Immune Regulation: What Immunodeficiency Disease Has Taught Us

DIANE W. WARA, M.D.
Department of Pediatrics, University of California, San Francisco, California, U.S.A.

"Immune regulation: what immunodeficiency disease has taught us" is reviewed by discussing three immunodeficiency disorders. Hypogammaglobulinemia, the first documented primary immunodeficiency disorder, has a well-defined and uniform clinical presentation which reflects a variety of underlying abnormalities involving the B cell, T cell, and monocyte. X-linked hypogammaglobulinemia, transient hypogammaglobulinemia of infancy common variable immunodeficiency, and their pathogenesis are discussed. Combined immunodeficiency with adenosine deaminase (ADA) deficiency first led to the now accepted concept that a biochemical abnormality may result in immunodeficiency. The clinical presentation, possible biochemical abnormalities resulting in the observed immunodeficiency, relative selectivity of the defect for the immune system, and potential applications of knowledge gained from the study of ADA deficiency are presented. Acquired immunodeficiency (AIDS) has resulted in the concept that a virus is cytotoxic for a specific population of T cells and that this, at least in part, results in the immunodeficiency seen in AIDS.

The title "Immune Regulation: What Immunodeficiency Disease Has Taught Us" should be extended to include "what we still have to learn". Rather than review immune dysregulation in a large number of immunodeficiency disorders, I have chosen three, each of which has presented a unique set of questions and answers. Hypogammaglobulinemia, the first documented primary immunodeficiency disorder, has a well defined and deceptively uniform clinical presentation which reflects a variety of underlying abnormalities involving the B cell, T cell, and monocyte. The clinical entity hypogammaglobulinemia has prompted the evaluation of the differentiation of the B cell in human. The second disorder, combined immunodeficiency with adenosine deaminase deficiency, first led to the now accepted concept that a biochemical abnormality may result in immunodeficiency. Finally, investigation of the pathogenesis of acquired immunodeficiency disease (AIDS), has resulted in the concept that a virus, human T-cell leukemia virus (HTLV III) is cytopathic for a specific population of T cells and that this, at least in part, results in the immunodeficiency seen in AIDS.

HYPOGAMMAGLOBULINEMIA

In 1952 Colonel O. Bruton [1] described the entity of congenital hypogammaglobulinemia in a young boy with severe bacterial infections. Subsequently, reports of hypogammaglobulinemia acquired in adolescence or adulthood appeared [2], now termed common variable immunodeficiency (CVI). Transient hypogammaglobulinemia of infancy was defined [3]. In each form, total serum IgG, IgM, and IgA is less than 250 mg/dl. Cell-mediated immunity is intact as reflected by total numbers of T cells and T-cell response to mitogens. Recurrent infection with polysaccharide-coated organisms such as Hemophilus influenza may result in pneumonia, sinusitis, and otitis media. Chronic diarrhea and malabsorption are frequently observed.

Normal maturation of B cells in human involves (1) presence of a large pre-B cell with cytoplasmic IgM; (2) progressive decrease in size of the cell with acquisition of cell surface receptors for Epstein-Barr virus (EBV), C3 components and the Fc portion of IgG; (3) acquisition of surface IgM and IgD followed by IgG; (4) final differentiation to an immunoglobulin secreting cell following interaction with specific antigen processed by monocytes and with T-helper cells. For the following discussion, an activated B cell is defined by immunoglobulin secretion, its principle differentiated function and by division, measured by radiolabeled thymidine uptake. In a typical immune response, division precedes differentiation to the secretory phase; division probably requires T-cell secreted B-cell growth factor. The immune system's most well defined secretory cell, the plasma cell, does not divide; differentiation to a plasma cell requires the T-cell secreted B-cell differentiation factor. A defect at any stage of B-cell maturation may result in the abnormal secretion of immunoglobulin and in hypogammaglobulinemia.)

