immature lymphocytes, especially those of the T-cell lineage. Hence there may be a greater reduction in the number of T lymphocytes than of B lymphocytes.

Several other less common causes of autosomal recessive SCID have been identified:

- Mutations in recombinase-activating genes (RAG) or other components of the antigen receptor gene recombination machinery prevent the somatic gene rearrangements that are essential for the assembly of T-cell receptor and Ig genes. This blocks the development of T and B cells.
- An intracellular kinase called Jak3 is essential for signal transduction through the common cytokine receptor γ chain (which is mutated in X-linked SCID, as discussed above). Mutations of Jak3 therefore have the same effects as mutations in the γc chain.
- Several mutations have been described in signaling molecules, including kinases associated with the T-cell antigen receptor and components of calcium channels that are required for entry of calcium and activation of many signaling pathways.

The histologic findings in SCID depend on the underlying defect. In the two most common forms (γc mutation and ADA deficiency), the thymus is small and devoid of lymphoid cells. In X-linked SCID the thymus contains lobules of undifferentiated epithelial cells resembling fetal thymus, whereas in SCID caused by ADA deficiency, remnants of Hassall's corpuscles can be found. In both diseases, other lymphoid tissues are hypoplastic as well, with marked depletion of T-cell areas and in some cases both T-cell and B-cell zones.

Currently, HSC transplantation is the mainstay of treatment, but X-linked SCID is the first human disease in which gene therapy has been successful. For gene therapy a normal γc gene is expressed using a viral vector in HSCs taken from patients, and the cells are then transplanted back into the patients. The clinical experience is small, but some patients have shown reconstitution of their immune systems for over a year after therapy. Unfortunately, however, about 20% of these patients have developed T-cell lymphoblastic leukemia, highlighting the dangers of this particular approach to gene therapy. The uncontrolled T-cell proliferation may have been triggered by the activation of oncogenes by the integrated virus together with the growth advantage conferred by the introduced γc gene. Current trials are using new vectors with safety features built in. Patients with ADA deficiency have also been treated with HSC transplantation and, more recently, with administration of the enzyme or gene therapy involving the introduction of a normal *ADA* gene into T-cell precursors.

X-Linked Agammaglobulinemia (Bruton Agammaglobulinemia)

X-linked agammaglobulinemia is characterized by the failure of B-cell precursors (pro-B cells and pre-B cells) to develop into mature B cells. It is one of the more common forms of primary immunodeficiency. During normal B-cell maturation in the bone marrow, the Ig heavy-chain genes are rearranged first, in pre-B cells, and these are expressed on the cell surface in association with a "surrogate" light chain, where they deliver signals that induce rearrangement of the Ig light-chain genes and further maturation. This need for Ig-initiated signals is a quality control mechanism that ensures that maturation will proceed only if functional Ig proteins are expressed. X-linked agammaglobulinemia is caused by mutations in a cytoplasmic tyrosine kinase, called *Bruton tyrosine kinase (Btk)*; the gene that encodes it is located on the long arm of the X chromosome at Xq21.22. Btk is a protein tyrosine kinase that is associated with the Ig receptor complex of pre-B and mature B cells and is needed to transduce signals from the receptor. When it is mutated, the pre-B cell receptor cannot deliver signals, and maturation stops at this stage. Because light chains are not produced, the complete antigen receptor molecule (which contains Ig heavy and light chains) cannot be assembled and transported to the cell membrane.

As an X-linked disease, this disorder is seen almost entirely in males, but sporadic cases have been described in females, possibly caused by mutations in some other genes that function in the same pathway. **The disease usually does not become apparent until about 6 months of age, as maternal immunoglobulins are depleted**. In most cases, recurrent bacterial infections of the respiratory tract, such as acute and chronic pharyngitis, sinusitis, otitis media, bronchitis, and pneumonia, call attention to the underlying immune defect. Almost always the causative organisms are *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Staphylococcus aureus*. These organisms are normally opsonized by antibodies and cleared by phagocytosis. Because antibodies are important for neutralizing infectious viruses that are present in the bloodstream or mucosal secretions or being passed from cell to cell, individuals with this disease are also susceptible to certain viral infections, especially those caused by enteroviruses, such as echovirus, poliovirus, and coxsackievirus. These viruses infect the gastrointestinal tract, and from here they can disseminate to the nervous system via the blood. Thus, immunization with live poliovirus carries the risk of paralytic poliomyelitis, and echovirus can cause fatal encephalitis. For similar reasons, *Giardia lamblia*, an intestinal protozoan that is normally resisted by secreted IgA, causes persistent infections in persons with this disorder. In general, however, most intracellular viral, fungal, and protozoal infections are handled quite well by the intact T cell–mediated immunity.

The classic form of this disease has the following characteristics:

- B cells are absent or markedly decreased in the circulation, and the serum levels of all classes of immunoglobulins are depressed. Pre-B cells, which express the B-lineage marker CD19 but not membrane Ig, are found in normal numbers in the bone marrow.
- Germinal centers of lymph nodes, Peyer's patches, the appendix, and tonsils are underdeveloped.
- Plasma cells are absent throughout the body.
- T cell–mediated reactions are normal.

Autoimmune diseases, such as arthritis and dermatomyositis, occur in as many as 35% of individuals with this disease, which is paradoxical in association with an immune deficiency. It is likely that these autoimmune