CASE 30 Lepromatous Lepro

T_H1 versus T_H2 responses in the outcome of infection.

Mature naive CD4 T cells emerging from the thymus can differentiate into effector CD4 T cells of several different phenotypes, each with different functions in the immune response. Two of these subsets are called T_H1 and T_H2 (Fig. 30.1). They develop from naive T cells activated by pathogen antigens in the presence of different signals provided by antigen-presenting cells and the local environment. These two types of effector T cell are distinguished chiefly by the cytokines that they secrete when they encounter their target cell. T_H1 cells secrete interleukin-1 (IL-2), interferon-γ (IFN-γ), and lymphotoxin (LT, formerly known as TNF-β); T_H2 cells, often called helper T cells, secrete IL-4, IL-5, and IL-10 (Fig. 30.2).

Topics bearing on this case:
Cytokine production in innate immunity
Differentiation of T_H1 versus T_H2 CD4 T cells
Role of cytokines in T-cell differentiation
Functions of T_H1 and T_H2 cells in immune responses
Responses to mycobacteria

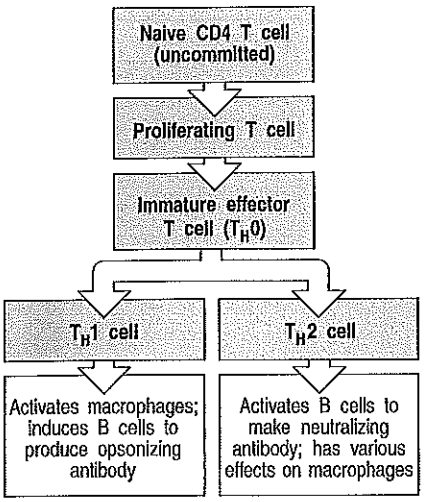

Fig. 30.1 Immature effector CD4 T cells can differentiate into either T_H1 or T_H2 cells. Naive CD4 T cells first respond to peptide:MHC class II complexes by making IL-2 and proliferating. These cells then differentiate into a cell type known as T_H0, which has some of the effector functions characteristic of T_H1 and T_H2 cells.The T_H0 cell has the potential to become either a T_H1 or a T_H2 cell. T_H0 cells might also have some effector actions in their own right.

The consequences of the decision to differentiate into T_H1 or T_H2 cells are profound, as selective production of T_H1 cells enables the immune response to activate macrophages and cell-mediated immunity, whereas selective production of T_H2 biases the response towards antibody production only. The decision as to which pathway a naive T cell will follow is made during its first encounter with antigen. An antigen that interacts strongly with the T-cell receptor causes the cell to mature into a T_H1 cell, whereas a weak interaction leads to T_H2 development. Differentiation is also dependent on cytokines. T_H1 differentiation is dependent on IL-12 and IFN-γ, whereas T_H2 differentiation is dependent on IL-4 (see Fig. 30.2). These cytokines trigger pathways of signal transduction; for example, mice deficient in the intracellular signaling molecule STAT6, which is induced by IL-4, fail to develop T_H2 cells.

Other factors influencing the T-cell phenotype are the amount of antigen present and thus which cells are most likely to present it. Large amounts of antigen are usually presented by dendritic cells, which produce IL-12 and therefore favor T_H1 differentiation. A limited amount of antigen leads to preferential presentation by antigen-specific B cells that take up antigen more avidly; they induce T_H2 differentiation. The co-stimulatory molecules (B7.1 versus B7.2) expressed by the antigen-presenting cells also influence the maturation process in that B7.1 (CD80) is more likely to provoke T_H1 development, and B7.2 (CD86) to provoke T_H2 development.

