Immunity Deficiency Syndromes

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Resistance to infection depends on many functions, and the outcome of any infective episode depends on the balance between the virulence of the organism and the efficacy of these mechanisms. Interesting reciprocal relationships occur; defect of a general system can lead to recurrent infection at one site, with resulting local damage, and work on germ-free animals shows that infection plays an important part in maturation of immune mechanisms (congenital rubella confirms this in humans). As it is normal for infection to occur, defective mechanisms of resistance can be recognised only by the statistically insecure concept of increased incidence of infection. With a story of recurrent infection, we look for such defects as are recorded in Table 1, but many individuals have a remarkable incidence of infection without evidence

TABLE 1. Some structures and functions relevant to resistance to infection with examples of deficiency diseases of each system, both quantitative and functional

Function/structure	Example diseases	
	Quantitative deficiency	Functional deficiency
Skin	Trauma	Eczema
Mucous membranes	Trauma	Cystic fibrosis
Polymorphonuclear leucocytes	Neutropenia	Chronic granulomatous disease
Complement	Hypocomplementaemia (C'_2)	—
Interferon	—	—
Immunoglobulins	Hypogammaglobulinaemia	Antibody deficiency syndrome without hypogammaglobulinaemia
Cellular immunity	Lymphopenia	Sarcoidosis

of these defects. The first four functions listed are non-specific but the last two are specific. Although this review is concerned with specific mechanisms, the non-specific defects deserve a mention. Chronic granulomatous disease of children, a familial disorder of males, is fascinating because there is a failure of the bacteriocidal action of polymorphonuclear leucocytes, although phagocytosis is normal. Thus, the infecting organism is transported in the leucocyte, safe from other mechanisms of immunity, to reach lymph nodes,

spleen, liver, and bone marrow where granuloma formation takes place as phase two of local protection. This defect seems to be associated with an *X*-linked enzyme defect of cell carbohydrate metabolism, and the mothers may well have chromosomal mosaicism (Holmes *et al.*, 1966). Another point of special interest is how mild is the symptomatology of patients with profound lack of the complement component C'_2, as described first by Silverstein (1960) and in detail by Gewurz *et al.* (1966). A postulated defect of interferon would presumably be related to an abnormality of response to virus infection and, also, a profound disturbance of cellular organisation, so that it might well be fatal *in utero* before infection could become a problem (but *see* Baron and Isaacs, 1962).

TYPES OF DEFECTS OF SPECIFIC IMMUNITY

Specific immunity is divided into humoral immunity, the function of antibodies, and cellular immunity, a function of lymphocytes. We know more about humoral than cellular immunity, but, as they usually occur together it is not easy to recognise, for certain, their relative roles in immunity. A study of the effects of their defects helps in this. Cellular immunity, also called delayed hypersensitivity, can be tested by cutaneous response of the tuberculin type (including the powerful sensitiser dinitro-chloro-benzene), by certain *in vitro* tests, which are difficult to qualitate, and, possibly, by survival of a foreign graft; one can also count lymphocytes in the peripheral blood, although this is an inaccurate reflection of the total lymphocyte population. There are many tests for antibodies, but these are by no means as straightforward as might be expected; estimation of the four (or more) immunoglobulins provides a reasonable but incomplete study of antibody deficiency.

Experimental separation of immune mechanisms can be demonstrated in the fowl. A profound defect of the cellular system is caused by neonatal thymectomy and a defect of humoral immunity results from removal of the Bursa of Fabricius, a lymphoid structure near the cloaca (Warner *et al.*, 1962). The separation is not so tidy in mammals, but thymectomy in rats produces a defect of cellular immunity, with a characteristic deficiency of certain cells of the lymph node architecture (Parrott and East, 1964), and it is claimed that extensive surgical removal of gastrointestinal lymphoid tissue in rabbits results in a defect of humoral immunity (Sutherland *et al.*, 1965). There is evidence that the thymus also has a role in humoral immunity.

