

Immunodeficiency states relevant to infection

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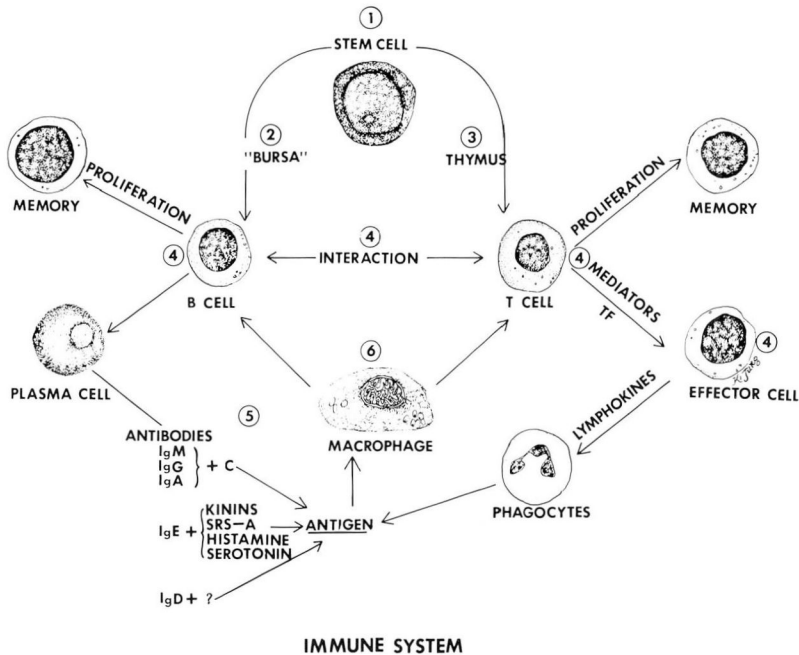
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The importance of immune mechanisms in resistance to infection is most apparent in persons with deficient immunity. Although immunodeficiency states are relatively uncommon, the study of patients with such defects has led to significant insights into the functioning of the normal immune system. Moreover, from a practical point of view, it is occasionally necessary to consider the differential diagnosis of immune deficiency in patients with repeated infections, or in patients with unusual infections. To approach an evaluation rationally, it is helpful to have some broad concepts about the organization of the immune system.

This paper presents a simple review of the functional and morphologic organization of the immune system, a discussion of the differential diagnosis of immunodeficiency states, and an orderly approach to the examination of patients suspected of having immune deficiency.

Organization of the immune system

Since the early work of Miller¹ in clarifying the role of the thymus gland and that of Cooper et al² in defining the function of the bursa of Fabricius in chickens, the binary structure of the immune system has become widely accepted. Primordial immunocytes from bone marrow mature along one of two pathways under the influence of the two central lymphoid organs, the thymus gland and the bursa or bursal equivalent (*Fig. 1*).



IMMUNE SYSTEM

Fig. 1. Organization of the immune system. Numbers refer to presumed defect sites and correspond to numbered paragraphs in the text. (Adapted from Cleve Clin Q 41: 128, 1974.)

The thymic influence leads to generation of the T-cell population, which includes the great majority of cells in the thymus gland itself, cells in the "thymic-dependent" areas of peripheral lymph nodes (paracortical areas), and a circulating population of small lymphocytes found in the blood and lymphatic vessels.³ Although it is not clear how many distinguishable subpopulations of T-cells exist or how the various functions are parceled out among them, recirculating mature T-cells, perhaps comparable to T-2 cells in mice,⁴ tend to be long-lived; their numbers are not greatly affected by thymectomy, but because they recirculate,⁵ they can be depleted rapidly by thoracic duct drainage, and are maximally accessible to antilymphocyte serum. These cells are responsible for delayed hypersensitivity,⁶ allograft re-

jection,⁷ graft versus host reactions,⁸ and probably play an important role in tumor surveillance.⁹ Adequate T-cell function is crucial in the defense against infection by intracellular parasites such as mycobacteria, brucella, many viruses, and *Pneumocystis carinii*.

A number of tests of T-cell function are available including delayed hypersensitivity skin tests, mitogen- or antigen-induced lymphocyte transformation, migration inhibition factor (MIF) production, mixed lymphocyte reactions, and in vitro cytotoxicity (especially relevant in tumor immunity). T-cells in circulation can be directly quantitated by taking advantage of their ability to form rosettes with sheep erythrocytes;¹⁰ normally, approximately 70% of peripheral blood lymphocytes are T-cells.