Congenital hypogammaglobulinemia is characterized by the absence of circulating small B lymphocytes bearing surface immunoglobulin or C3 receptors [4]. Cellular immunity is normal. However, pre-B cells have been demonstrated in the bone marrow of a subgroup of these patients. The bone marrow-derived cells may be transformed by EBV and long-term cell lines established. The cell lines do not always contain cells with surface immunoglobulin nor do they secrete immunoglobulin, however receptors for EBV are present [5]. This finding suggests that although some patients have absent B-cell precursors, others manifest congenital hypogammaglobulinemia from a failure of differentiation of normal early precursor cells. In contrast to the above situation, in transient hypogammaglobulinemia of infancy, differentiated B cells are present in normal numbers, but are not provided with T-cell help. Quantitative serum IgG in the full term neonate is equal to or greater than that in the mother, reflecting active transport across the placenta. The level of transplacentally acquired IgG falls rapidly during the first 3-4 months of postnatal life. Immunoglobulin synthesis begins immediately after birth, in response to colonization of the gastrointestinal tract, infections, and other antigenic stimulation; IgG synthesis is well established by 6 months of life. This combination of events results in a physi-
logical hypogammaglobulinemia normally present from 4–6 months of life and often associated with increased infection. In transient hypogammaglobulinemia of infancy, a delay in IgG production results in an extended period of hypogammaglobulinemia, usually resolving by 30–40 months of age.

Infants with prolonged transient hypogammaglobulinemia have normal numbers of circulating B cells with surface immunoglobulin which will synthesize immunoglobulin when stimulated with EBV. However, the cells synthesize decreased amounts of immunoglobulin in response to pokeweed mitogen (PWM), a T-cell dependent B-cell activator. Further, they have decreased numbers of and function of T-helper cells for age which normalize as their serum IgG increases. Thus, this form of hypogammaglobulinemia appears to reflect a transient deficiency of helper T cells rather than an abnormality of B cells [6].

The etiology of the acquired form of hypogammaglobulinemia (CVID) is complex. Patients with CVID have low serum levels of IgM, IgG, and IgA, but nearly normal numbers of peripheral blood B cells with surface immunoglobulin. Among these patients, some have circulating B cells with IgM/IgD and no IgG; others have increased numbers of surface IgG-positive cells and a third group has normal percentages [7]. In a study by Saiki et al [8], a portion of the patients had an intrinsic B-cell defect with no proliferation/division in response to B-cell mitogens. In a second group, proliferation/division was normal in response to pure B-cell mitogens, but cell differentiation did not progress to allow the secretion of immunoglobulin. In a final group, B cells proliferated normally to mitogens, but differentiated only to IgM-secreting cells and not to IgG- or IgA-secreting cells. In this particular study, B lymphocytes were isolated from several patients within each group and were assessed for the ability of T cells obtained from normal individuals or for T-cell replacing factors to enhance B-cell differentiation; none occurred. Likewise, the removal of patient T cells did not result in normal B-cell proliferation. The B-cell defect in these patients does not appear to be explained by a T-cell defect.

However, T-cell defects have been demonstrated in other patients with CVID. In 1972, Dr. Waldmann and associates reported that a subgroup of patients with CVID have increased functional T-suppressor cells [9]. These patients' lymphocytes were capable of suppressing immunoglobulin production by lymphocytes from normal individuals in response to an appropriate stimulus, PWM. Numerous studies have verified this initial report and suggested an additional defect, an absence of helper T cells in some patients.

More recently, factors produced by T cells and responsible for the activation and differentiation of B cells have been defined, namely B-cell growth factor and B-cell differentiation factor. Although specific defects of B-cell factors have not yet been identified in patients with CVID, further work in this area may define the basis of the T-cell help required for the proliferation and differentiation of B cells to functional immunoglobulin secreting cells. T-cell help may be abnormal because of defective production of T-cell factors. Interleukin 2 (IL-2) produced by T cells and necessary for antibody production but not implicated in B-cell differentiation, was absent in one patient with CVID [10].

