Diseases Associated with Immunosuppression
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Impairment of any of the major components of the immune system (T-cells, B-cells, phagocytes, complement) may result in clinical immunodeficiency. Immune defects can arise from intrinsic or heritable defects of lymphoid elements, failure of normal cellular differentiation, viral infection or other acquired causes. Clinical impairment of immunity is expressed as a marked susceptibility to opportunistic and pathogenic organisms which are difficult to control and by an increased risk of malignancy, allergy and autoimmune disease. Certain immunodeficiency disorders are associated with aberrant immune regulation. The major types of immune deficiency are characterized by unique patterns of infections depending on the level at which the defect occurs and the pathogenic mechanisms of the parasite. The basic defects of representative primary and secondary immunodeficiencies are discussed in relation to observed immunologic consequences.

Overview

Normal host defenses require the participation of four major immune systems: T-lymphocytes, B-lymphocytes, phagocytes and complement. Diseases associated with immunologic deficiency comprise a large group of disorders which are heterogeneous in their clinical expression and in their pathogenesis. It is possible to categorize immunodeficiency disorders in several ways (1). However, no completely satisfactory classification has thus far emerged. One approach is to distinguish between primary and secondary immunodeficiency (Table 1). Primary immunodeficiencies originate from a defect within one or more of the four immune systems. This group generally is subdivided into disorders of the T-cell system, the B-cell system or both B- and T-cells. Primary immunodeficiencies typically are hereditary and are manifest early in life as repeated infections caused by microorganisms which produce infections in normal children that are not serious. Secondary immunodeficiency may be defined as a disorder affecting host defenses in which the initiating factor arises outside of the immune system or is not restricted to immune elements. Secondary immune impairment occurs more frequently than primary immunodeficiency and commonly occurs in an older age group. Adenosine deaminase (ADA) and nucleoside phosphorylase (NP) deficiency can be considered in this category since the biochemical defect is not limited to lymphocytes. Excessive loss of lymphocytes or immunoglobulin from the gastrointestinal and genitourinary tracts or the lymphatic system due to congenital malformations, to surgical accidents, to disease or to other cause can also depress immunity. Another common cause of immunosuppression is infectious disease, especially viral disease, which impairs the function of lymphocytes or the development of lymphoid organs. The widespread use of immunosuppressive agents and cytotoxic drugs in recipients of organ transplants, cancer patients and patients with autoallergic disorders can lead to states of severe immunologic deficiency. Immunologic recovery following irradiation may require as long as a year. In protein-calorie malnutrition, a marked lymphopenia develops and defects in lymphocyte function may occur.

Recent advances have greatly improved our understanding of immunodeficiency disorders. The
advances include (1) the ability to isolate and identify distinct subpopulations of lymphoid cells, (2) the demonstration of functionally separate subpopulations of lymphocytes with unique surface antigens (2-5) and (3) the development of functional assays for the different lymphocyte subpopulations. These advances now permit immunologic defects to be localized to a particular developmental or regulatory pathway. Similar advances in leukocyte biology have identified and localized many defects in neutrophils, macrophages and the complement system. It should be emphasized that the various immune systems are closely integrated such that a defect in one system may have effects in other systems. Thus, deficient T helper cells may result in poor antibody responses. Improved understanding of the precise site of the defects in immune mechanisms could lead to a new classification of immunodeficiency based on mechanisms (Table 1). Already it is possible to distinguish several mechanisms of defects in specific and nonspecific immunity. For example, the defect can be intrinsic if an abnormality exists in hemopoiesis, lymphopoiesis or enzyme production, or there may be a failure in the differentiation pathway leading to effector T-cells or to antibody-secreting B-cells, resulting from abnormalities of the microenvironments which provide the short-range signals for T- and B-cell differentiation. Another likely possibility is that of disturbances of immune regulation involving T-cells, B-cells and macrophages. A second group of functional disorders are those that involve the nonspecific defense mechanisms. This latter group would include intrinsic defects in phagocytes affecting motility, phagocytosis or microbicidal mechanisms and defects in the system of complement proteins.