Immunocytes maturing under the influence of the bursa or bursal equivalent constitute the B-cell population, which includes most of the cells found in the bursa of Fabricius of birds, the cells found in the "bursal-dependent" areas of lymph nodes (germinal centers and far cortical areas), plasma cells, and a population of circulating lymphocytes.³ B-cells do not recirculate as extensively as T-cells and their life span is much shorter than that of T-cells.⁴ The major function of the B-cell system is antibody production. Antibody activity is borne by proteins called immunoglobulins, which are separable by antigenic, physical, and functional characteristics into five distinct classes: IgM, IgG, IgA, IgD, and IgE. IgM and IgG are the major circulating immunoglobulins, the former dominating primary immune responses and responses to polysaccharide antigens, the latter dominating secondary responses to protein antigens.¹¹ IgA is the major immunoglobulin of exocrine secretions,¹² although it is also found in the circulation. IgE is largely tissue-fixed,¹³ and only a small amount is present in the circulation. IgD is to a large extent bound to B-cells and may play a role in induction of the immune response.¹⁴ Antibodies are important in resistance to pyogenic bacterial infections and some viral infections.

B-cell function is assessed by measuring immunoglobulin levels and antibody responses. Circulating B-cells can be enumerated by staining lymphocytes with fluorescein-tagged anti-globulins,¹⁵ by rosette formation with sensitized sheep erythrocytes bearing complement components through C3,¹⁶ or by binding of fluorescein-tagged aggregated IgG.¹⁷ Normally

about 30% of peripheral blood lymphocytes are B-cells.

These two populations of cells give rise to cell-mediated and humoral immune responses when triggered by appropriate antigenic stimuli. The outcome of such responses depends on the activation of a wide variety of effector mechanisms. Effector mechanisms are, by and large, without specificity. When they are activated immunologically, their destructive effects are ordinarily brought to bear against the specific stimulating agent, although this may not always be the case. It should also be kept in mind that some of these effector mechanisms may be activated by nonimmunologic pathways.

When an immunogenic material enters the system, it eventually finds its way (sometimes after "antigen-processing" by macrophages) to appropriate antigen-sensitive T- or B-cells or both. The immunogen interacts with surface receptors on these cells, and in this way the antigen-sensitive cells are triggered, initiating the immune response. At this point, interactions may occur between the stimulated T- and B-cells which lead either to enhancement¹⁸ or suppression¹⁹ of the response. Activation of such antigen-sensitive cells has several results. In both T- and B-cell systems proliferation occurs, and this produces a much larger population of specific antigen-sensitive cells establishing immunologic memory. In the T-cell system, both by proliferation and recruitment, a population of cells is produced which launches a direct attack on the immunogen itself. In the B-cell system, the antibody production mechanism is activated, resulting in the production of various classes of immuno-

globulins which specifically combine with the antigen, and produce complexes which can activate several effector mechanisms.

Effectors of humoral immunity. Although the mere combination of antibody with antigen may alter the antigen in various ways, it generally does not result in destruction or rapid elimination of antigen from the body. Auxiliary mechanisms must be activated to accomplish this. The best understood of these auxiliary mechanisms is the complement system.

Complement is the effector system for antibodies in the major immunoglobulin classes; IgG and IgM antibodies activate the classical pathway,²⁰ and IgA antibodies may activate the alternate pathway.²¹ Current data indicate that antibodies of the other classes (IgD and IgE) are unable to activate the complement cascade, although there is some evidence to suggest that IgE may activate the alternate pathway.²² The complement system is a group of alpha, beta, and gamma globulins with potential enzymatic activity, which are activated sequentially in a fashion analogous to the coagulation mechanism. Their relationships are shown in *Figure 2*. The pivotal step in the cascade is activation of the third component of complement (C3), which may be accomplished in two major ways: immune complexes containing IgG or IgM antibodies may activate the classical pathway with sequential fixation of C1, C4, and C2; or immune complexes containing IgA (or possibly IgE) antibodies may evoke the alternate pathway with sequential activation of properdin, C3 proactivator convertase (C3Pase), and C3 proactivator (C3PA properdin factor B, GBG). Both

