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The Primary Immunodeficiency Diseases: Classification, Pathogenesis and Treatment*

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An attempt will be made in this brief space to review some current views on the classification, pathogenesis and treatment of some of the primary immunodeficiency diseases. (For further details the reader is referred to references[1, 2, 3] and [4]). Over the past two years, we have witnessed a rapid technological expansion in the recognition of lymphocyte subpopulations.[5–47] Approximately one-fifth of circulating lymphocytes carry easily detectable immunoglobulin on their outer membrane (mIg): such cells are bursal-derived or B-cells. Another three-fifths of the peripheral lymphocytes form rosettes spontaneously with sheep erythrocytes: these appear to be thymus derived or T-cells. While some laboratories claim to account for nearly 100 percent of the circulating lymphocyte population by using just these two markers,[34] most evidence suggests that other minor populations exist which do not have the characteristics of either B-cells or T-cells. Other markers include rosette formation of lymphocytes with sheep erythrocytes coated with antibody and complement (C3R), binding of aggregated IgG to the lymphocyte surface (FcR), cytoplasmic fluorescence with antiserum made against acute lympatic leukemia cells (HTLA) and complement-dependent killing by antisera made against thymocytes or lymphocytes from patients without mIg-bearing B-cells (anti-T).[38] While the HTLA and anti-T antisera cleary recognize lymphocytes within the T-cell compartment, much controversy

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exists at the present writing over interpretation of C3R and FcR bearing lymphocytes. While both of these markers are present on some B-cells, they are also present on some non-mIg bearing cells. Some of these cells may represent immature B-cells (see Table I). In general, studies of mIg-bearing lymphocytes in patients with primary immunodeficiency diseases have yielded two types of findings: those patients in both serum immunoglobulins (sIg) and mIg-bearing lymphocytes are absent and those in whom a discordance is found in that while serum immunoglobulin (sIg) is very low or absent, mIg-bearing lymphocytes are present in normal numbers. These studies have also provided evidence that some apparently "homogeneous" clinical disorders should be divided into several groups.

TABLE I

GUIDE TO LYMPHOCYTE SUBPOPULATION MARKERS

E	Rosettes are obtained directly with sheep erythrocytes. Reliable indicator of T-cells.
HTLA	Indirect IF of cytoplasm using antiserum made in rabbits against human acute lymphatic leukemia cells. Probably detects T-cells, possibly other cells also.
anti-T	Complement-dependent cytotoxicity of hetero-antisera against human thymocytes or leukocytes from patients without mIg-bearing lymphocytes.
FcR	Binding of labelled aggregated IgG or rosette formation with sheep erythrocytes coated with 7SIgG. Present on B cells and non T, non-B lymphocytes.
C3R	Rosettes obtained by first coating sheep erythrocytes with antibody (rabbit IgM) and then with human complement. Coated cells are incubated with test lymphocytes. Present on B-cells and on non-T, non-B lymphocytes. Always HTLA negative.[47]
mIg	Direct IF of cell membranes using antisera against μ, γ, α, λ, k. Reliable indicator of B-cells.

The modern era of clinical immunology began with the observation that patients lacking gamma globulins in their serum suffered an increased incidence of severe infections. It quickly became apparent, however, that despite this deficiency of gamma globulins, delayed hypersensitivity skin reactions were quite normal in such patients. These two types of immunologic functions were called "humoral" and "cell-mediated" on the basis of how such immunity could be transferred to a previously, unsensitized person. Humoral immunity, as demonstrated by Schick

testing, is transferable with serum (i. e. antibodies) alone; cell-mediated immunity, as demonstrated by tuberculin skin testing, is transferable with cells (i. e. lymphocytes) but not with serum alone. The patients described above appeared to have an isolated humoral deficiency. But to say *that* is to jump ten difficult years during which extensive animal work helped sort out the various immunologic functions into either humoral or cell mediated camps. With the discoveries of the bursa of Fabricius in chickens and of the impact of the fetal and neonatal thymus on immunological development, it was recognized that such functions as capacity to induce a graft-versus-host reaction in an immunodeficient host, transfer delayed hypersensitivity and rejection of skin grafts were mediated by cells coming under thymic influence during ontogeny. In contrast, formation of antibodies appeared, to be dependent upon bursal influence in chickens and could be shown, in animals where a bursa has yet to be anatomically defined, to be quite independent of thymus influence and thus, by inference, "bursal" dependent. Although the evidence was convincing that these two central lymphoid organs rather independently influenced the *development* of lymphoid elements from a common stem cell precursor into either thymus-dependent or thymus-independent lymphocytes, it was not until 1965 that a similar division of immunologic *function* was proposed. While more recent animal studies have produced incontrovertible evidence of cooperation, rather than independent *function* of the thymus-dependent and thymus-independent systems, convincing clinical evidence for cooperation between the two immunological compartments has been difficult to obtain. This present discrepancy is almost certainly the product of limited methodological capability in clinical situations: improved laboratory techniques will no doubt produce evidence of cooperation between the two components of the immunological system. Already in some disorders, such as selective IgA deficiency, there is reason to believe that the humoral deficiency may be the end result of a T-cell dysfunction. While it has recently become fashionable to describe the pathogenesis of immunodeficiency disorders in terms of T- and B-cell defects. These terms should be used carefully since they are only operational concepts. Furthermore, within each cell compartment additional subdivisions will most likely be necessary.

Congenital X-linked Hypoimmunoglobulinemia (CXLH)

This disorder is characterized by an isolated deficiency of humoral immune function which becomes apparent in the early months of life. Cell-mediated immunity remains intact. The diagnosis can only be

made with confidence if the family history reveals other similarly affected males and a pattern of X-linked inheritance. Clinically, CXLH patients form a rather homogeneous group. Before the advent of antibiotics these patients, no doubt, all died in early childhood from severe infections. Since that time, it has been possible with antibiotics, gammaglobulin and with aggressive pulmonary hygiene to allow such patients to live relatively normal functional lives. Lymphocyte subpopulation studies in patients with the X-linked form of hypoimmunoglobulinemia have revealed two groups. Group I patients are concordant with regard to absence of both sIg and mIg -bearing lymphocytes. The majority of patients with this disorder belong in Group I. Group II. patients are discordant for sIg and mIg in that normal or nearly normal percentages of mIg-bearing lymphocytes have been observed in the peripheral blood despite absent or low sIg levels.[10, 37, 48] Group I patients also lack lymphocytes bearing FcR.[40] Normal or near normal percentages of C3R lymphocytes have been described in some Group I CXLH patients recently studied by Aiuti et al[45] and Yata et al[46] suggesting the existence of either a non-B cell or a non-mIg-bearing B-cell population bearing the C3R marker. Others, however, have found the proportions of C3R lymphocytes to be low in these patients. E rosette forming lymphocytes are present in normal numbers.

The basic immunologic defect in Group I CXLH remains undefined (Fig. 1). Both serum Ig and B-cells are lacking. The defect may lie in a faulty microenvironment at the level of the bursa or bursal equivalent which does not allow immunologic precursor cells (i. e. immunoblasts) to differentiate properly into B-cells and plasma cells. An alternative hypothesis suggests that the microenvironmant is intact whereas the precursor cells cannot differentiate into the B-cell line perhaps as a result of an inherent enzyme defect. There is little evidence to refute either theory. The resolution of this dilemma would have obvious implications with regard to therapy by cellular reconstitution. Since the existence of Group II CXLH patients has only recently been recognized, little can be said regarding the pathogenesis of this disorder except to point out that the presence of B-cells in these patients suggests a post-bursal maturational defect.