T-cell regulatory function itself depends to a large extent on the modulatory action of macrophages which process antigen and present it to T cells in conjunction with L1 antigen expressed on their surface. Macrophage T cell interactions have been shown to be abnormal in 8 of 9 patients with CVID. It is possible that this defect may be related to still another cell product, interleukin 1, produced by macrophages and necessary for the stimulation of T-cell help [11].

Hypogammaglobulinemia, whether diagnosed in infancy or adulthood, presents with a common clinical picture. Cell-mediated immunity as assessed by total numbers of T cells and T-cell response to mitogens is generally normal or only slightly depressed. Primary B-cell abnormalities have been defined at different levels in patients with different forms of hypogammaglobulinemia. Infants with congenital hypogammaglobulinemia generally have decreased numbers of mature B cells with surface immunoglobulin but may have early B cells with receptors for EBV. Patients with CVID most commonly have normal numbers of circulating B-cells defined by surface immunoglobulin but a defect in either the proliferative or the differentiation step of B-cell maturation. T-cell abnormalities have been defined in all clinical groups. Increased T-cell suppression is present in approximately 50% of patients with CVID. Others with CVID have decreased T-cell help as do patients with prolonged transient hypogammaglobulinemia of infancy. A single patient with CVID has been defined with absent IL-2; other T-cell derived B-cell factors have not been assessed in patients with hypogammaglobulinemia. In addition, macrophage abnormalities appear commonly in patients with CVID. The production of immunoglobulin by a differentiated nondividing B cell relies on the presence of a pre-B cell and its orderly maturation; in addition, T cell and macrophage help provided both by cell interaction and by the release of appropriate factors are necessary for the secretion of immunoglobulin by a normally differentiated plasma cell. Defects at any of these levels may lead to hypogammaglobulinemia.

COMBINED IMMUNODEFICIENCY WITH ADENOSINE DEAMINASE DEFICIENCY

In 1972, Giblett et al described the first association between T- and B-cell immunodeficiency and enzyme deficiency in two female children with severe combined immunodeficiency disease (SCID). Both children lacked an enzyme in the purine salvage pathway, adenosine deaminase (ADA), which had severely impaired cellular immunity, lymphopenia, and a variable degree of hypogammaglobulinemia [12]. A subsequent review of 22 children with documented SCID and known ADA status revealed that 13 were ADA deficient [13], thus establishing the association, if not the causative nature, of the immunodeficiency and enzyme defect. Since the initial discovery of ADA deficiency, greater than 25 families with ADA deficiency and immunodeficiency have been carefully described in the literature (reviewed by Hirschhorn and Martin, 1978 [14]). A deficiency of purine nucleoside phosphorylase (PNP) was first described in 1975 by Giblett et al [15] in association with T-cell deficiency and relatively preserved B-cell function. This second association between absence of an enzyme in the purine salvage pathway and SCID supported a causative effect.

ADA deficiency is inherited in an autosomal recessive manner [16]. The majority of infected infants are seen usually within the first few months of life with multiple recurring infections and failure to thrive. The infections involve the respiratory tract, the skin, and the gastrointestinal system and are caused by a variety of organisms including fungi, protozoa, viruses, and bacteria. Mucocutaneous candidiasis is a common feature and overwhelming infections from Pneumocystis carinii and varicella zoster have been reported. Without therapy, most infants die within the first year of life. The clinical manifestations of this form of ADA deficiency result from significant abnormalities of T-cell immunity and moderate abnormalities of B-cell immunity. Severe lymphopenia is often present. Delayed hypersensitivity skin test responses are absent and in vitro lymphocyte responses to the mitogen phytohemagglutinin (PHA) and to alloantigens (mixed lymphocyte culture) are depressed. Quantitative immunoglobulins are low to absent and evidence for a specific antibody response to antigen is variably absent. The remainder of the group (approximately 10%) with ADA deficiency have a delayed clinical presentation. As the infants become older, susceptibility to infections increases. In this group, T-cell function is more severely affected than B-cell immunity [17].

