibility to experimental autoimmune uveitis involves more than a predisposition to generate a T-helper-1-like or a T helper-2-like response. J Immunol 1997;159:1004–1111.
45 Heurtier AH, Biotard C: T cell regulating in murine and human autoimmune diabetes: The role of Th1 and Th2 cells. Diabetes Metab 1997;23:377–385.
46 Pakala SV, Kurrer MO, Katz JD: T helper 2 (Th2) T cells induce acute pancreatitis and diabetes in immune compromised nonobese diabetic (NOD) mice. J Exp Med 1997;186:299–306.
47 Pennline KJ, Roque-Gaffney E, Monahan E: Recombinant human IL-10 prevents the onset of diabetes in the nonobese diabetic mouse. Clin Immunol Immunopathol 1994;71:169–175.
48 Wogensen L, Lee M-S, Sarvetnick N: Production of interleukin 10 by islet cells accelerates immune mediated destruction of β cells in non obese diabetic mice. J Exp Med 1994;179:1379–1384.
49 Shehadeh N, Calcinaro F, Bradley BJ, Bruchlim I, Vardi P, Lafferty KJ:

Effect of adjuvant therapy on development of diabetes in mouse and man. Lancet 1994;343:706–707.
50 Balasa B, Savetnick N: The paradoxical effects of interleukin–10 in the immunoregulation of autoimmune diabetes. J Autoimmunity 1997;9:283–286.
51 Williams RO, Feldmann M, Maini RN: Anti–tumor necrosis factor ameliorates joint disease in murine–collagen–induced arthritis. Proc Natl Acad Sci USA 1992;89:9784–9788.
52 Horsfall AC, Bulter DM, Marinova L, Warden PJ, William RO, Maini RM, Feldman M: Suppression of collagen–induced arthritis by continuous administration of IL–4. J Immunol 1997;159:5687–5696.
53 De Franco M, Gille–Perramant M–F, Mevel J–C, Coudere J: T helper subset involvement in two high antibody responder lines of mice (Biozzi mice): HI (susceptible) and H II (resistant) to collagen induced arthritis. Eur J Immunol 1995;25:132–136.
54 Kageyama Y, Koide Y, Yoshida A, Uchijima M, Arai T, Mijamoto S, Ozeki T, Hijoshi M, Kushida K, Inoue T: Reduced susceptibility to collagen–induced arthritis in mice deficient in IFN–gamma receptor. J Immunol 1998;161:1542–1548.
55 Romball CG, Weigle WO: Transfer of experimental autoimmune thyroiditis with T cell clones. J Immunol 1987;138:1092–1098.
56 Stull SJ, Sharp GC, Kyriakos M, Bickell JT, Braley–Mullen H: Induction of granulomatous experimental autoimmune thyroiditis in mice with in vitro activated effector T cells and anti–IFN–γ antibody. J Immunol 1992;149:2219–2226.
57 Jacob CO, van der Meide PH, McDevitt HO: In vivo treatment of (NZB X NZW)F1 lupus–like nephritis mice with monoclonal antibody to γ–interferon. J Exp Med 1987;166:798–803.
58 Ozmen L, Roman D, Fountoulakis M, Schmid G, Ryffel B, Garotta G: Experimental therapy of systemic lupus erythematosus: The treatment of NZB/W mice with mouse soluble interferon–γ receptor inhibits the onset of glomerulonephritis. Eur J Immunol 1995; 25:6–12.
59 Finck BK, Chan B, Wofsy D: Interleukin 6 promotes murine lupus in NZB/NZW FI mice. J Clin Invest 1994;94:585–591.
60 Ishida H, Muchamuel T, Sakaguchi S, Menon S, Howard M: Continuous administration of anti–interleukin 10 antibodies delays onset of autoimmunity in NZB/W mice. J Exp Med 1994;179:305–310.
61 Zhang J, Markovic–Plese S, Lacet B, Raus J, Weiner HL, Hafler DA: Increased frequency of interleukin 2–responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. J Exp Med 1994;179:973–984.
62 Tang L, Benjaponpitak S, Dekruyff RM, Umetsu DT: Reduced prevalence of allergic disease in patients with multiple sclerosis is associated with enhanced IL–12 production. J Allergy Clin Immunol 1998;102:428–435.
