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Cellular Immunity

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Cellular immunity is mediated by specifically activated lymphocytes and serves to enhance nonspecific immune functions. Unlike immunoglobulins which generally enhance protection against circulating or cell-free microorganisms or toxins, the cellular immune response has evolved to rid the host of infected or otherwise altered *host cells*. Cell mediated immunity (CMI) is responsible, therefore, for resolution or prevention of infection caused by intracellular bacteria (*Listeria monocytogenes*), certain viruses, fungi, and protozoa, and mycobacteria. CMI is also responsible for rejection of foreign tissue grafts and for elimination of some cancer cells.

These responses have been previously termed "delayed hypersensitivity." This phenomenon, however, is just one manifestation of CMI, although the first to be recorded. In the early 1800s, Jenner observed erythema and induration in the skin of individuals approximately 24 hours after inoculation of his cow pox vaccine in those who had had small pox or who had been previously vaccinated. Koch then studied the reaction in great detail in the host response to infection with tuberculosis. But it was not until the early 20th century that Landsteiner and Chase determined that delayed hypersensitivity was due to specific cells. Other workers subsequently determined that lymphoid cells previously exposed to the antigen in question are required for speci-

ficity but that macrophages were required to effect the response. In addition, if the thymus of the animal was removed, normal development of cellular immunity was impossible.

This chapter will explore the development and maturation of cellular immunity and its constituents, the thymus, lymphocytes and their products, and macrophages; in addition, the major congenital and acquired CMI deficiency states will be summarized.

BIOLOGY OF CELLULAR IMMUNITY

The thymus is responsible for converting hematopoietic stem cells into immunocompetent lymphocytes, which it supplies to the rest of the body. The thymus is formed along with the parathyroid glands from specialized epithelial cells lining the third and fourth pharyngeal pouches. As the thymus migrates in early embryonic life to its final location in the anterior part of the mediastinum, stem cells begin to enter it. The epithelial thymus appears to secrete hormones at this stage which initiate this migration. Once under the influence of the thymic environment, these cells differentiate into small lymphocytes and multiply rapidly as they migrate from cortex to medulla. From the medulla, thymic lymphocytes (T lymphocytes) enter the bloodstream bound for peripheral lymphoid tissues. The thymus gland elaborates other humoral substances which

enhance the functional capability of its daughter lymphocytes in extrathymic locations. T lymphocytes exit the circulating bloodstream and collect in the deep cortical areas of lymph nodes and cuffs around the small straight arteries of the spleen. After transient residence in these thymic-dependent areas of the peripheral lymphoid tissues, T lymphocytes enter the lymphatics and via the lymphatocovenous communications, reenter the bloodstream. This circular traffic pattern does not include a revisit to the thymus. Recognition of foreign substances by both B and T lymphocytes is apparently accomplished by surface receptor units. It is thought that each lymphocyte carries surface receptors capable of combining with a single antigen or a small group of closely related antigens. Receptors on B lymphocytes are clearly established as immunoglobulin molecules. Specific antigen receptors on T lymphocytes may also be immunoglobulins or immunoglobulin-like molecules. On contact with the appropriate antigen, B lymphocytes divide and differentiate into plasma cells and T lymphocytes are stimulated to begin a complex series of events, including secretion of several biologically active factors and transformation into blast cells. Lymphoblast transformation is followed by division into two daughter T lymphocytes bearing surface receptors for the same antigen as that to which the parent is responsive. In this way, "immunologic memory" is established in the form of an expanded population of lymphocytes capable of recognizing and initiating the immune response to the antigen. Lymphoblast transformation and products of lymphocyte factors by T lymphocytes may also be stimulated nonspecifically by plant mitogens such as phytohemagglutinin (PHA).

SUBPOPULATIONS OF T LYMPHOCYTES

Studies of cell surface membrane receptors and of cell functions indicate there are at least six functional subpopulations of T lymphocytes. These have been labeled *helper T cells*, *suppres-*

sor T cells, *antibody-dependent cytotoxicity T cells*, and *natural killer cells*, as well as two types of *primary effector cells*. Helper T cells enable B lymphocytes to differentiate into antibody-secreting plasma cells. This effect is particularly important when the B cell has been stimulated by certain antigens, typically proteins, referred to as T cell dependent antigens. T cell help is more necessary for production of IgA, IgE, and IgG antibodies than for production of IgM antibodies. T helper cells also enhance T cell maturation when stimulated by specific or nonspecific triggers.

Suppressor T cells act as regulators of B cell maturation, inhibiting the process and thereby controlling production of antibody. Suppressor T cells are thought to play a role in other immune regulatory phenomena including immunologic tolerance and antigen competition. Antigens presented to T cells in limited amounts appear to lead to T helper activation whereas excessive amounts of antigen induce T suppressor activity.