Drs. Hirschhorn and Martin [14] posed 4 major questions concerning the association between enzyme defects and im-
munodeficiency diseases. These questions were: "1. What is the metabolic mechanism(s) of the pathogenicity? 2. What is the basis of the remarkable organ systems specificity? 3. What are the pathogenic relationships if any, between the genetically distinct diseases associated with enzyme defects? 4. Do any of the above provide important insights into the basic mechanisms by which the immune system functions or means by which it may be manipulated?"

As basic laboratory work on ADA deficiency has resulted in a more complete understanding of the pathogenesis of this disease than work concerning PNP deficiency, I will confine my comments concerning pathogenesis to the first disorder.

ADA catalyzes the conversion and deamination of adenosine and deoxyadenosine to inosine and deoxynosine in the purine (deoxy) ribonucleoside catabolic pathway. Although there are several molecular forms of ADA in human tissue, erythrocytes as well as lymphocytes contain primarily the low molecular weight of ADA. It appears that the tissue, red cell, and lymphocyte form of ADA are deficient in patients with immunodeficiency and ADA deficiency, suggesting that they are all products of the same gene. The gene for ADA is located on chromosome 20 in the human. There is a single locus with 2 alleles [17]. An early theory that the immunodeficiency found in ADA deficient patients resulted from a linkage between the structural gene for ADA and the HLA locus was eliminated following the assignment of discrete structural genes for ADA, PNP, and the HLA locus on 3 separate human chromosomes.

It seemed most likely that the pathogenesis of the abnormal immune system in ADA deficiency followed general principles for inherited metabolic disorders. That is, the immunodeficiency results from (a) a deficiency of the product of the absent enzyme; (b) the accumulation of a toxic substrate; or (c) the accumulation of a toxic metabolite of a substrate of the absent enzyme.

The initial studies of purine metabolism in ADA deficient patients suggested that adenosine was the most likely candidate to produce lymphocyte toxicity because it was elevated in the plasma of an ADA-deficient child [18] and, in a series of studies, was found to be toxic to normal lymphoid cells in the presence of an ADA inhibitor in vitro [19,20]. Three suggestions were made concerning possible mechanisms of lymphocyte toxicity for adenosine or adenosine metabolites. First, the incubation of human peripheral blood lymphocytes with different concentrations of adenosine resulted in an increase in intracellular cyclic AMP; dipyridamole, a drug known to block adenosine uptake, did not block the effect of adenosine on the lymphocyte cyclic AMP level, suggesting that adenosine was active on an extra cellular site, presumably a cell surface receptor site [21,22]. Intracellular cyclic AMP is a known immunosuppressive agent. The increased serum adenosine in patients with ADA deficiency could saturate cell surface adenosine receptors, increase intracellular cyclic AMP through a receptor mechanism, and produce immunodeficiency. Secondly, it was hypothesized that adenosine pyrimidine nucleotides inhibit the growth of cultured cells by pyrimidine starvation which are necessary for DNA replication [23].

These studies were carried out on two established cell lines of lymphoid origin and, the end point was diminished growth in the presence of adenosine. However, this specific mechanism is no longer accepted as the primary cause of immunodeficiency in ADA-deficient cells, because the addition of a pyrimidine, uridine, to ADA deficient peripheral blood mononuclear cells did not result in normal growth. Further, a mutant cell line was developed lacking adenosine kinase, presumably necessary for pyrimidine starvation; this cell line was also susceptible [24].

The third explanation put forth for the toxicity of adenosine to lymphocytes in patients with ADA deficiency was that exogenous adenosine resulted in the intracellular accumulation of S-adenosyl-homocysteine, which in turn acts as an inhibitor of methylation reactions. Both in normal peripheral blood mononuclear cells [25] and in a human lymphoblastoid line [26] adenosine inhibits the uptake of radiolabeled thymidine and leucine, presumably by inhibiting methylation. Methylation reactions are necessary for the production of DNA. The inhibition of methylation by S-adenosyl homocysteine accounts for the observed uridine-resistant adenosine toxicity in human lymphoblastoid lines; this mechanism is felt by many investigators to at least contribute to the immunodeficiency in ADA deficient patients.

