Genetics of Immunity Deficiency Syndromes

The concept of immunity deficiency implies a definable range of normal immune reactivity from which a significant deviation can be detected and, perhaps, described in detail. In the past 20 years progress in experimental immunology has increased our understanding of both antibody and cell-mediated immunity, and of the thymus and lymphoid system as a whole. In clinical medicine a parallel advance, due in part to the prolongation of lives at risk by antibiotics, has led to the recognition of a variety of syndromes of immune deficiency. All are more or less rare but in many a hereditary element is clear and in some the basic pathology of the defect can be analysed. (For classification see Seligmann, Fudenberg, and Good, 1968.)

Many uncertainties remain. Thus, whereas most deficiencies are manifest in infancy or childhood and the genetic basis is quite plain, other defects may only be discovered in adult life when hereditary influences may be overlooked. The situation is further confused through the mimicry of genetic disease by infection, e.g. rubella, acquired *in utero*, and by the obscure role of materno-fetal immunocyte chimerism.

Modern analysis of specific immune processes in vertebrates has distinguished a number of components. These include 'effector' cells concerned with both antibody and cell-mediated immunity, as well as 'reactor' (antigen-sensitive) lymphocytes, memory cells, and macrophages. The latter, together with polymorphonuclear neutrophils and those cells that synthesize substances such as leucotaxins, are also primarily responsible for the function of the more primitive processes of non-specific immunity. The interdependence of all these components and the development of the whole system, comprising cell migration, proliferation, inductive processes, and differentiation, give rise to a large number of steps at which failure may occur but which also afford some opportunity for compensatory balance.

The most clearly defined and commonest group of disorders is that of the antibody-forming system,

essentially a failure of the effector end-cells, the plasma-cells. As the known number of different fractions of immunoglobulins increases, so the number of discoverable and discovered deficiencies grows. In congenital hypogammaglobulinaemia, as originally described by Bruton (1952), all classes of immunoglobulin are affected but in variable degree from one case to another and from one family to another. X-linkage is the commonest mode of inheritance but a similar syndrome affecting girls also is probably due to an autosomal recessive gene.

More selective deficiencies have been described such as that of IgM alone, which is associated with a tendency to overwhelming meningococcal infection (Hobbs, Milner, and Watt, 1967). Absence of IgA (Rockey *et al.*, 1964) is frequently a symptomless condition and has been estimated to have an incidence of 1 in 700 (Bachmann, 1965). Interest has been aroused by its detection in 4 out of 12 cases having congenital abnormalities of chromosome 18 (18q- or 18r), either a long arm deletion or a ring chromosome. Such a small number of cases might still be merely a fortuitous association but if confirmed an explanation is required. Finley *et al.* (1969) suggest that loss of a gene in a heterozygote is less probable than the persistence of a fetal pattern of immune activity (developmentally IgA is the latest globulin to be formed), and quote the analogy of fetal haemoglobin formation in trisomy D (Edwards') syndrome. However in Edwards' syndrome immunological abnormalities have not been observed. Possibly relevant is the finding of 18q- in a proportion of cases of various lymphomas (Spiers and Baikie, 1966; Millard, 1968; B. R. Reeves, 1970, personal communication); only a minority (6 out of 40) show this change in the neoplastic cells, but the several connexions which link states of immune deficiency with the formation or progression of lymphomas suggest that there is an interesting field for inquiry into the role of chromosome 18 in cells of the lymphoid system.

The number of possible antibody deficiencies is greatly increased if we add those conditions in which antibody formation is defective, though the levels of

the immunoglobulin fractions are normal (Fulginiti *et al.*, 1966; Blecher *et al.*, 1968). It is highly probable that such states, comprising a wide or narrow range of antibody defect, do exist, but they are, of course, less easy to detect and it is more difficult to distinguish an inherited from an acquired defect. The range of abnormalities may be ascertained when the precise mechanism of diversification in antibody-forming cells is known. There is some evidence (Hong, Pickering, and Good, 1968) that in congenital hypogammaglobulinaemia the small quantities of globulin which are formed lack heterogeneity in their structure, so that the basic fault may be in the process of cellular diversification rather than a rate-limited step in biochemical synthesis.