Di George Syndrome (III-IV Pharyngeal Pouch Syndrome)

Di George syndrome is characterized by neonatal hypocalcemic tetany, peculiar facies, ear defects (low-set, fused helix-anthelix, flattened pinnae), cardiac defects (sometimes including right-sided aortic arch) and other congenital anomalies. The tetany results from absence of

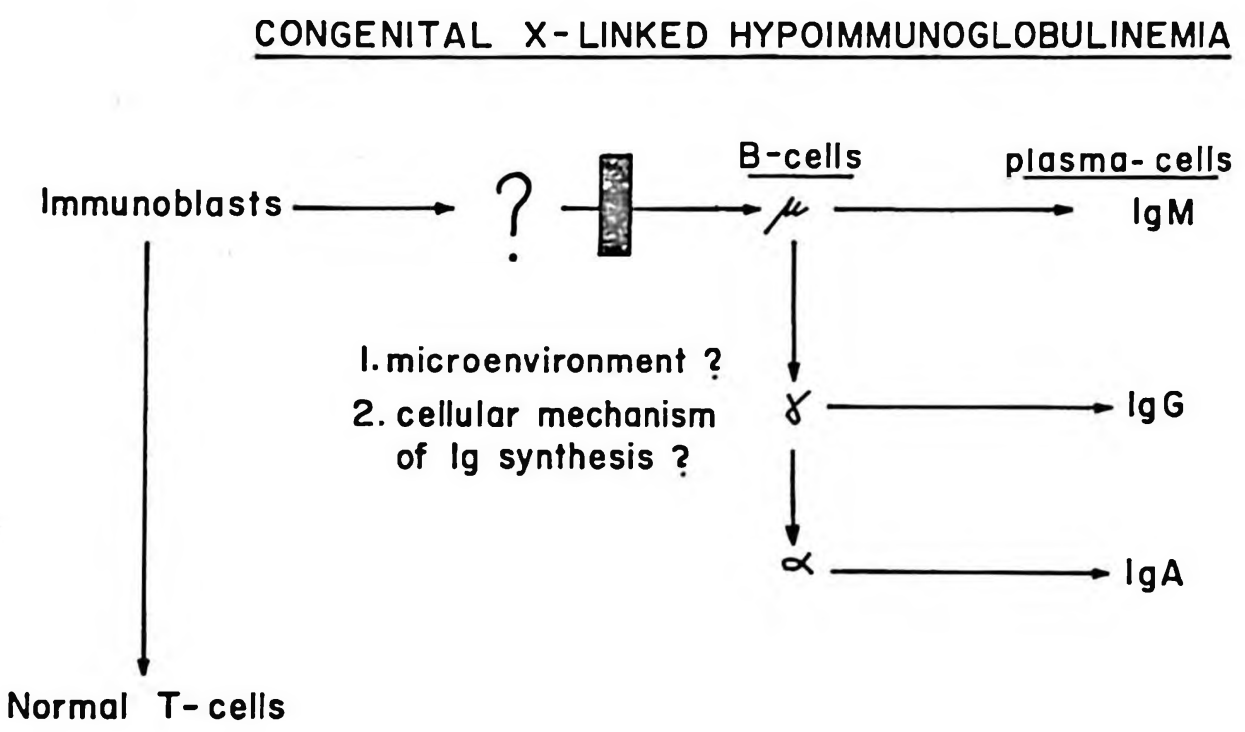

Figure 1

Schematic diagram of lymphoid differentiation depicting the probable site of malfunction in congenital X-linked hypoimmunoglobulinemia, Group I.

parathyroid glands; thymic hypoplasia or aplasia usually accompanies this embryonic maldevelopment of the third and fourth pharygeal pouches. Viral and fungal infections are usually severe, often fatal. Pneumocystis carinii pneumonitis is another common cause of death among these patients. Only one report exists of more than one child being affected in a family.[49] In this family, male and female half-siblings were affected and the mother had cell-mediated immunodeficiencies as well.

Lymphocyte subpopulation studies have demonstrated increased percentages of mIg-bearing lymphocytes in several patients.[50, 51] E rosette forming cells have been absent; HTLA positive lymphocytes have also been absent. In vitro lymphocyte responses to PHA and to PWM have been very low or absent. Mixed leukocyte culture (MLC) studies have not been performed on most of the patients with Di George Syndrome reported thus far. In one patient with this syndrome, the MLC was negative at three weeks of age but became positive at seven weeks of age.[52] Some infants with the Di George "syndrome" do not reveal any immunologic deficits, as tested by present methods.[35] Immunoglobulin levels have been completely normal in all but a few of the Di George patients, despite reports that nude athymic mice have very depressed levels of IgA.[54] At post-mortem examination, a very small

thymus remnant is often found in infants with Di George syndrome. Such remnants usually microscopically as normal thymus tissue with normal or slightly decreased numbers of Hassal's corpuscles. The diagnosis in such patients is termed "partial" Di George syndrome or thymic hypoplasia.

Severe Combined Immunodeficiency (SCID)

Four types of inherited SCID have been defined: 1) autosomal recessive, 2) X-linked, 3) that associated with short-limbed dwarfism and sometimes with ectodermal dysplasia as well and 4) an autosomal recessive form with an associated deficiency of adenosine deaminase.[55] The immunologic status of all four types is essentially the same with the qualification that the lymphopenia and the prognosis are sligtly less severe in the X-linked form. On occasion, the infants with immunodeficiency and dwarfism have enlarged lymph nodes rather than the small, difficult-to-palpate nodes usually found in patients with the other types of SCID. The reasons for this are not clear. Because patients with SCID are rare and die quickly if left untreated, studies of lymphocyte subpopulations have been performed on only a few infants. Membrane Ig-bearing lymphocytes were absent. HTLA positive cells were absent or very low in 4 of 5 patients studied by Yata et al.[47]

Although this group of patients initially appeared rather uniform from a clinical point of view, it is unlikely that all infants with severe immunodeficiencies of both compartments have a stem cell defect. One of the authors (MS) has studied an infant who had extremely high numbers of mIg-bearing lymphocytes in his peripheral blood. Some of these cells carried both μ and γ on their surfaces. In vitro responses to phytohemagglutinin (PHA) were absent despite a normal mixed leukocyte culture (MLC) response. The family history included three brothers who had died in infancy with SCID. Other patients have been described with positive MLC responses and otherwise deficient cell-mediated and humoral immune functions. Another infant recently studied by Soothill and Hayward presented at one year of age with a history of recurrent pneumonitis, diarrhea and weight loss. A brother had died at 7 months of age with pneumocystis carinii pneumonitis and post-mortem findings compatible with SCID. While sIg and mIg were both absent and delayed hypersensitivity skin tests and PHA responses were absent, 41% E rosette-forming lymphocytes were observed in the peripheral blood. Some of these patients may have congenital infections (viral ?) rather than hereditary disorders. No doubt, careful analysis of lymphocyte subpopulations in this group of patients will

reveal new entities with different pathogenetic mechanisms suggesting certain modifications in the approach to their cellular reconstitution.

