THE CLINICAL PRESENTATION OF THE PRIMARY IMMUNODEFICIENCY DISEASES
A PRIMER FOR PHYSICIANS

INTRODUCTION

The primary immunodeficiency diseases are a heterogeneous group of over 50 disorders which affect the cells, tissues and proteins of the immune system. These disorders were originally felt to be rare, to occur only in infants and young children and to be associated with severe clinical symptoms. However, as clinical experience with the primary immunodeficiency diseases has grown, it has become clear that they are much more common than originally appreciated, that they can be present in older children, adolescents, and adults, and that they can be associated in some patients with relatively mild clinical disease. The early detection of patients with primary immunodeficiency diseases is critically important. Effective therapy is available for virtually all of the different disorders, but is most beneficial when instituted before there has been damage to target organs (e.g. the lung) by infection or autoimmune disease. Similarly, early recognition of primary immunodeficiency may lead to a precise genetic diagnosis which in turn may be important to the family in planning their future reproductive options. This Primer has been written in an effort to alert primary care physicians to the signs and symptoms of primary immunodeficiency diseases in the hope that these patients will be diagnosed earlier in the course of their illness, allowing for more effective therapy and improved prognosis.

THE PRIMARY IMMUNODEFICIENCY DISEASES

The primary immunodeficiency diseases are a group of disorders in which the primary defect appears to be intrinsic to one or more components of the immune system. The immune system is conveniently divided into four functional compartments:

- The B-lymphocyte system
- The T-lymphocyte system
- the Phagocytic system
- The Complement system

Each of these functional compartments of the immune system plays a critical role in host defense against infection and inflammation. Although they each have specific roles in the normal function of the immune system, each works best when functioning in concert with the others.

Some of the more common primary immunodeficiency diseases are listed in the table. One of the most useful ways of classifying the primary immunodeficiency diseases is according t which functional compartment of the immune system is impaired. Thus, there are disorders that affect the B-lymphocyte system, disorders that affect the T-lymphocyte system, disorders that affect both the B- lymphocyte and T-lymphocyte systems, disorders that affect the phagocytic system, and disorders that affect the complement system.

FREQUENCY OF PRIMARY IMMUNODEFICIENCY DISEASES

The primary immunodeficiency diseases were originally thought to be quite rare. In fact, however, some of the primary immunodeficiency diseases are relatively common. For example, Selective IgA deficiency occurs in as many as 1/500-1/1000 individuals. Other primary immunodeficiency diseases are much less common and occur with a frequency of between 1/10,000 and 1/100,000. However because there are so many primary immunodeficiency diseases, when taken together as a group of disorders, they become a significant health problem, occurring with a frequency comparable to leukemia and lymphoma in children and four times as frequently as cy

CLINICAL MANIFESTATIONS OF THE
PRIMARY IMMUNODEFICIENCY DISEASES

Although the initial description of patients with primary immunodeficiency diseases focused on their increased susceptibility to infection, these patients may also present with a variety of other clinical manifestations. In fact, in some patients, the non-infectious manifestations, such as autoimmune disease and/or gastrointestinal disease, amy be the predominant clinical expression of their underlying immunodeficiency.

INFECTIOUS DISEASES:
An increased susceptibility to infection is the hallmark of the primary immunodeficiency diseases. In most patients, this is manifested by recurrent infections. Often, individual infections are not more severe than those that occur in a normal host. Rather, the striking clinical feature is the recurring and/or chronic nature of the infections. Typically, the infections do not occur only in a single anatomic site, but usually involve multiple organs or multiple sites within the same organ. For example, some patients will have recurrent otitis media in association with recurrent sinusitis and/or pneumonia, while other patients may have recurrent pneumonia, with episodes occurring in different lobes.

Recurrent sinopulmonary infections, such as otitis, sinusitis, bronchitis, and pneumonia, are the most common presenting manifestations of the primary immunodeficiency diseases, but recurrent systemic infections such as bacteremia and meningitis are also seen. Chronic changes of the lungs and sinuses are not unusual. In many instances, the patients not only have recurrent infections, but one or more of these is either unusually severe, leads to an unexpected or unusual complication, or is caused by an organism of relatively low virulence (i.e. an opportunistic organism). In fact, in some patients the first infection may be so severe or unusual that it raises the question of an underlying immunodeficiency. For example, a patient who presents with Pneumocystis carinii pneumonia is likely to be immunodeficient even if it is his/her first infection.