The converse of a pure antibody-deficiency syndrome, in which cellular immunity appears to be entirely normal, should be a syndrome of purely cell-mediated deficiency. Such a condition may exist but if so it is rare, and the slender evidence can be interpreted in other ways. Certainly in the very rare Di George syndrome (Di George, 1968), where the thymus is absent (together with absence of the parathyroids, anomalies of the aortic arch and sometimes other defects), cellular immunity is depressed and immunoglobulin levels are normal, but the antibody responses to certain antigens tend to be somewhat depressed also.

Nothing is known of the genetic basis of this condition, but therapy, in the form of thymic transplantation, confirms the notion that the lack of a thymus is the primary abnormality (Cleveland *et al.*, 1968; August *et al.*, 1968). Transplantation of fragments of fetal thymus have, in two cases, been rapidly succeeded by the development of normal cutaneous hypersensitivity tests, rejection of skin allografts, and responsiveness of lymphocytes to phytohaemagglutinin. Indeed the rapidity with which these changes occurred has raised questions as to the mode of action of the graft. In experimental animals it can be shown that these aspects of cellular immunity depend very much, in the short term at least, on donor type thymic cells (Davies *et al.*, 1968). These were not detected in the two treated cases and a more probable hypothesis postulates a thymic hormone as an essential mediator of graft function. Despite much controversy the existence of such a hormone must be counted as probable (Davies, 1969; Stutman, Yunis, and Good, 1969; Goldstein *et al.*, 1970).

The other syndrome in which cellular immune deficiency is associated with normal or near normal antibody synthesis has been termed the Nezelof syndrome (Nezelof *et al.*, 1964). It is exceedingly rare

so that the genetic basis remains uncertain; indeed the very existence of the syndrome as a separate entity is in some doubt. The thymus in the described cases is small and atrophic, resembling that in the somewhat commoner disorders of combined immunity deficiency of which it may be a variant for reasons outlined below.

As the name implies the combined immunity deficiency syndromes display both humoral and cellular defects, resulting in an extreme susceptibility to infections and a fatal outcome, usually in infancy. That originally described by Glanzmann and Riniker (1950) may be termed the 'Swiss' type (Hitzig, Barandun, and Cottier, 1968): it is inherited as an autosomal recessive and the peripheral lymphocyte count is characteristically low ($<1000/\text{cu. mm.}$). By contrast the 'American' type (Rosen, Gitlin, and Janeway, 1962; Miller and Schieken, 1967) seems to be inherited as a sex-linked recessive and blood lymphopenia is not a feature. In a third and perhaps distinct syndrome (Davis, 1966; Gatti *et al.*, 1969), there is also a dysplasia of cartilage with dyskeratosis of skin and oesophagus; and a similar histological pattern of thymic hypoplasia is also seen in another milder form of combined deficiency, that associated with cerebellar and vascular defects—the syndrome of ataxia-telangiectasia (Louis-Bar, 1941; Peterson, Cooper, and Good, 1966). This is determined by an autosomal recessive gene and has a more prolonged but always fatal course in which the development of a lymphoma may be the ultimate even.

Knowledge of the pathways of stem-cell migration and of the interactions of the lymphoid tissues suggests that the defects in these syndromes could lie either in the thymus or, more probably, in the primitive stem-cells from which the immune system as a whole is derived. The only direct evidence comes from recent attempts at transplantation. In contrast to the results in thymic aplasia, thymic transplants in the syndrome of combined immunity deficiency have given, at the best, a very temporary and partial effect (Hitzig, Kay, and Cottier, 1965; Kay, 1968). On the other hand stem-cell suspensions from bone-marrow or fetal liver, especially when typed for histocompatibility, have been able to colonize the lymphoid tissues, with resultant development of antibody and cellular immune capacities (Gatti *et al.*, 1969; De Koning *et al.*, 1969; J. F. Soothill and H. E. M. Kay, 1970, unpublished data). The primary defect must therefore lie in the native stem-cell population.