The principal manifestations of impaired host defenses are recurrent and severe infections caused by opportunistic microorganisms. These infections are difficult to treat with appropriate antibiotics. The types of infections provide important clues to the particular system(s) deficient in function (Table 2). For example, recurrent infections with encapsulated pyogenic bacteria could indicate a defect in either the B-cell system (immunoglobulin deficiency), the phagocyte system or the complement system. In contrast, patients with defective T-cell-mediated systems are especially susceptible to infections by intracellular parasites including fungi, bacteria and viruses, which present as pneumonia or as chronic infections of the skin, mucous membranes or other tissues. Complications of combined B- and T-cell deficiency generally are more serious than those caused by B-cell deficiency.

Table 1. Categories of impaired immune function.

| Category                                                                 | Immune Deficiency |
|-------------------------------------------------------------------------|-------------------|
| Primary immunodeficiency                                                | Defects of T-lymphocytes |
|                                                                          | Defects of B-lymphocytes |
|                                                                          | Combined T- and B-cell deficiency |
| Secondary immunodeficiency                                              | Multisystem biochemical defects |
|                                                                          | Loss of lymphocytes or immunoglobulin |
|                                                                          | Immunosuppressive infections  |
|                                                                          | Chemical or physical immunosuppression |
|                                                                          | Nutritional deficiency |
|                                                                          | Neoplasia |
| Defects of specific immune mechanisms                                   | Intrinsic defects of lymphoid cells |
|                                                                          | Impaired differentiation of lymphoid cells |
|                                                                          | Disorders of immune regulation |
| Defects of nonspecific defense mechanisms                                | Defects in phagocytosis or microbicidal killing |
|                                                                          | Defects of the complement system |

Table 2. Some complications of immunodeficiency.

| Defective system | Etiology                          | Pattern of infectious complications                                                                 |
|------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------|
| T-cells          | SCID, thymic hypoplasia, treated | Severe viral infections (chicken pox, measles, cytomegalovirus, herpessivirus)                      |
|                  | malignancy, immunosuppression     | Pneumonia caused by Pneumocystis carinii                                                            |
|                  |                                   | Opportunistic fungi (Candida, Aspergillus, Nocardia)                                                |
|                  |                                   | Intrauterine or post-transfusion graft-versus host disease                                           |
| B-cells          | IgG, IgM, or IgA deficiency       | Severe infections with pyogenic bacteria, hepatitis virus, ECHO virus, live poliovirus vaccine and protozoa (Giardia) |
| Polymorphonuclear leukocytes | Defective killing | Severe and/or recurrent pyogenic skin infections                                                     |
|                  |                                   | Superficial fungal infections                                                                       |
|                  |                                   | Chronic osteomyelitis (Klebsiella and Serratia sp.)                                                 |
| Complement       |                                   | Severe and/or recurrent pyogenic infections                                                          |
Immunodeficiency Associated with Intrinsic Defects in Lymphoid Cells

The most profound of the immunodeficiency diseases are included in a heterogenous group referred to as severe combined immunodeficiency (SCID), which is characterized by disorders in both the T-cell and B-cell systems (Table 3). The most severe of these is reticular dysgenesis arising from a defect at the level of hematopoietic stem cells which results in the virtual absence of T-cells, B-cells and neutrophils. In the Swiss type of SCID, lymphoid cells fail to develop, although hematopoietic stem cells are normal. T- and B-cells are greatly diminished, and neither responds to antigenic stimulation. Another type is SCID associated with a deficiency of adenosine deaminase (ADA). This enzyme deficiency prevents the conversion of adenosine to inosine and deoxyadenosine to deoxynosine, resulting in an accumulation of deoxy ATP, which is toxic, especially to lymphocytes. Some patients with SCID have normal numbers of B-cells. However, T-cell-mediated immunity is almost always deficient. Some cases of ADA deficiency have been reconstituted with red blood cell transfusions (7). The ADA in the red cells reduced the level of deoxy ATP and restored lymphocyte function. ADA-deficient SCID patients have also been successfully treated by bone marrow transplantation. Recently, Gelfand et al. (8) described a form of SCID with normal numbers of B- and T-lymphocytes. The lymphocytes from these patients failed to proliferate when stimulated in vitro. Investigation revealed that the lymphocytes were defective in lateral mobility of membrane receptors (frozen membrane) possibly caused by a defect in the assembly of cytoplasmic microtubules.