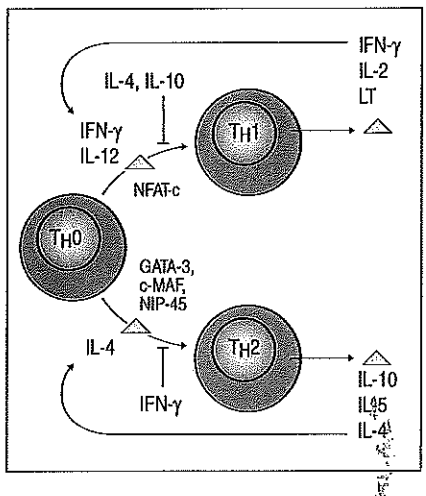

Fig. 30.2 Differentiation of T_H0 cells into either T_H1 or T_H2 cells depends on the cytokines present. IL-4 induces T_H2 differentiation, whereas IL-12 and IFN-γ induce differentiation into T_H1 cells. IL-4, which is secreted by T_H2 cells, also inhibits T_H1 development. Similarly, cytokines produced by T_H1 cells, for example IFN-γ, inhibit T_H2 differentiation. T_H1 or T_H2 development is driven by transcription factors induced by the cytokines. Induction of the transcription factors GATA-3, c-MAF and NIP-45 in naive T cells leads to T_H2 development, whereas induction of NFAT-c leads to T_H1 development.

The differentiation of T_H2 cells is favored by pathogens, such as parasites, that elicit IL-4 production from specialized subsets of cells that include mast cells, eosinophils, and thymic-derived T cells expressing both the NK1.1 marker and a T-cell receptor of restricted V_β and invariant V_α chain usage. This loop is amplified by the cytokines produced by T_H2 cells—IL-4 and IL-10. IL-4 promotes the development of T_H2 cells and IL-10 blocks T_H1 development (see Fig. 30.2).

Once one T_H phenotype becomes dominant in the course of a response, it is difficult to shift the antigen-specific response to the other. One reason for this is that the cytokine products of T_H1 and T_H2 cells are reciprocally inhibitory (see Fig. 30.2). The outcome of certain infections is greatly influenced by the type of T-cell response elicited. As we see in this case, infection with *Mycobacterium leprae*, the leprosy bacillus, is a good example.

The case of Ursula Iguaran: a T_H2 response to the leprosy bacillus has severe consequences.

Ursula first sought medical advice when she was 18 years old, having left her home in Colombia to attend Harvard University on a scholarship. From the age of 16, she had started to notice a gradual loss of sensation on the backs of her hands and had developed hypopigmented lesions over both arms. The lesions progressively became worse and she noticed that she was losing her eyelashes and hairs from her eyebrows. She also experienced recurrent nose bleeds. A month after first noticing the hair loss she decided to seek medical help.

18-year-old female; light-colored lesions on skin.

On examination at the physician's office, Ursula seemed to be well apart from her immediate symptoms. She reported a history of mild asthma, which required treatment with inhaled β_2-adrenergic agents on an as-needed basis. Multiple hypopigmented macules (coin-sized raised lesions with ill-defined borders) were evident on her skin, along with cutaneous nodules 1 cm in diameter. These lesions were predominantly on her elbows, wrists, and hands (Fig. 30.3) and showed traces of dried blood; she also had similar lesions on her knees, ears, and buttocks. The absence of eyelashes and the ends of her eyebrows was obvious.

Acid-fast bacilli (? mycobacteria) in skin lesions; leprosy?

Cardiovascular and abdominal examinations were normal; a neurological examination was negative except for a decreased response to pinprick on the outer edges of the right and left hand and the right fourth and fifth fingers. There was a flexion contracture of the fourth and fifth fingers of both hands so that she could not straighten these fingers completely.

On blood test, her hematocrit was 35.1%; white blood count was 7100 μl^{-1}, with 68% neutrophils, 23% lymphocytes, 5% monocytes, and 4% eosinophils (all normal values). Serum electrolytes were normal. Because her symptoms were becoming more severe, she was referred to a dermatologist. She told him that she had grown up in a small village on the Caribbean coast of Colombia where many people, including her mother, had leprosy. The dermatologist performed a biopsy of the lesions on her left arm and right forearm, which revealed numerous acid-fast bacilli in clumps. A routine hematoxylin and eosin stain of lesion tissue showed up numerous Virchow's cells (highly vacuolated cells of the macrophage lineage also known as foam cells) and few lymphocytes (Fig. 30.4). Cultures for acid-fast bacilli were negative.