Lymphocytes which lack typical T or B receptors (Null cells) but which have Fc receptors recognize antibodies on infected cells and lyse them. This mechanism is known as antibody-dependent cell-mediated cytotoxicity (ADCC). A fourth type of T lymphocyte is the natural killer cell. These cells require no specific antigenic stimulation, but are able to lyse infected or cancerous cells (1). Their activity is enhanced by interferons. Two other types of effector T lymphocytes are produced upon specific stimulation; T killer cells are capable of lysing infected or "foreign" cells (no antibody required). The second effector cell produces lymphokines, a conglomerate of biologically active factors with a variety of functions.

LYMPHOKINES

On stimulation with specific antigens or appropriate mitogens, both T and B lymphocytes produce lymphokines. At least a dozen such substances have been described, primarily in terms of the activity they promote rather than their physical-chemical properties. It seems likely, therefore, that some of the different activities

may be mediated by the same substance. Nevertheless, the elucidation and partial purification of several of these lymphokines have provided at least a tentative explanation of how T lymphocytes communicate with macrophages, and other lymphocytes to achieve the eventual rejection of invading microorganisms, foreign tissue, or cancer cells.

One of the best defined lymphokines is migration inhibitory factor (MIF), so named because it inhibits migration of macrophages from capillary tubes. The assay is performed in the following manner: A suspension of macrophages, sensitized lymphocytes from immunized donors in a sensitizing antigen are placed in capillary tubes; the cells are packed by centrifugation; and the extent of migration out of the open tube is measured. Lymphocytes and antigen can be removed to show that migration of a purified macrophage preparation can be inhibited by the cell-free supernatant of a mixture of sensitized lymphocytes and antigen or by a thermostable acidic glycoprotein purified from this supernatant. This protein may be responsible for the activation of the macrophages as well. Chemotactic factors for both macrophages and neutrophils have been demonstrated in lymphocyte-antigen supernatants using Boyden chemotaxis chambers. These factors are distinct from each other and from MIF. Cytotoxic or lymphotoxic factors have been described which are able to cause the death and lysis of target cells in culture. Mitogenic or blastogenic factors can be prepared by stimulating the sensitized lymphocytes from an immunized donor with specific antigen; the supernatants call sensitized lymphocytes to transform into lymphoblasts and divide. Soluble factors that can enhance or suppress antibody production have been described. Interferon elaborated from virus-infected or antigen-stimulated lymphocytes can inhibit virus replication in other cells. Leukocyte inhibitory factor acts to inhibit the migration of polymorphonuclear leukocytes. These and the other substances summarized by Rocklin (2) elicit responses from or effect other components of the immune

system. Lymphokines are then products which amplify the host response to a given antigen or insult with a purpose of mounting a concentrated effort to maintain homeostasis.

ROLE OF THE MACROPHAGE

The peripheral blood monocyte is transported from its birthplace in the marrow to its eventual home in the reticuloendothelial system where it becomes a free or fixed mononuclear phagocyte or macrophage; this process may include a sojourn in the thymus (3). Two divergent roles have been proposed for macrophages; whether the same cells participate in each is unclear. The first and more primitive role is that of a phagocytic killer cell. The second role is regulation of the immune response; in many instances the two roles are interrelated.

In a nonimmune host, macrophages initially come in contact with new antigens in regional lymphoid tissue. Foreign material is engulfed and may either be destroyed or persist in the cytoplasm. Antigens are somehow "processed" and remain on the surface of the macrophage. These cells then "present" the antigen to T or B lymphocytes to initiate lymphocyte activation and effector processes described above. During certain infections, these cells come under the influence of an intense stimulus and develop morphologic and functional alterations indicative of a state of activation. The morphologic changes consist of increased cell size and increased numbers of mitochondria, lysosomal granules, and fluid-filled vesicles with the cell. In terms of function, activated macrophages exhibit increased pinocytosis, enhancing spreading on glass, and, most importantly, increasing the killing of microorganisms.

The principal infections resulting in macrophage activation are due to organisms which are pathogenic because they can survive inside phagocytic cells, viz, viruses, fungi, parasites, and bacteria such as *Brucella*, *Listeria*, and *Mycobacterium*.

It is clear from the work of Mackaness and others that the small lymphocyte is integrally involved in the process of

macrophage activation (4). It has been shown, for example, that the transfer of small lymphocytes from an animal immune to the tubercle bacillus enables the recipient to rapidly accumulate activated macrophages at sites of tuberculous infection, as if the recipient himself were immune. Moreover, the state of enhanced immunity which has been transferred is specific for the immunizing antigen; it can be elicited only by exposing the transferred lymphocytes to that antigen. However, once the macrophage has been activated, it exhibits a nonspecific increase in microbicidal activity which may be directed against any organism. Thus, an animal which received tubercle bacilli along with lymphocytes from a donor immune to tuberculosis becomes resistant to challenge with *Listeria* because of the activated macrophages which are developed. In other words, sensitized lymphocytes generated by prior exposure to an antigen can, on exposure to that antigen, excite previously resting macrophages to a state of activation during which they have enhanced microbicidal activity for any organism.