Subsequently, attention turned to body fluids and tissues obtained either fresh or cultured from patients with ADA deficiency. Polmar et al first documented a ten-fold increase in lymphocyte adenosine triphosphate (ATP) in an untreated patient. ATP levels returned to normal after the infusion of irradiated erythrocytes containing ADA; immune function also normalized [27]. It was clear that the addition of ADA activity either in vivo (by erythrocyte transfusions) or in vitro allowed for the partial reconstitution of cellular immune function. Therefore, it appeared that ADA was removing some potentially toxic substrate(s). However, that toxin did not appear to be exclusively adenosine. Further studies revealed that erythrocytes of ADA deficient, immunodeficient patients had increased concentrations of deoxyadenosine and deoxy-ATP (dATP) [28]. These increased levels often return to normal following treatment, and dATP appear to correlate better with the reconstitution of immune function in patients than ATP levels. Therefore, it was postulated that the potential "toxin" was deoxyadenosine rather than adenosine.

Studies to substantiate the theory that ADA deficiency and immunodeficiency results in part from increased deoxycytosine and increased dATP rather than increased adenosine and ATP include the following. Peripheral blood mononuclear cells obtained from ADA deficient, immunodeficient patients were sensitive to 100–1,000 fold lower concentrations of deoxycytosine than were peripheral blood mononuclear cells obtained from normal individuals. This was in contrast to the previous experience utilizing adenosine. The mechanism of deoxyadenosine toxicity remained unknown. Deoxy-ATP is an inhibitor of the ribonucleotide reductase activities responsible for the production of deoxyribonucleotides and thus, ultimately, for the production of the substrates necessary for DNA synthesis. The theory that increased levels of dATP result in immunodeficiency via inhibition of ribonucleotide reductase is supported by a cell model system in which micromolar concentrations of deoxyadenosine result in a marked increase in intracellular dATP and a depletion of the deoxynucleotides, especially deoxyctydine. In this particular system, the toxicity of deoxyadenosine has been shown to be completely independent of cyclic AMP mediated effects [29,30]. One would predict that if the model is correct, the ADA induced immunodeficiency in man could be repaired in vivo by the infusion of deoxyctydine. However, in two infants with ADA deficiency and severe combined immunodeficiency, the infusion over long periods of time of large amounts of deoxyctydine, which accumulated intracellularly, did not result in clinical improvement or reconstitution of cellular immunity [31]. There are at least 3 explanations for these findings: (1) deoxyctydine did not reach the potential target cells; (2) the target cells were no longer present in the infants; or (3) the major mechanism for the toxicity in ADA deficiency is not limited amounts of dCTP resulting from the inhibition of ribonucleotide reductase deficiency. In support of this latter possibility, an effort to increase immunodeficiency in an infant with ADA deficiency, in order to prepare the infant for bone marrow transplantation, by infusing large amounts of the presumed toxic metabolite deoxyadenosine, resulted in a marked increase in intracellular dATP levels. However, no diminution of immune response measured either by lymphocyte response to lectins or to allogeneic cells was observed (M.J. Cowan, personal communication).

Therefore, a single explanation for the immunodeficiency observed in children with ADA deficiency is not available. Most likely, ADA deficiency results in a combination of defects,
including increased levels of deoxyadenosine and dATP with ribonucleotide reductase deficiency, increased intracellular cyclic AMP resulting from saturation of cell surface adenosine receptors, and inhibition of essential methylation reactions by S-adenosyl homocysteine.