The suspected diagnosis of lepromatous leprosy led to a more extensive immunologic work-up. Delayed hypersensitivity skin tests with intradermal injections of candida, mumps, and tuberculin antigens showed no reactions when the injection sites were inspected 48 and 72 hours later. Ursula's serum IgG was mildly elevated at 1800 mg dl^{-1} (normal 600–1100 mg dl^{-1}); her IgA and IgM levels were normal.

A diagnosis of lepromatous leprosy was made on the basis of the presence of acid-fast bacilli in the biopsy and Ursula's progressive neurologic symptoms. She was placed on a multiple drug regime consisting of dapsone, clofazamine, and rifampin, drugs that kill *M. leprae*. Her skin lesions gradually flattened and improved.

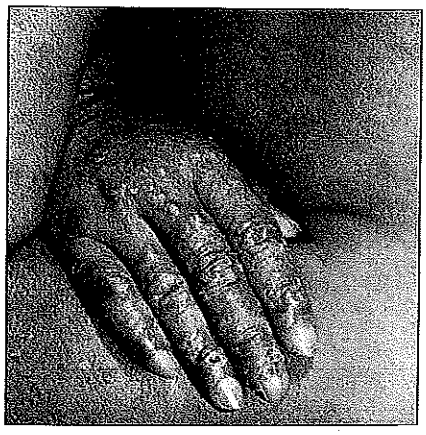

Fig. 30.3 Cutaneous nodules in lepromatous leprosy. Patients with lepromatous leprosy have multiple skin lesions. This photograph shows subcutaneous nodules on the hand. Photograph courtesy of E. Gonzalez.