The mechanism by which macrophages become activated has not been elucidated. However, it has been shown that purified MIF can induce in cultured macrophages some of the morphologic, metabolic, and functional alterations that comprise the activated state, including an increased capacity for ingestion and killing of bacteria. Thus, it seems likely that it is through MIF that sensitized lymphocytes induce macrophage activation.

By synthesizing what is known of macrophage activation with what is known about the activity of lymphocytic factors in vitro, it is possible to construct a hypothetical model of the events which surround the body's resistance to infection by intracellular microorganisms in the immune host. Since these organisms have the ability to survive inside phagocytes, phagocytosis by polymorphonuclear leukocytes would not halt the infection, even in the presence of adequate antibody levels. Within 12 hours, T lymphocytes would be attracted to the area and would encounter the invading organism. As a re-

sult, lymphokines would be elaborated which would expand the cellular immune response. Lymphocytotoxin might directly injure the invader. Chemotactic factor might recruit macrophages which could become activated and more microbicidal on exposure to MIF. If the invader were a virus, interferon would block its replication in infected cells. These events would be amplified in time by the replication of immune T lymphocytes, possibly enhanced by mitogenic factor and perhaps enhanced by the instruction of other T lymphocytes through the action of transfer factor, which could convey specific recognition capabilities to neighboring cells. Depending on the balance between the inoculum size and the virulence of the infecting organisms and the rate and intensity of the host response, the infection would be eliminated or would spread systemically.

Macrophages may also control T lymphocyte responses. At least in certain in vitro situations, lymphocyte response to mitogen and antigen are suppressed when macrophages comprise greater than 50% of the mixture. Whether this phenomenon occurs in vivo, has not been elucidated.

CELL-CELL COOPERATION

T and B lymphocytes interact directly with one another, with macrophages, and with antigens during the response to foreign substances or altered self substances. Inherent in these reactions are two basic principles: 1) recognition of antigens that are different from self, and 2) communication among autologous cells, ie, B-T cell interactions. In humans, each of these phenomena are dependent on the HLA (Human Leukocyte Antigen) system, a series of antigens which are expressed on chromosome 6 and appear to be associated with immune responses.

HLA antigens are present on all cells (except erythrocytes). This label was first studied in relation to the development of cancer in animals, but soon was recognized to be of prime importance in transplantation rejection.

The immune response to infection was subsequently found to be under the same

genetic control as the HLA system. In fact, it has been hypothesized that this system of identification of host cells evolved as defense against virus infections became important (5). Viruses replicate in animal cells by using the host's genetic material and production apparatus. Thus, virus antigens frequently become fused with host antigen. A system of discrimination to recognize virus-infected cells vs noninfected cells appeared to be necessary so that host defense mechanisms could intervene in a selective manner. The HLA system fulfills the criteria of identifying normal host cells, so that cells with additional antigen or altered host-antigen (infected cells) may be removed.

Experiments in both human and animal subjects have shown the Tk function (cell-mediated cytotoxicity) is dependent on HLA (A, B) identity between lymphoid cells and infected cells. Thus, lymphocytes must recognize both normal and altered antigens on infected cells (6).

Another type of genetic restriction found in the HLA region of chromosome 6 is based on another antigen called Ia. Ia may control cell-cell interaction per se, but not cytotoxicity reactions. In other words, communication between T and B cells, T cells and macrophages, and T-T cell interactions may be specifically related to Ia, rather than HLA-A or B. This requirement appears to be independent of the presence of antigens.

CLINICAL EVALUATION

It is clear from the study of patients and animals with defective cellular immunity and from correlated laboratory research that cellular immune mechanisms are required for defense against infection by intracellular parasites, including fungi, viruses, and some bacteria. Therefore, even in the presence of adequate amounts of antibody, deficient T lymphocyte function leaves the host susceptible to persistent or life-threatening disease due to microorganisms which are mildly pathogenic or even commensal in the normal host. For example, candidiasis may be severe and chronic in spite of all therapy, or

a patient may die of generalized vaccinia following smallpox vaccination, of disseminated herpes simplex infection, or of fulminant chickenpox or measles. Conversely, no better evidence of normal T lymphocyte function can be obtained than the history of a normal response to chickenpox, herpes zoster, measles, or live-measles virus vaccine. (It should be emphasized at this point that live virus vaccines should never be administered to an infant with possible immune deficiency.) Since contact hypersensitivity is a manifestation of cellular immunity, history of poison ivy or other contact allergy also indicates normal T lymphocyte function at the time of the event.