Another enzyme deficiency involves the enzyme purine nucleoside phosphorylase (PNP) which basically is a condition with impaired T-cell function but with normal B-cell function. The enzyme PNP catalyzes the conversion of inosine to xanthine and of guanosine to guanine in the purine catabolic pathway. The immunologic abnormalities in PNP deficiency consist of diminished delayed hypersensitivity responses, reduced numbers of circulating T-cells and reduced in vitro proliferative responses to mitogens, antigens and allogeneic cells. Serum immunoglobulin levels and antibody responses are normal. Evidence has been presented which suggests that deoxyguanosine triphosphate is a toxic metabolite responsible for the immunodeficiency (9).

Immunodeficiencies Involving Impaired Differentiation of Lymphoid Cells

Disorders thought to involve impaired maturation of T- and B-cells are listed in Table 4. Thymic hypoplasia (DiGeorge syndrome) is believed to result from an undefined intrauterine insult affecting the third and fourth pharyngeal pouches. Consequently, the microenvironment necessary for T-cell development fails to develop. Patients with the DiGeorge syndrome have increased susceptibility to sinusitis, recurrent pneumonia and diarrhea. The infections are often caused by Candida albicans and protozoa. The absolute lymphocyte count is usually normal, with a reduced percentage of T-cells and an increased percentage of B-cells. T-cell-mediated functions are decreased markedly, whereas B-cell functions are remarkably normal, considering that T-cells are required for initiation of immune responses to most antigens. Fetal thymus transplants have resulted in rapid restoration of T-cell function even when the thymus transplant was enclosed in a millipore filter, which suggests that a lack of thymic hormones may be responsible for this disease.

X-linked agammaglobulinemia is manifest by early onset of recurring infections with encapsulated pathogenic bacteria (i.e., staphylococci, pneumococci, streptococci and hemophilus) and with several viruses, specifically, hepatitis virus and enterovirus (ECHO virus and poliovirus). Patients

| Clinical diagnosis                  | Presumed level of basic defect | Immunologic defect | Cellular abnormalities | Functional deficiencies |
|------------------------------------|-------------------------------|--------------------|-----------------------|------------------------|
| SCID, reticular dysgenesis         | Hematopoietic stem cell       | T-, B-, and phagocytes | CMI, antibody, phagocytosis |
| SCID, Swiss type                   | Lymphocytic stem cell         | T-, B-cells        | CMI, antibody         |
| SCID with ADA deficiency           | Adenosine deaminase deficiency| T ± B cells        | CMI, antibody         |
| Purine nucleoside phosphorylase deficiency | Absent or abnormal enzyme     | T-cells            | CMI                   |

*After Waldmann et al. (6).
with this disorder exhibit low concentrations of all immunoglobulin classes except IgE. These patients lack circulating B-cells and plasma cells in sti-
mulated nodes. In contrast, the thymus is normal, and normal thymic-dependent areas are present in peripheral tissues. Evidence has been obtained which indicates that the defect occurs at the level of the transition from pre-B-cells to B-cells. Dosch et al. (10) demonstrated that a patient with X-linked disease possessed precursor B-cells which could develop surface IgM after a period of in vitro culture and that the transition from pre-B-cells to antibody-producing cells could occur in vitro.

Deficiency in transcobalamin II, a protein important in transport of vitamin B sub 12 in the blood, is associated with normal numbers of circulating B-cells and T-cells (11). However, plasma cells are absent and virtually no immunoglobulins or specific antibodies are produced. Following vitamin B sub 12 therapy the patient is able to make antibodies, suggesting that vitamin B sub 12 is necessary for the transformation of B-cells into immunoglobulin-producing plasma cells.

Common variable immunodeficiency comprises a heterogeneous group of disorders associated with high incidence of infections caused by encapsulated extracellular organisms and reduced immunoglobulins. One subgroup of common variable immunodeficiency apparently is caused by an intrinsic defect in B-cell differentiation. This inference is based on the demonstration that in vitro cultures of whole or separated cell populations stimulated with polyclonal B-cell mitogens did not synthesize or secrete immunoglobulin molecules (12).

Ataxia-telangiectasia is associated with recurrent sinopulmonary infections and an increased incidence of malignancy especially lymphoreticular tumors. Abnormalities of both T-cell and B-cell systems are present in most patients. The most prominent abnormality in the B-cell system is a deficiency of IgA and/or IgE. B-cells bearing surface IgA are present, which indicates that the defect probably is at the level of terminal differentiation rather than an inability to synthesize the alpha chain (H chain) of IgA.

