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Editorial

A Proposed Classification of Primary Immunologic Deficiencies*

RAPID expansion of reporting and analysis of patients with primary immunologic deficiencies has accentuated the need for an acceptable, workable and flexible classification of these disorders. Faced with this need at a recent WHO Conference focusing on genetic controls in immunologic processes, the undersigned found it possible to agree to major criteria upon which such a classification, at least temporarily, might be based, and herewith submit a tentative categorization of these disorders. It is obvious that an ideal classification must ultimately be based upon knowledge of etiology, genetic control or pathogenesis. Since such definitive information is still not available for most diseases or syndromes featured by immunologic deficiency, any present classification must be considered provisional and should have structured within it flexibility permitting alteration with increasing knowledge.

In recent years several attempts have been made to develop a classification of these disorders based upon pathogenetic mechanisms [*1,2*], genetic control of immunoglobulin polypeptide chain synthesis [*3*] and clinical analysis [*4,5*]. These classifications have had the drawback of leaving many cases unclassifiable and hence have not won general acceptance. To fill the needs outlined, we believe a classification should improve on present nosology in the following ways: (1) avoid eponyms and designations by country whenever possible; (2) avoid confusing, misleading and inaccurate terminology such as "congenital" versus "acquired," "dysgammaglobulinemia," "dysplasia"; (3) avoid numbers based on concepts of priorities, which are often disputable, or on immunoglobulin patterns, which may be variable; and (4) avoid hypothetic pathogenetic mechanisms. Although such concepts may be most useful in guiding future studies and analysis, they cannot be used in formal classification until they are established beyond question.

The classification we propose is based upon syndrome analysis in terms of quantifiable cellular (lymphocytes and plasma cells), immunoglobulin and functional defects (humoral and cellular), pathologic characteristics (emphasizing thymus and peripheral lymphoid tissues), associated disorders and, finally, genetic or etiologic considerations.

As a basis for this classification we have attempted to employ the minimum number of characteristics and have limited the criteria for our headings and subdivisions to those that seem to us most useful in distinguishing one form of immunologic deficiency disease from the others (Table 1).

With respect to the immunoglobulin findings,

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TABLE

Syndrome	Cellular Defects		Immunologic Defects		
	Number of Circulating Lymphocytes	Number of Plasma Cells	Immunoglobulin Deficiencies	Humoral Antibody Response	Cellular Immunity Responses
Infantile sex-linked agammaglobulinemia (A) [6–9]	Normal	Absent	All classes extremely deficient	Absent or extremely deficient to all antigens	Normal
Selective inability to produce one class of Ig* IgA [10–15]	Normal	IgA-producing plasma cells absent, particularly in lamina propria	Both exocrine and circulatory IgA absent; others generally normal; IgM may be increased in secretions	Normal except for IgA antibodies	Normal
Transient hypogammaglobulinemia of infancy [17]	Normal	Deficient	IgG primarily depressed; (may have low IgG and IgM later in life) [18]	Generally low or absent to most antigens	Normal
Nonsex-linked primary immunoglobulin deficiency with variable onset and expression,† (primary immunoglobulin aberrations) [2,4,8,9,19–29]	Usually normal	Usually deficient but variable	Immunoglobulin deficit invariably present but class involved, degree and direction of change variable	Constant deficiency of responses to most antigens	Inconstant deficiency of responses to some antigens but not to others
Agammaglobulinemia with thymoma (B) [30,31]	Low and progressive decline often to extremely low levels	Deficient or absent	All markedly reduced	Constant deficient responses to all antigens	Constant deficiency in responses to most antigens
Immune deficiency with thrombopenia and eczema (C) [32–35]	Usually low and progressive decline	Normal	Immunoglobulin deficit usually present but class involved, degree and direction of change variable; (low IgM and high IgA frequent)	Constant deficient responses to some antigens but not others; (in particular, isohemagglutinins absent and failure to respond to carbohydrate-membrane antigens)	Constant deficient responses to most antigens
Ataxia-telangiectasia (D) [36–40]	Variable (usually slight decrease)	Variable (usually present)	Immunoglobulin deficit inconstant but usually present; class involved, degree and direction of changes variable (often low IgA)	Inconstant deficiency in response to some antigens but not to others	Constant deficiency in response to some antigens but not to others
Primary lymphopenic immunologic deficiency (E) [41–48]	Low but variable	Variable	Immunoglobulin deficit invariably present but class involved, degree and direction of change variable	Constant deficiency in responses to some antigens but not to others	Constant deficient responses to most antigens
Autosomal recessive alymphocytic agammaglobulinemia (F)‡ [49–52]	Very low	Absent	All extremely deficient	Absent or extremely deficient to all antigens	Deficient responses to all antigens
Autosomal recessive lymphopenia with normal immunoglobulins (G) [53,54]	Low	Present	All normal	Antibodies present,# probably deficient	Deficient responses to all antigens#
Thymic aplasia (H) [55–58]	Variable; mostly in normal range	Present	All normal	Many apparently deficient responses#	Absent responses to all antigens#