classical and alternate pathways may on occasion be activated by nonimmune mechanisms. Activation of C3 to C3b leads to a positive feedback mechanism which utilizes some of the components of the alternate pathway in activating further molecules of C3. The potent biological effects of complement begin with C3 activation. The fixation of C3b leads to opsonization for phagocytosis of many antigens including most gram-positive bacteria. The subsequent activation of C5 leads to further opsonization and is required for phagocytosis of many gram-negative bacteria and *Staphylococcus aureus* as well as many fungi. Anaphylotoxins (C3a and C5a) are released with activation of the third and fifth components. Chemotaxis of phagocytes is produced by activation of C5, C6, and C7 with C567 complex formation. If the antigen is on a cell surface, activation of C8 and C9 produces damage at the antigenic site which may result in lysis of the cell. The complement system, then, is important in mediating the destruction of antigen and its elimination from the system. Its complexity, together with the presence of inhibitors at several steps, help to protect the host against self-infliction of damage by inappropriate activation of complement.

An important effector mechanism activated by immune complexes containing IgE antibody is the kallikrein-kinin system.²³ Kallikreins are enzymes which cleave oligopeptides called kinins from plasma alpha globulins. Kinins produce vasodilatation, increased vascular permeability and leukotaxis, thereby contributing to the inflammatory response. Immune complexes containing IgE antibody also cause the release of slow reacting sub-

stance of anaphylaxis (SRS-A), histamine, and serotonin.

Effectors activated by immune complexes containing IgD have not been described.

Effectors of cellular immunity. When antigen-sensitive cells of the T-cell system are stimulated, there ensues production of a number of poorly characterized substances called mediators and lymphokines. These materials are important in the recruitment of other lymphocytes to the response (transfer factor, lymphocyte transforming factor), actions on cells other than lymphocytes (macrophage MIF, macrophage agglutinating factor, macrophage activating factor, eosinophil chemotactic factor), and direct attack on the antigen (lymphotoxins and interferons). The exact interrelationships of these materials are not completely understood.

Immune deficiency states

During the past few years it has become increasingly obvious that diseases of immune deficiency are exceedingly heterogeneous. Although in no case is the exact nature of the defect completely understood, it is often possible to approximate the site of the defect on the scheme presented in *Figure 1*. A recent reclassification of the primary immunodeficiencies²⁴ attempts to de-emphasize assumptions about pathogenesis which characterized the old nomenclature. The numbers in the following discussion refer to the presumed location of defects on the scheme presented in *Figure 1*.

1. Stem cell defects. The most severe of all the immunodeficiencies is immunodeficiency with generalized hematopoietic hypoplasia (reticular dysgenesis).²⁵ In this disease none of the white

cells normally produced by the bone marrow, including lymphocytes, are present. It is incompatible with life, and the immunodeficiency associated with it is of little importance.

Severe combined immunodeficiency includes a heterogeneous group of diseases characterized by lack of stem cells which mature to effective immunocytes. The result of this is lymphopenic agammaglobulinemia, and affected patients have severe deficiencies both in cell-mediated and humoral immunity with susceptibility to all types of infection. The prototype of the severe combined immunodeficiencies is that associated with erythrocyte adenosine deaminase deficiency (Swiss type agammaglobulinemia).^{26, 27} This is an autosomal recessive disorder which, if untreated, ordinarily results in death from infection during the first year. Erythrocyte adenosine deaminase is severely deficient in these patients; adenosine deaminase is normal in other immunodeficiency states. Severe combined immunodeficiency may also occur in an x-linked recessive form (thymic aplasia)²⁸ which is not quite so severe, but which ordinarily results in death from infection before the patient is 2 years of age. These patients have variable numbers of lymphocytes and may have low but detectable levels of immunoglobulins. Severe combined immunodeficiency may also be associated with dysostosis (short-limbed dwarfism).²⁹

Because these patients appear to lack stem cell precursors for mature lymphocytes, the most rational treatment is bone marrow transplantation.³⁰ This requires the identification of donors, usually siblings, who are histocompatible with the patients. The result of an incompatible transplant

would be graft versus host disease and death. Compatibility can be established by demonstrating identity of H-LA antigens in donor and recipient using standard antisera, and this must be further confirmed by mixed lymphocyte cultures.

Another form of treatment under investigation is the use of a germ-free environment during early life, allowing time for immunocyte maturation.³¹ This period may be prolonged, however, and possible undesirable side effects of lengthy life-island incarceration need investigation.

A third method of treatment is a trial of transfer factor.³² This is usually unsuccessful but a few patients have benefited.

