Immune deficiency diseases

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Paediatricians have long been deeply concerned with problems of infection. The sharp decrease in childhood mortality in recent decades in highly developed countries is mainly due to progress in preventing and treating infection: for example, in Switzerland in 1973 there were about 88 000 births and only 16 deaths due to infection in children aged between 2 and 4 years in contrast to 76 killed by accidents. In underdeveloped countries more than 50% of the children die during childhood, infection being a predominant cause.

Individual differences in the ability to cope with pathogens have been assumed for a long time, but were not studied scientifically until the introduction of antibiotics had resulted in control of the major infections. At this time paediatricians began to pay more attention to constitutional and inherited diseases, and made observations on congenital deficiencies of selective defence mechanisms which have contributed to a better understanding of the normal immunological functions.

The basis of the currently used classification of primary immune deficiency diseases is the 'two-component concept' (Cooper, Paterson, and Good, 1965; Good and Fisher, 1971). Its main postulate, the distinction between T and B lymphocytes, is well known, and provides a useful working hypothesis clinically.

Methods of Study

Many methods for measuring immune reactions have been devised in the last two decades. They distinguish between cell-mediated and antibody-mediated immune reactions, which correspond almost completely with T- and B-cell-mediated reactions respectively.

Simple *in-vivo* procedures have been used for many years. Thus, circulating antibodies are detected by an immediate skin reaction after intracutaneous administration of the corresponding antigen. In contrast the cell-mediated reaction needs time to develop; it is therefore a reaction of delayed hypersensitivity. For both tests the patient must be exposed to the antigen, which is not only painful but involves

also the danger of hyperergic reactions. Therefore, *in-vitro* tests are preferable.

CELL-MEDIATED RESPONSES

The simple count of circulating lymphocytes gives one important figure. The size of some lymphoid organs can roughly be estimated by palpation. The thymus can be visualized radiologically, and its histology can be studied if a biopsy is available. Most important, however, are functional methods for measuring the reaction of the lymphocyte to an exogenous antigenic stimulus. The lymphocytes are activated to undergo mitosis, which can be assessed by various methods, most accurately by the measurement of incorporation of precursor substances such as ³H-thymidine into DNA. The stimulus may be homologous cells, specific antigens, or non-specific plant mitogens like phytohaemagglutinin (WHO report, 1970).

ANTIBODY-MEDIATED RESPONSES

Humoral immune mechanisms can be evaluated by the overall determination of circulating immunoglobulins but more accurately by titration of specific antibodies. When a functional method is used to determine the response to antigenic stimulation, the change in serum antibody titres can be measured as well as the anatomical changes in the lymphoid organs.

In addition to these classical methods, a new principle was introduced two years ago: by chance, a previously well known enzyme, adenosine deaminase (ADA), was shown to be important for immune reactions by observations on patients who had both congenital absence of the enzyme and immune deficiency. It turned out that ADA might be a key enzyme for the synthesis of DNA. This is of interest, because only the homozygous individual shows an immune deficiency, the heterozygous parents being phenotypically normal.

Classification

PRIMARY IMMUNE DEFICIENCY SYNDROMES

A number of clinical immune deficiency syndromes

Immunodeficiency Syndrome	Suggested Cellular Defect			Inheritance		
	B Cells		T Cells	X-linked	Autosomal Recessive	Other
	Absent	Present	Absent			
X-linked agammaglobulinaemia	x	(x)		x		
Thymic hypoplasia			x			x
Severe combined IDS	x	x	x	x	x	x
With dysostosis	x	?	x		x	
With ADA deficiency	x		x		x	
With generalized haemopoietic hypoplasia	x		x		x	
Selective Ig deficiency						
IgA	?	x	(x)			x
Others		?				x
X-linked IDS with increased IgM		x		x		
IDS with ataxia teleangiectatica		x	x		x	
IDS with thrombocytopenia and eczema (Wiskott-Aldrich syndrome)			x	x		
IDS with thymoma		x	x			x
IDS with normo- or hypergammaglobulinaemia	x	x	(x)			x
Transient hypogammaglobulinaemia of infancy		x				
Variable immune deficiencies (largely unclassified and very frequent)	x	or x	(x)		(x)	x

Table I Classification of primary immune deficiency syndromes (WHO Committee, February 1973)

can be convincingly classified on the basis of the T and B cell defects (Cooper *et al*, 1974) as shown in table I. There is also reason to hope that the concept will accommodate any new and more refined clinical findings in the future. However, some well delineated diseases, especially ataxia telangiectatica and thrombocytopenia with eczema, are not adequately explained on this basis (for detailed references see Stiehm and Fulginiti, 1973; Hitzig, 1974).