Still another group of patients with combined immunodeficiency exists who present after infancy. Here again, many variations have been observed, including those with serum IgM remaining and those with normal sIg levels but poor or absent antibody responses to antigenic stimulation. All of these have cell-mediated immunodeficiencies as well. Classification of such patients defies present understanding or nomenclature and overlaps with both SCID and the group of disorders termed "variable hypoimmunoglobulinemia".

Variable Hypoimmunoglobulinemia

Patients with this diagnosis should not really be discussed as a group since this classification probably includes several disease entities. Unfortunately, until now, it has not been possible to further subdivide them. In general, this group includes patients with severe depression of sIg levels and humoral immune responses. With progression of the disease, cell-mediated immune function also wanes. A number of years ago, Rosen et al[56] proposed a classification termed "dysgammaglobulinemia Types I, II and III" on the basis of serum immunoglobulin patterns. However, because these patterns often change with progression of the disease and within different members of a family this terminology was abandoned. Others have subdivided this group into "early" and "late-onset" patients. Recent studies of the mIg -carrying lymphocyte subpopulations have revealed two distinct patterns: 1) patients lacking B-cells, who are similar in this respect to the congenital X-linked hypoimmunoglobulinemia Group I patients and 2) patients with fairly normal percentages of B-cells carrying mIg of one, two or all of the Ig classes. Gatti and coworkers[44] have proposed to call these "Group I" and Group II" respectively (See Fig. 2).

Patients with early and late onsets appear in both groups.[40] The main drawback to grouping these patients on the basis of the percentages of B-cells in their peripheral blood is that during a severe infection these percentages may increase from very low levels to near normal.[37, 40] Further, Aiuti et al[57] has recently observed a patient who previously had B-cells in her peripheral blood and now no longer has such cells, a phenomenon not unlike changing Ig patterns which led us to abandon the dysgammaglobulinemia nomenclature. Taken together, these obervations suggest that the level of peripheral B-cells may reflect the progress of the disease. Thus, those patients lacking B-cells (Group I) may be in the late stage (Stage III) while those with B-cells (Group II) are in an early

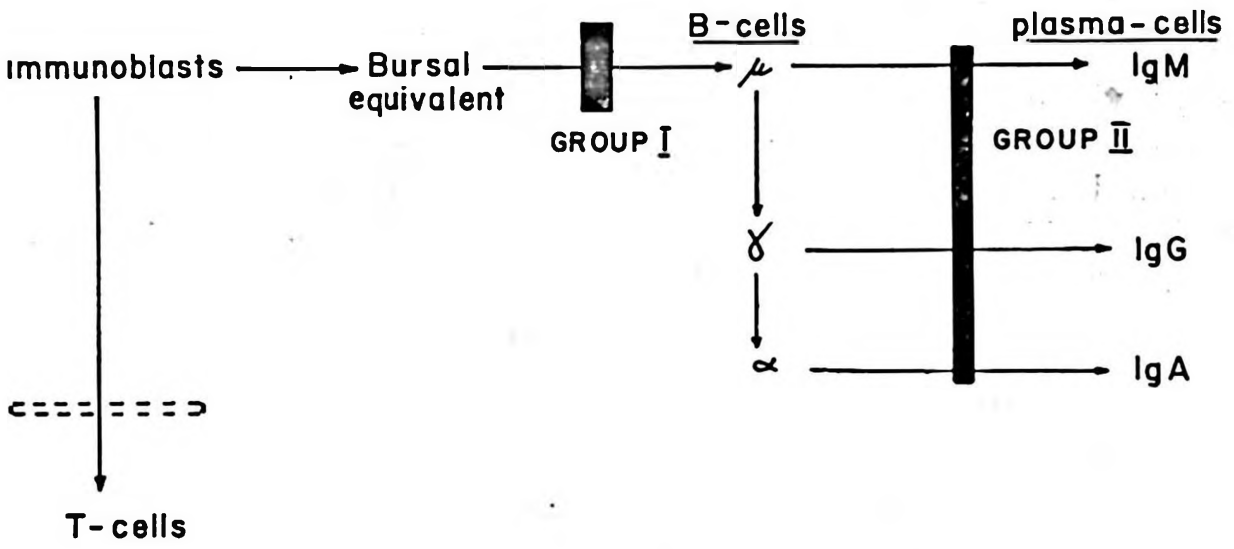

Figure 2

Schematic diagram of lymphoid differentiation depicting the probable sites of malfunction in variable hypoimmunoglobulinemia.

stage (Stage I). Patients whose levels increase from very low levels during severe infections may represent a transitional phase or Stage II.

It has been suggested that the lymph node hyperplasia in patients with variable immunodeficiency results from persistent antigenic stimulation since little antibody is released to neutralize the antigen. Assuming that lymphocytes which no longer contain immunoglobulin on their surface would no longer be capable of stimulation by antigen, it follows that patients without B-cells should not develop lymph node hyperplasia. From the data of Preud Homme et al,[40] this appears to be the case.

Some patients in this group have been reported to possess antibodies against IgM. One group of investigators reports a frequency as high as 5 of 7 patients studied.[58] This observation fits nicely with the work in chickens of Cooper et al[59] showing that embryos treated with anti-μ antisera develop agammaglobulinemia. However, Aiuti et al[57] have not found such antibodies to any of the immunoglobulins in nine patients studied thus far. Others have reported only an occasional patient with anti-Ig antibodies.

Selective IgA Deficiency

It is within this group of patients that the mIg lymphocyte marker has provided the most unexpected finding. Consistently, each patient studied has possessed normal or high percentages of IgA-bearing B-cells

in the peripheral blood despite absent or very low levels of serum IgA (Fig 3). The percentages of lymphocytes carrying IgM on their surface are usually elevated. One likely explanation of the pathogenesis in this disorder is a faulty mechanism for secretion of IgA into the serum and, indeed, Cooper and associates have been able to induce this release of IgA by treating lymphocytes from such patients *in vitro* with pokeweed mitogen.[60] The therapeutic implications of this finding are obvious. An alternative hypothesis of the underlying pathogenetic mechanism in these patients is the existence of an inhibitor of IgA release in the serum. Antibodies against IgA and autoantibodies are common in patients with selective IgA deficiency: it is conceivable that such factors might inhibit IgA secretion *in vivo*.