Selective IgA deficiency is manifested by respiratory and gastrointestinal disease as can be expected because IgA plays an important role in humoral immunity of mucosal surfaces. Moreover, IgA deficiency is associated with an increased risk of allergy, autoimmune disease and carcinoma. Antibodies to IgA are relatively frequent in individuals lacking this immunoglobulin. In the majority of patients an intrinsic defect in the B-cell system leads to failure of IgA bearing cells to develop into IgA synthesizing and secreting plasma cells (13). An excess of IgA suppressor cells does not seem to play a role in IgA deficiency.

### Disorders Involving Abnormalities of Immunoregulatory Cells

Aberrant immunoregulation is postulated for several autoimmune diseases (14) and immunodeficiency. Data supporting this hypothesis have been obtained by various in vitro methods including: determination of T sub M (IgM Fc receptor) and T sub G (IgG Fc receptor) bearing T-cells, mitogen-driven B-cell immunoglobulin synthesis and use of monoclonal antibodies to T-cell differentiation antigens. Using monoclonal antibodies, Reinherz and colleagues (15, 16) demonstrated disturbances in

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*After Waldmann et al. (6).*

| Diagnosis                                | Presumed level of basic defect                | Immunologic defect | Cellular abnormalities | Functional deficiencies |
|------------------------------------------|----------------------------------------------|--------------------|------------------------|-------------------------|
| Thymic hypoplasia                        | Failure of thymic development                | T                  |                        | CMI± antibody           |
| X-linked agammaglobulinemia              | Failure of pre-B maturation ± suppressor T-cells | B                  |                        | Antibody               |
| Transcobalamine II deficiency            | Failure of B-cell differentiation, vitamin B sub 12 deficiency | Plasma cells | Antibody and phagocytosis |
| Common variable immunodeficiency (one type) | Failure of pre-B to B-cell maturation       | B                  |                        |                         |
| Ataxia telangiectasia                    | Thymic failure and failure of terminal maturation of B sub a, B sub c cells | T, IgA, IgE plasma cells | CMI ± antibody         |
| Transient hypogammaglobulinemia (infancy) | Impaired terminal differentiation of B-cells | Plasma cells       | Antigbody              |
| Selective IgA deficiency                 | Failure of terminal differentiation of B sub a | IgA plasma cells   | IgA antibody           |

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*Table 4. Immunodeficiency diseases involving impaired differentiation of lymphoid cells.*
the normal immune homeostatic mechanisms in several immunodeficiency diseases, autoimmune disorders and other conditions (Table 5). Four different patterns of T-cell disturbances have been distinguished. The first type consists of a deficiency of helper T-cells, which is observed in one type of common variable immunodeficiency. A second group of conditions includes acute graft versus host disease (GVH), scleroderma, Sjögren's disease, hemolytic anemia and sarcoidosis. This group is reported to exhibit excessive numbers of activated helper T-cells and reduced numbers of suppressor T-cells. The third pattern is that of reduced numbers of suppressor T-cells with adequate numbers of helper T-cells. This pattern is consistent with results obtained by others who have enumerated the T_M (helper) and T_G suppressor subsets or have used mitogen-driven antibody secretion assays for functional studies. A fourth pattern is that of quantitatively increased numbers of activated suppressor T-cells. In this subset of common variable immunodeficiency, the suppressor T-cell abnormality probably plays a primary role. This is suggested by experiments in which purified B-cells and monocytes from which T-cells had been removed were able to synthesize immunoglobulins in vitro. Moreover, unseparated lymphocytes from these patients synthesized IgM normally when they were cultured in the presence of hydrocortisone succinate, a drug which inhibits activation of suppressor cells (13).

**Immunodeficiency Associated with Lymphoreticular Malignancies**

Neoplasms of B- and T-cells frequently are associated with disorders of cellular or humoral immune mechanisms. These immunodeficiencies are of particular interest in relation to mechanisms of immune regulation. Several examples of B-cell and T-cell malignancies will be considered.

