Section of Clinical Immunology and Allergy

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Immunological Deficiency Syndromes [*Abridged*]

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Classification of Immunological Deficiency Diseases

Resistance to infection depends on a number of structures and functions, some of which are listed in Table 1, with examples of quantitative and qualitative diseases of these functions. Specific immunity is the function of the last two systems shown and both quantitative and qualitative diseases of these occur, sometimes on their own, and sometimes together. All diseases need to be classified according to four systems – syndrome, structure, ætiological agent and ætiological mechanism (Soothill 1967) and we are making progress in doing this for the immunity deficiency diseases. We have come to recognize the effects of deficiency of humoral immunity – the antibody deficiency syndrome – as leading to recurrent bacterial infection, particularly to cocci (Gitlin *et al.* 1959) and the effects of deficiency of specific cellular immunity – the cellular immunity deficiency syndrome – with recurrent virus infections, moniliasis, pneumocystis carinii, diarrhœa and wasting, &c. (Nézelof *et al.* 1964, Fulginiti *et al.* 1966) – and the combined immunity deficiency syndrome with features of both (Hitzig & Willi 1961) (*see* Fig 1 and Soothill 1968).

Techniques for study of antibodies are far more advanced than those for study of cellular immunity. We have reason to believe that deficiency of the various immunoglobulins may occur in any combination, in patients with immunity deficiency states, sometimes even in individuals within the same family. We also have evidence that some patients' immunoglobulins may be functionally defective (Giedion & Scheidegger 1957, Soothill 1962) – present but lacking expected antibody activity (dysimmunoglobulinæmia); indeed some patients may respond to some antigens but not to others (Fulginiti *et al.* 1966, Blecher *et al.* 1968). Cellular immunity deficiency is sometimes associated with gross lymphopenia, but there may be normal numbers of circulating lymphocytes which do not respond to phytohæmagglutinin by transformation, so the possibility of 'dyslymphocytosis' must be considered. The analysis in Fig 1 points to at least 11 independent variables, and factorial 11 $\simeq$ 40 million possible syndromes. This is perhaps a less useful analysis than is provided by the three basic syndrome classes – antibody deficiency syndrome, cellular deficiency syndrome, and combined immunity deficiency syndrome (Soothill 1968). Though these three basic syndromes are not yet broken down into subdivisions associated with different clinical pictures, it seems likely that such will soon be recognized, as the different immunoglobulins almost certainly have different func-

Table 1

Some structures and functions relevant to resistance to infection with examples of deficiency diseases of each system, both quantitative and functional (reproduced from Soothill 1968 by kind permission)

	Example diseases	
Structure	*Quantitative deficiency*	*Functional deficiency*
Skin	Trauma	Eczema
Mucous membranes	Trauma	Cystic fibrosis
Polymorphonuclear leucocytes	Neutropenia	Chronic granulomatous disease
Complement	Hypocomplementæmia (C'_2)	–
Interferon	–	–
Immunoglobulins	Hypogammaglobulinæmia	Antibody deficiency syndrome without hypogammaglobulinæmia
Cellular immunity	Lymphopenia	Sarcoidosis

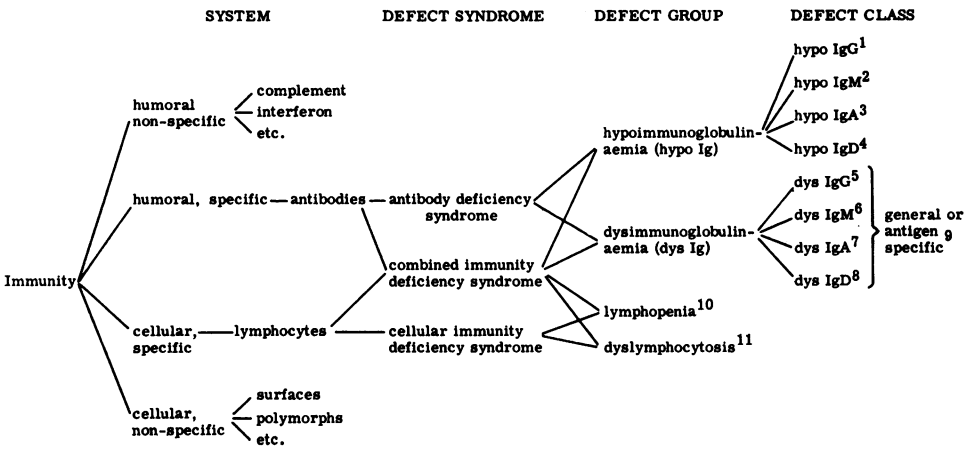

Fig 1 *A functional or syndrome classification of the immunity deficiency states, based on the current concept of the duality of specific immunity. Examples of nonspecific mechanisms are indicated but defects are not included. There is reason to believe that the eleven numbered parameters vary independently in these patients. (Reproduced from Soothill 1968, by kind permission)*

tions. The association of meningococcal meningitis with IgM deficiency (Hobbs *et al.* 1967) may well be one example, and the specific lack of IgA, which is especially secreted by mucous membranes would be expected to be specifically equated with gastrointestinal or upper respiratory infection though such patients may be remarkably symptomless (Rockey *et al.* 1964).