2. B-cell maturation defects. The prototype of this group is x-linked infantile agammaglobulinemia (Bruton-type agammaglobulinemia).³³ In this disease patients have exceedingly low levels of all immunoglobulins and they do not make humoral antibody responses to antigenic stimuli. Cell-mediated immunity is grossly intact, although allograft rejection may be somewhat slower than normal. The number of B lymphocytes, identifiable by surface immunoglobulins or C3-receptor sites, is significantly decreased in these patients who are quite susceptible to acute pyogenic bacterial infections.

The regular administration of gamma globulin generally provides adequate protection. The dose is 50 mg/kg each month, administered intramuscularly. Standard preparations of gamma globulin contain 165 mg/ml, and this results in an average intramuscular injection of approximately 20 ml per month in an adult. Unpleasant local effects can be dimin-

ished by dividing the total volume among several sites, by splitting the administration into two biweekly doses, and by mixing the gamma globulin with lidocaine. The administration of gamma globulin does not confer immunologic reactivity on the recipient, but supplies him with low levels of natural antibodies, protecting against the initial establishment of infection. Once infection is determined, vigorous antibiotic therapy is indicated.

3. T-cell maturation defects. In thymic hypoplasia (DiGeorge syndrome)³⁴ there is failure of development of thymus and parathyroid glands (derivatives of the third and fourth branchial arches). Symptoms of hypocalcemia appear very early in life; later viral, fungal, and mycobacterial infections begin. Although stem cell precursors of T-cells are present, they do not mature in the absence of thymus gland; B-cells and immunoglobulin synthesis are normal. These patients are unable to mount a cell-mediated immune response. A milder form of T-cell maturation deficiency is cellular immunodeficiency with lymphocytes (Nezelof syndrome).³⁵

Thymus transplantation has been successful in some patients with thymic hypoplasia.³⁶ In contrast with bone marrow transplantation, establishment of chimerism is not a goal of thymic transplantation. The transplanted fetal thymus provides the necessary microenvironment for maturation of the patient's own stem cells to functional T-cells. The risk of graft versus host disease is less severe after thymus transplantation than after bone marrow transplantation.

Immunodeficiency with ataxia telangiectasia³⁷ is characterized by mor-

phologic abnormalities of the thymus gland and deficient immune function, often with absent IgA and defective cell-mediated immunity. Some success in treating the immune deficiency associated with this syndrome has been reported with transfer factor³⁸ and thymic transplantation.³⁹

A variety of immunodeficiencies with thymoma have also been recorded, including hypogammaglobulinemia and deficient cell-mediated immunity.⁴⁰ Treatment generally includes removal of the thymoma as well as supportive treatment.

4. Peripheral defects. There is a large variety of defects leading to different combinations of partial or complete malfunction of either T- or B-cell system. Several of the more common constellations of abnormalities are recognized as separate syndromes. These diseases tend to be less severe and less immediately life-threatening than the more central defects.

Selective immunoglobulin deficiencies occur in a heterogeneous group of patients who lack one or more immunoglobulins without being totally agammaglobulinemic. The most common of these is selective IgA deficiency⁴¹ (Type III dysimmunoglobulinemia). The IgA levels of these patients are exceedingly low, but the other immunoglobulins tend to be present in normal amounts, except for IgE which may also be absent. Selective IgA deficiency occurs in about 1 of 600 of the general population. In some cases, it is associated with an increased tendency to respiratory infections (especially in the presence of IgE⁴²) and it appears also to be associated with a higher than expected incidence of autoimmune diseases, such as lupus erythematosus.⁴³ Secretory IgA is im-

portant in preventing entrance of antigenic material to the circulation via the gastrointestinal route; patients with a deficiency of IgA have a high incidence of milk antibodies.⁴⁴ No treatment is required for selective IgA deficiency, and the use of gamma globulin or other material which might lead to the production of antibodies against IgA is contraindicated. In IgA-deficient patients sensitized to IgA, severe hypersensitivity reactions may result if whole blood containing IgA is transfused to them.⁴⁵

Selective IgM deficiency (Type V dysimmunoglobulinemia⁴⁶) is a rare disorder; the patients have devastating bacterial infections with septicemia which are difficult to treat with antibiotics. *Streptococcus pneumoniae* is a common infectious agent. At least some of these patients are unable to respond to antigenic challenge by producing specific IgG antibody, although they have normal total levels of IgG. In these patients, gamma globulin therapy may be helpful.