NOTE: (A) Bruton's disease [59]; (B) Good's syndrome [30]; (C) Wiskott-Aldrich syndrome [60]; (D) Mrs. Louis Bar's syndrome [61]; (E) Gitlin's syndrome [41]; (F) Glanzmann and Riniker's lymphocytophthisis (Swiss type agammaglobulinemia) [62]; (G) Nezelof's syndrome [53]; (H) DiGeorge's syndrome [55].

* Such selective deficiency for other classes of immunoglobulin has not yet been well documented.

† This group includes "acquired" primary deficits, "dysgammaglobulinemias" and "congenital" nonsex-linked forms of previous nomenclatures.

Pathologic Characteristics				
Thymus	Peripheral Lymphoid Tissue	Associated Disorders	Clinical Features Due to Immunologic Deficiency	Genetics
Normal	Germinal centers regularly absent in both normal and stimulated nodes; paracortical regions of nodes usually normal		Recurrent infections with extracellular pyogenic pathogens	X-linked recessive
? Normal	Normal in structure		Bronchitis, sinusitis. Enteropathy with malabsorption syndrome and steatorrhea. Some such subjects remain perfectly healthy	Unknown. Some may be autosomal recessive [16].
	Germinal centers rare or absent		Recurrent infections with extracellular pyogenic pathogens	Familial, ? genetic
Usually normal but involuted; data insufficient for definitive analysis	Germinal centers usually but not always absent; paracortical tissue often deficient; reticulum hyperplasia, tonsilar hyperplasia, infrequently giant follicular hyperplasia in nodes and spleen	High frequency of auto-immune disorders and of lymphoreticular malignancy. Some may have amyloidosis	Recurrent infections primarily with pyogenic pathogens. May have deficient resistance to virus and fungus infections	Possibly autosomal recessive in some
Thymic enlargement of stromal epithelial spindle cell type	Germinal centers deficient or absent; paracortical lymphoid tissue may be deficient	*Thymoma.* Eosinophils regularly absent or grossly deficient in blood and marrow. Associated pure red cell aplasia in some cases	Recurrent infections primarily with pyogenic pathogens. May have deficient resistance to virus and fungus infections	? Genetic factor
Normal	Germinal centers present, may be decreased; progressive deficiency of lymphocytes in paracortical regions	*Eczema and central thrombocytopenia;* high frequency of lymphoreticular malignancy	Frequent infections with all kinds of pathogens (pyogens, virus, fungi)	X-linked recessive
Embryonic type lacking cortical and medullary organization; no Hassall's corpuscles	Germinal centers usually present, may be decreased; lymphocytes deficient in paracortical regions; reticular hyperplasia in some instances	Progressive cerebellar *ataxia; telangiectasia* in all tissues; may appear late; ovarian dysgenesis in females; high frequency of lymphoreticular malignancy	Frequent sinopulmonary infections in cases with low IgA	Autosomal recessive
Thymus hypoplastic; deficiency of lymphoid cells and Hassall's corpuscles	Lymphocytes in tissues markedly deficient but foci of lymphocytes often present in spleen and lymph nodes		Often die in early childhood of fungus, pneumocystis or virus infection §	X-linked recessive or autosomal recessive, ? genetic factor in some
Thymus hypoplastic, often undescended, lacks lymphoid cells and Hassall's corpuscles	Absence or marked deficiency of lymphocytes		Do not survive infancy §	Autosomal recessive
Thymus hypoplastic, lacks lymphoid cells and Hassall's corpuscles	Lymphocytes markedly deficient; germinal centers may be present		Frequent virus, fungus or pneumocystis infection §	Autosomal recessive
Absence of thymus; failure of development of epithelium of 3rd and 4th pharyngeal pouch	Germinal centers present; lymphocytes scarce in paracortical regions	*Absence of parathyroids;* usually recognized as tetany of the newborn; frequent cardiovascular malformations	Usually die in infancy; frequent virus, fungus or pneumocystis infection in most cases	No evidence of genetic mechanism

‡ De Vaal [63] has described a disease entitled "reticular dysgenesis" featured by absence of plasma cells, lymphocytes, polymorphonuclears and anemia. Although immunologic studies have not been carried out, this disease probably represents a generalized immunologic deficiency disorder. In a similar case, the thymus was hypoplastic without Hassall's corpuscles [64].

§ Terminal event often initiated by live organism vaccine.