Human specific immunity defects can be viewed in the light of these concepts, and two basic syndromes distinguished. The antibody deficiency syndrome (Barandum *et al.*, 1959) results in numerous infections by bacteria, usually coccal, involving many sites. The cellular immunity deficiency syn-

drome, clearly established in its pure form by Fulginiti *et al.* (1966), results in an abnormal susceptibility to virus and monilial infections. The two disorders may occur together as the combined immunity deficiency syndrome (Hitzig and Willi, 1961). There is also, as shown in Table 2, the interesting

TABLE 2. Immunity Deficiency States

	Syndrome	Deficient mechanism	Possible basic defect	Example diseases
1	Antibody deficiency syndrome	Humoral immunity	Gastrointestinal lymphoid tissue deficiency or disturbance of function or loss, etc.	Hypogammaglobulinaemia in boys Dysgammaglobulinaemia Nephrotic syndrome
2	Cellular immunity deficiency syndrome	Cellular immunity	Thymus dependent lymphoid tissue deficiency or disturbance of function	Thymus aplasia
3	Combined immunity deficiency syndrome	1 and 2	Perhaps 1 and 2 Perhaps a more profound thymus deficiency, or a defect of a more primitive cell line	Lymphopenic hypogammaglobulinaemia Ataxia telangiectasia
4	Combined immunity deficiency syndrome and neutropenia	All reticular structures	Reticular dysgenesis	Reticular dysgenesis

phenomenon of profound leucopenia, assumed to be a defect of reticular structures.

In the antibody deficiency syndrome there is usually a lack of plasma cells, and lymphoid tissue of the gastrointestinal tract is often deficient. In the cellular immunity deficiency syndrome there is a lack of lymphocytes, though not always of the circulating cells, and the thymus is hypoplastic, as it is in the combined deficiency syndrome (Peterson *et al.*, 1965). Attempts have been made to equate antibody deficiency syndrome with the bursectomised fowl, and the combined immunity deficiency syndrome with a deficient thymus. However, the absence of parathyroids and thymus, which arise close together in the brachial arches, is associated with cellular immunity deficiency and normal immunoglobulin production (di George *et al.*, 1967) so the defect of combined immunity deficiency syndrome is at a more basic level—presumably a common cell line from which both forms of immunity arise, but not as elementary as the cell deficiency in reticular dysgenesis.

DEVELOPMENT OF IMMUNITY MECHANISMS

A child is born with incomplete mechanisms of immunity. He has a limited capacity to produce immunoglobulins and, therefore, antibody, and, as each contact with antigen is his first, he has the characteristic primary response, slow, low, and transient; even this may be limited. On the other hand, cellular immunity can be induced from birth (Uhr *et al.*, 1960). These limitations are partly compensated for by IgG antibody passively acquired from the mother, but this protects only against antigens to which the mother formed antibody, and, when it is used up, more must come from the baby himself. IgG is the only immunoglobulin to cross the placenta in any quantity, and it decays in the first weeks of life. The child's own production of immunoglobulins increases in the first weeks of life, IgM being the first to appear and to reach adult concentration. Production of IgA is the slowest. Gitlin *et al.* (1963) have pointed out that IgM antibodies are particularly effective in complement-dependent bacteriocidal action on Gram-negative organisms, and the lack of IgM antibodies early in life may explain the special susceptibility of infants to *E. coli* infections.

Similarly, as IgA is secreted actively in mucus of the respiratory, gastro-intestinal, and urinary tracts (Tomasi *et al.*, 1965) it might have a special local protective role in these vulnerable sites. This speculation is doubtful because healthy subjects can have a complete absence of IgA in serum and mucus (Rockey *et al.*, 1964).