The type of infectious agent and the location of the infection may give valuable insight into the nature of the immunologic defect. For example, individuals who have B-cell deficiencies characteristically have an increased susceptibility to infection with encapsulated pyogenic bacteria, such as the pneumococcus and H.influenzae, and to enteroviruses. Patients who are deficient in T-cells may have infections with a variety of microorganisms but appear especially susceptible to fungi, viruses and Pneumocystis. Patients with complement deficiencies often present with blood- borne

infections, such as bacteremia and meningitis, caused by encapsulated bacteria. And, finally, patients with phagocytic disorders characteristically have infections of the skin and reticuloendothelial system.

AUTOIMMUNE AND RHEUMATIC DISEASES:
Patients with primary immunodeficiency diseases may also present with a variety of autoimmune or rheumatic disorders. Presumably, the underlying abnormality that leads to the development of the immunodeficiency also leads to faulty discrimination between "self" and "non-self" and thereby to autoimmune disease. In some patients the manifestations of the autoimmune disease may be limited to a single tissue or organ, such as occurs in autoimmune hemolytic anemia or autoimmune thrombocytopenia. In other patients with primary immunodeficiency, however, the clinical manifestations of the autoimmune disease may be more global and involve a number of different target organs, have an associated vasculitis, or resemble "classic" rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and/or dermatomyositis. Autoimmune and rheumatic diseases are more commonly seen in some of the primary immunodeficiency diseases than in others. For example, they are relatively common in Selective IgA Deficiency, Common Variable Immunodeficiency and deficiencies of the complement system and relatively uncommon in X-linked agammaglobulinemia.

GASTROINTESTINAL DISEASE:
Chronic diarrhea, malabsorption and even malnutrition may be important manifestations of primary immunodeficiency diseases, especially in infants and young children. In some instances, the cause is clearly infectious. Chronic giardiasis, rotavirus and cryptosporidium, among other infections, have each been significant problems in patients with primary immunodeficiency diseases. However, a variety of autoimmune or chronic inflammatory diseases which have no clear infectious etiology may also occur in patients with primary immunodeficiency diseases. These include inflammatory bowel disease, gluten-sensitive enteropathy, atrophic gastritis with pernicious anemia and nodular lymphoid hyperplasia.

HEMATOLOGIC DISEASES:
Anemia, thrombocytopenia, or leukopenia are seen frequently in patients with primary immunodeficiency diseases. In some instances, the hematologic abnormalities are the consequence of the underlying abnormality that is responsible for the immunodeficiency. For example, the Wiskott-Aldrich Syndrome is characterized by variable defects in B-lymphocyte and T-lymphocyte function. These patients also have intrinsic abnormalities of their platelets which result in small platelets and significant thrombocytopenia. In other instances, hematologic abnormalities are the consequence of the autoimmune diseases that are seen in patients with primary immunodeficiency. For example, a significant proportion of patients with autoimmune hemolytic anemia or ITP have an underlying primary immunodeficiency disease. Conversely, autoimmune hemolytic anemia, and/or thrombocytopenia, and/or neutropenia are often seen in patients with Common Variable Immunodeficiency or Selective IgA Deficiency, and the hyper IgM Syndrome.

LABORATORY DIAGNOSIS OF IMMUNODEFICIENCY

Once the question of a primary immunodeficiency disease has been raised, based on suggestive findings on history and physical examination, then laboratory testing is used to document and delineate the immunologic defect. The screening laboratory tests are relatively simple to perform and readily available, and can screen for more than one disorder at a time.

EVALUATION OF B-LYMPHOCYTE FUNCTION:
The initial screening test for B-lymphocyte function is the measurement of serum immunoglobulines. Neither serum protein electrophoresis, immunoelectrophoresis, nor immunofixation electrophoresis are sufficiently sensitive or quantitative to be useful. Quantitative measurements of serum IgG, IgA and IgM will identify patients with panhypogammaglobulinemia as well as patients who have a deficiency of an individual class of immunoglobulin, such as selective IgA deficiency. There are four subclasses of IgG and selective deficiencies of these have also been described. In some instances, the total serum IgG may be normal or near normal but the patient may still have an IgG subclass deficiency.

Thus, in the patient in whom there is a strong suspicion of a humoral immunodeficiency based on clinical grounds but the total IgG is normal, quantitative measurements of individual IgG subclasses are indicated. In addition to the measurement of serum immunoglobulin concentrations, some assessment of antibody function is a necessary part of the evaluation of humoral immunity. Antibody titers after immunization with protein antigens (e.g. tetanus or diphtheria toxoids) and polysaccharide (e.g. pneumococcal capsular polysaccharides) are most convenient. It should be emphasized, however, that immunization with live viral vaccines should be avoided whenever an immunodeficiency is suspected. If immunoglobulin levels and/or antibody titers are decreased, the evaluation should proceed with more advanced tests of B-lymphocyte numbers and function.