Further investigation of patients whose history suggests defective cellular immunity should begin with determination of the absolute lymphocyte count, x-ray of the chest for the thymic shadow, and application of skin tests for delayed hypersensitivity, as summarized in Table 1. Antigens used for skin testing should be stored in the lyophilized state at 4 C and reconstituted shortly before use, care being taken that the expiration date has not been reached. The injection of 0.1 ml should be made intradermally with a 25- or 27-gauge needle. Reactions should be examined at 4 to 6 hours for the appearance of an antibody-mediated Arthus reaction, which could be confused with a delayed hypersensitivity response. Most infants who have received two DPT (diphtheria, pertussis, tetanus) immunizations should have a positive delayed reaction to tetanus toxoid (7), and most children over 12 months of age should have a positive delayed response to Candida antigen and streptokinase-streptodornase (SKSD). Tetanus toxoid should be used at a 1:100 dilution; if the response is less than a 5-mm induration, a 1:10 dilution should be administered. Candida and Trichophyton antigens should be diluted 1:100 before use in adults and 1:10 for children but should be given undiluted if the initial testing is negative. Streptokinase-streptodornase should be given at a concentration of 5 units of streptokinase per 0.1 ml; if no reaction occurs, 40 units should be given. A positive response to any of the

TABLE 1. Clinical Assessment of Cellular Immunity

Method	Material	Normal Finding
History		Poison ivy, contact hypersensitivity No difficulty with thrush, viral infections, or vaccines
Lymphocyte counts	Peripheral blood	>4,000/cu mm in first year; >2,000/cu mm in childhood
Chest x-ray		Visible thymus
Skin tests	<i>Candida</i> (Hollister-Stier)	>5-mm induration after 48 hr
	SKSD (Varidase) (Lederle)	>5-mm induration after 48 hr
	<i>Trichophyton</i> (Hollister-Stier)	>5-mm induration after 48 hr
	PPD, histoplasmin, coccidioidin	>5-mm induration after 48 hr
	Tetanus toxoid (Lilly)	>5-mm induration after 48 hr

SKSD, streptokinase-streptodornase; PPD, purified protein derivative.

skin test antigens suggests strongly that cellular immunity is intact.

T lymphocytes can be identified and enumerated in samples of blood or lymphoid tissues. One convenient technique for distinguishing T lymphocytes from B lymphocytes is by virtue of the chance discovery that T lymphocytes can bind sheep erythrocytes (8). In this assay, the lymphocyte mixture is incubated at a 1:100 ratio with sheep erythrocytes at room temperature for 30 minutes and then overnight in the refrigerator. The cells are then resuspended by gentle mixing and examined by counting the percentage of lymphocytes which bind sheep erythrocytes in a rosette pattern. This procedure is referred to as the E-rosette or T-rosette assay. T cells can also be directly enumerated by their reaction with antiserum to the antigens found on T lymphocytes but not on B lymphocytes.

T cells can also be identified by specific membrane antibodies or by rosetting with IgM or IgG coated erythrocytes yielding T_H (helper) or T_S (suppressor) subjects respectively (9).

If the delayed hypersensitivity skin tests are negative, other tests of cellular immune function must be employed, since skin tests may be negative in a small percentage of otherwise normal individuals, especially if they have a concurrent viral illness. Measurement of the response of peripheral blood lymphocytes to PHA is a valuable screening test for T lymphocyte abnormalities. When the PHA induces lymphocytes to undergo blast transforma-

tion and divide, radiolabeled nucleic acid (eg. tritiated thymidine) is incorporated into new cells as DNA. The culture is terminated by precipitating the cellular material with acid, and the precipitated radioactivity count reflects the amount of nuclear material formed. Lymphocytes from patients with defective cellular immunity respond subnormally to the mitogenic effect of PHA. A variety of other stimuli can be used to activate lymphocytes in culture, including specific antigens and cells of a second individual, ie. in the mixed lymphocyte culture.

MIF and other lymphokine activity, as well as T cell subset function, may be determined by the assays mentioned above in which patients' lymphocytes are tested in the presence of antigen to which the lymphocytes have been exposed.