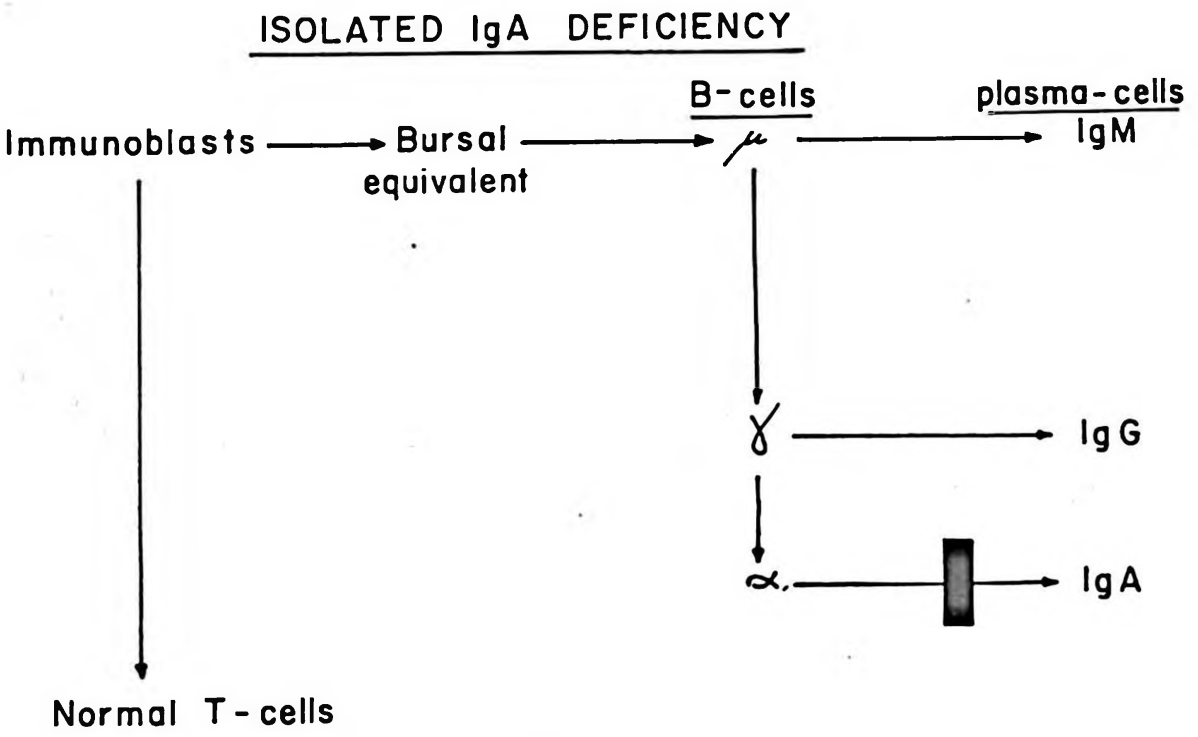

Figure 3
Schematic diagram of lymphoid differentiation depicting the probable site of malfunction in selective IgA deficiency.

The possibility must also be considered that the serum IgA deficiency may reflect a defect in B-T cell cooperation or even a primary defect in T-cell function. IgA levels are very low in nude nice, a strain which is born with little or no thymus.[54] IgA levels are also low in neonatally thymectomized rabbits.[61] J. F. Bach and coworkers have recently measured serum levels of "thymus factor" in IgA deficient patients and found them to be depressed.[62] Finally, despite earlier reports of normal cell mediated immunity in these patients, recent studies reveal that some patients with selective Ig-A deficiency have decreased numbers of E rosette-forming lymphocytes in their peripheral blood.

Vitiligo has been observed in a small number of patients with selective IgA deficiency[63] and in one patient following thymectomy.[93] Since one of the most likely pathogenetic mechanisms for the development of vitiligo appears to be autoantibodies against melanocytes, this is not a surprising association in a group of patients where autoantibodies are frequently found. Vitiligo is also a common finding among nude-mice·[93] On the other hand, most patients with vitiligo do not have IgA deficiency.[64]

Ataxia Telangiectasia

This disease is characterized by a progressive neurological degeneration of cerebellar function manifested by ataxia and accompanied by the eventual appearance of telangiectases which are especially notable around the eyes and ears. Sinopulmonary infections and bronchiectasis occur frequently. About half of these patients have decresed levels of IgA. As in selective IgA deficiency, the number of circulating B-cells carrying IgA on their surface remains normal despite the serum IgA deficiency, (Fig. 4). Since these patients also have gross anatomical and histologic changes in their thymus at post-mortem examination, it is quite possible here also that the IgA deficiency reflects a defect in function of the thymus dependent compartment. Further investigations of lymphocyte subpopulations in patients with ataxia telangiectasia have not yet been completed. An important recent finding has been the high alpha-fetoprotein levels in these patients reported by Waldman et al.[65]

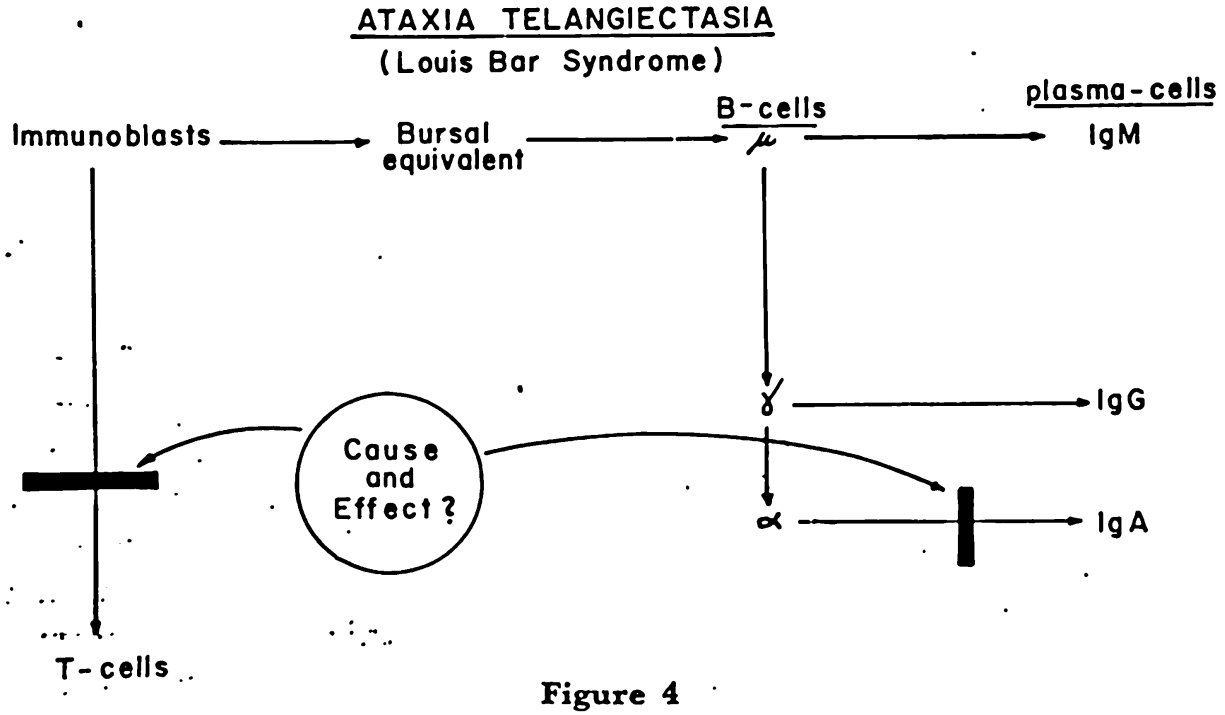

Figure 4

Schematic diagram of lymphoid differentiation depicting the probable sites of malfunction in ataxia telangiectasia.