EVALUATION OF T-LYMPHOCYTE FUNCTION:
Testing for defects in T-lymphocyte function is relatively difficult because of the lack of inexpensive and reliable screening tests. Delayed type hypersensitivity (DTH) skin tests using a panel of ubiquitous antigens can be used as a screening test in older children and adults. The presence of a positive DTH skin test generally indicates intact T-cell function and cell mediated immunity. However, there are some important limitations to DTH skin testing.

A positive DTH skin test to some antigens does not insure that the patient will have normal cell mediated immunity to all antigens or microorganisms. For example, patients with chronic nucocutaneous candidiasis may have a limited defect in which cell mediated immunity may be intact to a wide variety of microorganisms except to candida. Furthermore, some normal individuals may have transiently depressed DTH reactions during certain viral infections. And finally, a positive DTH skin test requires prior exposure and sensitization to the antigen. Infants and young children may not have had sufficient prior exposure to have developed positive DTH skin tests.

Thus, negative DTH skin tests may not necessarily reflect abnormal T-lymphocyte function. Indirect information about T-lymphocyte function may be obtained by enumerating peripheral blood T-lymphocytes using monoclonal antibodies. The number of total T-lymphocytes (CD2 or CD3), T- helper lymphocytes (CD4) and T-

suppressor/cytotoxic lymphocytes (CD8) in peripheral blood can be quantitated with the appropriate monoclonal antibodies. More specialized tests of T-cell function include an assessment of lymphocyte proliferation in response to nonspecific mitogens (e.g. phytohemagglutinin), specific antigens (e.g. candida) and/or mononuclear cells from an unrelated, histoincompatible individual (mixed leukocyte reaction). It is also possible, in specialized laboratories, to measure the production of a number of different cytokines that are involved in T- and B- lymphocyte regulation (e.g. Interleukin 2, interferon-gamma).

EVALUATION OF PHAGOCYTIC FUNCTION:
The evaluation of phagocytic cells generally entails assessment of both their number and their function. For example, disorders such as congenital agranulocytosis or cyclic neutropenia are characterized by reductions in phagocytic cell number in the peripheral blood and, therefore, can be detected by using a white blood cell count and differential. Assessment of phagocytic cell function requires a number of different assays. In vitro assays of directed cell movement (chemotaxis), ingestion (phagocytosis), and intracellular killing (bactericidal activity) are available but usually require specialized laboratories. Importantly, there are simpler assays that indirectly assess phagocytic killing by measuring the metabolic events which accompany and/or are responsible for intracellular killing. The most common of these assesses the ability of phagocytic cells to respond with an oxidative burst by measuring the reduction of nitroblue tetrazolium (NBT test).

EVALUATION OF THE COMPLEMENT SYSTEM:
Most of the genetically determined deficiencies of the classical activating pathway (C1, C4 and C2), of C3, and of the terminal components (C5, 6, 7,8, and 9) can be detected by using antibody sensitized sheep erythrocytes in a total hemolytic complement (CH50 assay since this assay requires the functional integrity of C1 through C9. Deficiencies of alternative pathway components Factors D, H and I and properdin can be detected by a hemolytic assay that used unsensitized rabbit erythrocytes which are potent activators of the alternative pathway. The identification of the individual component which is deficient rests on specialized functional and immunochemical tests which are specific for each component.

SPECIFIC IMMUNODEFICIENCY DISEASES

There are over 50 different primary immunodeficiency diseases which affect virtually every functional compartment of the immune system. Space limitations do not allow a discussion of all of the primary immunodeficiency diseases so only those that are the most prevalent or most illustrative will be presented.

X-LINKED AGAMMAGLOBULINEMIA (XL-A):
This X-linked recessive disorder is due to a developmental arrest in B-lymphocyte differentiation. Males with X-LA have decreased numbers of mature B-lymphocytes in blood and severe panhypogammaglobulinemia. Cell-mediated immune function is normal. Affected males are usually well for the first few months of life and then begin to develop frequent or severe infections, particularly of the paranasal sinuses and the lungs. Individual infections may be no more severe than in the general population but they may be chronic or recurrent. The most frequent identified pathogens are S. pneumoniae, H. influenza type b, streptococcus and staphylococcus. Non-typeable H.

influenzae, a variety of gram negative bacilli and mycoplasma may also become important pathogens in those patients with chronic lung disease.

