VOLUME 2

PROGRESS IN CLINICAL IMMUNOLOGY

EDITED BY

Robert S. Schwartz, M.D.

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Preface

Since the first volume of *Progress in Clinical Immunology* appeared, several important advances have been made. Among the most interesting of these is work on the nature of the lymphocyte membrane, and especially the immunoglobulins found on the surfaces of B cells. Identification of these constituents of the membrane has numerous implications. For example, the demonstration of antigen-specific immunoglobulin receptors on lymphocytes—which, incidentally, confirms Paul Ehrlich's brilliant insights—permits an appreciation of the power of the clonal selection theory of the immune response. And, as an immediate consequence of this, our understanding of certain lymphoproliferative disorders as disturbed clones of lymphocytes is clarified. Moreover, the development of relatively simple means of enumerating T and B cells has resulted in an explosive growth of the literature, with no end in sight.

These technics, when coupled with certain tests of lymphocyte function, allow an extraordinarily complete and entirely in vitro assessment of the immunologic capabilities of human subjects. When compared to methods available ten years ago, the results are nothing short of revolutionary. Two reviews in this volume deal with these important matters. In the first, Preud'Homme and Seligmann take up the question of surface markers on lymphocytes, and in the second, Rocklin analyzes the extensive literature on the in vitro assessment of lymphocyte function. Taken together, these two articles review one of the most dynamic and rewarding areas of immunological research.

Recently, I had the most interesting experience of participating in the treatment of Col. Bruton's historic patient with agammaglobulinemia. Now in his thirties, he required an adjustment in the schedule of γ-globulin injections. He is an assistant manager of a bank and is an unusually well informed and instructive patient. His case, reported in 1952 by Bruton in a masterful example of clinical observation and reasoning, was one of the seminal discoveries in contemporary immunology. Twenty-two years later, the field of immunological deficiency diseases is fluorishing. In this volume, two aspects of the problem are reviewed. Hong surveys the interesting associations between *apparently* unrelated,

but simultaneously occurring congenital disorders, one of which is an immune deficiency and the other a bizarre failure of development involving cells unrelated to the lymphoid system. Hitzig and Grob take up the very complex problem of transfer factor, an as yet unidentified, dialyzable substance found in lymphocytes that can transmit cellular immunity from one person to another. Discovered over 20 years ago, the status of transfer factor as a treatment of deficient cellular immunity is still mired in uncertainty. Hitzig and Grob conclude that the major reason for this is our ignorance of the chemical nature of transfer factor. This means that standardized, reproducible investigations of its therapeutic value are not yet possible. However, the pace of investigation into transfer factor has quickened substantially, and it seems reasonable to predict a breakthrough within five years.

Three other topics have been selected for this volume. Their diversity indicates the sweep of modern immunology. Costanza and Nathanson extensively review carcinoembryonic antigens. Sir Peter Medawar has recently written, "I feel that the discovery of cross-reactivity between tumor and embryonic antigens is the best lead we have had in cancer research since the discovery of syngeneic tumor immunity, because it offers a possible way out of the impasse of strict antigenic specificity and individuality of tumors—properties which, if they were true without qualification, would virtually prohibit the use of tumor antigenicity for diagnostic or therapeutic purposes."* It now appears that, at least in some cases, the detection of fetal antigens may have value in the diagnosis of cancer, but as Costanza and Nathanson have pointed out, the situation is far more complex than originally envisioned.

Although the NZB mouse is not, strictly speaking, a "clinical" subject, it has provided many valuable insights into autoimmune diseases of man. This, in fact, is the point of view taken by Talal in his review. A particularly interesting development is the role of the suppressor T cell in preventing autoimmunization. Now that the NZB model has elucidated this important possibility, a burst of research dealing with suppressor T cells in humans can be anticipated.

Finally, aficionados of complement should be tempted by the review of Petz and Garratty, which deals with that subject in the context of immunohemolytic anemia. It is now evident that, in many instances, coating by an immunoglobulin cannot by itself lead to the premature destruction of an erythrocyte. Although the role of complement in this process is complex—a complexity which the uninitiated may find all the more difficult because of the nomenclature—the subject is nevertheless becoming more accessible to the generalist, thanks to the clarifying research on immunohemolytic anemia.

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*Medawar, P. Introduction to session on cross-reactive antigens. Cancer Res. 34:2053, 1974.

