been termed *delayed-type hypersensitivity reactions*. The term *delayed* has been used to contrast a secondary cellular response that appears 48–72 h after antigen exposure with an *immediate* hypersensitivity response generally seen within 12 h of antigen challenge and initiated by basophil mediator release or preformed antibody. For example, in an individual previously infected with *M. tuberculosis* organisms, intradermal placement of tuberculin purified protein derivative as a skin test challenge results in an indurated area of skin at 48–72 h, indicating previous exposure to tuberculosis.

The cellular events that result in classic delayed-type hypersensitivity responses are centered on T cells (predominantly, although not exclusively, IFN-γ, IL-2, and TNF-α-secreting T_H1-type helper T cells) and macrophages. Recently NK cells have been suggested to play a major role in the form of delayed hypersensitivity that occurs following skin contact with immunogens. First, local immune and inflammatory responses at the site of foreign antigen upregulate endothelial cell adhesion molecule expression, promoting the accumulation of lymphocytes at the tissue site. In the general schemes outlined in Figs. 372e-2 and 372e-3, antigen is processed by DCs and presented to small numbers of CD4+ T cells expressing a TCR specific for the antigen. IL-12 produced by APCs induces T cells to produce IFN-γ (T_H1 response). Macrophages frequently undergo epithelioid cell transformation and fuse to form multinucleated giant cells in response to IFN-γ. This type of mononuclear cell infiltrate is termed *granulomatous inflammation*. Examples of diseases in which delayed-type hypersensitivity plays a major role are fungal infections (*histoplasmosis*; **Chap. 236**), mycobacterial infections (*tuberculosis*, *leprosy*; **Chaps. 202 and 203**), chlamydial infections (*lymphogranuloma venereum*; **Chap. 213**), helminth infections (*schistosomiasis*; **Chap. 259**), reactions to toxins (*berylliosis*; **Chap. 311**), and hypersensitivity reactions to organic dusts (*hypersensitivity pneumonitis*; **Chap. 310**). In addition, delayed-type hypersensitivity responses play important roles in tissue damage in autoimmune diseases such as *rheumatoid arthritis*, *temporal arteritis*, and granulomatosis with polyangiitis (Wegener's) **(Chaps. 380 and 385)**.

CLINICAL EVALUATION OF IMMUNE FUNCTION

Clinical assessment of immunity requires investigation of the four major components of the immune system that participate in host defense and in the pathogenesis of autoimmune diseases: (1) humoral immunity (B cells); (2) cell-mediated immunity (T cells, monocytes); (3) phagocytic cells of the reticuloendothelial system (macrophages), as well as polymorphonuclear leukocytes; and (4) complement. Clinical problems that require an evaluation of immunity include chronic infections, recurrent infections, unusual infecting agents, and certain autoimmune syndromes. The type of clinical syndrome under evaluation can provide information regarding possible immune defects **(Chap. 374)**. Defects in cellular immunity generally result in viral, mycobacterial, and fungal infections. An extreme example of deficiency in cellular immunity is AIDS **(Chap. 226)**. Antibody deficiencies result in recurrent bacterial infections, frequently with organisms such as *S. pneumoniae* and *Haemophilus influenzae* **(Chap. 374)**. Disorders of phagocyte function are frequently manifested by recurrent skin infections, often due to *Staphylococcus aureus* **(Chap. 80)**. Finally, deficiencies of early and late complement components are associated with autoimmune phenomena and recurrent *Neisseria* infections (Table 372e-16). **For further discussion of useful initial screening tests of immune function, see Chap. 374.**