Wiskott Aldrich Syndrome

This syndrome is defined by eczema, corpuscular thrombocytopenia and recurrent infections and occurs only in males. In cases with mild infections and without a clear family history of X-linked inheritance, it is sometimes difficult to distinguish this entity from several other forms of congenital thrombocytopenia. Patients with Wiskott Aldrich Syndrome manifest a very poor antibody response to stimulation with polysaccharide antigens, such as pneumococcus types I and II and blood group substance, despite normal responses to other antigens such as tetanus and diphtheria toxoids. Recent preliminary data also suggests that the antibody responses of these patients to stimulation with hemophilus B polysaccharide antigen are normal.[66]

Although in vitro lymphocyte responses to allogeneic cells to mitogen often appear normal, deficient responses can be demonstrated in some of these patients by using suboptimal stimulating doses of PHA, for instance. Further, these patients are usually anergic and have decreased numbers of E rosette forming lymphocytes in their peripheral blood. Where studied, the typically low serum levels of IgM have been accompanied by correspondingly low percentages of IgM-bearing B-cells. Serum IgE levels are greatly elevated in some patients with this disorder however these levels do not appear to correlate with the appearance or severity of the eczema.

Treatment

In general terms, the treatment of isolated humoral immunodeficiencies has been limited thus far to replacement therapy using gammaglobulin or other globulin fractions supported by antibiotics and antifungal agents when necessary. When gamma globulin is used to maintain IgG levels above 3 mg/ml (see ref. 67 for details), the incidence and severity of infections is markedly reduced. Anaphylactic reactions have been observed in occasional patients and are most likely due to IgG aggregates. The treatment of cell-mediated immunodeficiencies has proved more challenging, however. Until the initiation of thymus transplantation in 1968,[68] little could be done for these patients. Patients with severe combined immunodeficiency were also beyond our therapeutic capabilities until 1968 when successful immunological reconstitution was first accomplished with bone marrow transplantion.[69] Prior to that time treatment of these infants with gammaglobulin and antibiotics alone did not extend their lifespan much beyond one year of age.

Patients with severe cell-mediated immune defects are also susceptible to an iatrogenic disorder, graft-versus-host (GVH) disease.[70] This

disease may result from the transfusion of histoincompatible blood or bone marrow into a patient lacking the ability to reject such cells. Viable lymphocytes in the transfused blood products then reject the host, a process which usually terminates in the death of the patient within two weeks of the histoincompatible transfusion. ABO mismatching is not responsible for such reactions. HL-A matching, except between siblings of the patients, is inadequate at the present time for selecting a proper blood donor and impractical in any case. Therefore, if the administration of blood products to a patient with severe cell-mediated deficiency becomes necessary, the blood should first be irradiated with 2000 Rads. Such treatment does not result in significant harm to erythrocytes or platelet function.

The administration of blood transfusions to patients with selective IgA deficiency is also accompanied by a unique hazard. Certain of these patients, although by no means all of them, possess antibodies against IgA. Following the administration of even a few milliliters of whole blood to such patients, severe anaphylactic responses have been observed.[71, 72] These can be largely avoided by administering well-washed packed cells or whole blood from IgA deficient patients.

Bone marrow transplantation to patients other than with dual system immunodeficiecy has been mostly unsuccessful in the few attempts that have been made, probably because the marrow has been rejected by the patients residual cell-mediated immune function. Two notable exceptions exist. A patient with Wiskott-Aldrich syndrome was successfully transplanted following heavy immunosuppression with cyclophosphamide for five days prior to transplantation of the marrrow.[73] Although this patient still suffers from the disease, this condition is improved and he is definitely chimeric. A 12-year-old boy suffering from variable immunodeficiecy was transplanted with marrow following immunosuppression with methotrexate; the transplant resulted in partial immunological reconstitution.[74] Bone marrow transplantation for the treatment of severe combined immunodeficiecy was originally designed to replace of deficient stem cell population and has been succesfully accomplished in more than a dozen patients around the world since 1968.[75-82] Until recently, this has only been possible when an HL-A/MLC identical sibling has been available as a marrow donor and, even then, has only been successful in approximately two thirds of all attempted marrow transplants.

In 1972, marrow from a maternal uncle differing from the patient by both HL-A haplotypes was employed to successfully reconstitute cell-

mediated immune function and partially restore humoral immunity to such a child.[80] The uncle's lmyphocytes were unresponsive in MLC to the patients's leukocytes, although the latter's cells were capable of stimulating lymphocytes from an unrelated person. Only a mild GVH reaction was observed beginning on day 12 with a morbiliform rash which lasted until day 21 following transplantation. This experience underscores the common belief that HL-A typing, previously thought to be important in avoiding fatal GVH reactions in such situations, is only of minor importance by itself and that MLC responsiveness is the main locus controlling histocompatibility matching for transplantation.

On the other hand, since the HL-A loci appear to be on the same chromosome pair as the MLC loci, the former markers can be utilized in family studies to identify the two chromosomal haplotypes of the patient which must be "matched" by the potential marrow donor. Hopefully, within the near future it will be possible to match at the MLC locus among unrelated persons; such donor-recipient pairs are expected to allow bone marrow transplantation without fatal GVH reactions This would be a major step toward successful transplantation of all organs if present theoretical considerations are correct.

Thymus transplantation has been employed mainly in patients lacking thymus. This procedure has been remarkably successful in reconstituting cell-mediated function, sometimes within hours of fetal thymus implantation, of almost all patients with thymic hypoplasia of Di George who have been transplanted.[52, 68, 83-85] Fatal GVH reactions have not been observed, although the implanted thymuses have all been obtained from unrelated fetal donors. Little is understood of how the immunologic reconstitution is accomplished in these infants since it has not been advisable to carry out investigative studies on such patient following transplantation. The reconstituted T-cells are of host origin:[86] the transplanted thymus was no longer detectable by biopsy of the transplant site (rectus abdominis muscle) in one patient thusly studied.[87] Implantation of thymus tissue inside a millipore chamber with a filter size which would prevent cells from entering or leaving the transplanted thymus, also resulted in a conversion of PHA responsiveness at six hours after implantation.[49] This approach does not seem justifiable as treatment for such patients, however, since animal studies have failed to document long-lasting immunologic reconstitution under similar experimental conditions.[88] In one instance of thymus transplantation to a seven-week-old infant with Di George syndrome, spontaneous improvement of in vitro lymphocyte responsiveness to allogenic cells was documented, in retrospect, just before the fetal thymus was implanted.[52]

This observation suggests again that many of the patients with Di George syndrome possess small amounts of thymus tissue which with time, might reconstitute their cell-mediated immune deficiencies without further treatment. On the other hand, if one weighs the almost negligible hazards of fetal thymus transplantation against the prognosis of infants with truly severe deficiencies of cell-mediated immunity, it does not seem advisable to wait very long for spontaneous recorvery to occur before attempting a transplant, even though immunologic reconstitution following thymus transplantation in many such infants may represent only an acceleration of an otherwise spontaneous recovery.