Chronic lymphoblastic leukemia (CLL) is a neoplasm characterized by the accumulation of excessive numbers of small lymphocytes in the blood, bone marrow or other tissues. In more than 95% of cases, the cells express surface immunoglobulin that is restricted as to heavy-chain type, light-chain type and antibody specificity. These findings indicate that the CLL cells are clonally derived. CLL frequently causes a secondary immunodeficiency which is characterized by decreased humoral responses and immunoglobulin levels together with some diminution of cell-mediated immunity (17). Decreased synthesis is the major factor in the reduced serum immunoglobulin levels (18). The cause of the decreased immunoglobulin production has not been defined, but does not appear to be caused by excessive suppressor T-cell activity (19).

Multiple myeloma is a disease characterized by monoclonal proliferation of plasma cells in the bone marrow and lytic bone lesions. Usually, serum or urine monoclonal myeloma paraproteins are present. The paraproteins represent a homogeneous population of immunoglobulins or Ig subunits, especially light (L) chains (kappa or lambda). In some cases myeloma proteins are found to have specific antigen binding activity, often directed against phospholipid moieties common to cell membranes.

In certain animal models, the proliferation of monoclonal plasma cells has been found to be regulated by T-cells and macrophages, similar to the amplification and suppression of normal B-cell differentiation. The function of residual polyclonal B-cells is often markedly impaired in patients with multiple myeloma leading to depression of humoral immunity and to reduced heterogeneity of Ig molecules in immunoelectrophoresis determinations. To a lesser extent, nonspecific host defenses and cell-mediated immunity also are impaired (20, 21). A summary of the immunologic abnormalities is shown in Table 6.

| Disease | Presumed abnormality | T4 * | T5 * | I_A * |
|---------|----------------------|------|------|-------|
| Subset of patients with common variable immunodeficiency | Deficient T_H cells | ↓ | n | n |
| Acute GVH, scleroderma, Sjogrens, sarcoid, hemolytic anemia | Excessive T_H cells (act.) with deficient T_S cells | ↑ | ↓ | ↑ |
| Systemic lupus erythematosis | Deficient T_S cells | n | ↓ | n |
| Subset of patients with common variable ID; infectious mononucleosis, cytomegalovirus, chronic GVH | Excessive T_S cells (act.) | n | ↑ | ↑ |

* n = normal numbers of a T-cell subset; I_A * = nonpolymorphic determinant of I-region associated-like protein; T_H = T_H cell antigen defined by a monoclonal antibody; T_S = T_S cell antigen defined by a monoclonal antibody.
Table 6. Immunologic features of multiple myeloma.

| Humoral immunity                                      | Non-specific host defenses                        | Cell-mediated immunity                           |
|-------------------------------------------------------|---------------------------------------------------|--------------------------------------------------|
| Serum paraproteins (80%)                              | Reduced levels of serum complement (Clq, C2, C4)  | Decreased ability to develop primary DH responses|
| Urinary paraproteins (50%)                            | Decreased granulocyte migration and adhesiveness  | Insufficient depression of delayed hypersensitivity to |
| Moderately reduced levels of nonmyeloma immunoglobulins| Decreased granulocyte lysozyme concentration      | common antigens                                   |
| Reduced or absent natural antibodies                   |                                                  |                                                  |
| Impaired antibody formation                            |                                                  |                                                  |
| Decreased synthesis and increased catabolism of immuno-|                                                  |                                                  |
| globulins                                               |                                                  |                                                  |
| Reduced numbers of circulating B-cells                 |                                                  |                                                  |
| Suppression of mitogen-induced immunoglobulin synthesis|                                                  |                                                  |

Recurrent bacterial infection is a common complication of multiple myeloma. Bacterial infection is the presenting feature in about 25% of myeloma patients (22) and may be the immediate cause of death (29). The major type of infections are pneumonia caused by pneumococci or staphylococci and urinary tract infections caused by gram-negative organisms (E. coli, Pseudomonas, Proteus and Kelbsiella) (24). The major immunologic defect observed in myeloma patients is in the humoral system. Broder and Waldmann (25) recently concluded that at least one mechanism for the humoral deficiency observed in myeloma patients is a block in polyclonal B lymphocyte maturation and immunoglobulin synthesis. However, these patients also have defects in antigen nonspecific host defenses that include dysfunction of granulocytes and of the complement system. These authors also conclude that if a clinically significant abnormality of cellular immune function exists, it is smaller in magnitude compared to deficiency of humoral immunity. In one study, untreated myeloma patients were found to have circulating suppressor cells that inhibited mitogen-induced immunoglobulin synthesis (26). The suppressor cells were Fc receptor-positive and nonphagocytic.