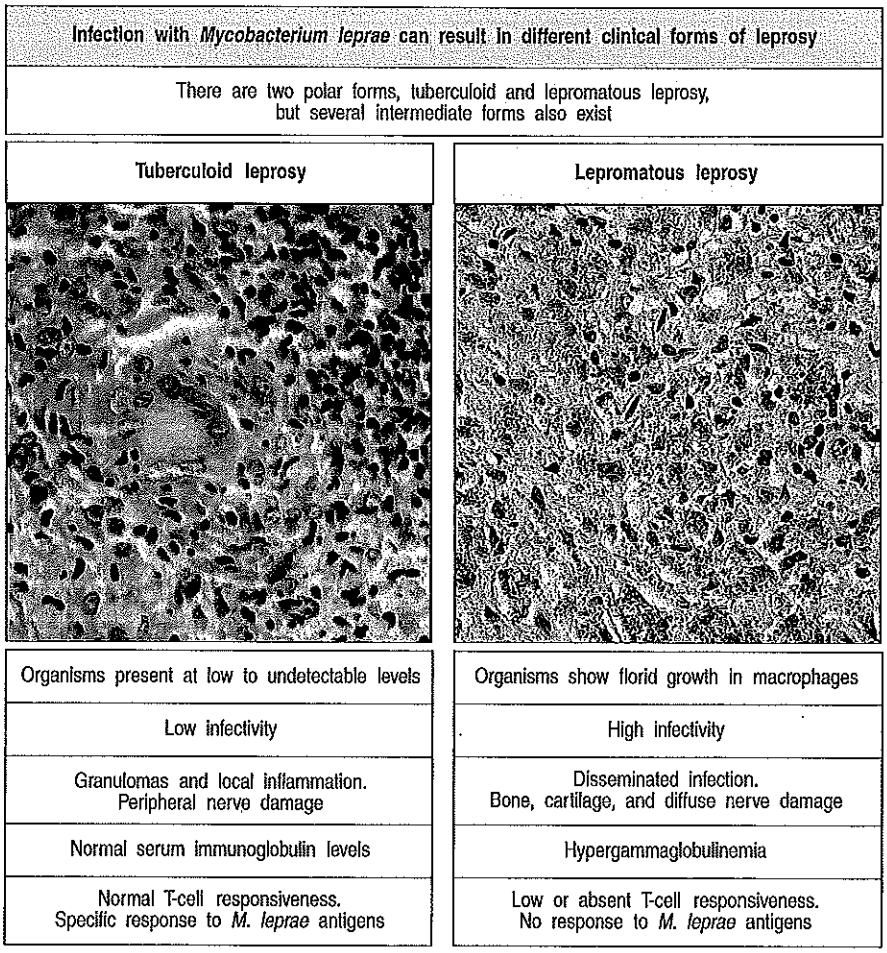

Fig. 30.4 Responses to *M. leprae* are sharply differentiated in lepromatous and tuberculoid leprosy. The photographs show sections of lesion biopsies stained with hematoxylin and eosin. Infection with *M. leprae* bacilli, which can be seen in the right-hand photograph as numerous small dark red dots inside macrophages, can lead to two very different forms of the disease. In tuberculoid leprosy (left), growth of the microorganism is well controlled by T_H1-like cells that activate infected macrophages. The tuberculoid lesion contains granulomas (see Case 2) and is inflamed, but the inflammation is localized and causes only local peripheral nerve damage. In lepromatous leprosy (right), infection is widely disseminated and the bacilli grow uncontrolled in macrophages. In the late stages there is severe damage to connective tissues and to the peripheral nervous system. There are several intermediate stages between these two polar forms. Photographs courtesy of G. Kaplan.

Lepromatous leprosy.

The classical clinical feature in patients with leprosy is the association of cutaneous lesions, neuropathologic changes, and deformities. Leprosy is caused by *Mycobacterium leprae*, which colonizes macrophages and other host cells and multiplies within them. Mycobacteria within macrophages are protected from attack by antibody and can be eliminated only when their host macrophages are activated and produce increased amounts of nitric oxide, oxygen radicals, and other microbicidal molecules. *M. leprae* grows best at 30°C and therefore lesions tend to appear on the extremities—the colder areas of the body—for example the hands, ears, and buttocks as in Ursula's case. Unlike *M. tuberculosis*, *M. leprae* does not grow in culture.

The clinical symptoms of leprosy vary depending on the type of immune response to the mycobacteria. The clinical spectrum is typically divided into two polar forms, tuberculoid and lepromatous leprosy, although intermediate forms exist. Tuberculoid leprosy is associated with a vigorous cell-mediated (T_H1) response against the bacillus. This results in macrophage activation with efficient killing of intracellular mycobacteria, localized tissue damage, and usually a milder clinical picture. In the lepromatous form, the T_H1-cell

mediated response is defective and a T_H2 response predominates; this leads to a vigorous but ineffective antibody response against *M. leprae* and dissemination of the bacilli to other sites in the body, which results in further tissue destruction and aggravation of the symptoms. The importance of T_H1-derived IFN-γ in containing mycobacterial infections is further illustrated by the observation that infants with genetic defects in the IFN-γ receptor die from disseminated mycobacterial infections (see Case 21).

Infection with *M. leprae* illustrates a situation in which the same microorganism, in different individuals, can trigger either a T_H1 or a T_H2 response. A T_H1 response predominates in tuberculoid leprosy, in which the mycobacteria are contained within well-circumscribed granulomas and propagate poorly, usually accompanied by subsequent minimal tissue damage. In contrast, a T_H2 response predominates in lepromatous leprosy, in which the mycobacteria propagate rapidly, with resulting extensive tissue damage. Analysis of mRNA isolated from lesions of patients with lepromatous and tuberculoid leprosy illustrates the cytokine patterns in the two forms of the disease. T_H2 cytokines (IL-4, IL-5, and IL-10) dominate in the lepromatous form, whereas T_H1 cytokines (IL-2, IFN-γ, and LT) dominate in the tuberculoid form (Fig. 30.5).