Well studied in only one published case.

it has seemed most useful to classify patients in the following way: (1) those in whom all immunoglobulin levels are extremely depressed; (2) those with entirely normal immunoglobulin levels; (3) we have purposely lumped together patients in whom all immunoglobulin levels are low but less depressed and those with a deficiency of only one or two immunoglobulin classes whereas the remainder are normal or increased (within this last group all combinations may occur and variable immunoglobulin patterns may be observed from time to time in the same patient or variations from one subject to another within the same family); (4) from the data available we have been able to accept only one form of immunoglobulin deficiency as a truly selective deficiency involving failure of production of a single immunoglobulin, without any other immunologic abnormality. This is, of course, the selective IgA deficiency originally described by Rockey et al. [*10*]. Doubtless, as the search continues, other instances of selective inability to produce IgM, IgG, IgD or IgE will be defined and will be included in this group. The recently described IgM deficiency in children dying of fulminating meningococcal septicemia [*65*] might represent such an example. The classification has been made flexible particularly in this regard. Some patients have normal or increased levels of each of the immunoglobulins but are deficient in both humoral and cellular immune responses [*66*]. No evidence of genetic mechanism has been established. This group has not been included in the present classification.

The classification seeks to bring out whether the patients have cellular or humoral immunologic deficits or both, whether these deficits hold for all antigens studied or only for some, and whether the deficits are constantly or inconstantly present. Included with cellular immunity responses can be those based on either *in vivo* (delayed hypersensitivity reactions) or *in vitro* responses. As the relationship of *in vitro* to *in vivo* responses becomes more clearly defined, the *in vitro* responses of peripheral lymphoid cells will surely play a role of increasing importance in evaluation of the immunologically defective patient. It must also be emphasized that deficiency of cellular immunity may be associated with normal numbers of circulating lymphocytes which do not respond to phytohemagglutinin and other stimuli [*58*].

In considering the immunologic deficits, we have not included homograft rejection in our definition. The immunologic process associated with graft rejection has been purposely eliminated for two reasons: (1) homograft rejections may reflect different immunologic mechanisms under different circumstances and (2) perhaps of greater importance is the consideration that ultimate attempts to achieve immunologic reconstitution of patients with immunologic deficiency may be compromised by prior experience with transplantation antigens.

The pathologic features brought into focus by our classification include thymic size and structure as well as histologic architecture of the peripheral lymphoid tissues. These features are difficult to evaluate quantitatively, but nonetheless represent a basic characteristic of diseases involving functions of the lymphoid cells.

It is to be recognized that our group of "primary immunoglobulin aberrations" (the nonsex-linked primary immunoglobulin deficiencies with variable onset and expression) probably represents a "waste basket" necessary at present because of inadequate information. Included in this group are all cases previously classified as "congenital" nonsex-linked or sporadic hypogammaglobulinemia, primary "dysgammaglobulinemias" of both childhood and adult life, "acquired" agammaglobulinemias and hypogammaglobulinemias. We grouped these forms together since none alone represents a homogeneous group. We believe that, at present, neither the date of onset nor the numerous immunoglobulin patterns justify separate classifications since much variability in both features has been noted from patient to patient in any subgroup and within families with multiple cases. For instance, patients with uniform depression of all immunoglobulins have been described in families in which several members have had one or another form of so-called "dysgammaglobulinemia." Moreover spontaneous variations in immunoglobulin levels have been observed from time to time in the same patient, and children described as having "dysgammaglobulinemia" with elevated IgM levels have at a later time been found to have very low levels of all immunoglobulins. Inversely, patients in this whole group of primary immunoglobulin aberrations seem to share other features which may justify a common grouping for the present. Careful study of many of the patients in this category has often revealed defects of cellular immunity responses. These pa-

tients also share a high frequency of lymphoid malignancy, autoimmune diseases and amyloidosis. It seems likely that as this group of patients is more definitively studied several subclasses based on established hereditary mechanisms or etiologic factors will be defined, making it possible to enlarge and strengthen the classification.

Other diseases featured by a combined (humoral and cellular) immunity deficiency with frequent "dysgammaglobulinemia" require separate consideration because of the precisely defined associated disorders and genetic transmission. They are, of course, the ataxia-telangiectasia syndrome and the Aldrich syndrome. Evidence is accumulating to indicate that the immunologic defect in the Aldrich syndrome involves primarily the processing of antigen—the afferent limb, so to speak.