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Contents

Richard Hong

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Immunodeficiency: Enigmas and Speculations

The immune mechanism is but one of the vast array of biologic systems which operate in concert with each other to maintain the support of life. Derangements in one system affect the others: often cause and effect are predictable and proximate. In other cases, the relationships are ill defined. The enigmatic and more speculative aspects of the immune system's interrelationships with other body systems comprise the substance of this chapter.

Development of normal immunity involves the appropriate maturation and differentiation of cell systems which ultimately arise from the bone marrow. Some of the cells develop under the influence of the thymus gland, and hence are known as T cells. Others mature independently of thymic factors and are designated B cells. In addition to T and B cells interacting with each other and with macrophages, B cells further combine with humoral systems such as complement, and T cells elaborate a number of substances known as lymphokines. The result of these secondary phenomena is to generate inflammatory tissue reactions, mobilize white cells, macrophages, and other elements to augment host defenses and more efficiently contain or eliminate invading organisms. These interrelationships have been recently reviewed.[1,2]

From the foregoing it can be seen that immunodeficiency disorders would result from defects in any number of the diverse mechanisms involved in attaining competent immunity.

In addition to defense processes dependent upon immune mechanisms, granulocytes play a major role in protection. However, defects of the granulocytes and complement disorders will not be considered in this discussion.

Although the precise pathogenetic mechanisms are unknown, many of the well-described immunodeficiency syndromes are felt to represent a failure of development of B cells or T cells or both. Isolated T cell deficiency states may simply be due to a lack of thymic development. The DiGeorge syndrome is thought to represent an embryologic fault of the III and IV pharyngeal pouches with maldevelopment of the thymus and parathyroid glands.[3] Successful correction of the defect by thymic transplantation supports this theory.[4,5] In contrast to

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Table 1-1
Enigmatic Relations of the Immune System

1. Well-defined syndromes not thought to involve primarily the lymphoid apparatus but associated with immunodeficiency
   A. Ataxia-telangiectasia
   B. Exomphalos-macroglossia-gigantism (Wiedemann-Beckwith syndrome)
   C. Omenn's disease
   D. Short-limbed dwarfism
      1. Cartilage-hair hypoplasia
      2. Other forms
2. Deficiency due to unclear mechanisms
   A. Adenosine deaminase deficiency
   B. Antibodies to immune elements
   C. Chronic mucocutaneous candidiasis and lepromatous leprosy
   D. Protein calorie malnutrition
3. Effects of immunodeficiency on nonlymphoid systems
   A. IgA deficiency
   B. T suppressor cell deficiency

these obvious relationships, B and T cell deficiency states have now been observed in a number of well-defined syndromes which seem to bear no relation to the immune system in terms of the major organs involved in the primary disorder. Anomalies involving the skeletal system comprise one such group. It is the purpose of this discussion to point up a number of these associations and provide speculation as to their relation to immune disorders. I will also discuss unusual disease processes which result in deficiency and instances in which deficiency states have resulted in complications extending beyond the lymphoid apparatus (Table 1-1).

DIAGNOSIS OF DEFICIENCY STATES AND ASSESSMENT OF IMMUNITY

These matters are extensively discussed in recent publications,[1,6-8] and only a few pertinent comments will be included here. The morphology of the thymus, spleen, and lymphoid tissues of the gut and peripheral nodes is of great importance in assigning deficiency to T or B cell systems or both. In evaluating these studies it is important to remember that many diverse processes can result in a single pathological picture. Thus, the etiology is not always immediately apparent from histological assessment. A prime example is found in thymic studies. The embryonal thymus without thymocytes and Hassall's corpuscles was for many years considered the primary organ at fault in all forms of T cell deficiency. In vitro studies of Owen and Ritter,[9] however, clearly show that the thymus cannot develop normal morphology without appropriate lymphoid invasion. Thus, the marked hypoplasia of the thymus seen in nearly all T cell deficiencies can be a secondary as well as a primary fault.

