Immunodeficiency is a common thought among both patients and physicians when confronted with what is perceived as an excessive number, duration, or severity of infections. Because of this, the starting point for evaluating patients for suspected immunodeficiency is based on what constitutes "too many infections." It generally is agreed that children with normal immune systems may have an average of 6 to 8 respiratory tract infections per year for the first decade of life. Even after a pattern of abnormal infection is established, questions of secondary immunodeficiency should first be raised. The relatively uncommon primary immunodeficiency diseases are statistically dwarfed by secondary causes of recurrent infection, such as malnutrition, respiratory allergy, chronic cardiovascular, pulmonary, and renal disease, and environmental factors. On the other hand, a dizzying spiral of progress in our understanding of the genetics and immunology of primary immunodeficiency disease has resulted in improved diagnostic and therapeutic tools. Twenty-five newly recognized immunologic disease genes have been cloned in the last 5 years. It has become arguably more important than ever for us to recognize the clinical and laboratory features of these relatively uncommon, but increasingly treatable, disorders.

CLASSIFICATION

The immune system has been classically divided into four separate arms: The B-cell system responsible for antibody formation, the T-cell sys-
tem responsible for immune cellular regulation, the phagocytic (polymorphonuclear and mononuclear) system and the complement (opsonic) system. The World Health Organization (WHO) expert committee recently has classified the primary immunodeficiencies to reflect the interactions of these four components and the different variants that have been recognized.\textsuperscript{26,37} This includes immune deficiency diseases with a primary defect in humoral immunity, immunodeficiency defects in cellular immunity, partial combined immunodeficiency diseases, and disorders of complement and phagocytic cells (Table 1).

**GENERAL FEATURES**

Several excellent, recent reviews of the primary immunodeficiency disorders are available.\textsuperscript{4,24,30} This article concentrates on some of the representative and common features of primary immunodeficiency that may present to the primary care physician. These clinical presentations are placed in the context of our recent advances in the understanding of their molecular genetics.

**Incidence**

The incidence of congenital immunodeficiencies varies from the relatively common, selective IgA deficiency (1:400) to the rare, severe, combined immunodeficiency (1:100,000 to 1:500,000). Chronic granulomatous disease has been estimated to occur at a 1:200,000 incidence, and common variable immunodeficiency occurs 1:75,000. These disorders present with a male to female ratio of 5:1 in infants and children and with no discernible sex difference in adults. This is because of the respective frequency of X-linked primary immunodeficiency disorders in childhood, and the relatively frequent occurrence of late-onset, common-variable immunodeficiency in females. The primary immunodeficiency disorders are seen more commonly in infants and children than in adults. It has been estimated that 40% of cases are diagnosed in the first year of life, another 40% by age 5 years, another 15% by age 16 and only 5% in adulthood.\textsuperscript{5}

**Physical Examination**

The physical stigmata of the primary immunodeficiency diseases can be divided into consequences of recurrent infection (such as persistent sinusitis and bronchiectasis) and associated congenital defects. The skin may show monilial infection (T-cell deficiency), eczema (Wiskott-Aldrich syndrome, hyper IgE syndrome), petechia (Wiskott-Aldrich syndrome), partial albinism (Chediak-Higashi syndrome, immunodeficiency with partial albinism), rash secondary to graft-versus-host disease (GVHD) (T-cell disease or Ommen's syndrome), or telangiectasia (ataxia telangiectasia). There may be abnormal features, such as the facial dysmorphology
### Table 1. COMMON CLINICAL FINDINGS IN REPRESENTATIVE PRIMARY IMMUNODEFICIENCY DISEASES

<table>
<thead>
<tr>
<th>Immune System Defect</th>
<th>Example of Disease</th>
<th>Common Age of Onset</th>
<th>Clinical and Laboratory Pearls</th>
<th>Common Organisms</th>
<th>Common Sites of Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary defects in humoral immunity</td>
<td>XLA</td>
<td>6 m–2 y</td>
<td>Absence of tonsils and lymphatic tissue</td>
<td>Strep/staph/echovirus</td>
<td>Sinuses and Lungs</td>
</tr>
<tr>
<td>Primary defects in cellular immunity</td>
<td>SCIDS caused by ADA deficiency</td>
<td>Birth to 1</td>
<td>Lymphopenia and osseous anomalies</td>
<td>Viruses, fungi, and bacteria</td>
<td>Septicemia &amp; Severe candidiasis</td>
</tr>
<tr>
<td>Partial combined immunodeficiency diseases</td>
<td>Wiskott-Aldrich Syndrome</td>
<td>Birth to 2 y</td>
<td>Microcytic thrombo cytopenia, eczema</td>
<td>Viruses and bacteria</td>
<td>Septicemia</td>
</tr>
<tr>
<td>Disorders of Complement</td>
<td>C5–C9 Deficiency</td>
<td>Variable</td>
<td>CH50 Abnormal</td>
<td>Neisseria</td>
<td>Meninges, Lung</td>
</tr>
<tr>
<td>Disorders of Phagocytes Killing</td>
<td>CGD</td>
<td>Birth to 3 y</td>
<td>NBT Abnormal</td>
<td>Staph, Pseudomon as an Aspergillus</td>
<td>Deep tissue abscesses</td>
</tr>
<tr>
<td>Disorders of Phagocytes Chemotaxis</td>
<td>LAD</td>
<td>Variable</td>
<td>Delayed umbilical stump separation</td>
<td></td>
<td>Severe gingivitis and skin disease</td>
</tr>
</tbody>
</table>
of DiGeorge’s syndrome or coarse facies of hyper IgE syndrome. Children with leukocyte adhesion defects can present with severe gingivostomatitis and dental erosion as a consequence of abnormal leukocyte function.