Concerning the lymphopenic immunologic deficiencies, it is surely necessary to have more than one group. The basis of inheritance sharply separates the sex-linked form first described in Boston from the autosomal recessive forms. Absolute lymphocyte counts and degree of lymphoid development in the peripheral lymphoid tissues seem to provide a sufficient basis for another separation. The few cases in which the levels of all immunoglobulins are normal also justify separate consideration. Viewed from this perspective it seems to us likely that there are at least four groups: (1) patients with autosomal recessive inheritance and with almost complete lack of lymphocytes and plasma cells; patients with either (2) sex-linked or (3) autosomally transmitted diseases in which peripheral lymphoid development is much less completely depressed. In both of the latter genetic forms so-called "dysgammaglobulinemia" may be observed, plasma cells may be found and immunologic deficits may involve some antigens and not others. The similarities in the symptomatic, immunologic and pathologic analysis seem to warrant placing these two forms together provisionally. In addition, similar syndromes may be observed without evidence of a genetic mechanism. The fourth group, with autosomal recessive inheritance, is characterized by a profound deficiency of cellular immunity contrasting with normal immunoglobulin levels and a relatively intact humoral antibody response. In patients with the lymphopenic forms of immunologic deficiency, lymphoid cell chimerism always must be considered and represents an ever-present threat of confusion when one tries to analyze experiences with these patients. The foreign lymphoid cells could derive from blood transfusions [*67*] or from maternal transmission of lymphoid cells across the placenta [*68*]. Such chimerism should always be sought, particularly if the patient is male.

The precisely defined developmental abnormality of the immunologic deficiency described by Di George (congenital *absence* of the thymus due to defective embryogenesis) justifies separate classification. Of all syndromes presently defined, this one would seem the most approachable from a therapeutic point of view. A recent study suggests that this defect already may have been corrected by a transplant of embryonic thymus.

We do not make the question of the pathogenetic basis of the immunologic deficiency a major issue in this classification largely because of remaining uncertainties concerning the nature of thymic influence and the nature and site of the type of influence contributed by the bursa of Fabricius in birds.

The ultimate importance of etiologic considerations, and more precisely of processes of a nongenetic nature, has been brought into sharp focus by the study of patients with congenital, continuing rubella infection. Many affected infants have markedly deficient levels of IgG and increased levels of IgM during the virus excretory period, and in some persistent hypogammaglobulinemia has been observed [*69*]. In addition, circulating lymphocytes of these patients fail to respond to phytohemagglutinin [*70*] and this lymphocyte defect seems to be a direct effect of the rubella virus [*71*]. To judge from several reported cases it would seem that more profound immunologic deficiency and even "acquired congenital" agammaglobulinemia with histologic abnormalities of thymus and spleen may be one consequence of rubella virus infection occurring during the embryonic period. These observations point to the influence of environmental factors *in utero* on the development of the immunologic functions and this may become an important etiologic mechanism of some "primary" immunologic deficiencies. Inversely, many findings suggest that the so-called "acquired" agammaglobulinemias are often genetically determined: consanguinity in distant ancestors [*72*] and occurrence of the disease in siblings [*66,73*] have been observed; family studies have shown a high incidence of quanti-

tative immunoglobulin abnormalities and anti-gamma globulin factors in the asymptomatic relatives [*74–76*]; and, more recently, defects in lymphocyte metabolism have been reported in the parents of some of these patients [*77*].

The classification calls for needed attention, we believe, to the importance of studying in all detail possible and with the best quantitative methods available, many features in patients suspected of immunologic deficiency. The immunoglobulins of all classes must be quantified. In view of the recent finding of qualitative immunoglobulin abnormalities in some of these patients [*78–80*], it is also important for future analysis and better classification to quantify light chain types and heavy chain subgroups, to search for any tendency to electrophoretic homogeneity and for defects in biologic functions such as complement fixation. All these tests should, if at all possible, be performed prior to treatment with parenteral immunoglobulins. Of obvious importance is evaluation of responses of both humoral and cellular types to a standardized panel of antigens. In these evaluations live virus vaccines should be avoided because of the threat to many patients with immunologic deficiency of overwhelming or uncontrollable infections with the viruses thus introduced. We believe that *in vitro* lymphocyte response tests will be of increasing importance to classification as these tests become standardized and related to lymphocyte functions *in vivo*. It seems almost unnecessary to mention that a single blood lymphocyte count may be misleading and that serial counts may be needed to detect and define patients with lymphopenic agammaglobulinemia. The thymic region should be studied by appropriate roentgenologic technics. Rectal biopsies, and regional lymph node biopsies, especially following antigenic stimulation, are useful. Family studies should always be performed as well as careful search for prenatal infections or other prenatal influences. Chromosome analyses and a search for mosaicism of blood groups should be made and would help to establish the existence of chimerism. The greatest effort must be made to be certain that postmortem description should include the gross and histologic characteristics of thymus, lymph nodes, spleen, Peyer's patches, ileum, appendix and tonsils.

In conclusion, the classification here proposed seems to us to have some advantages over nosology and classifications currently employed. We present it with the hope that after suitable study and trial it can form the basis for the consideration of a universally acceptable nosology of immunologic deficiencies by an appropriate international body.

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