Bacterial meningitis, sepsis, arthritis, and osteomyelitis occur much less often, but with higher frequency than in the normal population. The diagnosis of X-LA is usually suggested by frequent and/or severe bacterial infections. When present, a positive family history of previously affected males can be helpful in suggesting the presence of an immunodeficiency. However, a positive family history is not always present since not all cases have previously affected family members. Early recognition and initiation of immunoglobulin (gamma globulin) therapy are key to the prevention of chronic pulmonary disease. Regular infusions of intravenous immunoglobulin are of real benefit in this disorder and prevent and/or delay the development of chronic lung disease.

COMMON VARIABLE IMMUNODEFICIENCY:
The term common variable immunodeficiency (CVID) describes a heterogeneous group of disorders in patients who have hypogammaglobulinemia with a variable degree of T-cell dysfunction. The etiologic basis for this group of diseases is unclear. There is no recognizable pattern of inheritance, although CVID may cluster in some families. Most patients with CVID do not manifest symptoms until the second or third decade of life; a smaller number of patients have clinical symptoms during the first decade of life. The most common manifestations of CVID are chronic/recurrent infections of the respiratory and gastrointestinal tracts. Individuals without a significant prior history of infections may develop recurrent otitis media or bronchitis.

The spectrum of respiratory tract disease is very similar to what is seen in X-LA patients. In addition, there is a surprisingly high incidence of gastrointestinal disease; chronic diarrhea occurs in as many as 30% of patients. Giardia lamblia and bacterial overgrowth of the small bowel are the most frequently identified pathogens. Patients with CVID also have a variety of associated illnesses which are believed to be the result of immune dysregulation. Chronic idiopathic diarrhea with malabsorption is common. There is an increased incidence of inflammatory bowel disease, gluten-sensitive enteropathy and nodular lymphoid hyperplasia.

Hematologic abnormalities include autoimmune hemolytic anemia, immune thrombocytopenia, leukopenia, pernicious anemia, and persistent splenomegaly. Rheumatoid arthritis and other collagen vascular diseases also occur more commonly than expected. The diagnosis of CVID is usually suggested by frequent and/or severe sinopulmonary infections. The mainstay of treatment for CVID is the prophylactic use of immune globulin and aggressive management of infection.

SELECTIVE IGA DEFICIENCY:
Selective IgA deficiency is the most prevalent primary immunodeficiency disease, occurring in approximately 1/500 to 1/1000 individuals in the general population. Patients have serum IgA levels less than 5 mg/dl with normal levels of other immunoglobulin classes, normal serum antibody responses, and normal cell mediated immunity. However, this definition may be overly restrictive. individuals with low but not absent IgA(5-10 mg/dl) share some of the same clinical manifestations. Furthermore, many patients previously classified as having "selective" IgA deficiency are now known to have associated immunologic abnormalities, the most common of

which are deficiencies of IgG2 and/or IgG4. As with common variable immunodeficiency, most cases occur sporadically.

However, in some patients, selective IgA deficiency is seen in a familial setting. Some, but not all, patients with selective IgA deficiency have an increased susceptibility to infections. As might be expected by the role of IgA as the predominant secretory immunoglobulin, the most common sites of infection are mucosal surfaces; bacterial sepsis and meningitis are rare. As many as 50% of patients with IgA deficiency have chronic otitis, sinusitis or pneumonia. those IgA deficient patients with chronic respiratory infections are most likely to have an associated IgG subclass deficiency. Since the latter is treatable with immunoglobulin, IgG subclass quantitation and testing for antibody response to capsular polysaccharide vaccines should be included in the work-up of all IgA deficient patients.

The second major mucosal target for infections is the small intestine. Giardia lamblia is the most frequently identified pathogen in this group of patients, although the disease is often unrecognized because the symptoms are chronic and indolent. Autoimmune and rheumatic diseases are also associated with selective IgA deficiency. These include juvenile rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, pernicious anemia, inflammatory bowel diseases and gluten-sensitive enteropathy. Immunoglobulin therapy is generally contraindicated in selective IgA deficiency.

Commercial immunoglobulin preparations contain trace amounts of IgA which are sufficient to sensitize the patient to IgA, or which can react with existing anti-IgA antibodies and on rare occasions induce an anaphylactic response. However, this is a relative and not an absolute contraindication to immunoglobulin therapy. Patients with associated IgG subclass or antibody deficiencies who suffer from recurrent infections may benefit from immunoglobulin prophylaxis.