Short stature is associated specifically with X-linked hypogammaglobulinemia with growth hormone deficiency and generally with recurrent infection. Many of the immune deficiency states are associated with neurologic disorders, including seizures associated with hypocalcemia in the newborn (DiGeorge’s syndrome), cerebellar degeneration (ataxia and telangiectasia), echovirus encephalitis (humoral syndromes associated with absence of B cells), intracranial hemorrhage (Wiskott-Aldrich syndrome), and lymphomas involving the brain (Wiskott-Aldrich syndrome and ataxia telangiectasia). Paucity of peripheral lymphatic tissue is characteristic of X-linked agammaglobulinemia, although lymphadenopathy is a common feature of Omenn’s syndrome and common variable immune deficiency.

**Laboratory Investigation**

Most immunodeficiency disorders can be ruled out at little cost to the patient if the proper choice of screening tests is made. A great deal of immunologic-related data can be obtained from a complete blood count and differential (Fig. 1). Neutropenia, lymphopenia, and abnormalities in white blood cell morphology can be found directly. Anemia may be supporting evidence of chronic illness, or may be secondary to hemolysis from autoimmune dysregulation or parvovirus infection. Normocytic thrombocytopenia is characteristic of bone marrow failure and autoimmune disease, and microcytic thrombocytopenia is highly suggestive of the Wiskott-Aldrich syndrome. If an infant’s neutrophil count is persistently high in the absence of malignancy and active infection, a leuk-

<table>
<thead>
<tr>
<th>LYMHOCYTES</th>
<th>PLATELETS</th>
<th>NEUTROPHILS</th>
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<tbody>
<tr>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>SCIDS due to ADA</td>
<td>Omenn Syndrome</td>
<td>Decreased</td>
</tr>
<tr>
<td>or IL-2 R deficiency</td>
<td>or SCID with GVHD</td>
<td>Bone marrow failure</td>
</tr>
<tr>
<td></td>
<td>Wiscott Aldrich Syndrome</td>
<td>Bone marrow failure</td>
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<tr>
<td></td>
<td>Microcytic decrease</td>
<td>Normocytic decrease</td>
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<td></td>
<td>Bone marrow failure</td>
<td>L.A.D.</td>
</tr>
</tbody>
</table>

*Figure 1. Characteristic changes in the complete blood cell count in selected primary immunodeficiency disorders.*
kocyte adhesion deficiency should be suspected. If the absolute lymphocyte count is elevated or normal, it is less likely that the patient has a severe T-cell defect. If the pattern of infection suggests predominant humoral or cellular immune system involvement, specific studies should be directed as described in the following sections.

**Humoral Immune System Evaluation**

The evaluation of humoral immunity should begin with quantification of serum immunoglobulins (Fig. 2). At term birth, IgG is present at maternal levels because of placental transport of IgG from the mother. IgG levels decline and normally reach a nadir at 3 to 6 months. The adult concentration of IgM (1.4 +/− 0.6 mg/mL) is reached at 1 year, IgG (12.6 +/− 2.6 mg/mL) at 5 to 6 years, and of IgA (2.6 +/− 1 mg/mL) at puberty.\(^\text{31}\) Quantification of serum IgA levels is a particularly cost-effective study in that IgA levels are low in almost all permanent types of agammaglobulinemia and in selective IgA deficiency. Measurement of serum IgE levels would be appropriate in patients with suspected atopy, Wiskott-Aldrich syndrome, or suspected hyper IgE syndrome. The WHO also recommends screening for isohemagglutinins as an initial screening study of humoral immunity. Isohemagglutinins are IgM antibodies that cross-react with polysaccharide blood group A or B antigens found in all normal individuals, with the exception of those with type AB red cells. By the age of 3 years, 98% of normal persons with type A, B or O blood have titers of isohemagglutinins at least 1:16.\(^\text{20}\) These studies usually are adequate to rule out a deficiency of humoral immunity; however, when patients are potential candidates for replacement intravenous immunoglobulin (IVIG) therapy, or if there remains a dissociation between normal screening studies and the patient’s clinical course, studies of functional antibody responses are more definitive tests of humoral immunity. Antibody responses are measured by obtaining serum samples before and 3 to 4 weeks after immunization with such representative protein antigens as diphtheria and tetanus toxoids and such polysaccharide antigens as *pneumococcus*. In addition, B cells can be identified and enumerated by the presence of unique surface proteins (such as CD19 and CD20), which are identified by immunofluorescent-tagged monoclonal antibodies and quantified by flow cytometry. IgG subclass testing should not be used for routine screening of patients with suspected immunodeficiency, but may help in defining syndromes of poor antibody formation and borderline low serum IgG levels.