IMMUNOTHERAPY

Many therapies for autoimmune and inflammatory diseases involve the use of nonspecific immune-modulating or immunosuppressive agents such as glucocorticoids or cytotoxic drugs. The goal of development of new treatments for immune-mediated diseases is to design ways to specifically interrupt pathologic immune responses, leaving nonpathologic immune responses intact. Novel ways to interrupt pathologic immune responses that are under investigation include the use of anti-inflammatory cytokines or specific cytokine inhibitors as anti-inflammatory agents, the use of monoclonal antibodies against T or B lymphocytes as therapeutic agents, the use of intravenous Ig for certain infections and immune complex–mediated diseases, the use of specific cytokines to reconstitute components of the immune system, and bone marrow transplantation to replace the pathogenic immune system with a more normal immune system **(Chaps. 80, 374, and 226)**. In particular, the use of a monoclonal antibody to B cells (rituximab, anti-CD20 MAb) is approved in the United States for the treatment of non-Hodgkin's lymphoma **(Chap. 134)** and, in combination with methotrexate, for treatment of adult patients with severe rheumatoid arthritis resistant to TNF-α inhibitors **(Chap. 380)**. The U.S. Food and Drug Administration (FDA) approved the use of CTLA-4 antibodies in 2010 to block T cell anergy for use in cancer immunotherapy, and it was the first agent to demonstrate survival benefit in patients with advanced melanoma. Early-stage clinical trials have now shown that PD-1 blockade to reverse T cell exhaustion can induce tumor regression.

Cell-based therapies have been studied for many years, including ex vivo activation of NK cells for reinfusion into patients with malignancies and DC therapy of ex vivo priming of DCs for enhanced presentation of cancer antigens, with reinfusion of primed DCs into the patient. One such strategy for DC therapy has been approved by the FDA for treatment of advanced prostate cancer.

Cytokines and Cytokine Inhibitors Several TNF inhibitors are used as biological therapies in the treatment of rheumatoid arthritis; these include monoclonal antibodies, TNF-R Fc fusion proteins, and Fab fragments. Use of anti-TNF-α antibody therapies such as adalimumab, infliximab, and golimumab has resulted in clinical improvement in patients with these diseases and has opened the way for targeting TNF-α to treat other severe forms of autoimmune and/or inflammatory disease. Blockage of TNF-α has been effective in *rheumatoid arthritis*, *psoriasis*, *Crohn's disease*, and *ankylosing spondylitis*. Other cytokine inhibitors are recombinant soluble TNF-α receptor (R) fused to human Ig and anakinra (soluble *IL-1 receptor antagonist*, or IL-1ra). The treatment of autoinflammatory syndromes (Table 372e-6) with recombinant IL-1 receptor antagonist can prevent symptoms in these syndromes, because the overproduction of IL-1β is a hallmark of these diseases.

TNF-αR-Fc fusion protein (etanercept) and IL-1ra act to inhibit the activity of pathogenic cytokines in rheumatoid arthritis, i.e., TNF-α and IL-1, respectively. Similarly, anti-IL-6, IFN-β, and IL-11 act to inhibit pathogenic proinflammatory cytokines. Anti-IL-6 (tocilizumab) inhibits IL-6 activity, whereas IFN-β and IL-11 decrease IL-1 and TNF-α production.

Of particular note has been the successful use of IFN-γ in the treatment of the phagocytic cell defect in *chronic granulomatous disease* **(Chap. 80)**.

Monoclonal Antibodies to T and B Cells The OKT3 MAb against human T cells has been used for several years as a T cell-specific immunosuppressive agent that can substitute for horse antithymocyte globulin (ATG) in the treatment of solid organ transplant rejection. OKT3 produces fewer allergic reactions than ATG but does induce human anti-mouse Ig antibody—thus limiting its use. Anti-CD4 MAb therapy has been used in trials to treat patients with rheumatoid arthritis. While inducing profound immunosuppression, anti-CD4 MAb treatment also induces susceptibility to severe infections. Treatment of patients with a MAb against the T cell molecule CD40 ligand (CD154) is under investigation to induce tolerance to organ transplants, with promising results reported in animal studies. Monoclonal antibodies to the CD25 (IL-2a) receptor (basiliximab) are being used for treatment of graft-versus-host disease in bone marrow transplantation, and anti-CD20 MAb (rituximab) is used to treat hematologic neoplasms, autoimmune diseases, kidney transplant rejection, and rheumatoid arthritis. The anti-IgE monoclonal antibody (omalizumab) is used for blocking antigen-specific IgE that causes *hay fever* and *allergic rhinitis* **(Chap. 376)**; however, side effects of anti-IgE include increased risk of anaphylaxis. Studies have shown that T_H17 cells, in addition to T_H1, are mediators of inflammation in Crohn's disease, and anti–IL-12/IL-23p40 antibody therapy has been studied as a treatment.