HYPOIMMUNOGLOBULINAEMIA

The simplest explanation of antibody deficiency syndrome is lack of IgG, the predominant immunoglobulin. The low production rate of the newborn is physiological but a transient prolongation of this phase can occur (Gitlin and Janeway, 1956). Different types of disturbance are listed in Fig 1. The 'primary' causes are genetic or unknown. The best recognised familial syndrome is the sex-linked, which affects boys, but other familial syndromes, often associated with a defect of humoral immunity (as in Aldrich's syndrome and ataxia telangiectasia), indicate a variety of genetic causes (Good *et al.*, 1962). The association of hypogammaglobulinaemia with congenital rubella (Soothill *et al.*, 1966) indicates that 'congenital' may actually be 'acquired'. For the rest, 'cause unknown' is an appropriate label. Speculations on an autoimmune aetiology have been raised because of the appearance of autoimmune phenomena in patients or their families (Fudenberg *et al.*, 1962). These classifications can be applied with confidence only to certain cases.

Apart from such an attempt at an aetiological classification of patients with 'primary' hypogammaglobulinaemia, it is also possible to classify them by

levels of the other immunoglobulins. Despite some striking exceptions, it has been possible to show a significant tendency for consistency of immunoglobulin concentrations in the individual (Soothill *et al.*, 1967) but there is a considerable range of concentrations of the other immunoglobulins in patients

Cause	IgG	IgA	IgM	IgD
1. Physiological	→	→	→	→
2. Transient	↓	↓→	↓→	?
3. Loss	↓	↓→	↑→	?
4. Myelomatosis	↑^{x}→↓	↑^{x}→↓	↑^{x}→↓	↑^{x}→↓
5. Other secondary diseases of production	↓	↓→	↓→	?
6. Familial				
a) Sex-linked	↓	↓→	↓→↑$^{(x)}$	↓→
b) Non sex-linked (Thymus dysplasia)	↓→	↓→	↓→	?
7. Congenital rubella	↓	(↓)→	↑	?
8. Cause unknown	↓→(x)	↓→	↓→$^{(x)}$↑$^{(x)}$	↓→↑

x = immunoglobulin without detectable antibody function

(x)= immunoglobulin sometimes without detectable antibody function

↑ → ↓ = raised normal or low for age

Fig. 1. Antibody deficiency syndrome: quantitative disturbance of immunoglobulins.

with low levels of IgG, whether they are of the sex-linked form, the lymphopenic form, or not. Indeed, members of the same family with low IgG concentrations may have widely different concentrations of the other immunoglobulins (Soothill, 1967). Above all, it seems likely that the various defects are never absolute ones.

DYSIMMUNOGLOBULINAEMIA

The varied concentrations of different immunoglobulins have not been correlated clearly with syndromes. Moreover, the concentration of an immunoglobulin does not indicate its capacity as antibody; a qualitative defect of one immunoglobulin can be associated with a quantitative defect of another (Giedion and Scheidegger, 1957); for instance, IgM concentration may be low, normal or high in patients with IgG deficiency. Although

always absent when the IgM concentration is low, the iso-haemagglutinin and antibody activity expected of this protein cannot be correlated with its serum concentration (Soothill, 1962). It is also possible to have fatal antibody deficiency syndrome, with gross failure of antibody response to some antigens but not to others, but with normal concentrations of all immunoglobulins (Blecher *et al.*, 1967); this may well be so in Aldrich's syndrome (Krivit and Good, 1959).

Current literature in this field contains two diagnostic and semantic confusions. Patients, deficient in IgG, may have abnormal susceptibility to infection in spite of having abnormally high levels of IgM, which is effective antibody (Kekwick *et al.*, 1961; Cruchaud *et al.*, 1962) and which produces a normal γ globulin band on electrophoresis. On the other hand, immunoglobulin may be present, providing a normal γ band which is not effective antibody. Currently the word dysgammaglobulinaemia is used to cover both of these two fundamentally different situations. I suggest that the word