**Cellular Immune System Evaluation**

The presence of a thymic shadow on a chest radiograph is comforting, but nonspecific, reassurance when questions of T-cell deficiency are raised in a newborn. The laboratory evaluation of cellular immunity should begin with quantification of an absolute lymphocyte count (Fig. 3). This is obtained by multiplying the total white blood cell count by the percentage of lymphocytes. Lymphocyte counts persistently below 1500 per cubic
Documented increased number, severity or duration of infections?

**Primary Immunodeficiency**

- Measure serum immunoglobulins and isohemagglutinins

**Secondary Immunodeficiency**

- Rule out respiratory allergy
- Rule out chronic cardiovascular, respiratory or renal disease
- Rule out maternal risk factors for HIV 1 Infection

**Normal**

- Primary humoral defect not probable.
- Reassess for secondary immunodeficiency. Re-evaluate in 6 months if continued pattern of infection

**Decreased or absent**

- Less than two years of age
  - Measure functional antibody responses to diphtheria and tetanus toxoids
    - Normal
    - B cell disease is not probable

- More than two years of age
  - Measure functional antibody responses to diphtheria, tetanus and pneumococcal antigens
    - Deficient
    - Reimmunize with respective vaccines. If still deficient, candidate for IVIG replacement therapy.

**Figure 2.** Laboratory evaluation of suspected primary defects in humoral immunity.

Millimeter may signify a defect in the T-cell system. Lymphocyte counts in infants normally are very high in comparison with adult values. In addition, false elevation of peripheral lymphocyte counts may result from engraftment of maternal lymphocytes in T-cell deficient newborns or may
be secondary to proliferation of an uncontrolled T-cell clone as seen in Omenn’s syndrome. T-cell function may be screened for in vivo by measuring delayed hypersensitivity responses to skin test antigens. Intradermal testing material, with such common recall antigens as mumps, Trichophyton, purified protein derivative (PPD), Candida, tetanus and diphtheria toxoid, and keyhole-limpet hemocyanin, is available widely. The maximum wheal resulting from intradermal injection of 0.1 mL of appropriate dilutions of these antigens should be read 48 to 72 hours after injection. These studies have excellent positive predictive values of intact cellular immunity, but negative tests may not be informative in very young children. More definitive in vitro studies of T-cell function involve the measurement of uptake of radioactive thymidine into new DNA in response to substances that stimulate lymphoblastogenesis. This includes such mitogens as concanavalin A (Con A) and phytohemagglutinin (PHA) or recall antigens such as candida or PPD. Flow cytometry may be used to characterize the presence of surface markers unique to different T-cell subtypes.
Treatment

Although attempts at immunomodulation and gene replacement therapy are ongoing and promising, the treatment of choice for severe defects in humoral immunity is passive antibody replacement with IVIG, and the standard treatment for most severe T-cell defects is bone marrow transplantation.

Treatment for Immune Defects with Primary Humoral Defects

Patients with primary humoral immune defects may often require prolonged and aggressive antimicrobial therapy to clear pyogenic bacteria from sino-pulmonary sites. Even with IVIG replacement, these patients may have relative defects in mucosal immunity that require aggressive management with postural drainage and prolonged oral and occasional intravenous antibiotic coverage. Some authors have recommended rotating oral antibiotic coverage to help minimize development of bacterial resistance in patients requiring repeat courses of oral antibiotics for sinusitis or bronchiecatic disease. Prophylactic antibiotic coverage also has been considered in patients with subtle antibody formation defects with hypogammaglobulinemia.

Immunoglobulin replacement therapy is indicated for patients at risk for recurrent pyogenic infections caused by an inability to make specific antibody. Their rapid degradation and relative lack of clinical efficacy limit intramuscular products. All of the currently licensed intravenous products in the United States meet acceptable standards of safety and efficacy. The most common side effect of immunoglobulin replacement therapy is an anaphylactoid type reaction, which may include fever and chills. This is largely secondary to rate of infusion, can be controlled by reducing infusion speeds, and can be minimized by pretreatment with acetaminophen and antihistamines. There have been no reports of HIV transmission with IVIG. The Cohn fractionation process of serum proteins destroys HIV and a viricidal detergent treatment is now routine. Reports of Hepatitis C transmission with two IVIG products has resulted in the donor pool being limited to patients with no antibodies to Hepatitis B and HIV. Many IVIG have been withheld from distribution because of the threat of transmission of Jakob-Cruetsfeldt disease from an inadvertent donor.