63 Windhagen A, Anderson DE, Carrizosa A, Balashov K, Weiner HL, Hafler DA: Cytokine secretion of myelin basic protein reactive T cells in patients with multiple sclerosis. J Neuroimmunol 1998;91:1–9.
64 Vandevyver C, Motmans K, Stinissen P, Zhang J, Raus J: Cytokine m–RNA profile of myelin basic protein reactive T cell clones in patients with multiple sclerosis. Autoimmunity 1998;8:77–89.
65 Hohnoki K, Inoue A, Koh CS: Elevated serum levels of IFN–γ, IL–4 and TNF–α/unelevated serum levels of IL–10 in patients with demyelinating diseases during the acute stage. J Neuroimmunol 1998;87:27–32.
66 Link H : The cytokine storm in multiple sclerosis. Mult Scler 1998;4:12–15.
67 Panitch HS, Hirsch RL, Schindler J, Johnson KP: Treatment of multiple sclerosis with γ interferon: Exacerbations associated with activation of the immune system. Neurology 1987;37:1097–1102.
68 Laman JD, Thompson EJ, Kappos L: Balancing the Th1/Th2 in multiple sclerosis. Immunol Today 1998;19:489–490.
69 Kusaba M, Honda J, Fukuda T, Oizumi K: Analysis of type 1 and type 2 T cells in synovial fluid and peripheral blood of patients with rheumatoid arthritis. J Rheumatol 1998;25:1466–1471.
70 Elliott MJ, Maini RN, Feldmann M, Fox–Long A, Charles P, Katsikis P, Brennan M, Walker J, Biji H, Ghrayeb J, Woody J: Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to TNF–α, safety, clinical efficacy and regulation of acute phase response. Arthritis Rheum 1993;-36:1681–1686.
71 Cope AP, Londei M, Chu NR, Cohen SBA, Elliott MJ, Brennan F, Maini RN, Feldmann M: Chronic exposure to tumor necrosis factor (TNF) in vitro impairs the activation of T cells through the T cell receptor/CD3 complex: Reversal in vivo by anti–TNF antibodies in patients with rheumatoid arthritis. J Clin Invest 1994;94:749–760.
72 Verhoef CM, Van Roon JA, Vianen ME, Bruijnzeel–Koomen CA, Lafeber FP, Bijlsma JW: Mutual antagonism of rheumatoid arthritis and hay fever; a role for type 1/type–2 T cell balance. Ann Rheum Dis 1998;75:275–280.
73 Raziuddin S, Bahabri S, Al–Dalaan A, Siraj AK, al–Sedairy S: A mixed Th1/Th2 cell cytokine response predominates in systemic onset juvenile rheumatoid arthritis: Immunoregulatory IL-

10 function. Clin Immunol Immunopathol 1998;86:192–198.
74 Del Prete G, Maggi E, Pizzolo G, Romagnani S: The cytokines and HIV infection: A complex and fascinating link. Immunol Today 1995;16:76–80.
75 Llorente L, Zou W, Levy Y, Richaud–Patin Y, Wijdenes J, Alcocer–Verela J, Morel–Fourrier B, Brouet J–C, Alarcon–Segovia D, Galanaud P, Emilie D: Role of interleukin–10 in the B lymphocyte hyperactivity and autoantibody production of human systemic lupus erythematosus. J Exp Med 1995;181:839–844.
76 Heusser CH, Brinkmann V: Immune response and pathophysiology of the allergic reaction. Ther Umsch 1994;51:14–18.
77 Romagnani S: Lymphokine production by human T cells in disease states. Annu Rev Immunol 1994;12:227–257.
78 Maggi E: The Th1/Th2 paradigm in allergy. Immunotechnology 1998;3:233–244.
79 Umetsu DT, DeKruyff RH: Th1 and Th2 CD4$^+$ cells in the pathogenesis of allergic diseases. Proc Soc Exp Biol Med 1997;215:11–20.
80 Zurawaski G, de Vries JE: Interleukin 13, an interleukin 4–like cytokine that acts on monocyte and B cells, but not on T cells. Immunol Today 1994;15:19–26.
81 Kiniwa M, Gateley M, Chizzonite R, Fargeas C, Delespesse G: Recombinant interleukin 12 suppresses the synthesis of immunoglobulin E by interleukin 4 stimulated human lymphocytes. J Clin Invest 1992;90: 262–266.