As will be discussed in greater detail later, not all in vitro tests of T and B cells can with certainty define a fundamental fault of the cellular machinery. A simple viral infection can result in in vitro tests of lymphocyte function of sufficient abnormality to suggest a severe congenital deficiency state. Yet the function returns to normal when the infection resolves.[10,11]

The point in the natural evolution of the disease process at which examination is accomplished is of great significance in postulating the nature and degree of the defect. In many disorders (severe combined immunodeficiency, for example) the defect is of such magnitude and death occurs so early that pathological examination is virtually unchanged regardless of the time of performance. In others, the disease assumes a stable or at worst only a slowly deteriorating course so that, again, tissue assessment remains essentially unchanged regardless of when it is performed. In a number of instances, however, the pathological changes are not static. Progressive diminution of immunologic capability or other changes with time are seen. For example, a characteristic immunoglobulin distribution consisting of marked elevation of serum IgA and decrease in serum IgM is seen in the Wiskott-Aldrich syndrome.[12] Early in the course of the disease, however, immunoglobulin levels may be normal. Progressively more severe changes in the lymphoid morphology occur with time.[13] (See also ataxia-telangiectasia below.) Therefore, it is incumbent upon the investigator to consider the various tests of immune function in the context of general state of health, presence of possible confounding factors, and possibility of progressive changes with time.

It is also now apparent that subpopulations of T and B cells exist.[14] In older studies T cell function was assessed solely on the basis of thymus and lymph node morphology plus counts of peripheral blood lymphocytes. The various in vitro tests of lymphocyte function assess the different subpopulations to varying degrees —thus several different stimulatory agents must be used—mitogens (phytohemagglutinin), bacterial or fungal antigens as well as histocompatibility antigens. When several different methods are used, it is apparent that diseases involve the subpopulations to different degrees.[15,16] In vitro assessment must also be supplemented by in vivo tests since, again, disparity has been observed.[17] It seems quite likely that some of the mysterious associations to be described will become more understandable with more extensive characterization of the immunologic defect(s).

WELL-DEFINED SYNDROMES

Ataxia-Telangiectasia

Ataxia-telangiectasia, first described in 1926,[18] is characterized by a number of neurological faults of which ataxia is the most prevalent and usually the presenting symptom. It was not until some 30 years after the original description, however, that Boder and Sedgwick[19] pointed out the high frequency of sinopulmonary infections in the disorder. Further investigation led to the observation of T cell, selective IgA, and combined IgA and IgE deficiencies in these patients.[20–22] The high frequency of malignancy observed as a terminal event may also be due to immunodeficiency.

Of unusual interest in the syndrome is the development of endocrine abnormalities. Ovarian dysgenesis,[19] testicular atrophy,[23] abnormality of growth hormone response,[24] and pathologic changes in the anterior pituitary[23] have been observed. An unusual form of diabetes characterized by insulin resistance, absence of ketosis, hypersecretion of insulin, and hepatic disease was noted by Schalch et al.[25]

The T cell deficiency in ataxia-telangiectasia is the most constant immuno-

logic aberration. Other faults, such as those involving IgA, are present in 60 to 80 percent, and IgE deficiency is even less common. Progressive decline in immunologic capability occurs with the passage of time. For example, Cawley and Schenken[26] studied a patient with ataxia-telangiectasia over a 5-year period. When first evaluated, the peripheral blood lymphocyte count and serum immunoglobulins were normal. Later, profound changes in immunoglobulin amounts and electrophoretic behavior were noted. IgM became monoclonal as IgA disappeared and IgG became markedly reduced. Significant lymphopenia occurred simultaneously. The gradual loss in lymphoid function seen in ataxia-telangiectasis is not readily understood. One explanation may relate to the continuous assault upon lymphoid tissue as a result of recurrent infections. Eckstedt[27] has shown that a severe wasting syndrome with virtually complete destruction of the lymphoid apparatus occurs as a result of injecting killed bacterial vaccines into the thymus. Although in his experiments it was necessary to perform the injections within the first day of life of these otherwise normal animals, an analogous mechanism might still obtain in man if continuous stimulation by infectious agent occurred in patients with originally compromised immune systems. Exhaustion or attrition can be seen when the T-cell reservoir is ablated. Infectious agents will produce wasting in neonatally thymectomized mice; maintenance in a germ-free environment prevents the lymphoid exhaustion.[28] Stimulation by Freund's adjuvant or endotoxin similarly has been shown to produce lymphoid depletion.[29]

It is important to stress that lymhpoid attrition syndromes may require one of two conditions. The assault could occur in utero or in early neonatal life before massive lymphoid proliferation and dissemination of T cells occurred, or the assault could occur at any time in an individual whose original T and/or B cell mass was diminished. In diseases such as ataxia-telangiectasia, the original complement of immune clones might be less than that of normal or be unable to expand in response to increased stimulation with age and greater antigenic exposure. Thus, the lymphoid tissue could be envisioned as being consumed with time, unable to replenish itself.