IVIG replacement therapy for primary immunodeficiency disease commonly begins at a dose of 400 mg/kg/m. Trough serum titers and clinical response are used to titrate the infusion dose. If extensive bronchiectasis or disseminated echovirus infection is present, consideration of high dose or intrathecal IVIG may need to be given. Patients with relatively low immunoglobulin levels but normal antibody responses usually are not candidates for IVIG replacement therapy.

Treatment for Immune Defects with Predominant Cellular Defect

The therapeutic options for cellular immune defects are dependent on rapid recognition of these potentially lethal disorders. Early risks in-
clude exposure to live viral vaccines. These patients should receive protective isolation and avoid live viral vaccines and any household contact to a host recently immunized with a live viral vaccine. If blood products are needed, they should be irradiated with 3000 cGy, and ideally be cytomegalovirus-free. Therapeutic options include bone marrow transplantation and gene therapy.

**Bone marrow transplantation.** Transplantation of bone marrow cells from genotypically human leukocyte antigen (HLA)-identical siblings has led to complete immunologic reconstitution of patients with severe combined immunodeficiency disorder (SCID), Wiskott-Aldrich syndrome, leukocyte adhesion defects, and major histocompatibility complex (MHC) Class II deficiencies.\(^1\) Engraftment of donor cells usually is seen 2 to 3 weeks after transplantation. Risks associated with this procedure include intercurrent infection (especially when ablative immunosuppressive regimens are needed with partially HLA matched donors), engraftment failure, and GVHD. Acute GVHD involves donor lymphocytes engrafting in the host and resulting in skin, liver, and gastrointestinal injury. The chronic form of GVHD may result in a debilitating scleroderma-like illness. If an HLA-identical donor is not available, different strategies to reduce the risk of GVHD from haplo-identical donors have been developed. This includes depleting donor T cells with monoclonal antibodies and soy lectins. Haplo-identical bone marrow transplantation usually requires ablative therapy with immunosuppressive agents.

**Gene therapy.** SCID secondary to a genetic defect in ADA expression was the first primary immunodeficiency disease treated by somatic gene therapy. This initial trial involved cloning the gene encoding for ADA and placing it into a retroviral expression vector, which was introduced into the patient's peripheral lymphocytes in vitro.\(^1\) The ongoing regular infusions of these ADA-gene-corrected autologous lymphocytes has been associated with both clinical and immunologic improvement. More recently, several neonates have received autologous bone marrow transplantation of ADA-transfected stem cells from cord blood resulting in gene expression in circulating lymphocytes.\(^15\)

**IMMUNODEFICIENCY DISEASE WITH PRIMARY DEFECT IN HUMORAL IMMUNITY**

These disorders are linked by antibody deficiency and have been extensively and recently reviewed.\(^20,24\) They typically result in recurrent sinopulmonary infections and septicemias with pyogenic encapsulated bacteria such as Haemophilus influenzae, pseudomonas, Staphylococcus aureus, and Streptococcus pneumoniae during early childhood. Although the end point of antibody-deficiency–induced recurrent infection is common to these disorders, there is considerable heterogeneity among their genetic basis and immunologic expression.
X-Linked Agammaglobulinemia (XLA)

The characteristic clinical features of this disease were well described by Bruton in 1952. He recognized a group of male infants that appeared to do well during the first months of life, but developed progressive, recurrent sino-pulmonary infections. Advances in protein chemistry allowed him and others to link this relative infection-free period during the first months of life to active maternal transport of IgG across the placenta. Recent epidemiological studies have shown that most children develop clinical problems during the first year of life, but as many as 21% first presented clinically as late as 3 to 5 years of age. Although recurrent sino-pulmonary infections are the most common infections in XLA, septicemia, septic arthritis, and osteomyelitis may present in untreated children. The sequel of untreated XLA includes chronic sinusitis and progressive bronchiectasis. Once these entities have become well established, aggressive antimicrobial therapy often is needed as adjunctive care in spite of IVIG replacement. A chronic enteroviral infection of the central nervous system, which can develop in the face of gammaglobulin replacement, remains a poorly understood complication. Patients also may develop a dermatomyositis-like syndrome as a consequence of enteroviral infection. This involves development of peripheral edema and a shuffling gait secondary to flexion contractures from the underlying fasciitis and myositis. The disease gene for X-linked agammaglobulinemia was identified in 1993 as encoding Bruton tyrosine kinase (Btk). Defective Btk results in an inability to develop B cells from pre-B cells. Diagnosis is made by extremely low or absent immunoglobulin and few or no B cells. Specific mutation detection or measurement of Btk kinase activity can confirm the genetic cause in patients without an X-linked family history. Reductions in hospitalizations and infection rates have been well documented in patients receiving high dose (>400 mg/kg every 3 weeks) IVIG, and maintaining trough levels of IVIG above 500 mg/dL is a reasonable standard of care.