X-linked immunodeficiency with hyper-IgM (Type I dysimmunoglobulinemia⁴⁷) is also characterized by inability to produce IgG antibodies. In addition, patients may have exceedingly low levels of IgA and increased levels of IgM; they are able to produce IgM antibodies. Gamma globulin therapy is often helpful.

Immunodeficiency with normal or hypergammaglobulinemia (Type VI dysimmunoglobulinemia⁴⁸) is characterized by the inability to produce antibodies, although immunoglobulin levels are normal. This is a rare condition. It can only be detected by immunization studies.

The variable immunodeficiencies include common variable hypogamma-

globulinemia⁴⁹ in which immunoglobulins of all classes are reduced with accompanying inability to mount antibody responses. B-cells may lack surface immunoglobulins while maintaining C3 receptor sites. Recent data suggest that at least some cases may result from abnormal T-cell-B-cell interaction in which T-cell suppressor function is greatly increased.⁵⁰ Gamma globulin is the treatment of choice.

Variable immunodeficiencies can also produce abnormalities of cell-mediated immunity, which vary in severity from nearly total ablation of all manifestations of cell-mediated immunity to limited defects in the ability to respond against certain antigens. This collection of disorders often results in the clinical syndrome of chronic mucocutaneous candidiasis,⁵¹ in which there is chronic monilial infection of skin and mucous membranes, often accompanied by endocrine abnormalities or autoimmunity or both. Treatments have ranged from the use of transfer factor and lymphocyte transfusions to thymic transplants and bone marrow transplantation. Although the candidal infection may be disfiguring, it tends not to be systemic and is generally not fatal. Consequently, it seems prudent to avoid the use of drastic life-threatening treatments such as bone marrow transplantation. Transfer factor therapy is relatively benign and sometimes effective. The use of short courses of intravenous amphotericin-B is occasionally followed by long (>1 year) remissions. It is important to monitor endocrine functions since these patients may die of sudden endocrine catastrophes such as Addisonian crisis.

Transient hypogammaglobulinemia of infancy⁵² may be mistaken for a

serious immunodeficiency. In this condition, there is a delay between the disappearance of maternal IgG from the circulation and the appearance of the infant's own immunoglobulins. This can be distinguished from primary immunodeficiency by performing rectal biopsy with immunofluorescent staining of plasma cells. If IgA-bearing plasma cells can be seen in the biopsy material, the diagnosis of transient hypogammaglobulinemia of infancy can be made, and treatment is not required.

5. Primary complementopathies. The humoral immune system requires a number of effectors in order to exert an effect on antigen. As noted in the previous section, antigen-binding by antibody generally produces very little effect on antigen. The major effector of humoral immunity is the complement system. There are a few severe defects in the complement system that may lead to a state of susceptibility to infection clinically resembling hypogammaglobulinemia, despite the fact that antibody formation proceeds normally. The worst of these defects involve early steps in the final common pathway (*Fig. 2*) which begins with the activation of C3. C3 deficiency states lead to absence of complement-mediated immunoadherence and opsonization as well as failure to activate subsequent complement components. C3 may become deficient by three different mechanisms: (1) failure of synthesis of C3 protein, (2) absence of C3 INA leading to hypercatabolism of C3, and (3) cleavage of C3 to two inactive products (C3c and C3d) by C3ase, an enzyme which is normally inhibited by a stabilizer.⁵³ In C3 deficiency, repeated infections with pyogenic bacteria are the rule. Treatment consists

which is generally not as severe as the primary types discussed above.

Complement components may be consumed at a high rate in diseases characterized by the presence of immune complexes, such as lupus erythematosus. The contribution of this to the unusual tendency of patients with lupus erythematosus⁶³ to develop infections has not been clarified.

Acquired abnormalities may also lead to defective synthesis of immunologic materials. Malignancies and infections (particularly viral) are the best examples of this. Sarcoidosis may also fall into this category.