Evidence for such a mechanism in man derives from a number of observations. In a case studied by West et al.,[12] a child undergoing intense stimulation because of a hypersensitivity reaction to milk showed marked lymphadenopathy in the axillary, cervical, and inguinal areas. Lymphoid hyperplasia was so marked that a malignancy was suspected. Ig levels were elevated to 2–3 times normal values. Removal of milk from the infant's diet was attended by complete regression of the hyperplastic lymphoid tissue. Ig levels fell progressively and finally reached almost nondetectable levels. Over a 12-month period the Ig's slowly returned to normal. Since the patient's inherent immune apparatus was intact, it is assumed that recovery was possible on this basis. A child recently studied by us with severe combined immunodeficiency syndrome had normal levels of Ig's, although no functioning antibody was produced. During a 1-year observation period repeated bouts of sepsis and one episode of *Pneumocystis* pneumonia occurred, and his Ig levels fell to barely detectable values. Further evidence of restricted clonality of the Ig-producing cells was demonstrated by the monoclonal character of the Ig's which were essentially all IgG3, lambda, and Gm (f+) (studies performed by Dr. S. Litwin, New York, New York). A 19-month-old-boy, apparently normal except for thrombocytopenia, suddenly developed cutaneous

candidiasis and massive bleeding. A blood transfusion resulted in graft-versus-host disease, attesting to T cell deficiency. His sister developed progressive loss of immunologic function manifested by decrease in Ig levels and development of lymphopenia. Thus, after a normal infancy she too succumbed to sepsis at 2 years of age. A process of immunologic attrition was suggested.[30]

There is yet a third mechanism by which lymphoid attrition may occur. We have been impressed by the variability in onset of symptoms, the progression of symptoms with time, and the multiple organ systems involved in ataxia-telangiectasia. One mechanism by which multiple effects might occur at varying rates would relate to autoagression. Ammann and Hong[31] showed autoantibodies in 8 of 18 patients with ataxia-telangiectasia. Antibodies to smooth muscle, mitochondria, thyroglobulin, parietal cells, and tubular basement membrane were seen. The finding of common antigenic determinants of T cells and brain cells, the brain-associated theta antigen,[32] is most provocative in considering the gradual decline in neurologic and lymphoid function. Could an autoantibody directed against theta or theta-like antigens possibly be important in producing both progressive T cell and CNS deterioration?

Another unifying hypothesis for the myriad of manifestations seen in ataxia relates to a fault of mesenchymal development. The mesenchymal fault is manifested by the vascular abnormalities and also results in defective differentiation of the thymus gland.[33] While this hypothesis does not explain the progressively changing nature of the disease or the progressive neurological and immunological deficiencies, further support is lent by the recent observation of elevated alpha-1 fetoprotein values in patients with ataxia-telangiectasia.[34] Fifty-five percent of patients with ataxia-telangiectasia have significant liver disease and the elevation of alpha-1 fetoprotein is presented as evidence for failure of liver maturation. Thus, ataxia-telangiectasia might also be considered a state of persistent immaturity of several systems due to inappropriate mesodermo-ectodermal relationships in utero.

Exomphalos-Macroglossia-Gigantism (EMG) Syndrome

This disorder, first described in 1963, is characterized by visceromegaly, omphalocele, hypoglycemia, macroglossia, and somatic gigantism.[35] Combined immunodeficiency (CID) also was recently reported.[36] T cell immunity was diminished in all parameters. Tests of B cell immunity revealed only a modest diminution in total immunoglobulin levels; however, functional assessment revealed no evidence of specific antibody formation. Family history and postmortem tissue examination indicated that the patient's two brothers were probably also afflicted with a severe immunodeficiency syndrome—one died of necrotizing *Pseudomonas* pneumonia and the other of giant cell pneumonia. Neither of the brothers possessed the phenotype of the EMG syndrome. Since immunoglobulin production was present and, in fact, was at normal levels for IgA, the defect was midway in severity between severe combined immunodeficiency without any significant immunoglobulin production and pure T cell deficiency with functional immunoglobulin production. It was suggested, therefore, that perhaps the major defect was in the T helper cell population.