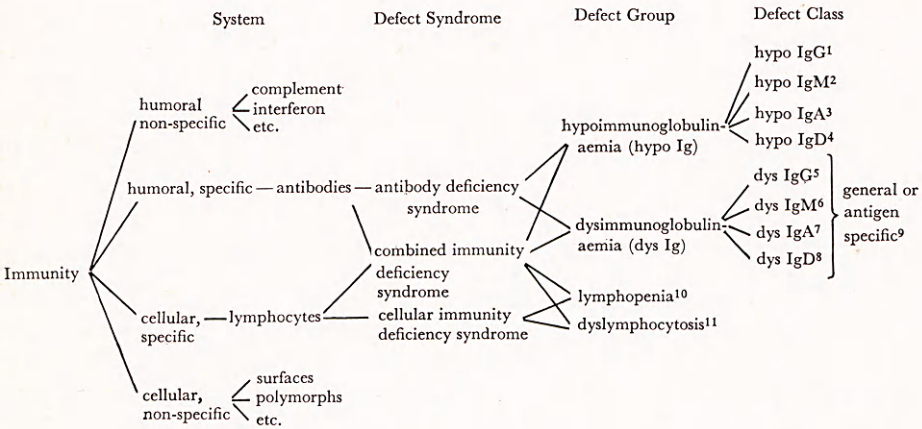

Fig. 2. A rational syndrome or functional classification of immunity deficiency states. The superior figures 1 to 11 indicate possibly independent variables in these conditions.

dysimmunoglobulinaemia, if awkward, should be kept clean and used only to describe functionally ineffective immunoglobulin.

CLASSIFICATION OF IMMUNITY DEFICIENCY STATES

Merely numbering the deficiency states leads to mathematical chaos as so many variables are involved. A systematic approach to classification, based on syndrome, is outlined in Fig. 2. The structure of this classification permits tidy thought and advances in methodology will allow an expansion of the details.

TREATMENT

The possible methods of treatment, as yet of limited value, are listed in Table 3. Individual infections respond well to available chemotherapy. These include tuberculosis (Soothill, 1967) and the interesting *Pneumocystis carinii* pneumonia

TABLE 3. Possible Lines of Treatment for Immunity Deficiency States

1. Chemotherapy of individual infections
2. Prophylactic antibacterial drugs
3. Replacement of γ-globulin
4. Replacement of deficient cells
5. Immunisation
6. Suppression of causative diseases
7. Prevention

(Marshall *et al.*, 1964), the commonest cause of death in boys with hypogammaglobulinaemia. Progressive virus infections, such as vaccinia, associated with the cellular immunity deficiency syndrome, are a challenging problem for viral chemotherapy.

Prophylactic antibacterial drugs and γ globulin have a place in treatment. The use of γ globulin is, however, not without risk. Alarming and sometimes fatal reactions may occur, although boys with affected male relatives apparently do not suffer from them (Soothill *et al.*, 1967).

As patients affected by cellular immunity deficiency accept foreign grafts, there is the possibility of more fundamental treatment for them. Attempts to replace their immune mechanisms are under way in many centres but so far no useful therapy has been evolved, although some effect of treatment has been demonstrated. Since it is probable that none of these defects is absolute, immunisation would seem worth while. But only dead antigens should be used, to avoid the risk of dissemination of attenuated organisms, with potential return of their virulence.

If autoimmunity does play a part in some of these diseases, suppressive therapy could play a part, and there is some evidence of its effect (Soothill, 1967).

But medicine's main role must be prevention. Apart from a eugenic approach, the recognition of antibody deficiency syndrome due to congenital rubella (Soothill *et al.*, 1966) permits a more active and immunological approach, by immunisation of all women against rubella.

CONCLUSION

I have confined my remarks to defects of immunity mechanisms in these patients and have omitted any reference to other aspects of these syndromes

that present fascinating fields for speculation and study. More detailed reviews have been written by Gitlin *et al.* (1959), Good *et al.* (1962, 1967), Peterson *et al.* (1965) and Soothill (1967). We know that the recognised phenomena explain the abnormal susceptibility of only a very small proportion of the patients with an impressive tendency to recurrent infection. Even these defects are very incompletely understood, and clearly there are many more defects to be found, investigated, treated and prevented.

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