Progress is being made in the syndrome classification. Many descriptions of the morbid anatomy of immunity deficiency states have appeared, but there is need for systemization. Peterson *et al.* (1965) reviewed the morbid anatomy in terms of

Table 2
Morbid anatomical classification of immunity deficiency states

Peripheral lymph nodes	*Spleen*
Absent or few	Deficiency of follicles, lymphocytes, and plasma cells (IgG, A or M)
Reticular structures only with scanty small round cells	Or normal, hyperplasia of any component, or infiltrated
Small, with few follicular structures or plasma cells (IgG, A or M) but otherwise normal	
Lack of parafollicular zone	
Or normal, hyperplastic or infiltrated	
Gastrointestinal lymphoid tissue (including appendix and tonsil)	*Thymus*
Little or no organized lymphoid tissue	None detectable (? parathyroids absent)
Few lymphocytes in lamina propria	Small, deficient lymphoid cells and absent or deficient Hassall's corpuscles
Few plasma cells in lamina propria (IgG, A or M)	Normal structure with cortical lymphocyte depletion
Or normal	Normal structure with generalized lymphocyte depletion
	Or normal, hyperplastic, infiltrated, or necrotic

Present information suggests that there can be any combination of these defects of the different organs

the hypothesis of dual origin of immunity mechanisms – the thymus and a postulated equivalent of the avian bursa of Fabricius. But a statistically verifiable test of some of the impressions of correlations is needed, and Berry (1968) provides perhaps the first of these. The picture is almost certainly not a simple one but, apart from organs damaged by the effects of the immunity deficiency, the basic defects would be expected in peripheral lymph nodes, gastrointestinal tract lymphoid tissue, thymus, spleen and bone marrow. An indication of the range of observed defects is given in Table 2, and we really have no clear idea how they are related. Probably some of these distinctions are important. For instance, it is far more likely that it will be possible to populate with grafted immunologically competent cells a child with combined immunity deficiency if he has organized lymph nodes which lack lymphoid cells, than if he has virtually no lymph nodes at all.

We know so little about ætiology, in most cases, that it seems wisest to consider ætiological agents and ætiological mechanisms together (*see* Table 3). Even the effects of loss are not quite straightforward (Hobbs 1968), and, as knowledge advances, such concepts as primary or secondary, and acquired or congenital immunity deficiency become increasingly insecure.

The acquired congenital hypogammaglobulinæmia due to congenital rubella (Soothill *et al.* 1966) and the familial late-onset hypogammaglobulinæmia associated with a familial incidence of high levels of immunoglobulins, and other immunological abnormalities, possibly pointing to autoimmune phenomena (Fudenberg *et al.*

Table 3
Ætiological classification of immunity deficiency states

Genetic
Sex-linked → ADS
? Autosomal recessive (? other) → ADS, CIDS, combined IDS
Reticular dysgenesis
Aldrich's disease
With ataxia telangiectasia
DiGeorge's disease (with hypoparathyroidism)
Late-onset ADS with familial immunological abnormalities
Physiological
Neonatal IgM and IgA ADS
IgG trough
Transient ADS
Loss
Urine, gut, &c. → ADS
Experimental thoracic duct cannulation → CIDS
Environmental
Drugs, poisons, X-rays → ADS or combined IDS
Congenital rubella → ADS (? combined IDS)
? *Autoimmune* (? genetic)
Associated with neoplasia → ADS, CIDS and combined IDS

ADS = antibody deficiency syndrome
CIDS = cellular immunity deficiency syndrome

1962, Wollheim *et al.* 1964), illustrate this. None the less, there is good reason to believe that there is a sex-linked abnormality of antibody deficiency syndrome associated with deficiencies of one or more immunoglobulins, though even here there may be qualitative as well as quantitative deficiency of immunoglobulins (Soothill & Rowe 1968). The association of demonstrable immunity deficiency with odd symptom complexes which are familial, but for which there is no satisfactory unifying hypothesis, provides evidence of recognizable disease entities of genetic cause, such as Aldrich's disease, and immunity deficiency and ataxia telangiectasia. The details of the immunity deficiency syndromes in these diseases (they are probably of the combined type) need further study.

We can therefore make a start in the four-tier system of classification of immunity deficiency states, but the detection of correlations between these systems is only in its infancy.

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Secondary Antibody Deficiency

The antibody deficiency associated with certain conditions is believed to result somehow from those conditions and has, therefore, been called secondary. After defining criteria, I will consider the incidence and five ætiological categories of secondary antibody deficiency.

In 107 normal adults the serum immunoglobulin levels showed a log-normal distribution. The 2 SD ranges in mg/100 ml were γG 500–1,600, γA 125–425, γM 47–170: levels below these limits are called subnormal. *Severe hypogammaglobulinæmia* here follows the MRC criterion and is defined as a serum γG level of less than 200 mg/100 ml. At this very low level 70% of patients are known to suffer excessive infection due to antibody deficiency (Hobbs 1966). Hypogammaglobulinæmia can, of course, be detected by simple serum electrophoresis, but it is possible for an apparently normal γ-globulin to be associated with antibody deficiency, a condition for which the term dysgammaglobulinæmia is used. Strictly speaking,

Table 1
Frequency of immunoglobulin deficiency among patients at the Hammersmith Hospital

Subnormal serum γG levels of secondary type were found in 445 (2%) patients, though only 106 were proven as below 200 mg/100 ml. Secondary deficiency is commoner than primary

Severe hypogammaglobulinæmia (γG <200 mg/100 ml)	*No. of cases*
Total examined	20,000
Primary	10
Secondary	106 (0·5%) + 24●
Dysgammaglobulinæmia (γM/γA deficiency only)	
Total examined	11,000
Primary	59
Secondary	112 (1%)

● In this consecutive series 24 patients with γG-myelomatosis had severe reduction of normal serum immunoglobulins, but normal γG could not be measured