disorders are caused by a breakdown of self-tolerance resulting in autoimmunity, but chronic infections associated with the immune deficiency may play a role in inducing the inflammatory reactions. The treatment of X-linked agammaglobulinemia is replacement therapy with immunoglobulins. In the past, most patients succumbed to infection in infancy or early childhood. Prophylactic intravenous Ig therapy allows most individuals to reach adulthood.

DiGeorge Syndrome (Thymic Hypoplasia)

DiGeorge syndrome is a T-cell deficiency that results from failure of development of the third and fourth pharyngeal pouches. The latter give rise to the thymus, the parathyroids, some of the C cells of the thyroid, and the ultimobranchial body. Thus, individuals with this syndrome have a variable loss of T cell–mediated immunity (resulting from hypoplasia or lack of the thymus), tetany (resulting from lack of the parathyroids), and congenital defects of the heart and great vessels. In addition, the appearance of the mouth, ears, and facies may be abnormal. Absence of cell-mediated immunity is caused by low numbers of T lymphocytes in the blood and lymphoid tissues and poor defense against certain fungal and viral infections. The T-cell zones of lymphoid organs—paracortical areas of the lymph nodes and the periarteriolar sheaths of the spleen—are depleted. Ig levels may be normal or reduced, depending on the severity of the T-cell deficiency.

In many cases, DiGeorge syndrome is not a familial disorder. It results from a deletion that maps to chromosome 22q11. This deletion is seen in more than 50% of patients, and DiGeorge syndrome is now considered a component of the *22q11 deletion syndrome*, discussed in Chapter 5. One gene in the deleted region is *TBX1*, which is required for development of the branchial arch and the great vessels. Notably, *TBX1* is involved by loss-of-function mutations in a few cases of DiGeorge syndrome that lack 22q11 deletions, strongly suggesting that its loss contributes to the observed phenotype.

Other Defects in Lymphocyte Maturation

Many other, rare causes of immunodeficiency resulting from defective lymphocyte maturation have been documented. One of these, the *bare lymphocyte syndrome*, is usually caused by mutations in transcription factors that are required for class II MHC gene expression. Lack of expression of class II MHC molecules prevents the development of CD4+ T cells. CD4+ T cells are involved in cellular immunity and provide help to B cells, and hence class II MHC deficiency results in combined immunodeficiency. Other defects are caused by mutations in antigen receptor chains or signaling molecules involved in T- or B-cell maturation.

Defects in Lymphocyte Activation and Function

With our improving understanding of the molecular pathways in lymphocyte activation and function, there has also been an increasing recognition of immune deficiencies caused by mutations affecting various components of these pathways. Some of the mutations cause well-defined syndromes, and others are rare but informative.

Hyper-IgM Syndrome

In this disorder the affected patients make IgM antibodies but are deficient in their ability to produce IgG, IgA, and IgE antibodies. It is now known that the defect in this disease affects the ability of helper T cells to deliver activating signals to B cells and macrophages. As discussed earlier in the chapter, many of the functions of CD4+ helper T cells require the engagement of CD40 on B cells, macrophages and dendritic cells by CD40L (also called CD154) expressed on antigen-activated T cells. This interaction triggers Ig class switching and affinity maturation in B cells, and stimulates the microbicidal functions of macrophages. Approximately 70% of individuals with hyper-IgM syndrome have the X-linked form of the disease, caused by mutations in the gene encoding CD40L located on Xq26. In the remaining patients the disease is inherited in an autosomal recessive pattern. Most of these patients have loss-of-function mutations involving either CD40 or the enzyme called activation-induced cytidine deaminase (AID), a DNA-editing enzyme that is required for Ig class switching and affinity maturation.

The serum of persons with this syndrome contains normal or elevated levels of IgM but no IgA or IgE and extremely low levels of IgG, although the number of B and T cells is normal. Clinically, patients present with recurrent pyogenic infections, because the level of opsonizing IgG antibodies is low. In addition, those with CD40L mutations are also susceptible to pneumonia caused by the intracellular organism *Pneumocystis jiroveci*, because CD40L-mediated macrophage activation, a key reaction of cell-mediated immunity, is also defective. Occasionally, the IgM antibodies react with blood cells, giving rise to autoimmune hemolytic anemia, thrombocytopenia, and neutropenia. In older patients there may be a proliferation of IgM-producing plasma cells that infiltrates the mucosa of the gastrointestinal tract.

Common Variable Immunodeficiency

This relatively frequent but poorly defined entity encompasses a heterogeneous group of disorders in which the common feature is hypogammaglobulinemia, generally affecting all the antibody classes but sometimes only IgG. The diagnosis of common variable immunodeficiency is based on exclusion of other well-defined causes of decreased antibody production.

Both sporadic and inherited forms of the disease occur. In familial forms there is no single pattern of inheritance. Relatives of such patients have a high incidence of selective IgA deficiency (see later). These studies suggest that at least in some cases, selective IgA deficiency and common variable immunodeficiency may represent different expressions of a common genetic defect in antibody synthesis. In contrast to X-linked agammaglobulinemia, most individuals with common variable immunodeficiency have normal or near-normal numbers of B cells in the blood and lymphoid tissues. These B cells, however, are not able to differentiate into plasma cells.

Both intrinsic B-cell defects and abnormalities in helper T cell–mediated activation of B cells may account for the antibody deficiency in this disease. Families have been reported in which the underlying abnormality is in a receptor for a cytokine called BAFF that promotes the survival and differentiation of B cells, or in a molecule called ICOS