SYNDROMES OF DEFICIENT CELLULAR IMMUNITY

In respect to pathogenesis, it is artificial to separate all defects of cellular immunity into one category distinct from defects of immunoglobulin synthesis. However, an absence or even a partial depression of cellular immunity bears common and severe clinical consequences which dominate the symptomatology and the problems of management. Moreover, these syndromes illustrate most of the basic concepts described above. Therefore, for the purposes of this discussion, all syndromes of deficient cellular immunity have been grouped and subdivided, as summarized in Table 2, according to

TABLE 2. Defects of Cellular Immunity

Abnormality	Diagnostic Studies	
	Suggestive	Confirmatory
Without immunoglobulin deficiency		
Chronic mucocutaneous candidiasis	<i>Candida</i> skin test	Lymphocyte transformation (normal); MIF
Thymic hypoplasia	Thymic shadow; skin tests; immunoglobulins (normal); calcium	Lymphocyte transformation; parathormone response; E rosettes
Thymic dysplasia with abnormal immunoglobulin synthesis	Thymic shadow; skin tests; immunoglobulins and antibodies; lymphocyte counts	Lymphocyte transformation; E rosettes
Secondary deficiencies	Thymic shadow; skin tests; immunoglobulins and antibodies; lymphocyte counts	Lymphocyte transformations to nonspecific and specific stimuli
Combined with immunoglobulin deficiency		
Severe combined immunodeficiency	Thymic shadow; skin tests; immunoglobulins and antibodies; lymphocyte counts	Lymphocyte transformation; E rosettes; adenosine deaminase, nucleoside phosphorylase assays
Immunodeficiency with dwarfism	Thymic shadow; skin tests; immunoglobulins and antibodies; lymphocyte counts; bone x-rays	Lymphocyte transformation; E rosettes
Ataxia-telangiectasia	Skin tests; immunoglobulins; lymphocyte counts	Lymphocyte transformation
Wiskott-Aldrich syndrome	Skin tests; immunoglobulins; lymphocyte counts; isohemagglutinins; platelet count	Lymphocyte transformation (normal to PHA); antibody response to polysaccharides
Immunodeficiency due to enteropathy	Skin tests; immunoglobulins; lymphocyte count; albumin	Gastrointestinal tract studies
Immunologic amnesia	Skin tests; immunoglobulins; lymphocyte count	Lymphocytotoxic antibody; response to antigens
Thymoma	Skin tests; immunoglobulins; lymphocyte count; chest x-ray	Surgery

MIF, migration inhibitory factor; PHA, phytohemagglutinin.

whether or not there is an associated immunoglobulin deficiency.

Without Immunoglobulin Deficiency—Chronic Mucocutaneous Candidiasis

Patients with this disorder suffer chronic and severe candidiasis of the buccal mucosa, tongue, vagina, nails, and skin. Invasion of deeper tissues rarely occurs. Many endocrinologic abnormalities have been associated with this entity, often appearing years before or after the onset of chronic candidiasis. The more common ones include hypoparathyroidism. Less common are diabetes, pernicious anemia, and gonadal dysgenesis. This relationship has not been explained, but

these patients have an increased incidence of antibodies to mitochondria, parietal cells, or adrenal, ovary, thyroid, or parathyroid tissue.

Evaluation of cellular immunity has given variable results from patient to patient: almost all patients have had a negative *Candida* skin test; many have had a negative response to other delayed hypersensitivity skin tests; and lymphocytes from most have transformed normally in vitro on exposure to PHA or specific antigens including *Candida albicans*. It has been shown that some patients' lymphocytes may lack the ability to elaborate MIF on exposure to *Candida*. This deficiency may account for the failure of local surface immunity in the presence of nor-

mal lymphocyte transformation on exposure to the organism. Treatment of the endocrinopathy, if present, may cure the candidiasis; no other treatment, including toxic doses of amphotericin B, has given more than temporary relief. However, it has been demonstrated that if lesions have been cleared with amphotericin B therapy, their recurrence may be suppressed by the administration of transfer factor obtained from donors with normal cellular immunity to *C albicans*; this treatment may prove effective for some patients.

Thymic-Parathyroid Hypoplasia

Faulty embryonic development of the third and fourth pharyngeal pouch epithelium can result in congenital absence of the epithelial thymus and the parathyroid glands. Infants with this disorder suffer tetany and recurrent severe infections, including meningitis, septicemia, peritonitis, subcutaneous abscesses, and pneumonitis due to bacteria, viruses, or *Pneumocystis carinii*. Diarrhea, persistent mucopurulent rhinorrhea, oral candidiasis, and growth retardation are other common manifestations. Developmental abnormalities of related anlagen and their clinical consequences have been a prominent part of the syndrome and have included, in various combinations, esophageal atresia, right-sided aortic arch, congenital heart defects, thyroid hypoplasia, and facial anomalies, consisting of micrognathia, shortened philtrum of the upper lip, midline cleft of the nose, high-arched or cleft palate, hypertelorism, and malformed, asymmetric, or low-set ears. The glands may be hypoplastic rather than absent, in which case the tetany and recurrent infections are less severe and may disappear in time.