The following syndromes are of importance for clinical chemists.

Sex-linked agammaglobulinaemia

In 1952 Bruton described a patient with severe widespread infections due to pyogenic organisms, including cutaneous infections with abscess formation, respiratory infections including otitis, sinusitis and severe bronchopneumonia, gastrointestinal infections, and finally blood stream invasion resulting in purulent meningitis and septicaemia. The detection of a complete lack of immunoglobulins gave the name to the disease, and stimulated investigations of the role of immunoglobulins as specific antibodies. The normal antibody response to stimulation by specific antigens is completely absent, and this is in keeping with the morphology of the lymphoid system which shows severe atrophy and absence of germinal centres and plasma cells. In a number of families the heredity of the disease could be demonstrated; the phenotypically healthy mothers transmit the disease only to their sons. This proves that the anomalous gene is located on the X chromosome. The importance of antibody deficiency in this syndrome is shown by the therapeutic success of the

injection of human gamma globulin preparations.

In these patients B lymphocytes are usually absent. In the normal human fetus B cells appear around the eleventh gestational week, ie, long before the actual secretion of specific antibodies. Animal experimentation has clearly demonstrated that the synthesis of the three main immunoglobulin classes is acquired in a rigidly fixed sequence, starting with IgM, proceeding to IgG, and finally followed by IgA (Lawton, Self, Royal, and Cooper, 1972). This sequence recapitulates the phylogenetic development of antibodies as demonstrated in a large number of different animal species (Good, Finstad, Gewurz, Cooper, and Pallora, 1967). It must therefore be concluded that in congenital sex-linked agammaglobulinaemia this development is lacking, and several authors claim that the absence of membrane immunoglobulins as markers of B lymphocytes is the most sensitive test for the early diagnosis of this disease.

A few cases, however, were not consistent with this concept, since they had normal membrane immunoglobulin but virtually no circulating immunoglobulins or specific antibodies. It was therefore concluded that in this disease the normal differentiation into functional B cells is blocked, and that the site of the block can vary; in the first instance there is a failure of transition of the primitive stem cell into the B cell, whereas in the second instance the B cells produce immunoglobulins but do not release them.

A recent study of an unusual patient seems to throw some light on the mechanism of this transition (Hitzig and Kenny, 1975). The parents were first cousins and had already lost two boys from

pancytopenia, which was diagnosed as Kostmann's syndrome (infantile genetic agranulocytosis). This male infant was born by Caesarean section under sterile conditions and immediately transferred into a sterile laminar airflow cabinet, where he was nursed for 78 days without any bacterial contamination. During this time extensive investigations excluded Kostmann's syndrome, but agammaglobulinaemia with inability to synthesize specific antibodies developed. During this time, however, B lymphocytes in normal number were detected by immunofluorescence, thus proving that the patient belonged to the rare category of agammaglobulinaemia with B lymphocytes. About two months after exposure to bacterial contamination, respiratory and intestinal infections appeared which did not respond to appropriate intramuscular gamma globulin therapy; the boy slowly developed pancytopenia exactly like his two siblings and rapidly deteriorated. Haematological investigations revealed the morphological changes of pernicious anaemia in the presence of normal serum vitamin B₁₂ levels, and, almost at the last minute, made us suspect the syndrome of transcobalamin II deficiency described by Hakami, Neimann, Canellos, and Lazerson (1971). Transcobalamin II is a beta globulin (table II)

	TC I	TC II	TC III
Electrophoresis	alpha 1	beta	alpha 2
Molecular weight	120 000	35 000	120 000
B ₁₂ clearance	10 days	10 min	?
Free B ₁₂ -binding capacity	Low	High	?
Biological function	Storage	Transport	Fetal binder
HeLa cell uptake	No	Yes	No