Common Variable Immune Deficiency (CVID)

CVID is a diagnosis of exclusion, as the genetic basis remains unknown. It is clinically indistinguishable from the other primary B-cell disorders and shares features of hypogammaglobulinemia, recurrent pyogenic infection, and impaired antibody responses. In contrast to XLA, the onset usually is in the second or third decade of life. The clinical, immunologic, and genetic diversity of CVID suggests that this may represent a common clinical framework for several genetically distinct disorders. In addition to the features of impaired humoral immunity, up to 50% of CVID patients exhibit some alteration of T-cell function. This has included low CD4/CD8 ratios, low expression of T-cell activation molecules, abnormal responses to T-cell mitogens, and reduced lymphokine production. Passive replacement therapy with high dose IVIG has been shown
to reduce the incidence of pyogenic infections and is a standard of care for this group of illness.

**Selective IgA Deficiency**

Although this is the most common of the primary immunodeficiency diseases (with an estimate of 1:400 of the population affected), it remains one of the more poorly understood. Most immunologists believe that only a small percentage of patients with selective IgA deficiency seek care for recurrent upper respiratory tract infections or pulmonary or gastrointestinal disease. On the other hand, patients diagnosed with selective IgA deficiency have been found to have increased risk of numerous infectious, autoimmune, and malignant disorders. Recognition of IgA deficiency is of potential clinical significance in the setting of transfusion reactions. Patients with selective IgA deficiency may mount IgE antibodies to trace amounts of IgA in blood products and experience risk of anaphylactic reaction.

**X-Linked Immunodeficiency with Hyper IgM**

The initial clinical presentation of this X-linked disorder is similar to XLA; however, the frequency of Pneumocystis carinii pneumonia, associated lymphoproliferative diseases, and a rare parvoviral-induced form of hemolytic anemia suggested early on that aberrant T-cell control was present. As the name suggests, the immunologic hallmark is elevated serum IgM levels at the expense of low IgG, IgA and IgE levels. The genetic basis for this failure of isotype switching is attributed to a gene encoding a T-cell receptor known as the CD40 ligand. Failure of interaction between CD40 on B cells and the CD40 ligand on T cells results in a defect in B-cell differentiation characterized by inability to undergo immunoglobulin isotype switching. Although the elucidation of the genetic basis of this disorder holds the promise of more specific genetic therapy, current treatment of X-linked hyper IgM syndrome is limited to the provision of passive immunity with IVIG.

**IgG Subclass Deficiency**

This group of disorders includes patients with low levels of IgG subclasses, with normal IgG and IgA levels, who have depressed antibody levels. For children older than the age of two, this means that the IgG1 level should be less than 250 mg/dL, the IgG2 level less than 50 mg/dL and the IgG3 level less than 25 mg/dL. The IgG4 level may be undetectable in up to 10% of the normal population. It is difficult to distinguish patients with IgG1 deficiency from CVID, as it is commonly associated with other Ig subclass deficiencies. IgG2 deficiency is paired frequently with IgG4 and IgA deficiency; however, it is still uncertain whether the
absent subclass is significant clinically, or whether this is a marker for immune dysregulation. The presence of genetic deficiency of IgG2 and IgG4 in healthy individuals suggests that subclass deficiency may in itself not be of great clinical significance. The propensity to have recurrent infections correlates most closely with the inability to make specific antibodies rather than IgG subclass concentration.

**Specific Antibody Deficiency**

Immunologists have debated the potential clinical significance of lacunar gaps in the arsenal of specific antibody formation. Patients with a history of recurrent pyogenic infection have been reported with normal serum immunoglobulin and IgG subclass concentrations, but defective antibody production to polysaccharide antigens. Patients older than 5 years of age who have an inability to respond to polysaccharide antigens may be at risk for recurrent pyogenic infections and may require treatment with prophylactic antibiotics or IVIG.

**Transient Hypogammaglobulinemia of Infancy**

Whenever children present with hypogammaglobulinemia, consideration needs to be given to the potential for these children to be immunologically competent, but statistically delayed in the rise in serum immunoglobulin concentrations. These children have normal ability to respond to protein antigens, but have serum immunoglobulin concentrations two standard deviations below the normal range. Some of these patients may have an inability to respond to polysaccharide antibodies later in life, but the vast majority remains immunologically normal. The incidence and severity of infection in these infants largely dictates consideration of therapy with prophylactic antibiotics or IVIG.