An additional question, remaining to be answered in infants with ADA and related enzyme deficiencies, is an explanation for the specific susceptibility of the immune system and of its components. There are at least 3 explanations for this specific susceptibility. First, lymphocytes are rapidly proliferating cells, requiring large amounts of DNA. Any defect resulting in abnormal DNA formation would favor destruction of lymphocytes over other cells. Second, the concentration of ADA is high in peripheral lymphoid tissue, especially tissue correlating with differentiation of competent T cells. In cell models, ADA deficiency appears to produce increased toxicity via increased amounts of deoxyadenosine during the early stages of T-cell development. Finally, deoxyadenosine is a freely diffusible compound which is phosphorylated intracellularly by a specific kinase. The specific kinase activity is largely localized to lymphoid cells, allowing only these cells to phosphorylate and therefore to trap the diffusible deoxyadenosine [34]. In this cell model, all lymphocytes contain the specific kinase for deoxyadenosine and appear equally susceptible to ADA deficiency. However, in infants with ADA deficiency, the T-cell system is more severely affected than the B-cell system. Numerous investigators have attempted to explain the "protection" of B cells to ADA deficiency. T helper cell activity and the ability of B cells to differentiate to the antibody secreting stage are differentially protected in vitro when incubated with ADA inhibitors and deoxyadenosine; T suppressor activity is markedly affected in the studies [35]. In a single study, normal peripheral blood B cells appeared to degrade deoxynucleotide; thus, B cells did not accumulate toxic dATP [36]. It is hypothesized that the ecto-5' nucleotidase, present on the surface of B cells in larger concentrations than on the surface of T cells, is responsible for the intracellular degradation of the deoxynucleotides. In this model, dATP would not accumulate intracellularly, ribonucleotide reductase would not be inhibited and DNA synthesis would proceed more normally in B cells than in T cells.

It is clear that understanding the mechanism(s) for the immunodeficiency found in ADA deficient patients will help to define the normal immune response. Further, understanding the differential effects of accumulated metabolites on B and T lymphocytes may help to define their unique characteristics. It is already obvious that the recognition of the immunologic disorder associated with ADA deficiency will provide a means of manipulating the normal immune system. The use of pharmacologic agents with adenosine deaminase inhibitor activity may well add to the treatments available for leukemias. Although early trials with 2' deoxycoformycin as an adjunct treatment of lymphoid malignancies have been disappointing [37,38], future studies utilizing a similar approach may yield new therapeutic modalities.

ACQUIRED IMMUNODEFICIENCY SYNDROME

During the past four years, first in the United States and subsequently in other parts of the world, investigators have described an acquired immunodeficiency syndrome (AIDS). This syndrome is characterized by lymphopenia with a decreased percentage of helper T-lymphocytes and an increased percentage of suppressor T-lymphocytes [39–46]. AIDS has occurred primarily in homosexuals, drug users, and Haitians, but has been reported in hemophiliacs and in both infants and adults receiving blood transfusions from an individual with documented AIDS [47]. The syndrome appears to have a latency period between 6 months to 2 years and may be preceded by a lymphadenopathy syndrome (LAS).

The risk of Kaposi's sarcoma in this population is at 100-fold greater than in the general population. An additional association is that of opportunistic infection from a variety of microbial agents, including pneumocystis carinii. The mortality and apparent irreversibility of AIDS in patients with Kaposi's sarcoma and/or opportunistic infections has encouraged investigators to define the immune status and to search for an underlying infectious etiology in this patient population.

A common denominator in patients with AIDS is a profound selective defect in cellular immunity [48,49]. The most consistently observed defect has been a depression in the ratio of T helper/inducer cells (defined by OKT-4 or Leu-3 monoclonal antibodies) to suppressor/cytotoxic cells (defined by OKT-8 or Leu-2 monoclonal antibodies). Recently, retrovirus termed AIDS-related virus (ARV), lymphadenopathy associated virus (LAV), or HTLV III by various investigators, has been identified in patients with AIDS. The virus has a selective tropism for and subsequent cytopathic effect in helper/inducer T-lymphocytes, probably explaining the decreased numbers of these cells seen in patients with AIDS [50]. T-cell functions (defined by lymphocyte response to T dependent mitogen, antigens and alloantigens) is depressed in patients with AIDS but is most abnormal in patients with opportunistic infections [48,49]. An explanation, in addition to decreased numbers of helper cells, for the abnormal T-cell function and immunoregulation observed in these patients may be the elaboration of soluble suppressor factors (SSF) [51,52]. SSF is elaborated by AIDS or LAS T cells following interaction with autologous or normal adherent cells. SSF can inhibit T-cell response to antigen and PWM-induced B-cell proliferation by normal peripheral blood mononuclear cells.