Hodgkin's disease is a malignant lymphoma which is associated with increased incidence of infection (27) and defects in T-cell-mediated immunity (28). The abnormalities of cell-mediated immunity and lymphocyte function are seen in a proportion of untreated cases with early disease (stage I and II). Moreover, the degree of depression is related to the clinical stage of disease, i.e., deficiency is more marked in advanced stages of disease (stage III and IV), independent of treatment (radiotherapy or chemotherapy) which is itself immunosuppressive. Pretreatment absolute lymphocyte counts are significantly correlated with clinical stage, skin test reactivity and life expectancy in Hodgkin's disease (29, 30). Reduced skin test reactivity to common microbial antigens or to primary sensitization with dinitrochlorobenzene (DNCB) is commonly observed (31-33). Decreased delayed hypersensitivity is not specific for any single antigen (anergy). In some cases, lymphocyte function as assessed by lymphocyte proliferation in vitro, is reduced at only low PHA concentrations (34). In more severe disease, decreased proliferative responses to all concentrations of PHA are observed (35). Significant reduction in the percentages of E-rosette-forming cells (T-cells) is an inconsistent finding (36, 37) which may be related to the occasional finding that patient plasma or serum can inhibit E-rosette formation (38) and lymphocyte transformation (39). The inhibitors present in plasma from active Hodgkin's patients may be due to the presence of T-cell antibodies (lymphocytotoxins) (40) or nonimmunoglobulins, especially lipoproteins.

Several investigators have suggested that excessive suppressor cell activity may be responsible for the immune deficiency in Hodgkin's disease. For example, Engleman et al. (41) reported that 41 of 70 (58%) of Hodgkin's disease patients had a disproportionate number of circulating suppressor cells capable of inhibiting mixed lymphocyte reactions. Goodwin et al. (42) obtained data indicating that the suppressors are glass-adherent, prosta
glandin E2-producing mononuclear cells, which suggests that macrophages are responsible for the suppression. Interestingly, a defect in the ability of peripheral monocytes from patients to ingest and kill Candida organisms by a myeloperoxidase independent system was reported recently (43).

The data strongly suggest that abnormal functioning macrophages are important in the pathogenesis of immunodeficiency in Hodgkin's disease.

Several neoplasms of immunoregulatory T-cells have been investigated in recent years. Sezary's syndrome is a form of T-cell lymphoma with circulating malignant cells which have a propensity for infiltrating the epidermis. About one half of Sezary syndrome patients have a homogeneous population of neoplastic but functional helper T-cells (44). Another interesting malignant disease of regulatory cells is a T-cell leukemia of adult onset which has been reported in Japan, near the site of an atomic bomb explosion on the island of Kyushu. In these cases there was no mediastinal mass. The leukemia cells were identified as T-cells on the basis of E-rosette formation and by cytotoxicity.
using a heterologous T cell antiserum. Japanese adult T-cell leukemia differs from Sézary syndrome in that typical Sézary cells are absent, cellular infiltration of the skin occurs in the dermis rather than the epidermis and infiltration of the bone marrow occurs.

Immunodeficiency Associated with Infectious Disease

Specific immunity to several viral diseases, such as herpes, measles, rubella and vaccinia depends on T-cell-mediated immunity. Primary or secondary immunodeficiency of the T-cell system is associated with recurrent and often fatal viral disease, as previously noted. Conversely, certain viruses themselves are immunosuppressive when they infect immunocompetent cells. The best examples of immunosuppression secondary to viral disease are the paramyxovirus infections (measles, mumps and influenza). In these viral infections, delayed hypersensitivity is depressed within the first few days and persists for several weeks. The exact mechanism responsible for anergy following measles infection remains uncertain. However, at least three mechanisms can be considered. First, measles virus infection produces a lymphopenia, leaving fewer effector cells available for eliciting delayed hypersensitivity reactions. Second, measles virus can infect stimulated and proliferating lymphocytes and thus may directly interfere with the function of lymphocytes which are engaged in specific immune responses. Third, measles virus may compete with antigen for receptors on the lymphocyte surface.