82 Yamamoto S, Hamasaki Y, Ishii E, Ichimaru T, Miyazaki G: Unbalanced production of interleukin –5 and interkeukin–2 in children with atopic dermatitis. Ann Allergy Asthma Immunol 1997;78:517–523.
83 Hamid Q, Nasser T, Minshall EM, Song YL, Boguniewicz M, Leung DY: In vivo expression of IL–12 and IL–13 in atopic dermatitis. J Allergy Clin Immunol 1996;98:225–231.
84 Thepen T, Langeveld–Wildschut EG, Bihari IC, van Wichen DF, van Reijsen FC, Mudde GC, Bruijnzeel–Koomen CA: Bi phasic response against aero allergen in atopic dermatitis showing a switch from an initial Th2 response to a Th1 response in situ: An immunocytochemical study. J Allergy Clin Immunol 1997;97:828–837.
85 Bohm I, Bauer R: Th1 cells, Th2 cells and atopic dermatitis. Hautartz 1997;48:223–227.
86 Sugimara K, Hashiguchi S, Takahashi Y, Hino K, Kurimoto M, Fukuda K, Ohyama M, Yamada G: Th1/Th2 response profiles to the major allergens Cry j 1 and Cry j 2 of Japanese cedar pollen. Allergy 1996;51:732–740.
87 Ebner C, Siemann U, Bohle B, Willheim M, Wiedermann U, Schenk S, Klotz F, Ebner H, Kraft D, Scheiner O: Immunological changes during specific immunotherapy of grass pollen allergy: Reduced lymphoproliferative responses to allergen and shift from Th2 to Th1 in T–cell clones specific for Phl p 1, a major grass pollen allergen. Clin Exp Allergy 1997;27:1007–1015.
88 Laan MP, Baert MR, Vrendendaal AE, Savelkoul HF: Differential mRNA expression and production of interleukin–4 and interferon–γ in stimulated peripheral blood mononuclear cells of house–dust mite–allergic patients. Eur Cytokine Netw 1998;9:75–84.
89 Munoz–Bellido FJ, Monteserin FJ, Escribano MM, Delgad J, Velazquez E, Conde J: Effect of seasonal exposure to pollen on non-specific interleukin–4, interleukin–5, and interferon–γ in vitro release by peripheral blood mononuclear cells from subjects with pollinosis. Allergy 1998;53:420–5.
90 Probst P, Kuntzlin D, Fleischer B:Th2–type infiltrating T cells in nickel–induced contact dermatitis. Cell Immunol 1995;165:134–140
91 Crimi E, Gaffi D, Frittoli E, Borgonovo B, Burastero SE: Depletion of circulating allergen–specific Th2 lymphocytes after allergen exposure in asthma. J Allergy Clin Immunol 1997;99:788–797.
92 Noon L: Prophylactic inoculation against hay fever. Lancet 1991;-i:1572–1573.
93 Bousqust J, Becker WM, Hejaoui A, Chanal CP, Lebel B, Dhivert H, Michel FB: Clinical and immunological reactivity of patients allergic to grass pollens and multiple pollen species. II. Efficacy of a double–blind placebo–controlled, specific immunotherapy with standardized extracts. J Allergy Clin Immunol 1991;89:43.
94 Secrist H, Chelen CJ, Yan W, Marshall JD, Umetsu DT: Allergen immunotherapy decreases IL–4 production in CD4$^+$ T cells from allergic individuals. J Exp Med 1993;178:2123–2130.
95 Hamid QA, Schotman E, Jacobson MR, Walker SM, Durham SR: Increases in IL–12 messenger RNA$^+$ cells accompany inhibition of allergen–induced late skin responses after successful grass pollen immunotherapy. J Allergy Clin Immunol 1997;99:254–260.
96 Manetti R, Parronchi P, Guidizi MG, Piccini M–P, Maggi E, Trinchieri G, Romagnani S: Natural killer cell stimulatory factor interleukin 12 (IL–12) induces T helper type 1 (Th1)–specific immune responses and inhibits the development of IL–4 producing Th cells. J Exp Med 1993; 177: 1199–1204.
97 Magnan A, Vervloet D. Allergies: determinants of T2 lymphocyte polarization and desensitization mechanisms. Rev Mal Respir 1997;14:173–181.