**IMMUNODEFICIENCY DISEASE WITH PRIMARY DEFECT IN CELLULAR IMMUNITY**

Abnormalities of T-cell immunity are characterized clinically by infection with many different organisms. This includes disseminated viral, fungal, and parasitic infections. Common presentations include severe mucocutaneous candidiasis; overwhelming viremia; and progressive interstitial pneumonia with parainfluenza, cytomegalovirus, varicella, and Pneumocystis carinii. These T-cell disorders may be caused by embryologic misadventures of the branchial arches, inborn errors of T-cell signaling, and receptor expression or specific T-cell toxicity from genetic forms of enzyme deficiency. These T-cell disorders may be similar clinically to pediatric acquired immunodeficiency syndrome (AIDS), but can be distinguished by the absence of HIV-1 on culture or HIV DNA by polymerase chain reaction. The following descriptions highlight the ge-
ngetic basis and clinically distinguishing features of some representative disorders.

**Thymic Hypoplasia (DiGeorge's Syndrome)**

Embryologists define this disorder as a developmental field defect involving the third and fourth branchial arches. These structures are needed for the normal development of the thymus, parathyroid glands, and the great vessels of the heart. Defective function of these organs accounts for the respective features of variable immunodeficiency, neonatal hypocalcemia secondary to hypoparathyroidism, and congenital cardiac defects. Abnormal ear, maxilla, and mandible development accounts for the characteristic facies of this disorder. Parathyroid and thymic deficiency also have been described in a disorder of peroxisomes known as Zellweger syndrome. When the DiGeorge's syndrome phenotype is paired with cleft palate and learning disorders, the term velocardiofacial syndrome is used. Diagnosis in newborns should be suspected when hypocalcemia is paired with such relatively uncommon cardiac anomalies as an interrupted aortic arch type B, right-sided aortic arch or truncus arteriosus. Ninety percent of DiGeorge's syndrome patients have associated chromosome disorders, with the majority involving chromosome 22. The immunologic findings are variable, and spontaneous improvement in the immunologic defect has been described. In its severest form, bone marrow transplantation may be required.

**Severe Combined Immunodeficiency (SCID)**

This term is used to describe a group of disorders that involve both the B and T cells. Most of the B-cell abnormalities appear secondary to the lack of T-cell help, which points again to the critical role of the T cell as the leader of the immune system. The consequence of absent T-cell function is opportunistic infections and overwhelming septicemia, with such pathogens as Pneumocystis carinii, vaccinia, varicella and measles. These infants also are at risk for lethal GVHD if given transfusions with nonirradiated blood products. Lymphopenia is a common finding in X-linked SCID, but may be masked by the presence of maternal T cells, which have crossed the placenta and engraftment in the infant. Rarer forms of SCID may present with lymphocytosis secondary to proliferation of clones of dysfunctional T cells. The severity of these immunologic disorders has made them logical, early candidates for such advances in treatment as bone marrow transplantation and gene replacement therapy. Early diagnosis and availability of matched donors for bone marrow transplantation remains the most important prognostic factor for this group of severe disorders. SCID has become recognized as a heterogeneous group of disorders of stem cell and thymic differentiation, surface receptor expression, cellular signaling and enzyme deficiency.
**Surface Receptor Defects**

**IL-2 receptor defect (X-LINKED SCID).** This is the most common form of SCID. In 1993, common X-linked SCID was found to be caused by defects in the gamma chain of the IL-2 receptor gene. Defects in the function of this protein result in lymphocyte progenitors being unable to receive differentiation signals that are necessary for normal T and B cell function, and in severe lymphopenia. X-linked SCID is seen only in males, although healthy female carriers can be detected by nonrandom X inactivation in their lymphocytes. The best treatment is HLA-matched bone marrow transplantation. Methods of prenatal diagnosis and experimental trials of in utero bone marrow transplantation have been described.

**The bare lymphocyte syndrome.** The bare lymphocyte syndrome is recognized as a combination of disorders characterized by deficient expression of MHC class I (HLA-A, -B, and -C) antigens, class II (HLA-DR, -DQ, and -DP) MHC antigens, or both. It results in faulty communication between T cells and other cells. In contrast to other forms of SCID, T-cell function, as measured by in vitro response to PHA and ConA; numbers of circulating B and T cells may be normal. It is clinically indistinguishable from the other forms of SCID.

**Cellular Signaling Defects**

Additional forms of SCID with normal gamma chain expression have been recently described. This includes a clinically indistinguishable form of SCID with normal IL-2 receptor genes. These patients are defective in an intracellular kinase, Jak 3, which serves as an activation signal between the lymphokines IL-2 and IL-4.

**Immunodeficiency with Enzyme Deficiency**

**Adenosine deaminase (ADA) deficiency.** ADA was the first form of SCID in which a genetic basis was described. The genetic deficiency of this enzyme results in an accumulation of purine metabolites, such as deoxyadenosine, which are exquisitely toxic to T cells. Most patients with ADA deficiency present with a pathognostic pattern of radiographic findings. This includes cupping and flaring of the ribs and squaring of the scapula tip. Diagnosis depends on the measurement of low, red-blood cell ADA enzyme levels and high levels of purine metabolites, such as deoxyadenosine. In addition to the preferred treatment of HLA-matched bone marrow transplantation, attempts at enzyme replacement with ADA coupled to polyethylene glycol have proven beneficial. Intrauterine treatment with autologous cord blood in which the normal gene for ADA was transduced has been attempted.