Although a tragic birth defect, in its complete form the syndrome of thymic-parathyroid hypoplasia has represented an opportunity for delineation of the role of the thymus and T lymphocytes in human immunity. Indeed, patients have been found to lack all in vitro and in vivo manifestations of T lymphocyte-mediated immunity, including positive reaction to

delayed hypersensitivity skin tests, lymphocyte transformation by PHA or antigens, MIF production, graft rejection, and resistance to viral, fungal, and bacterial infection. Immunoglobulin levels may be normal or even elevated. The quality or quantity of the antibody response in these patients has not been clearly elucidated. The few who have been studied when not deathly ill have had a normal primary response to a variety of antigens but have had another primary response rather than a secondary response on restimulation with the same antigen. As was predicted from studies of the role of the thymus in experimental animals, implantation of fetal thymus tissue into the abdominal wall has restored T lymphocyte function and the ability to resist severe infection in patients with the syndrome. There is evidence that the thymic implant supplies a humoral factor that enables stem cells to mature into T cells.

Several children with this affliction (also known as DiGeorge's Syndrome) who were immunodeficient at birth, have spontaneously regained immune function after 3 to 4 months of life. The cardiac defect may dictate the final outcome in these patients.

Thymic Dysplasia With Immunoglobulin Synthesis

As originally described by Nezelof, this disorder was believed to represent thymic dysplasia (irregularly organized epithelial stromal cells with few lymphocytes and no Hassall's corpuscles) with complete sparing of antibody-producing machinery, i.e., a pure T lymphocyte defect like that of thymic aplasia but due to an abnormally functioning thymus. As additional cases have been described, however, it has been shown that these patients do not synthesize antibodies normally in spite of their normal immunoglobulin levels. Moreover, other patients with the pathologic picture of thymic dysplasia have had either deficient IgG and IgA and normal IgM, isolated IgA deficiency, or another partial immunoglobulin defect. In one instance, the partial defect differed in two siblings. Some of these pa-

tients have lived beyond 2 years of age. Their clinical pictures have been very similar no matter what the immunoglobulin pattern. Thus, it is not possible to separate these disorders on meaningful clinical grounds. In regard to etiology, this disorder could result from abnormal T cell and B cell interaction or a basic stem-cell defect.

Secondary Cellular Immune Deficiencies

Diminished but not absent cellular immunity may also accompany lymphoma, chronic lymphomatic leukemia, lepromatous leprosy, sarcoidosis, congenital rubella, primary biliary cirrhosis, protein malnutrition (10), and commonly steroid or antimetabolite therapy. Some patients with these disorders have also had deficient antibody production.

With Immunoglobulin Deficiency: Severe Combined Immunodeficiency

The primary defect in this disease in most instances is unknown. Successful therapy with transplanted bone marrow, as well as defects in B and T lymphocyte function have supported the concept of a stem-cell defect. Many of these patients may have immature T or B cell activity and an abnormally functioning thymus, suggesting a spectrum of defects to account for this syndrome (11, 12).

Affected infants begin within their first 6 months to exhibit intractable diarrhea, wasting, candidiasis, persistent morbilliform rash, and frequent localized and generalized infections due to almost any virus, bacterium, or fungus. Many have died of vaccinia, chickenpox, or measles. The thymus cannot be seen on chest x-rays; homograft rejection, dermal delayed hypersensitivity, and in vitro lymphocyte functions usually are completely lacking; and the levels of circulating small lymphocytes and all immunoglobulins are very low.

The disease may appear in families as an autosomal recessive or X-linked recessive gene defect, or it may occur sporadically. The X-linked recessive type has tended to have milder clinical and patho-

logic changes; lymphocyte counts have occasionally been nearly normal in this form. Transplantation of histocompatible bone marrow cells (usually from a sibling) or liver cells from very young fetuses have repaired the combined immunodeficiency in several affected children.

Deficient activity of the enzyme adenosine deaminase (ADA) has been reported in red blood cells and lymphocytes from several children with severe combined immunodeficiency. These patients have the same clinical problems but also may have bony abnormalities resembling rachitic rosary and flaring of the ends of the ribs on x-ray. Heterozygous carriers of this autosomal recessive defect are unaffected clinically but can be detected by enzyme studies. Prenatal diagnosis is possible by analysis of amniotic fluid fibroblasts. Some of these patients have been treated successfully with intermittent transfusions of irradiated red blood cells, which are rich in ADA. Deficiency of a second enzyme, nucleoside phosphorylase, has been described in a few patients with severe combined immunodeficiency. Both of these enzymes are involved in purine metabolism (13).