Two recent attempts, in collaboration with Aiuti and his coworkers in Rome, to recontitute cell-mediated immune function in older children with clearly documented deficiencies af T-cell populations, using again implantation of fetal thymus, have resulted in remarkable clinical improvement and normalization of percentages of T-and B-cells in the peripheral blood.[57] It was considered that perhaps both of these children were not suffering from a *primary* immunodeficiency but instead from a chronic, unresolved viral infection with concomitant depression of cell-mediated immunity and that the transplanted fetal thymuses acted to restore previously existing host responses to a point where the infection might be overcome. While such an interpretation is tenable it is difficult to ignore the family history of similarly involved siblings of both of these children, In one family, the mother also suffers from a cell-mediated immune defect and T-cell deficiency. Additional clinical experience will be necessary before these questions can be resolved.

One additional therapeutic approach deserves review: "transfer factor" (TF). While it is far from clear what this dialyzable extract from peripheral blood lymphocytes actually transfers along with delayed hypersensitivity skin reactivity to the antigens setted, some patients appear to be "improved" following its administration. Table II provides a very simplified overview of the results of two sizable studies.[89-91] testing the efficacy of TF on patients with various types of immunodeficiencies. About one-half of the patients with Wiskott-Aldrich syndrome have shown some clinical "improvement" following TF administration and conversion of skin test reactivity. This improvement has been mainly limited to a very dramatic disappearance of the eczema within several days of treatment. Platelet levels have not been significantly raised. The severity of subsequent infections and bleeding has been somewhat reduced in a few cases. Approximately one-half of the patients with chronic mucocutaneous candidiasis (CMC) have shown various degrees of clearing of the mucocutaneous candidiasis. Conversion of previously defici-

ent in vitro MIF production to relevant antigens following TF therapy has also been documented in some these patients.[89, 90, 92] In both the CMC and the Wiskott-Aldrich patients, it has been necessary to give multiple doses in most patients and the effect of TF apparently wanes after 5 or 6 months, necessitating repeated courses of treatment. In view of the heterogeneous nature of CMC and the singular resistance of this infection to therapy with antifungal agents, even these limited results are encouraging.

The efficacy of TF in the treatment of two cases of severe combined deficiency is difficult to explain without redefining the pathogenesis of the disease itself. Not shown in Table II, 4 of 7 patients with this diagnosis in Spitler's series demonstrated conversion of delayed hypersensitivity skin reactions; 3 of these 4 also produced MIF in vitro after TF administration. The "improvement" observed in two of seven patients was with regard to clearing of infections: in one child a disseminated herpes simplex infection was arrested. In the other patient, the MLC response was positive- an atypical finding in this disease as it has been heretofore defined (see discussion above).

TABLE II

TREATMENT WITH TRANSFER FACTOR

	"Improvement"
Spitler (78 patients)	
Wiskott Aldrich	12/24
Severe Combined IDD	2/7
Chronic Candidiasis	5/11
Common Variable IDD	1/2
Ataxia Telangiectasia	0/1
Partial Di George	1/1
Griscelli (14 patients)	
DCNB (+)	5/13
Ataxia Telangiectasia	3/5
Wiskott Aldrich	2/4
Severe Combined IDD	0/2
Common Variable IDD	0/2
Chronic Candidiasis	1/1

Finally, Griscelli et al.[91] have demonstrated that delayed hypersensitivity skin reactions to 2, 4 dinitrochlorobenzene (DNCB) became positive in 5 of 13 patients following administration of transfer factor

derived from lymphocyte donor who were not sensitive to DNCB themselves. This observation emphatically underscores our lack of understanding of TF and the mechanisms through which these empirical observations have been accomplished.

REFERENCES

1. Cooper, M. D., Faulk, W. P., Fudenberg, H. H., et al.: Classification of primary immunodeficences, N, Engl. J. Med. 288: 966, 1973.
2. Gatti, R. A., and Good, R. A.: Immunological deficiency diseases, Med. Clin. North. Am. 54: 281, 1970.
3. Report of a World Health Organization Committe: Primary immunodeficiencies, Pediatrics 47: 927, 1971.
4. Seligmann, M., Preud'Homme, J. L. and Brouet, J. C.: B and T cell markers in human proliferative blood diseases and primary immunodeficiencies, with specidal reference to membrane bound immunoglobulins, Transplant-Reviews. 16: 85, 1973.
5. Coombs, R. R., Feinstein, A., and Wilson, A. B.: Immunoglobulin determinants on the surface of human lymphocytes, Lancet 2: 1157, 1969.
6. Raff, M. C.: Two distinct populations of peripheral lymphocytes in mice distinguishable by immunoflourescence, Immunology 19: 637, 1970.
7. Klein, E., Eskeland, T., Inoue, M., et al: Surface immunoglobulin-moieties on lymphoid cells, Exp. Cell Res. 62: 133, 1970.
8. Brain, P., Gordon, J., and Willets, W. A.: Rosette formation by peripheral lymphocytes Clin. Exp. Immunol. 6: 681, 1970.
9. Pernis, B., Forni, L., and Amante, L.: Immunoglobulin spots on the surface of rabbit lymphocytes, J. Exp. Med. 132: 1001, 1970.
10. Siegal, F. P., Pernis, B. and Kunkel, H. G.: Lymphocytes in human immunodifeciency states: a study of membrane-associated immunoglobulins, Eur. J. Immunol. 1ı 482, 1971.
11. Rabellino, E., Colon, S., Grey, H. M., et al: Immunoglobulins on the surface of lymphocytes. I. Distribution and quantitation, J. Exp. Med. 133: 156, 1971.
12. Preud'homme, J. L., Klein. M., Verroust, P., et al.: Immunoglobulines monoclonales de membrane dans des leucemies lymphoides chroniques, Rev. Eur. Etud. Clin. Biol. 16: 1025, 1971.
13. Wilson, J. D., and Nossal, G. J.: Identification of Human T and B lymphocytes in normal peripheral blood and in chronic lymphocytic leukaemia, Lancet 2: 788, 1971.
14. Cooper, M. D., Lawton, A. R., and Bockman, D. E.: Agammaglobulinaemia with B lymphocytes. Specific defect of plasma-cell differentiation, Lancet 2: 791, 1971.
15. Papamichail, M., Brown, J. C., and Holborrow, E. J.: Immunoglobulins on the surface of human lymphocytes, Lancet 2: 850, 1971.
16. Fröland, S., Natvig, J. B., and Berdal, P.: Surface-bound immunoglobulin as a marker of B lymphocytes in man, Nature (New Biol.) 234: 251, 1971.