SEVERE COMBINED IMMUNODEFICIENCY:
Severe Combine Immunodeficiency Disease (SCID) is a disorder characterized by a marked deficiency of both B-lymphocyte and T- lymphocyte function. There are many forms of SCID. Some are inherited in an X-linked recessive fashion, while others are inherited as autosomal recessive traits. One form of the autosomal recessive disease is due to a deficiency of Adenosine Deaminase. A complete blood count, including WBC and differential, may be very useful in alerting the physician to the possibility of SCID since many (but not all) patients will be lymphopenic (<1000 lymphocytes/mm3).

Usually, these children are too young for delayed-type hypersensitivity skin testing to be of help. Therefore, enumeration of peripheral blood T-cell number and function is indicated. Serum levels of IgG, IgA, and IgM are usually markedly reduced. However, if the infant is only a few months old, the IgG level may be normal or near normal because of maternally derived IgG. SCID typically presents in the first several months of life. A typical SCID patient may have failure to thrive, and chronic respiratory, GI and/or cutaneous infections. However, it is not unusual for the first indication of SCID to be a single clinical problem such as interstitial pneumonitis. SCID should be considered in any infant with prolonged, unexplained chest disease, diarrhea or intractable candida.

The early diagnosis of SCID is crucial to these infants. Undiagnosed and untreated patients usually die in the first year of life. Bone marrow transplantation is very effective but the chances of a successful transplant depend in part on the degree of infection and/or failure to thrive present at the time of transplantation. Therefore, SCID patients should be identified and referred for transplantation as soon as possible.

WISKOTT-ALDRICH SYNDROME:

Patients with this X-linked recessive disorder become symptomatic in infancy or early childhood with the clinical triad of thrombocytopenia, eczema and recurrent infections. The immunologic dysfunction involves both humoral and cell-mediated immunity. Patients usually have elevated IgA and IgE, low IgM, and impaired responses to polysaccharide antigens; there is a variable degree of T-cell dysfunction. The diagnosis is confirmed by the finding of small platelets. The inability to respond to polysaccharide antigens leads to a high incidence of pyogenic bacterial infections, usually of the ears, sinuses, and lungs.

T-cell dysfunction may manifest itself by severe infections with herpes viruses and Pneumocystis carinii. In addition, there is an increased incidence of malignancies, particularly lymphomas, and autoimmune diseases. Treatment combines the use of prophylactic immunoglobulin with aggressive management of acute infections. Immunoglobulin may also be helpful in treating the thrombocytopenia, although some patients may require splenectomy. If a suitable donor is available, bone marrow transplantation may completely cure the disease. With earlier diagnosis and better supportive therapy, many of these patients reach adult life.

ATAXIA-TELANGIECTASIA:

Ataxia-telangiectasia (A-T) is an autosomal recessive disorder characterized by progressive development of cerebellar ataxia, oculocutaneous telangiectasia, and immunodeficiency. Patients with A-T have defective mechanisms of DNA repair, and their cells therefore have frequent chromosomal breaks and translocation. The diagnosis can be confirmed by the finding of an elevated serum a- fetoprotein level. The immunologic defect in ataxia-telangiectasia is variable, and frequently evolves over time. Individual patients may be immunologically normal, but the majority will eventually develop some dysfunction of humoral and/or cell-mediated immunity, most commonly a deficiency of serum IgA, IgE and/or IgG subclasses.

Chronic sinopulmonary infections are a major clinical problem in patients with ataxia-telangiectasia. The predisposition to infections is related both to the immunodeficiency and to neurologic abnormalities which interfere with the patients' ability to clear respiratory tract secretions. In addition to infection, patients with ataxiatelangiectasia have a marked predisposition to develop malignancy, particularly lymphoma and lymphocytic leukemia. Of note, the asymptomatic obligate carriers of this disease are also at an increased risk of developing certain cancers.

Therapy of this disorder includes gamma globulin if IgG or IgG subclass deficiency is present, supportive care for neurologic attrition, and strict attention to pulmonary toilet. Progression of neurologic and immunologic deficiencies is highly variable and do not always parallel each other. Many of these patients survive to adult life.