Recently several children with CNS dysfunction, candida dermatitis, keratoconjunctivitis, and alopecia who had absent skin test and in vitro lymphocyte responses to *C. Albicans* have been described. One child had absent IgA and absence of antibody production when immunized with pneumococcal polysaccharide vaccine at age 3 years. An abnormality in biotin-dependent carboxylase function was suspected on the basis of metabolic acidosis and excessive excretion of appropriate metabolites in the urine. Treatment with biotin was associated with clinical improvement, but immune function remained depressed (14).

Immunodeficiency with generalized hematopoietic hypoplasia (reticular dysgenesis) is a rapidly fatal variant in which both lymphocytes and granulocytes are lacking, perhaps because of a faulty stem cell for both of these elements of the hematopoietic system.

Although no specific relationship between immunodeficiency syndromes and

the HLA system has been detected, one patient with SCID who completely lacked HLA-A and B surface antigens has been described. It was hypothesized that lack of these antigens adversely affected development of the immune system (15).

Immunodeficiency With Short-Limbed Dwarfism

The clinical and pathologic findings of severe combined immunodeficiency have been found in association with dwarfism resembling, but not identical to, achondroplasia. Some affected children have also had ectodermal dysplasia or neutropenia.

A milder form of the disorder has occurred with cartilage-hair hypoplasia, a syndrome of short-limbed dwarfism and abnormally fine hair. Such children have had recurrent bacterial respiratory infections, including pneumonia, and have nearly died of chickenpox.

Immunodeficiency With Ataxia-Telangiectasia

Children with this autosomal recessive syndrome of ataxia and oculocutaneous telangiectasia often, but not invariably, develop chronic sinusitis and progressive bronchiectasis. Almost all have an immunologic deficiency state which varies from patient to patient but is usually characterized by 1) partial immunoglobulin defects (most frequently deficient IgA, less commonly deficient IgE and IgG) and 2) "blunted" cellular immunity manifested by depressed but not absent lymphocyte transformation by PHA, prolonged rejection of skin grafts, cutaneous anergy in most cases, and lymphopenia in some cases, but no difficulty with candidal, viral, or other fungal infections, including vaccinia. The thymus at autopsy has shown consistent abnormalities, including the absence of Hassall's corpuscles. Lymphoreticular and other malignancies have occurred frequently in these children.

Immunodeficiency With Thrombocytopenia and Eczema (Wiskott-Adrich Syndrome)

The syndrome of eczema, thrombocytopenic purpura, and recurrent infections occurs in boys as an X-linked recessive trait. As in ataxia-telangiectasia, there are associated immunoglobulin defects (deficient IgM, elevated IgA and IgE), lymphopenia, blunted cellular immunity, and a propensity to develop malignancy. Unlike ataxia-telangiectasia, however, the thymus at autopsy is normal, the antibody response to polysaccharide antigens is abnormal (eg, isohemagglutinins are deficient), and patients may suffer severe or lethal infections due to viruses and fungi, although bacterial infections tend to predominate early in life.

Mild Combined Immunodeficiency Due to Enteropathy

Intestinal lymphangiectasia is characterized by protein-losing enteropathy with mild fat malabsorption, hypoalbuminemia, edema, panhypogammaglobulinemia, lymphocytopenia, and, in some patients, failure to thrive.

The disease is due to dilated intestinal lymphatics which permit the loss of protein and lymphocytes into the bowel lumen. The same condition, although usually in a milder form, may be associated with Whipple's disease, regional enteritis, or constrictive pericarditis.

Most patients with the disorder do not have undue susceptibility to infection even though cutaneous anergy and failure to reject skin grafts are the rule. When frequent infections occur, they tend to be mild and confined to the respiratory tract in adults, but in children they may be systemic, chronic, and lethal. The infecting organisms are bacteria; apparently, the small numbers of normal lymphocytes that are present are adequate to resist viral and fungal infection.

Several patients have experienced elevation of serum protein levels and lymphocyte counts, as well as weight gain, on a diet rich in medium-chain triglycerides.

84 INFECTIONS IN CHILDREN

Episodic Lymphopenia With Lymphocytotoxin (Immunologic Amnesia)

The administration of antilymphocyte serum (ALS) to humans or animals can inhibit both primary and secondary antibody responses and suppress the development of cellular immunity.

A syndrome of recurrent severe bacterial and viral infections, eczema, and episodic lymphopenia in which the immunologic findings resemble closely those of ALS-treated animals has been described. Affected children have been capable of initiating primary lymphocyte-dependent responses such as rejection of skin grafts and transformation with PHA, but they have lacked immunologic "memory" so that they do not manifest delayed hypersensitivity reactions to commonly encountered antigens and mount no more than a short, transient, primary type of antibody response on repeated stimulation with the same antigen. There has been a depletion of lymphocytes from thymus-dependent areas of lymph nodes and spleen and a normal (although involuted) thymus in cases studied at autopsy. A complement-dependent lymphocytotoxic factor (probably antibody) has been found in patients' serums during episodes of lymphopenia. Quantitation of serum immunoglobulins has shown a consistent abnormality: IgA levels have been markedly elevated, IgM levels have been low or absent, and IgG levels have been normal or elevated.