**Purine nucleoside phosphorylase (PNP) deficiency.** PNP deficiency is a rare disorder of purine metabolism with considerable clinical heterogeneity. In its severe form, it is clinically indistinguishable from other forms of SCID. Milder forms have been reported later in childhood with diverse neurologic findings such as developmental delay, hypotonia, and
spasticity. This disorder differs from ADA by the low uric acid levels, absence of associated skeletal anomalies, and presence of Hassal's corpuscles in thymic tissue.

Other Forms of Predominant Cellular Immune Defects

Omenn's syndrome. The unique clinical features of this form of SCID include the presence of lymphadenopathy, desquamating erythroderma, eosinophilia, high IgE levels, hepatosplenomegaly and relatively normal lymphocyte counts and serum IgG, IgM, and IgA levels. The pathologic cutaneous findings in Omenn's syndrome are similar to those of acute GVHD disease, but usually no maternal engraftment of lymphocytes is present. Omenn's syndrome involves cytotoxic autologous T cells attacking target organs such as the skin. The pathogenesis and genetic basis of this rare disorder remain unknown. Bone marrow transplantation has been successful with several patients.

Cellular immunodeficiency with immunoglobulins (Nezelof syndrome). This form of combined immunodeficiency is associated commonly with hemolytic anemia, thrombocytopenia, and lymphoreticular malignancies. It is distinguished from X-linked SCID caused by 11-2 receptor deficiency by the presence of lymphatic tissue, (though histologically abnormal), hepatosplenomegaly, and normal serum immunoglobulins.

PARTIAL COMBINED IMMUNODEFICIENCY DISEASES

Wiskott-Aldrich syndrome

This is an X-linked disorder characterized by an altered cell surface glycoprotein structure (CD43 or sialophorin) common to lymphocytes and platelets. Its classic clinical features include a microcytic thrombocytopenia that distinguishes this disorder from idiopathic thrombocytopenic purpura and other forms of normocytic thrombocytopenia. The immunologic findings are variable but usually include impaired humoral responses to polysaccharide antigens and elevated serum IgA and IgE levels. Atopic dermatitis and recurrent pyogenic infections of the upper respiratory tract are common but variable associated clinical features. Since the gene for sialophorin is located on chromosome 16, it was apparent that a genetic deficiency of sialophorin could not account for all the features of this X-linked disorder. More recently, the gene for Wiskott Aldrich syndrome has been identified and codes a large molecular weight signal transduction protein expressed on lymphocytes, megakaryocytes, spleen, and thymus. Techniques for both gene carrier detection and in utero diagnosis have been described.

Ataxia Telangiectasia

Ataxia telangiectasia is an autosomal recessive disorder clinically characterized by progressive oculocutaneous telangiectasia, which be-
comes present between 3 and 6 years of age. Progressive cerebellar ataxia secondary to Purkinje's cell degeneration typically results in loss of ambulation by 10 to 12 years of age. Progeric changes of the skin and hair often are present. Immunologic features often include selective IgA and IgG2 subclass deficiency and depressed but not absent in vitro lymphocyte responses. These patients also display exquisite toxicity to chemotherapy and irradiation and should not receive these forms of diagnostic and therapeutic studies. This often poses difficult clinical decisions as 15% of affected patients are estimated to develop malignancy. The ataxia telangiectasia gene was identified in 1995 and has been referred to as a potential Rosetta stone of the human genome because of its wide-ranging roles. The postulated roles of this gene include detecting DNA damage, controlling immune system responses, preventing genomic rearrangements in malignancy, and preventing programmed cell death. It is believed that up to 1.4% of the population has one defective AT gene and the gene could account for up to 8% of all breast cancers. Treatment is limited to supportive care and no cure is available. Because the incidence of infection is so variable, bone marrow transplantation usually is not advised.

**DISORDERS OF PHAGOCYTIC CELLS AND ADHESION MOLECULES**

Genetic defects in the stages of neutrophil production, leukodiapedesis and oxidative function have been well described and result in characteristic clinical phenotypes. Patients with defective neutrophil function or number generally are at risk for deep tissue and cutaneous infection with such bacteria as Pseudomonas, Serratia, Staphylococcus aureus and such fungi as aspergillus and candida. An algorithm for the evaluation of common defects in neutrophil number and function is given in Figure 4. Representative disorders of neutrophil movement include the leukocyte adhesion defects, although chronic granulomatous disease is a prototype of defective neutrophil NADPH oxidase function.