The neurologic damage in leprosy has two main causes. It can arise from bacterial multiplication within Schwann cells—the cells that form the insulating myelin sheath around some nerve cell axons. Disruption of the myelin sheath interferes with the normal conduction of nerve impulses along the axon. In the tuberculoid form, nerve damage also arises from the formation of granulomas and inflammation of the tissue surrounding the nerve. The nerve damage results in dysfunctional nerve terminals, resulting in decreased sensation and eventually a loss of motor function.

The nose bleeds that Ursula experienced are common in leprosy. They are due to large numbers of *M. leprae* in the nasal tissue with extensive involvement of the nasal mucosa, leading to congestion and breakage of blood vessels.

The T_H2 response can influence the course of the infection in various other ways. By binding to mycobacterial antigens displayed on the surface of infected cells, antibodies to the leprosy bacillus can interfere with the action of

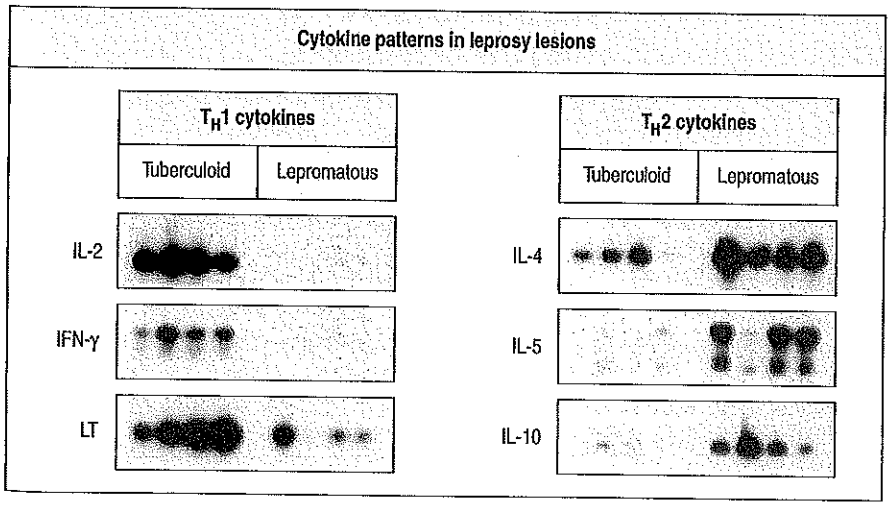

Fig. 30.5 Cytokine patterns in leprosy lesions. The cytokine patterns in the two polar forms of leprosy are distinctly different, as shown by Northern blot analysis of the mRNA from lesions of three patients with lepromatous leprosy and three patients with tuberculoid leprosy. Cytokine mRNAs typically produced by T_H2 cells predominate in the lepromatous form whereas cytokines produced by T_H1 cells predominate in the tuberculoid form. Cytokine blots courtesy of R.L. Modlin.

cytotoxic CD8 T cells. CD8 T cells can, in addition to their cytolytic function, also respond to antigen by secreting cytokines. Patients with lepromatous leprosy have CD8 T cells that suppress the T_H1 response by making IL-10 and LT. IL-10 inhibits the development of T_H1 cells and inhibits both cytokine release from macrophages and their capacity to kill internalized microorganisms. LT also inhibits macrophage intracellular killing capacity. Inhibition of macrophages leads to decreased production of IL-12, fewer T_H1 cells, and more T_H2 cells. In contrast, patients with the less destructive tuberculoid leprosy lack suppressor CD8 T cells and thus make a vigorous T_H1 response, leading to macrophage activation and the destruction of the leprosy bacilli.

Questions.

1 *Ursula did not respond to candida and mumps antigens, which are common recall antigens, with a delayed-type hypersensitivity reaction. Give a possible explanation.*

2 *Which cytokine might be beneficial to a patient with lepromatous leprosy?*

3 *Describe the mechanism for Ursula's hypergammaglobulinemia.*

4 *Why would Ursula be prone to asthma?*