Immunodeficiency With Thymoma

Thymoma is a usually benign tumor which develops in the fourth to eighth decades of life. Some patients with thymoma have acquired pan-hypogammaglobulinemia or a partial immunoglobulin defect 1 or 2 years before or after the discovery of the tumor on chest x-ray. Most of these patients have suffered recurrent infections, particularly bronchitis and pneumonia. Lymphocytopenia with skin anergy and prolonged skin graft rejection, aregenerative anemia, eosinopenia, and myasthenia gravis have

also occurred concomitantly; the interrelationships between these, the hypogammaglobulinemia, and the thymoma have not been elucidated.

THERAPY

Therapy for the cell-mediated deficiency syndromes is unsatisfactory at best. The most successful form of therapy is bone marrow transplantation. Until recently, this form of therapy had been reserved for children with SCID and no immune function so that engraftment would take place. Marrow from an HLA-identical sibling was required to prevent a graft vs host reaction. Bone marrow transplantation after irradiation and chemotherapy in syndromes with residual immune function has now succeeded in other immunodeficiency syndromes, ie, Wiskott-Aldrich. This form of therapy is still experimental, however.

If the patient has a combined defect, replacement of immunoglobulins is the only routine therapy available. Treatment of the immune defect per se is often only palliative or designed to augment immune function because the primary defect is unknown. The principles of these forms of therapy are summarized elsewhere in these volumes.

REFERENCES

1. Moller G (ed): Natural killer cells. *Immun Rev* 44, 1979
2. Rocklin RE: Mediators of cellular immunity. In Fundenberg HH, Stites DP, Caldwell JL, Wells JV (eds): *Basic and Clinical Immunology*. Los Altos, Ca: Lange, 1980, p 144
3. Jones JF, Meyskens FL, Nagle R: The human thymus: I. Partial characterization of non-lymphoid cells. *Thymus* 2:147, 1980
4. Mackaness GB: The mechanism of macrophage activation. In Mudd S (ed): *Infectious Agents and Host Reactions*. Philadelphia: Saunders, 1970, p 61
5. Zinkernagel RM, Doherty PC: MHC-restricted cytotoxic T cells: Studies on the biological role of polymorphic major transplantation antigens determining T cell restriction-specificity, function and responsiveness.
6. Benacerraf B, Unanue ER: *Textbook of Immunology*. New York: McGraw-Hill, 1974

- nology. Baltimore. Williams and Wilkins, 1979, p. 125
7. Franz ML, Carella JA, Galant SP: Cutaneous delayed hypersensitivity in a healthy pediatric population: Diagnostic value of diphtheria-tetanus toxoids. *J Pediatr* 88:975, 1976
 8. Ross GD, Winchester RJ: Methods for enumerating lymphocyte populations. In Rose NR, Friedman H (eds): *Manual of Clinical Immunology*. Washington, DC: American Society for Microbiology, 1980, p 213
 9. Moretta L, Ferrarini M, Cooper MD: Characterization of human T cell subpopulations as defined by specific receptors for immunoglobulins. *Contemp Top Immunobiol* 8:19, 1978
 10. Carney JM, Warner MS, Borut T, et al: Cell-mediated immune defects and infection: A study of hospitalized children. *Am J Dis Child* 134:824, 1980
 11. Cooper MD, Percy DY, Peterson RDA, et al: The two-component concept of the lymphoid system. In Bergsma D, Good RA (eds): *Immunologic Deficiency Diseases in Man*. New York: The National Foundation, 1968, p 7
 12. Pyle KW, Dosch H-M, Ipp MM, et al: Demonstration of an intrathymic defect in a case of severe combined immunodeficiency disease. *N Engl J Med* 293:424, 1975
 13. Ammann AJ, Hong R: Disorders of the T cell system. In Stiehm ER, Fulginii VA (eds): *Immunologic Disorders of Infants and Children*. Philadelphia: W.B. Saunders, Inc., 1980, p 286
 14. Cowan MJ, Packman S, Wara DW, et al: Multiple biotin-dependent carboxylase deficiencies associated with defects in T-cell and B-cell immunity. *Lancet* 2:115, 1979
 15. Touraine JL, Betuel H, Souillet G, et al: Combined immunodeficiency disease associated with absence of cell-surface HLA-A and -B antigens. *J Pediatr* 93:47, 1978