17. Lay, W. H., Mendes, N. F., Bianco, C., et al.: Binding of sheep red blood cells to a large population of human lymphocytes, Nature (Lond.) 230: 531, 1971.
18. Pernis, B., Forni, L., and Amante, L.: Immunoglobulins as cell receptors, Ann. N.Y. Acad. Sci 190: 420, 1971.
19. Grey, H. M., Rabellino, E., and Pirofsky, B.: Immunoglobulins on the surface of lymphocytes. IV. Distribution in hypogammaglobulinemia cellular immune deficiency, and chronic lymphatic leukamia, J. Clin. Invest. 50: 2368, 1971.
20. Kincade, P. W., Lawton, A. R., and Cooper M. D.: Restriction of surface immunoglobulin determinants to lymphocytes of the plasma cell line. J. Immunol. 106: 1421, 1971.
21. Nussenzweig, V., et al.: Receptors for C_3 on B lymphocytes: Possible role in the immune response. In Progress in Immunology. Ed. D. B. Amos, New York. Academic Press, 1971, .p 73.
22. Unanue, E. R., Grey, H. M., Rabellino, E., et al.: Immunoglobulins on the surface of lymphocytes. II. The bone marrow as the main source of lymphocytes with detectable surface-bound immunoglobulin, J. Exp. Med. 133: 1188, 1971.
23. Rabellino, E., and Grey, H. M.: Immunoglobulins on the surface of lymphocytes. III. Bursal origin of surface immunoglobulins on chicken lymphocytes, J. Immunol. 106: 1418, 1971.
24. Bach, J. F., Biozzi, G., Greaves, M. F., et al.: Summary of round-table dissussion on the technical aspects of the rosette test, Transplant. Proc. 4: 335, 1972.
25. Preud'homme, J. L., and Seligmann, M.: Primary Immunodeficiency with increased numbers of B lymphocytes contrasting with hypogammaglobulinemia, Lancet 2: 442, 1972.
26. Preud'homme, J. L., and Seligmann, M.: Immunoglobulins on the surface of lymphoid cells in Waldenström's macroglobulinemia, J. Clin. Invest. 51: 701, 1972.
27. Preud'homme, J. L., and Seligmann, M.: Surface bound immunoglobulins as cell marker in human lymphoproliferative diseases, Blood 40: 777, 1972.
28. Fröland, S. S., and Natvig, J. B.: Surface-bound immunoglobulin on lymphocytes from normal and immunodeficient humans, Scand. J. Immunol. 1: 1, 1972.
29. Papamichail, M., Holborow, E. J., Keith, H. I., et al: Subpopulations of human peripheral blood lymphocytes distinguished by combined rosette formation and membrane immunofluorescence, Lancet 2: 64, 1972.
30. Dickler, H. E., Kunkel, H. G.: Interaction of aggregated gamma globulin with B lymphocytes J. Exp. Med. 136: 191, 1972.
31. Froland, S. S.: Binding of sheep erythrocytes to human lymphocytes. A probable marker of T lymphocytes, Scand J. Immunol. 1: 267, 1972.
32. Stjernsward, J., Jondal, M., Vanky, F., et al.: Lymphopenia and change in distribution of human B and T lymphocytes in peripheral blood induced by irradiation for mammary carcinoma, Lancet 1: 1352, 1972.
33. Vitetta, E. S., Bianco, C,. Nussenzweig, V., et al.: Cell surface immunoglobulin. IV. Distribution among thymocytes, bone marrow cells, and their derived populations, J. Exp. Med. 136: 81, 1972.
34. Jondal, M., Holm, G., and Wigzell, H.: Surface markers on human T and B lymphocytes. I. A large population of lymphocytes forming non immune rosettes with sheep red blood cells, J. Exp. Med. 136: 207, 1972.

35. Lawton, A. R., Royal, S.A., Self, K. S., et al: IgA determination on B-lymphocytes in patients with deficiency of circulating IgA, J. Lab. Clin. Med. 80: 26, 1972.

36. Wybran, J., Carr, M. C., and Fudenberg, H. H.: The human rosette-forming cell as a marker of a population of thymus-derived cells, J. Clin. Invest. 51: 2537, 1972.

37. Aiuti, F., Lacava, V., and Fiorilli, M.: B lymphocytes in agammaglobulinaemia, Lancet 2: 761, 1972.

38. Aiuti, F. and Wigzell, H.: Funciton and distribution pattern of human T lymphocytes. I. Production of anti-T lymphocyte specific sera as estimated by cytotoxicity and elimination of function of lymphocytes, Clin. Exp. Immunol. 13: 171, 1973.

39. Dwyer, J. M., Bullock, W. E., and Fields, J. P.: Disturbance of the blood T:B lymphocyte ratio in lepromatous leprosy. Clinical and immunologic correlations, N. Eng. J Med. 288: 1036, 1973.

40. Preud'homme, J. L., Griscelli, C., and Seligmann, M.: Immunoglobulins on the surface of lymphocytes in fifty patients with primary immunodeficiency diseases, Clin. Immunol. Immunopathol. 1: 241, 1973.

41. Gajl-Peczalska, K. J., Park, B. H., Bigger W. D., et al.: B and T lymphocytes in primary immunodeficiency disease in man, J. Clin. Invest. 52: 919, 1973.

42. Gajl-Peczalska, K. J., Lim, S. D., Jacobson, R. R., et al.: B lymphocytes in lepromatous leprosy, N. Engl. J. Med. 288: 1033, 1973.

43. Wybran, J., Levin, A. S., Spitler, L. E., et al.: Rosette-forming cells, immunologic deficiency diseases and transfer factor, N. Engl. J. Med. 288: 710, 1973.

44. Aiuti, F., Fontana, L. and Gatti, R. A.: Membrane-bound immunoglobulin (Ig) and invitro production of Ig by lymphoid cells from patients with primary immunodeficiencies, Scand J. Immunol. 2: 9, 1973.

45. Aiuti, F. and Wigzell, H.: Function and distribution pattern of human T lymphocytes. II. Presence of T lymphocytes in normal humans and in humans with various immunodeficiency disorders Clin. Exp. Immunol. 13: 183, 1973.

46. Yata, J., Tsukimoto, I. and Tachibana, T.: Human lymphocyte subpopulations. Human thymus-lymphoid tissue (HTL) antigen-positive lymphocytes forming rosettes with sheep erythrocytes and HTL antigen-negative lymphocytes interacting with antigen-antibody-complement complexes. Clin, Exp. Immunol. 14: 319, 1973.

47. Yata, J. ,Gatti. R. A., Klein, G. Good, R. A. and Tsukimoto, I.: Lymphocyte subpopulations in immunodeficiency disorders. I. Human thymus-lymphoid tissue antigen, Clin. Immunol. Immunopath (in press)

48. Geha, R. S., Rosen, F. S. and Merler, E.: Identification and characterization of subpopulations of lymphocytes in human peripheral blood after fractionation on discontinuous gradients of albumin: the cellular defect in X-linked agammalobulinemia J. Clin. Invest. 52: 1726, 1973.

49. Steele, R. W., Limas, C., Thurman. G. B., et al.: Familial thymic aplasia. Attempted reconstitution with fetal thymus in a millipore diffusion chamber, N. Engl. J. Med. 287: 787, 1972.

50. Gajl-Peczalska, K. J., Biggar, W. O., Park, B. H., et al.: B lymphocytes in DeGeorge's syndrome, Lancet 1: 1344, 1972.

51. Lischner, H. W. Valdez-Dapena, M. A., Biggin, J. Hann, S. and Amoni, N.: Proliferative responsiveness of human B and T lymphocytes to phytohemagglutinin

(PHA) and Pokeweed mitogen (PWM). Presented at the Seventh Leukocyte Culture Conference. Quebec, Canada. 6-11 June 1972.