Depressed delayed hypersensitivity is also associated with certain bacterial and fungal infections, especially disseminated and granulomatous infections with intracellular organisms. Classic examples are miliary tuberculosis and active pulmonary tuberculosis, coccidiomycosis, histoplasmosis, blastomycosis and lepromatous leprosy (46). Anergy has been significantly associated with both lymphocytopenia and leukocytosis. However, functional abnormalities of lymphocytes or macrophages probably are responsible for anergy in these diseases. Several laboratories have studied the regulation of delayed hypersensitivity in experimental animal models (47-49). Transient suppression of delayed hypersensitivity can be accomplished by administration of specific soluble antigen to animals with established skin test responsiveness. Antigen-induced suppression of delayed hypersensitivity exhibits several features that resemble that seen in anergy. Animals sensitized to multiple antigens and challenged with mg quantities of a single specific antigen exhibit a profound, but transient, period of complete anergy which may persist for several days or weeks. This period of nonspecific unresponsiveness is followed by a second phase of hyporesponsiveness which is specific for the challenge antigen (49). Dwyer et al. (48) obtained evidence which strongly suggests that lymphocytes of a desensitized animal are competent but are actively suppressed in vivo. These investigators suggested that the products of stimulated suppressor T-cells exert a local effect on bystander lymphocytes (50). Presumably both specific and nonspecific suppressor factors are active at different times in order to explain both phases of anergy.

More recently, the relationship between granuloma formation and delayed hypersensitivity was studied in our laboratory (51). The results of this study indicated that dermal delayed hypersensitivity and allergic granuloma formation in the skin are both suppressed in sensitized animals following systemic challenge with specific antigen. In this model, pulmonary granulomas were unaffected. This data indicated to us that delayed hypersensitivity and allergic granulomatous responses which depend on circulating T-cells are controlled by the same regulatory system.

Immunodeficiency Associated with Autoimmune Disease

Immunodeficiency can occur in patients with B-cell hyperreactivity as in systemic lupus erythematosus (SLE). An increased risk of infection prior to therapy is likely, although firm evidence is lacking. Pyelonephritis, pneumonia and septicemia are relatively common. Organisms causing these infections typically are pyogenic bacteria, especially Staphylococci. Although the basis of this predilection of infections is uncertain, possible explanations could include low serum complement levels, abnormal leukocyte function and abnormalities in regulatory T-cells. Individuals with IgA deficiency seem to be predisposed to develop autoantibodies and autoimmune disease. This association may be the result of an inability of the host to prevent the entrance of antigens from mucous surfaces that are sufficiently similar to autologous antigens to induce an immune response to autologous tissue antigens or both.
Disorders Involving Excessive Loss of Immunoglobulins and Lymphocytes

Hypoglobulinemia may result from loss of protein into the urinary and gastrointestinal tract (Table 7). Loss of protein into the urine occurs when there is a defect in the renal glomerular membrane or in renal tubules. In nephrotic syndrome there is selective loss of the 7S immunoglobulins (IgG, IgA, etc.) with little or no loss of 19S IgM.

Protein can also be lost into the gastrointestinal tract; however, this rarely leads to clinically evident immunodeficiency. Intestinal lymphangiectasia is an exception because in this disease, loss of immunoglobulins is accompanied by loss of lymphocytes secondary to abnormalities of lymphatic channel development or other disease processes. Patients with this disorder have abnormalities in both cellular and humoral immunity. Serum concentrations of IgG, IgM and IgA are reduced although the rate of synthesis is normal. The defect in cell-mediated immunity is more profound than that in humoral immunity. These patients become markedly lymphopenic and are depleted in long-lived lymphocytes, which is analogous to thoracic duct drainage, a well-known and effective immunosuppressive procedure.

Disorders of Neutrophilic Phagocytes

Neutrophils are short-lived cells which are specialized for ingestion and destruction of certain classes of microorganisms. Failure of chemotaxis (directed locomotion), phagocytosis or intracellular killing results in increased susceptibility to opportunistic infections with bacteria; however, patients do not generally experience difficulties with viruses or protozoa.