An intriguing possibility is that the basic fault in the EMG syndrome relates

to abnormal epitheliomesodermal interaction during development. In most cases, this abnormality results in disturbances of organ growth (somatic gigantism). Intrauterine visceromegaly would prevent fusion of the abdominal skin resulting in omphalocele; the uncontrolled growth potential would be expressed in other organs, such as the tongue, by macroglossia. In other structures in which appropriate epitheliomesodermal interaction is important, such as the thymus, failure of normal development could result in T-dependent immunodeficiency. However, the morphology of the thymus is not such that this aberration can be distinguished from other conditions of thymic deficiency.

As in cartilage-hair hypoplasia, the immunodeficiency associated with EMG seems to be a rather uncommon manifestation. Documented deficiency has been observed only in 3 of 100 reported cases; however, exhaustive immunologic testing has not always been performed. In 2 other cases, atrophy of the thymus and splenic follicles was described.[37]

Omenn's Disease

In 1965, Omenn described an infant with a generalized skin eruption, hepatomegaly, lymphadenopathy, and eosinophilia whose illness was rapidly fatal.[38] Twelve other affected children were found in a family study, and the incidence suggested an autosomal recessive mode of inheritance. The disease was called familial reticuloendotheliosis with eosinophilia and has subsequently been referred to as Omenn's disease. The association of an immunodeficiency disorder was first suggested by Cederbaum et al.[39] and subsequently by Barth et al.[40] Detailed immunologic testing was not performed, but abnormalities of the thymus and lymphoid tissue consistent with the diagnosis of combined immunodeficiency were observed both in 2 patients in Omenn's original series and in the cases described by Cederbaum and Barth. Death from *Pneumocystis carinii* pneumonia in the propositus in Omenn's series and in Cederbaum's patients is also extremely suggestive of a defective immunologic apparatus.[38,39]

Although eosinophils are normally thought to be increased in situations of hypersensitivity and results of studies of their mechanism of accumulation imply attraction by antigen-antibody complexes or activation by sensitized lymphocytes,[41,42] eosinophilia in immunodeficient states is probably related to another phenomenon. We[36,43] and others[44] have observed an increase in eosinophils during infection which has been interpreted as representing a primitive response in an individual incapable of the normal cellular mobilization mechanisms in response to invasive processes.

In contrast to usual immunodeficiency states, the lymphoid tissue in Omenn's disease is markedly enlarged. However, the morphology of the lymph nodes shows considerable derangement. Rather than the normal architecture of highly stimulated nodes with active germinal center, and lymphoid follicle formation with the development of many mature plasma cells, these nodes are filled by a monotonous sheet of histiocytes. This observation has led to the erroneous diagnosis of Letterer-Siwe's disease or histiocytosis X. It now seems clear that the syndrome bears no relation to histiocytosis X, in which immunologic deficiency has not been described. Furthermore, the histiocytes observed in Omenn's disease do not have the malignant characteristics of those in Letterer-Siwe's disease. Another inter-

pretation of the lymphoid morphology would be that a primitive cell unable to differentiate appropriately within the lymphoid apparatus is stimulated to proliferation and fills an empty node incapable of developing normal architecture. The lymph nodes in Letterer-Siwe's disease do not show complete replacement by histiocytes. In Omenn's disease replacement by histiocytes is observed not only in the lymph nodes but also in the spleen. The thymus abnormality is indistinguishable from other T cell deficient states. There is fatty infiltration and absence of both Hassall's corpuscles and lymphocytes.[39,40]

The association of a generalized erythematous, papulovesicular, and desquamative skin eruption with heavy scaling in the area of the scalp and eyebrows had also suggested a clinical similarity to histiocytosis X. Skin biopsy showed infiltration of the corium by eosinophils, lymphocytes, and histiocytes with surrounding inflammation of the blood vessels and skin appendages—a microscopic picture inconsistent with that of histiocytosis X. Although extensive data concerning the histopathology of the cutaneous eruption is not available, the association of total alopecia—including the eyebrows—is highly suggestive of intrauterine graft-versus-host disease. The histopathology of this disorder, however, is not always absolutely diagnostic. Dyskeratosis, lymphocytic infiltration of the epidermis, and confinement of the cellular infiltrate to the upper layers of the corium are some of the more distinctive features,[45,46] but differentiation from other chronic dermatoses can be quite difficult.