52. Gatti, R. A., Gershanik, J. J., Levkoff, A. H., et al.: DiGeorge syndrome associated with combined immunodeficiency. Dissociation of Phytohemagglutinin and mixed leukocyte culture responses, J. Pediatr. 81: 920, 1972.
53. Gatti, R. A., Gershanik, J. J., Levkoff, A. H., Wertelecki, W. and Good, R. A.: Combined system immumodeficiency with Di George Syndrome and dissociation of PHA/MLC responses In: Microenvironmental Aspects of Immunity. (Ed. B. D. Jankovic) Plenum Press. New York 1972 pp. 327.
54. Luzzati, A. L. and Jacobson, E. B.: Serum immunoglobulin levels in nude mice. Eur, J. Immunol. 2: 473, 1972.
55. Giblett, E. R., Anderson, J. E., Cohen, F., et al.: Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity, Lancet 2: 1067, 1972.
56. Rosen, F. S., and Janeway, C. A.: The gamma globulins. 3. The antibody deficiency syndromes, N. Engl. J. Med. 275: 769, 1966.
57. Aiuti, F., Businco, L. and Gatti, R. A.: Reconstitution of T-cell disorders following thymus transplantation In: Second International Conference on Immunodeficiency Diseases. Editor, J. Finstad-Good. National Foundation Press. New York (in press).
58. Abdou N. I., Casella, S. R., Abdou, N. L. and Abrahamsohn, I. A.: Comparative Study of bone marrow and blood B cells in infantile and acquired agammaglobulinemia J. Clin. Invest. 52: 2218, 1973.
59. Kincade, P. W., Lawton, A. R., Bockman. D. E., et al.: Suppression of immunoglobulin G synthesis as a result of antibody-mediated suppression of immunoglobulin M synthesis in chickens, Proc. Natl. Acad. Sci. U.S.A. 67: 1918, 1970.
60. Wu, L. Y. F. Lawton, A. R., Greaves, M. F. and Cooper, M. D.: Evaluation of Human B lymphocyte differentiation using Pokeweed mitogen (PWM) stimulation: in vitro studies in various antibody deficiency syndromes. In: Seventh Leuk. Conf. (Ed. F. Daguillard) Acad. Press, New York 1973. pp. 485.
61. Good, R.A., and Wortis, H. H.: Immune deficiency disease Thymic aplasia. Prog. in Immunology Ed. D.B. Amos, NewYork, Academic Press, 1971. p. 1271.
62. Bach, J. F., et al.: Personal communication.
63. Gatti, R. A.: Aetiology of vitiligo, Lancet 1: 91, 1972.
64. Ruiz-Maldonado, R., Mejia- Laguna, J., and Tamayo. L.: Actiology of vitiligo, Lancet 2: 1201, 1972.
65. Waldman, T. A., and McIntire, K. R.: Serum-alpha-fetoprotein levels in patients with ataxia-telangiectasia, Lancet 2: 1112, 1972.
66. Oxelius, V.: Unpublished observation.
67. Gatti, R.A., and Good, R.A. In: Current Pediatric Therapy 6. (Ed. S. Gellis and B. Kagan,) Philadelphia, W. B. Saunders, 1973, p. 143.
68. Cleveland, W. W., Fagol, B. J., and Kay, H. E.: Implant of fetal thymus in an infant with the III-IV Pharyngeal Pouch syndrome, J. Clin. Invest. 47: 20a, 1968.
69. Gatti, R. A., Meuwissen, H. J., Allen. H. D., et al.: Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet 2: 1366, 1968.
70. Gatti, R. A., Kersey, J. H., Yunis, E. J. and Good, R. A.: Graft-versus-host disease Prog. Clin. Path. 5: 1, 1973.

71. Vyas, G. N., Perkins, H. A., and Fudenberg, H. H.; Anaphylactoid transfusion reactions associated with anti-IgA, Lancet 2: 312, 1968.

72. Leikola, J., Koistinen, J. and Lehtinen, M.: IgA-induced anaphylactoid transfusion reactions. A report of 4 cases. Blood 1973 (in Press).

73. Bach, F. H., Albertini, R. J., Joo, P., et al.: Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome, Lancet 2: 1364, 1968

74. Rubenstein, A., Speck, B., and Jeannet, M.: Successful bone-marrow transplantation in a lymphopenic immunologic deficiency syndrome, N. Engl. J. Med. 285: 1399, 1971.

75. DeKoning, J., Van Bekkum, D. W., Dicke, K. A., et al.: Transplantation of bone marrow cells and fetal thymus in an infant with lymphopenic immunological deficiency, Lancet 1: 1223, 1969.

76. Amman, A. J., Meuwissen, H. J., Good, R. A., et al.: Successful bone-marrow transplantation in a patient with humoral and cellular immunity deficiency, Clin. Exp. Immunol. 7: 343, 1970.

77. Levey, R. H., Gelfand, E. W., Klemperer, M. R., et al: Bone-marrow transplantation in severe combined immunodeficiency syndrome Lancet 2: 571, 1971.

78. Stiehm, E. R., Lawlor, G. J., Jr, Kaplan, M. S., et al.: Immunologic reconstitution in severe combined immunodeficiency without bone-marrow chromosomal chimerism, N. Engl. J. Med. 286: 797, 1972.

79. Yamamura, M., Newton, R. C., James, D. C., et al.: Uncomplicated HL-A matched sibling bone marrow graft for combined immune deficiency, Br. Med. J. 2: 265, 1972.

80. Koch, C., et al.: Bone-marrow transplantation from an HL-A non identical but mixed lymphocyte-culture identical donor. Lancet 1: 1146, 1973.

81. Griscelli, C., and Seligmann, M.: to be published.

82. See Second International Conference on Immunodeficiency Diseases. Ed. J. Finstad-Good, National Foundation Press. New York (in press).

83. August, C. S., Rosen, F. S., Filler, R. M., et al.: Implantation of a foetal thymus, restoring immunological competence in a patient with thymic aplasia (Di George's syndrome), Lancet 2: 1210, 1968.

84. Cleveland, W. W., Fogel, B. J., Brown, W. T., et al.: Foetal thymic transplant in a case of DiGeorge's syndrome, Lancet 2: 1211, 1968.

85. Good, R. A. et al.: To be published.

86. Good, R. A., Gatti, R. A., Meuwissen, H. J., et al. Treatment and analysis of the DiGeorge syndrome, Lancet 1: 946, 1969.

87. Cleveland, W, W.: Personel communication.

88. Miller, J. F.: Thymus tissue as a therapeutic measure, N. Engl, J. Med. 287: 818, 1972.

89. Spitler, L. E., Levin, A. S., Stites, D. P., et al.: The Wiskott-Aldrich syndrome. Results of transfer factor therapy, J. Clin. Invest. 51: 3216. 1972.

90. Spitler, L. E., Levin, A. S. and Fundenberg, H. H.: Transfer factor II. Results of therapy. In: Second International Conference On Immunodeficiency Diseases, Ed. J. Finstad-Good, National Foundation Press, New York (in press).

91. Griscelli, C. Revillard, J. P., Betuel, H., Herzog, C. Touraine, J. L.: Transfer factor therapy in immunodeficiencies, Biomedicine 18: 220, 1973.

92. Rocklin, R. E., Chilgren, R. A., Hong, R., et al.: Transfer of cellular hypersensitivity in chronic mucocutaneous candidiasis monitored in vivo and in vitro. Cell Immunol. 1: 290, 1970.

93. Thivolet, T. et al.: First International workshop on nude mice. Aarhus, Denmark Oct. 1973.