Immunologic investigation

An orderly approach to the immunologic investigation begins with a

Table. Immunologic investigation

<p>I. History and physical examination</p> <p>A. Infections: type, frequency, age of onset</p> <p>B. Family history</p> <p>C. Review of systems and examination</p> <ol style="list-style-type: none"> 1. Skin changes (e.g., eczema, telangiectases) 2. Tonsils, nodes, spleen 3. Gastrointestinal symptoms 4. Arthritis 5. Bleeding tendency due to thrombocytopenia 6. Neurologic signs and symptoms 7. Endocrine signs and symptoms <p>II. Routine laboratory tests</p> <p>A. Complete blood count (with differential count and platelet estimate)</p> <p>B. Serum protein electrophoresis</p> <p>C. Serum calcium</p> <p>D. Endocrine function tests, such as glucose tolerance test</p> <p>E. Cultures</p> <p>III. Roentgenography</p> <p>A. Chest</p> <ol style="list-style-type: none"> 1. Acute and chronic lung changes 2. Thymus shadow <p>B. Nasopharynx, for tonsillar tissue</p> <p>C. Sinuses, for evidence of inflammation</p> <p>IV. Tests of T-cell function</p> <p>A. Screening</p> <p style="padding-left: 20px;">Delayed hypersensitivity skin testing</p> <p>B. Advanced</p> <ol style="list-style-type: none"> 1. T-cell count (E-rosettes) 2. Lymphocyte transformation (phytohemagglutinin, concanavalin A, specific antigens) 	<ol style="list-style-type: none"> 3. Migration inhibition factor (MIF) production 4. Immunization studies (dinitrochlorobenzene, keyhole limpet hemocyanin) 5. Mixed lymphocyte cultures <p>C. Not recommended</p> <p style="padding-left: 20px;">Skin allografting</p> <p>V. Tests of B-cell function</p> <p>A. Screening</p> <ol style="list-style-type: none"> 1. Immunoglobulin levels 2. Schick test (for IgG function) 3. Isohemagglutinin titers (for IgM function) <p>B. Advanced</p> <ol style="list-style-type: none"> 1. B-cell count (EAC rosettes, surface immunoglobulins) 2. Immunization studies (typhoid, keyhole limpet hemocyanin, boiled sheep erythrocyte stromata) 3. Lymphocyte transformation (pokeweed mitogen) <p>C. Special</p> <p style="padding-left: 20px;">Immunoglobulin turnover studies</p> <p>VI. Effectors of immunity</p> <p>A. Complement (whole, components, inhibitors, inactivators, stabilizers, and others)</p> <p>B. Neutrophils (count, morphology, phagocytosis, nitroblue tetrazolium reduction)</p> <p>C. Macrophages (morphology, phagocytosis, chemotaxis)</p> <p>D. Overall—Rebeck skin window</p> <p>VII. Tissue examinations</p> <ol style="list-style-type: none"> A. Bone marrow aspiration B. Lymph node biopsy C. Rectal biopsy
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detailed history and physical examination and proceeds through routine laboratory studies, and finally to the sophisticated (and expensive) newer methods of studying the immune system. An outline of this approach is shown in the *Table*. It is generally not necessary to do all of the studies listed for any individual patient.

After obtaining a detailed history, physical examination, and routine laboratory studies, T- and B-cell function should be evaluated.

The major screening test for T-cell function is the application of a battery of intradermal delayed hypersensitivity skin tests. A typical group of antigens would be monilia, mumps, trichophyton, streptokinase-streptodornase, tuberculin purified protein derivative, and dermatophyton. Most normal adults will have positive reactions to one or more of the above antigens. If the skin tests are negative, advanced tests including T-cell count, lymphocyte transformation tests, MIF tests, and immunization tests (e.g., 2,4 dinitrochlorobenzene sensitization) will help to define the site of the defect. If bone marrow transplantation is contemplated, mixed lymphocyte reactions between cells from potential donor and recipient should be assessed. Skin allografting as a test of T-cell function is no longer done because of the potential hazard of introducing immunocompetent cells to a deficient recipient with subsequent production of graft versus host disease.

B-cell screening tests include measurement of serum immunoglobulin levels by radial immunodiffusion (IgM, IgG, and IgA) and functional tests for IgM (isohemagglutinin titers) and IgG (Schick test). If abnormalities are found, advanced tests including B-

cell count, lymphocyte transformation to pokeweed mitogen, and immunization studies should be performed. Turnover studies using isotopically tagged immunoglobulins are occasionally helpful in determining whether an immunoglobulin deficiency is due to decreased synthesis or increased catabolism.

After studying a few patients with immunodeficiency disease, it quickly becomes obvious that each patient is different and that there are very few "pure" cases of the syndromes listed above. With an approach such as the one suggested here, however, one can determine rather closely the nature of the defect in a given patient and rationally arrive at a suitable treatment program.

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