Table II Transport proteins for vitamin B₁₂

which is normally present in concentrations of about 25 µg/l plasma. It is necessary for the transport of vitamin B₁₂ from the gut wall to the cells, and probably also for its penetration into the cells. After the administration of large doses (1000 micrograms twice weekly) of vitamin B₁₂ the boy made a spectacular recovery, the blood picture returned to normal, and the gastrointestinal and respiratory infections disappeared (Döhmann, Gimpert, Vischer, Plüss, and Hitzig, 1974). Gamma globulin injections were continued, but in the course of the next two months it was suspected that he had started to synthesize his own immunoglobulins, since he exhibited very high IgM levels which could not be accounted for by the injected material which consisted almost entirely of IgG. The gamma globulin injections were stopped, and the rise of immunoglobulins continued. In addition, specific antibodies to diphtheria and tetanus appeared, much to our surprise, as although diphtheria and tetanus toxoids

had been given with KLH¹ three times during the first three months of life, no antibodies had appeared previously. Now, six months after the last antigen injection, significant titres appeared, and after a single booster injection these titres rose to very high values within 10 days. To characterize the nature of this antibody response further, the serum samples taken three and 10 days after the booster injection were fractionated in the ultracentrifuge and proved to contain IgG antibodies exclusively (Hitzig and Kenny, 1975).

In this case there is evidence that the lymphoid cells showed normal differentiation initially, since shortly after birth B lymphocytes with all three classes of membrane Igs were present in approximately normal numbers (Cooper, Lawton, and Kincade, 1972). For these cells to proceed to antibody secretion, however, two conditions are necessary, namely, antigenic stimulation and normal metabolism. In the sterile surroundings in which the boy was nursed during the first months of life, bacterial antigens were excluded, but specific and long-lasting stimulation was provided by sterile toxoids. From other patients reared under sterile conditions we know that antibody formation is perfectly possible, and the failure to produce antibodies in this patient is therefore attributed to an insufficiency of vitamin B₁₂. When B₁₂ was administered, antibody secretion occurred. A booster injection elicited an anamnestic response, thus proving that the first three antigen injections had left an impression on the immunological system with formation of memory cells. We conclude, therefore, that differentiation of these cells had proceeded before birth in the usual way but that clonal expansion and the synthesis and secretion of antibody was dependent on adequate concentrations of vitamin B₁₂. The lymphoid system thus appears to have behaved like the haematopoietic system and the intestinal mucosal epithelium, both of which have rapid cell replication dependent on B₁₂.

Thymic hypoplasia (third and fourth branchial pouch syndrome)

In 1968 DiGeorge and Lischner described several children with congenital absence of the thymus and the parathyroids. This defect, which is often combined with other malformations such as hypoplasia of the mandible or aortic arch, is easily explained embryologically as an inhibition of the differentiation of the organs derived from the third and fourth branchial pouch.

The sequence of clinical signs is very important. Within the first days of life severe tetany due to

¹KLH = keyhole limpet haemocyanin, a strong stimulant of T cells —ED.

hypoparathyroidism becomes manifest. Only after appropriate treatment of this life-threatening manifestation do the patients survive and, at a later date, produce the signs of immune deficiency, ie, infections mainly localized in the respiratory system, and the additional signs of a severe cellular immune deficiency, associated with a normal lymphocyte count. Total immunoglobulin levels are normal, but specific antibody formation may be deficient.

Significantly a transplant of fetal thymus almost completely reverses the signs of immune deficiency.

Severe combined immune deficiency

The most severe and probably also the most common hereditary immune deficiency syndrome involves both the antibody- and cell-mediated immune mechanisms (Swiss type, thymic lymphoplasia). Accordingly the clinical symptoms and signs are very severe (Hitzig, Barandun, and Cottier, 1968). Infections start in early infancy, and all contact surfaces of the body are involved, namely, the gastrointestinal tract (leading to severe malnutrition), the respiratory tract (with lung damage and an early severe pertussoid cough), and the skin which shows morbilliform rashes; blood stream invasions are frequent. All kinds of microorganisms are responsible for these infections, pyogenic and saprophytic bacteria, viruses, protozoa and fungi, especially *Candida albicans*. These infections almost invariably lead to death within the first weeks or months of life, malnutrition playing an important additional role.