The main hazard in transplantation is that a graft-against-host reaction may occur, clinically manifest by dermatitis, diarrhoea, wasting, fever, and death.

Only when tissue-typed compatible sibs have been available as donors has the outcome been truly successful, and even in these circumstances a mild reaction has been noted. In the absence of compatibility the benefits of graft function have been rapidly succeeded by the ill consequences of graft-against-host disease (Hong *et al.*, 1968). The pathological signs of this reaction include two of some interest and importance: bone-marrow aplasia which is rapid and may be accompanied by histiocytosis (Hathaway *et al.*, 1965), and plasma cell proliferation in the bone-marrow and lymph nodes (Harboe *et al.*, 1966).

Similar consequences have also followed lesser procedures such as fresh blood transfusion. As little as 125 ml. blood containing 250 million lymphocytes has been fatal in an infant of 11 months (Hathaway *et al.*, 1967), and it is pertinent to ask whether similar effects may occur if enough maternal lymphocytes cross the placenta to colonize the fetus. This may occur transiently (Turner, Wald, and Quinlivan, 1966) but is unlikely to cause any great disturbance after the development of the immune system at the end of the first trimester, since the maternal cells could be rapidly rejected.

In an immune-deficient fetus, however, rejection would not occur and the maternal cells may persist and function as has been observed in 3 cases (Kadowaki *et al.*, 1965; Di George, 1968; Githens *et al.*, 1969). The precise consequences then depend on the histocompatibility relationships of mother and fetus and the number of cells that cross the placenta. Antifetal reactions will usually predominate, but there might be instances where the absence of strong fetal antigens or other circumstances would induce a partial tolerance on the maternal cells which might then be available to act as effector cells against third party antigens. Such could be the case in those examples of immunity deficiency with cellular impairment but normal globulin levels. In suitable cases the true situation could be deduced, since, in addition to chromosome analysis of lymphocytes, it would sometimes be possible by allotyping of serum globulins to detect that these contained an antigen determined by a paternal gene if, in fact, the globulins were made by the infant's own cells. In an instructive investigation of this sort, it was shown that cells transplanted from a fetal donor were the source of all the globulin formed in a recipient infant (Harboe *et al.*, 1966).

Clearly the role of materno-fetal chimerism has to be further explored. At present it would be unwise to assume either that such chimerism when detected has been responsible for the immune deficiency or that the failure to demonstrate maternal cells in

affected infants excludes their presence or their role in the disease.

It is interesting also to speculate whether fetuses with a normally developing immune system might ever be affected by maternal immunocytes. It is probable that transgression of the placental barrier in the early stages of gestation, before the fetal lymphoid system is developed, would be attended with fatal results. Later, maternal cells would be rejected except in the rare instances where they contained no antigen foreign to the fetus—an experimental parallel is the transplantation of pure line to F1 hybrid animals causing graft-against-host reactions. This might occur by chance very rarely, and the risk would be very much increased if there were consanguinity in the maternal lineage causing homozygosity of maternal histocompatibility antigens.

Two other conditions affecting specific immune mechanisms need to be mentioned. The first is the Wiskott-Aldrich syndrome which has a sex-linked recessive inheritance and is manifest in childhood rather than infancy (Cooper *et al.*, 1968). The defect appears to be confined to reactions to polysaccharide and mucoprotein antigens such as blood group substances and some bacterial antigens; both cellular and humoral functions are affected. Cooper has suggested that the fault lies in a failure by macrophages to process the antigen in such a way that the immunocytes can react specifically. In the early stages there are no anatomical abnormalities but later there is histiocytic hyperplasia and lymphomas may develop. The precise pathogenesis of the lymphomas in this condition and in ataxia-telangiectasia is uncertain but the possibility that viruses, which fail to be rejected because of immune defects, are causative has some experimental support (Allison, 1970).