The establishment of the diagnosis of intrauterine graft-versus-host disease is of great importance since it can be present only in the face of T cell deficiency of the host and, therefore, would serve as further evidence of the immune deficiency. The proof of graft-versus-host disease in the absence of convincing morphologic data can best be obtained by the demonstration of lymphoid chimerism. In the case of male infants, the demonstration of XX/XY chimerism of the leukocytes proves the presence of two populations of cells. The female population can only have been derived from the mother while the patient was in utero or from a blood transfusion given postnatally. The survival of these cells proves the child's deficiency and provides support for the clinical diagnosis of cutaneous graft-versus-host disease.[47] When the affected patient is a female, proof of the chimerism can be obtained by appropriate lymphocyte testing in which two lymphocyte populations are demonstrated by appropriate HL-A tests. Since there are two segregant series, in the normal infant four sets of HL-A antigens would be expected, one haplotype being derived from each of the parents (fewer antigens would be detected if both parents possessed the same antigen at a given locus). Lymphoid chimerism is implied by the finding of all four antigens from the mother in addition to one or both antigens from the father.[48] It is important to distinguish these kinds of findings from cases of immunodeficiency in which extraneous antigens are found on the lymphocytes. In these patients, the antigens cannot be perfectly accounted for by the parentage and may exceed 6 in number.[48a] The The cause of this phenomenon is unknown; it may reflect a basic fault of the lymphocyte membrane resulting in the deficiency disease.

Interestingly, one of Cederbaum's patients demonstrated a normal response to phytohemagglutinin and another had a low response.[39] A single case which we studied showed a normal response to phytohemagglutinin, normal mixed leukocyte culture reactivity, and normal responses to antigens. Antibody formation was

normal with the exception of a lack of immune response to measles antigen shortly after the live virus vaccine was given. This patient developed a chronic persistent measles infection, which ultimately led to his death.[49] Omenn's disease represents an important clinical entity in that the major clinical manifestations which suggest immune deficiency are the presence of lymphopenia in association with markedly large nodes infiltrated by histiocytes. The tests of lymphoid function, however, are normal. A number of treatments given to these children probably results in an acceleration of the fatal course of the disease. Cyclophosphamide was given in one case, and in others blood transfusions were administered. In our case, routine immunization with live measles vaccine was employed. In the latter 2 instances and perhaps also in the first, death was due to iatrogenic causes. Therefore, it is important to be alert to the danger of accepted medical practices in the face of lymphopenia or unexplained cutaneous eruptions or both. The normality of in vitro tests of T cell function defies explanation for the moment. Repeated therapeutic attempts at reconstitution with thymus, transfer factor, and radiated leukocyte infusions were unsuccessful in our experience.[40]

Short-limbed Dwarfism

Deficiencies involving T or B cell systems or both have been described in deficiency states associated with short-limbed dwarfism. Two major clinical varieties are known: cartilage-hair hypoplasia and short-limbed dwarfism with immunodeficiency. In addition to the metaphyseal disease, cartilage-hair hypoplasia includes abnormality of the hair which lacks a central pigment core and is of small diameter (less than 55 μ), and hyperextensibility of the joints. Patients with cartilage-hair hypoplasia were first described by McKusick[50] in Amish patients, but non-Amish cases are also known. The deficiency state in cartilage-hair hypoplasia is unique. Neutropenia is a constant feature and in vitro tests of T cell function are uniformly abnormal.[51] Nevertheless, the T cell defect is not complete as demonstrated by patients' ability to reject a skin homograft (albeit in a delayed manner) and the fact that susceptibility to infections in cartilage-hair hypoplasia is restricted to varicella and vaccinia viruses. Rosette-forming cells in one case studied comprised 13.5 percent (normal: 46.8 $\pm$ 12.8). Since these patients are rare and their infectious complications have been successfully treated, postmortem studies of the thymus are not frequent. In one case we observed perfectly normal thymic morphology except that the total mass of the gland was small; serial sectioning revealed a diminished number of Hassall's corpuscles, a finding similar to that described for the DiGeorge syndrome.[52] Thus, we view cartilage-hair hypoplasia as a disorder in which there is a deficiency of thymic mass. Since T cell immunity is sufficient, such that common manifestations of complete T cell deficiency—such as chronic *Candida* infection and complete acceptance of skin graft—are not seen. However, T cell mass is inadequate to produce normal in vitro tests of T cell function. Although the data are limited, studies of this disorder indicate that the in vitro tests of lymphocyte function are quite sensitive and are readily depressed, even though a modest amount of thymic tissue is present. The reason for the neutropenia is unknown. Neutropenia has, however, been noted in other thymic deficiency states, such as ataxia-telangiectasia[53] and the Nezelof syndrome.[54]