**Leukocyte Adhesion Defects (LAD Type 1 and 2)**

These patients may present in the perinatal period with delayed separation of the umbilical cord and poor wound healing caused by reduced peripheral neutrophil presence. Although the clinical spectrum is large, they are prone to develop severe periodontal disease and recurrent pyogenic infection later in childhood. The hematologic hallmark of LAD I is neutrophilia, with absence of neutrophils at sites of infection. Leukocyte adhesion defect Type I is diagnosed by flow cytometry with monoclonal antibodies directed against a leukocyte surface structure known as CD 18. More specifically, the molecular defect has been characterized as an absence of the 95-kDa beta chain of the CD 18 molecule. This chain is a common subunit of three leukocyte surface heterodimers leukocyte func-
Absolute neutrophil count

Decreased

Bone Marrow Failure

Congenital

Acquired

Neutrophils absent in peripheral tissue

Leukocyte Adhesion Defect?

Systemic Infection?

Increased

Neutrophils present in peripheral tissue

Screen for neutrophil function

(Quantitative N.B.T. Slide test)

Normal

Deficient

Primary neutrophil oxidative dysfunction not probable

Refer to tertiary care center

Figure 4. Laboratory evaluation of primary neutrophil defect.

...n-associated antigen (LFA-1, CD11a/CD18), iC3b (Mac-1, CD11b/CD18) and p150, 95 (CD11c/CD18) that play a critical role in chemotaxis and adhesion. For example, LFA-1 serves as an important receptor for the vascular endothelium adhesion molecule known as ICAM-1. Leukocyte adhesion defect type 2 is a clinically similar disorder characterized by normal CD11/CD18 expression and a defect in fucosylation accounting for faulty neutrophil receptors for E-selectin (CD 62E). Treatment options for these clinically variable syndromes include aggressive antibiotic therapy and consideration of bone marrow transplantation in the face of difficult-to-manage life-threatening infections.

Chronic Granulomatous Disease (CGD)

The clinical phenotype of CGD was recognized in the 1950s by the unique pattern of infection affecting these patients. Children with CGD present with recurrent abscess formation of the lymph nodes, liver, lungs,
bones and gastrointestinal tract caused by a relatively narrow spectrum of catalase-positive organisms such as Staphylococcus aureus, Aspergillus species, Chromobacterium violaceum and Pseudomonas cepacia. The molecular basis for several forms of this disorder have been described in relation to genetic defects in the oxidase system that is used by leukocytes to kill bacteria. This includes the common X-linked form, with a lack of cytochrome b-558 on the cell membrane, and an autosomal recessive form with a normal membrane cytochrome b-558, but a defective cytosol component of the oxidase system. Neutrophil oxidative function can be screened with the nitroblue tetrazoleum (NBT) slide test. This colorimetric assay involves formazan being converted to nitro blue tetrazolium in the presence of a normal oxidative burst. Prophylaxis with trimethoprim-sulfamethoxazole and recombinant human interferon gamma have become standards of care for this disorder.

DISORDERS OF COMPLEMENT

These are the rarest of the primary immunodeficiency disorders, accounting for 2% to 3% of these diseases. Deficiencies of essentially all of the components of the complement cascade have been described and extensively reviewed. Some unique clinical features include the susceptibility to recurrent Neisseria infections that characterizes patients with deficiencies of the terminal complement components (C5-C9) of complement and the increased risk of developing rheumatic disorders in relation to deficiency of C2, C4, and C3. Deficiency of C2 is the most common complement component deficiency. C3 deficient patients have a more severe phenotype because of involvement of both the classical and alternate complement pathways. A normal CH50 test is an effective screening tool to rule out complement deficiencies. One clinically unique form of complement dysregulation is hereditary angioneurotic edema.

Hereditary Angioedema (C1 Esterase Inhibitor Deficiency, HAE)

This autosomal dominant disorder is characterized by recurrent, potentially life-threatening episodes of angioedema. In contrast to IgE-mediated mechanisms of mast cell and basophil histamine-induced angioedema, urticaria is not a part of this clinical syndrome. These patients are characterized by the presence of a positive family history of angioedema, swelling episodes in relation to trauma and surgical stress, and associated abdominal pain. The diagnosis is established by measurement of defective C1 esterase inhibitor function and supported by evidence of decreased C2 and C4 levels during symptomatic periods. Acquired forms of C1 esterase inhibitor dysfunction have been described primarily in the setting of B-cell lymphoproliferative diseases. In contrast to patients with HAE, these patients have normal C1 esterase inhibitor structure and decreased levels of C1.
CONCLUSION

The primary immunodeficiency diseases remain a rare but increasingly definable and treatable group of disorders. Recognizing the diversity of their clinical presentations is essential for timely intervention and improved prognosis. Screening studies of host immunity should be considered in the setting of recurrent infection. The age of onset, microbes encountered, complete blood count, and target organs of infection often give clues to appropriate use of diagnostic studies. Replacement IVIG and bone marrow transplantation remain the respective treatments of choice for the most severe forms of humoral and cellular immune defects. Ongoing advances in the genetic and immunologic understanding of these disorders hold the promise of more specific, cost effective, and successful therapy.

References


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