The other group of immune deficiency diseases which may have in part a hereditary origin are those appearing late in life and often spoken of as 'acquired' (Wollheim, 1968). Careful inquiry among relatives of cases of adult agammaglobulinaemia has often revealed other cases or other states of immune dysfunction, including macroglobulinaemia, autoimmune haemolytic anaemia, etc. The precise factor that might be inherited and the mode of transmission are obscure but the most plausible hypothesis is of an inherited instability in the homeostasis of immune activity or of a defect in the mechanism for antigen recognition. However the part played by viruses or mycoplasmas cannot be ignored. In congenital rubella their causative role in a deficiency, which is of both antibody and cell-mediated forms, is clear, and similar

infective factors may be operative in families with adult agammaglobulinaemia. The fact that a similar predisposition to autoimmune phenomena can be accompanied by constitutional abnormalities of the X chromosome does not deny the possible aetiological primacy of an infective agent. The subject has been discussed in detail by Fudenberg (1967) and by Fialkow (1969).

There remain the disorders of the non-specific system of immunity in which certain factors such as leucotaxins (Miller *et al.*, 1968; Chilgren *et al.*, 1969; Ward and Schlegel, 1969) or the components of the complement system may be deficient (Austen, Klemperer, and Rosen, 1968). Most of these syndromes are too rare for their genetic basis to be certain, but hereditary angioneurotic oedema due to absence or non-function of the inhibitor of the first component of complement is inherited as an autosomal dominant. The disease has an appreciable mortality through the complication of laryngeal oedema, which implies that the incidence of spontaneous mutation must be fairly frequent. The existence of non-functional inhibitors in some pedigrees may indicate the occurrence of several different mutations leading to the same end-result.

Absence or inhibition of leucotaxins is responsible for chronic cutaneous candidiasis; the condition is rare, but one case appears to have been cured by a transplant of paternal bone-marrow cells though only incomplete evidence of graft persistence by leucocyte typing was obtained (Buckley *et al.*, 1968). The case raises again the possibility that minority populations of foreign cells may persist and function without being readily detectable by chromosomal or other techniques.

Perhaps the most fascinating genetic problem in this group of disorders is that posed by chronic granulomatous disease. The defect resides in the inability of polymorphonuclear granulocytes to kill ingested bacteria and appears to depend, in one form at least, on a biochemical fault in the hexose monophosphate shunt. The typical patients are all boys, and the published pedigrees (Windhorst *et al.*, 1968) strongly support the natural hypothesis of an X-linked recessive gene. Tests have been devised to diagnose the disease and also, it is claimed, to detect the carrier state among the female relatives. The results from these tests are not as consistent and well defined as one would wish, but they do accord with the assumption of random clonal inactivation of the X chromosome in the female even to the point of minor degrees of morbidity (recurrent furunculosis) in a few females.

This clear sky of hypothesis has recently been darkened by the discovery of Soothill and his

colleagues (Thompson *et al.*, 1969) that the fathers and other male relatives of the affected boys may also show abnormalities in leucocyte function tests similar to those of the heterozygous carrier females. They postulate, therefore, an autosomal recessive gene, the expression of which is influenced by sex, females being more severely affected. The rarity of females with the disease is ascribed to early lethality in homozygous females; homozygous boys, of course, show the classical disease, while a few heterozygous females may, as has been noted, show a minor degree of leucocyte dysfunction.

Both hypotheses leave questions to be answered: is there a deficit of female births? how common is consanguinity in the parents? what is the meaning of the minor leucocyte abnormality in the fathers of patients? and very probably the answer will be that both methods of inheritance are possible and that two or more similar conditions exist, in either of which there is wide variation in gene expression. If so, the syndrome will fall in line with other immunity deficiencies, most of which have proved on inquiry to be a complex of related disorders rather than a single entity. Their study, complicated though it is by inevitable infections and other extraneous influences, will continue to provide valuable evidence on the mechanisms of immune function in man and their genetic control.

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Corrigendum

Annotation: Genetics of Immunity Deficiency, Syndromes, by Kay, December 1970, Vol. 7, p. 310, in the section discussing IgA deficiency, column 2, lines 29-31 should read

... the analogy of fetal haemoglobin formation in trisomy-D (Patau's syndrome). However in trisomy-E (Edwards' syndrome) immunological abnormalities have not been ...