Antibody-mediated immunity has been described as normal or overactive with normal or elevated immunoglobulins in AIDS patients. However, primary antibody responses to antigens, such as keyhole limpet hemocyanin, are severely depressed [53]. Evaluation of B-cell function in vitro in patients with AIDS has revealed the "spontaneous" polyclonal activation of B-cell lymphocytes with an increased number of cells secreting immunoglobulin. In the same patients, decreased proliferative responses to T-cell dependent B-cell mitogens, reflecting abnormal resting B cells, were reported [54]. A possible explanation for the discrepancy between the decreased absolute number of T-helper cells and the increased polyclonal activation of B cells is a decrease in the subset of T-helper cells not normally required for help in B-cell responses with the preservation of the subset required for help [55].

All investigators' evaluations of B-cell function in AIDS suggest that in addition to abnormalities of T-cell regulation, a fundamental but as yet unidentified defect in B cells exist [54,55]. The pathogenesis of B-cell polyclonal activation remains unknown. Possible explanations include the transformation of B cells by cytomegalovirus (CMV), EBV or a related agent in addition to infection with HTLV III. Patients with either LAS or AIDS have serologic evidence of recurrent infection with both EBV and CMV. It is unlikely that EBV is functioning as a B-cell polyclonal activator in patients with AIDS. Following the long term culture of B-cell enriched peripheral blood mononuclear cells obtained from individuals with LAS, the polyclonally activated cells secreted abnormally increased amounts of IgG. Cells infected with EBV secrete primarily IgM. Epstein-Barr nuclear antigen could not be detected in the cells at the termination of culture [56]. This finding, in addition to the cellular secretion of IgG in preference to IgM effectively excludes EBV as an in vivo polyclonal activator. CMV has also been reported as a polyclonal activator of B lymphocytes and has not been systematically investigated in B cells of patients with AIDS.

During the past four years it has been established that only a small subpopulation of men with LAS progress to develop AIDS. However, most men with LAS have elevated antibody titers to CMV, EBV and, most recently LAV/HTLV III/ARV
The recent documentation that a specific retrovirus (LAV/HTLV III/ARV) nicely explains the observation of decreased T-helper cells in men both with LAS and with AIDS, it alone is not a complete explanation for the development of AIDS. Infectivity with the retrovirus may result in AIDS in a yet not identified group of patients with a specific genetic background. Alternatively, AIDS may result from a "double hit" mechanism; that is, infection with a retrovirus followed by or simultaneous with infection with a virus similar to CMV/EBV, may induce the polyclonal activation of B lymphocytes and other immune abnormalities seen in AIDS.

SUMMARY

Abnormal immune response and dysregulation is found in patients with a variety of primary or secondary immunodeficiency disorders. The three I have chosen to discuss represent a general pattern of dysregulation in immunodeficiency without the common pathogenesis: (hypogammaglobulinemia), an enzyme deficiency resulting in severe combined immunodeficiency disease (adenosine deaminase deficiency), and the infection of a subpopulation of T lymphocytes by a cytotropic virus resulting in an abnormal immune response (acquired immunodeficiency syndrome). The pathogenesis of none of these disorders is completely understood. Hypogammaglobulinemia (congenital, prolonged transient, common variable immunodeficiency) may result from an intrinsic abnormality of B cells, T cells, and/or monocytes. Although the relationship between absent ADA and the immunodeficiency observed in a subpopulation of infants with severe combined immunodeficiency disease is established, the exact pathogenesis of the disordered immune response remains unknown. Most likely, both abnormal methylation and increased quantities of intracellular deoxyadenosine and dATP result in the immunodeficiency observed. The recent documentation that a specific retrovirus (LAV/HTLV III/ARV) is cytotoxic and cytopathic for human T-helper cells in men with AIDS alone does not provide a completely satisfactory explanation for the immunologic findings described in men with this syndrome.

REFERENCES