DIGEORGE ANOMALY (SYNDROME):

Infants with this immunodeficiency have a developmental defect of their pharyngeal pouches which affects embryogenesis of their parathyroids, thymus and hearts. As a result, they may be born with hypoparathyroidism and hypocalcemia, thymic aplasia and T- lymphocyte deficiency and congenital heart disease. Infants with DiGeorge Anomaly usually present in the first weeks of life either because of their congenital heart disease, their hypocalcemia, or their increased susceptibility to infection. The clinical expression of the syndrome varies. Some patients have involvement of all three organs (i.e. heart, thymus and parathyroids) while others have involvement of only two. The thymic defect can also be very variable with partial defects in T-cell function.

CHRONIC GRANULOMATOUS DISEASE:

Chronic granulomatous disease (CGD) is a disorder of phagocytic cells in which the ability of both polymorphonuclear leukocytes and monocytes to kill certain intracellular bacteria and fungi is markedly deficient. Phagocytic cells from these patients are unable to reduce molecular oxygen and produce reactive oxygen products, such as hydrogen peroxide and superoxide, which are necessary for the intracellular killing of bacteria and fungi. As a result, patients are unduly susceptible to those bacteria and fungi that are catalase positive and have no net production of peroxide; organisms that are catalase negative, and produce peroxide, supply the missing metabolite to the phagocytic cell and are readily killed. The disorder can be caused by a variety of genetic defects which affect components of the electron transport system. There are both X-linked recessive and autosomal recessive forms of the disorder. patients with CGD usually present in infancy and childhood but there are many patients with milder variants in whom the diagnosis is not made until adolescence or later. Because of the selective nature of their killing defect, these patients are susceptible only to a limited variety of bacteria (such as Staphylococci, E, coli, Pseudomonas, Klebsiella, Serratia and Salmonella), and certain fungi (such as Candida and Aspergillus). The infections most commonly involve the lungs, lymph nodes, soft tissues, bone, skin and urinary tract and are characterized histologically by granuloma formation. Treatment has traditionally involved antibiotics for both prophylaxis and the treatment of specific infections. The results of clinical trials have suggested that recombinant gamma interferon may prove beneficial as both a prophylactic and a therapeutic agent.

LEUKOCYTE ADHESION DEFICIENCY:

Leukocyte adhesion deficiency (LAD) is an autosomal recessive disorder of phagocytic cells. The molecular basis of LAD involves a family of glycoproteins on the surface of phagocytic cells which are responsible for the ability of leukocytes to adhere and migrate into sites of infection and inflammation. These patients have recurrent infections of their skin, subcutaneous, and deep tissues caused by a variety of bacteria.

COMPLEMENT DEFICIENCIES:

there are over 20 components of the complement system, and genetically determined deficiencies have been described for each. Most are inherited as autosomal recessive traits although one, properdin deficiency, is X-linked recessive, and another, C1 esterase inhibitor deficiency, is autosomal dominant. The clinical presentation of complement deficiencies depends to some extent on the component which is deficient.

The third component (C3) is an important opsonin, while C5-C9 assemble into a membrane attack complex and are responsible for bactericidal activity.

Deficiencies of C1, C4, C2 and C3 are characterized by an increased susceptibility to a wide variety of encapsulated bacteria as well as a variety of rheumatic disorders such as systemic lupus erythematosis. In contrast, patients with deficiencies of C5, C6, C7, C8 or C9 have a selective susceptibility to systemic meningococcal and gonococcal infections since normal host defense against these organisms depends in large part on serum bactericidal activity. Although the clinical expression of complement of deficiencies can occur in childhood, many patients do not demonstrate an increased susceptibility to infection or rheumatic diseases until adult life. There is no specific therapy for complement deficiencies but immunization against H. influenzae, S. pneumoniae, and N. meningitides probably is of some value.

REFERRAL TO AN IMMUNOLOGIST

Most patients with a primary immunodeficiency disease should have the benefit of a consultation with a clinical immunologist. The primary care physician has a critical role to play in identifying those patients who may have a primary immunodeficiency disease. However,the clinical immunologist can be of real benefit to the patient in a number of important areas. First, the clinical immunologist can be helpful in interpreting screening laboratory tests, suggesting and performing more sophisticated and definitive tests, and in making a precise diagnosis.

In addition, since many of the primary immunodeficiency diseases are genetically determined, a precise diagnosis is critically important, not only for an accurate prognosis and effective therapy, but also for appropriate genetic counselling, and the clinical immunologist can be helpful in that regard as well. Finally, the clinical immunologist has valuable experience in the management of patients with this heterogeneous group of disorders and can be very helpful in planning and implementing specific therapy and in addressing common and rare complications.