Disorders of neutrophil function may be divided into intrinsic and extrinsic defects (Table 8). In chronic granulomatous disease (CGD), granulocytes and monocytes are deficient in NADH or NADPH oxidase or NADPH reductase. The defect in killing appears to be at the level of post-phagocytic oxygen metabolism involved with the generation of hydrogen peroxide (H₂O₂) or O₂·. Organisms causing infection in CGD are almost always catalase producers (e.g., Staphylococcus aureus, Serratia marcescens, Aspergillus). Catalase-producing organisms rapidly destroy hydrogen peroxide, whereas catalase-negative organisms, such as pneumococci, do not destroy the available hydrogen peroxide of the phagocyte which the cell uses to effect microbial killing, most likely by interaction with myeloperoxidase and halide (32).

Chediak-Higashi syndrome is a rare multisystem disorder. The striking morphologic disorder consists of giant cytoplasmic inclusions derived from azurophilic granules (lysosomes) which are present in many cells, including granulocytes and monocytes. Both types of phagocytes are deficient in microbial and chemotactic activity. A primary defect in tubulin affecting microtubule polymerization and degranulation has been suggested as the basis of the disorder.

Extrinsic causes of neutrophil dysfunction are numerous and are often related to leucopenia or decreased opsonization, abnormal chemotaxis or other defects. When the total number of functioning neutrophils is reduced below a critical level (~1000/µl), infection is likely to ensue. Leukopenia is frequently drug-induced. Anti-inflammatory drugs (e.g., corticosteroids) characteristically induce abnormalities in neutrophil adherence and migration in addition to many other actions. Another mechanism is the premature destruction of neutrophils resulting from formation of neutrophil antibodies, as in autoimmune neutropenia, which may cause removal of neutrophils via antibody-dependent lymphocyte-mediated cytotoxicity (ADCC). In drug-induced immune neutropenia, the cells may absorb drug-antibody immune complexes which may result in neutrophil destruction via an innocent bystander mechanism.

Abnormal phagocytosis can be secondary to a large number of other disorders. In diabetes, for example, chemotaxis and bacterial ingestion is decreased. Decreased phagocytic function is also

| Diagnosis                                | Presumed level of basic defect                        | Immunologic defect            |
|------------------------------------------|------------------------------------------------------|-------------------------------|
| Familial hypercatabolic hypoproteinemia  | Hypercatabolism of serum proteins                     | Decreased Ig levels           |
| Myotonic dystrophy                       | Hypercatabolism of IgG                                | Decreased IgG levels          |
| Nephrotic syndrome                       | Sieving property of glomerular membrane               | Decreased IgG levels          |
| Intestinal lymphangiectasia              | Disorder of lymphatic channels with loss of lymph fluid and cells | Diminished CMI ± A_b           |
secondary to burns, alcoholic cirrhosis malnutrition and sickle cell disease.

Myeloperoxidase deficiency in leukocytes can be hereditary or secondary to refractory anemias or leukemias. In some cases, an increased susceptibility to Candida or staphylococci have been noted. Myeloperoxidase reduces hydrogen peroxide and in the presence of intracellular halide (iodine) leads to production of a lethal substance, as previously mentioned. The intracellular killing of these organisms in vitro is delayed compared to normal leukocytes.

### Disorders of the Complement System

The physiologic role of complement is clearly illustrated by the diseases which occur in complement deficiency states or when complement is activated under inappropriate circumstances. Patients with deficiencies in early components of the classic pathway (i.e., Clq, C1s, C4, and C2) have increased susceptibility to systemic lupus erythematosus or other collagen vascular diseases. This finding may indicate the role of complement in efficient destruction of viruses or in the removal or inactivation of some types of immune complexes. Complement C3 and C3b deficiency is associated with recurrent infections with pyogenic bacteria. About half of patients with deficiencies of the terminal components, i.e., C5, C6, C7 and C8, have recurrent infections with Neisseria organisms (gonococci and meningococci), apparently because cytolsis with these organisms is complement-dependent.

In conclusion, clinically apparent immunodeficiency is associated with frequent and persistent infections. Recurrent infections with the same organism or with organisms of low pathogenicity together with an incomplete response to appropriate antibiotics are suggestive of impaired immunity. Other features of certain immunodeficiency disorders include an increased risk of malignancy, autoallergic disease and allergy. Specific hereditary immunodeficiencies manifest additional anatomic and constitutional features. Impaired T-cell immunity generally is more serious than deficient B-cell immunity. In secondary immunodeficiency, normal function generally is restored once the underlying disease or condition is corrected.

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