Relatively simple laboratory data are sufficient to confirm the diagnosis as soon as the clinical suspicion is aroused. The patients are usually lymphopenic and the lymphocytic functions are invariably deficient. The thymus shadow on an antero-posterior radiograph is absent and at necropsy the pathologist finds either no thymus at all or a very hypoplastic one high up in the neck. The severe depression of immunoglobulin synthesis becomes manifest only after the age of 3 or more months, ie, when the maternal supply of IgG has been used up. The more tedious and time-consuming test of antibody formation is always negative. Postmortem findings are very characteristic with a marked diminution in the amount of lymphatic tissue. Even more striking are the histological findings: the lymph nodes are few and very small and exhibit a severely disturbed architecture—no lymphocytes, no germinal centres and no plasma cells. The intestinal mucosa shows severe atrophy of the lymphoid tissue which is very obvious in the appendix; this finding might explain the gastrointestinal infections. Subsequent atrophy of the intestinal villi leads to malabsorption. The changes in the thymus, if the thymus can be found

at all, are pathognomonic: the architecture can barely be recognized, there are very few lymphocytes, the predominant cells are large, clear reticulum cells, and there are no Hassall's bodies at all.

Before the two-component theory it was suspected that a failure in the development of the thymus was the sole causative factor. When it became known that the antibody-mediated functions were also severely impaired, a separate analogous defect in the development of this system (or in modern terminology, lack of T and B lymphocytes) was postulated. This, however, seems improbable, and a defect of the stem cell from which both chains of lymphocyte develop is a much more logical explanation, and this is accepted by most investigators today. Different genetic forms have been distinguished on purely clinical grounds, namely, autosomal-recessive X-linked and sporadic forms, but the hereditary basis is not clear.

Almost two years ago a new finding threw some light on at least one group of these patients (Giblett, Anderson, Cohen, Pollara, and Meuwissen, 1972). During the search for genetic markers the absence of adenosine deaminase (ADA) was found in two such patients. The parents of these children showed significantly reduced enzyme activity, and it was considered that they were heterozygous, whereas the children were homozygous for the deficiency. Very little was known about the frequency of this special subgroup of severe combined immune deficiency, and we decided therefore to investigate again all the families of our previously deceased patients. Eight families were available for study, and in three pairs of parents the enzyme deficiency was present. One was a family described previously as an apparently incomplete manifestation of this syndrome (Hitzig, Landolt, Müller, and Bodmer, 1971). We reviewed, therefore, the data from all our patients and compared them with the findings in the literature. We now suspect that the 'normogammaglobulinaemic antibody deficiency syndrome with severe lymphopenia' might be the clinical counterpart of ADA deficiency. It seemed possible that the Nezelof syndrome, which usually is regarded as a special entity, is also an example of this newly defined deficiency disease. Preliminary estimates indicate a frequency of one quarter to one half of all cases of severe combined immune deficiency.

The following hypothesis has been presented to explain the pathogenesis of the severe combined immune deficiency syndrome: ADA catalyses the critical metabolic step leading from adenosine to inosine. In its absence adenosine monophosphate accumulates and this product has been shown to be toxic to lymphocytes. On the other hand, the consequential fall of inosine concentration might be

a limiting factor in cell metabolism. Presumably T cells are more sensitive than B cells.

Such a hypothesis suggests new therapeutic approaches, eg, attempts to remove toxic substances or to avoid their accumulation, or to increase the concentration of the metabolites beyond the block, in this case presumably inosine.

Selective IgA deficiency

The complete absence of IgA from the blood is apparently the most frequent hereditary immunoglobulin deficiency. It was found in one per 700 apparently normal blood donors (Bachmann, 1965). According to phylo- and ontogenetic studies, the formation of the IgA system seems to be the latest developmental step. Apparently it is often missed. Each patient studied up to now has possessed a normal or high percentage of IgA-bearing B cells in the peripheral blood. The most likely explanation of the pathogenesis of this disorder is therefore a faulty mechanism for secreting IgA into the serum, and indeed Cooper and Lawton (1972) have been able to induce this release of IgA by treating lymphocytes from such patients *in vitro* with pokeweed mitogen. An alternative possibility is the existence of a serum inhibitor of IgA release; antibodies against IgA and other autoantibodies are commonly found in selective IgA deficiency and conceivably might inhibit IgA secretion *in vivo*. Finally, animal experiments suggest that a defect of B and T cell cooperation or even a primary defect of T cell function might be the basic failure; IgA levels are very low in nude mice, an inbred strain with congenital aplasia of the thymus, and in rabbits thymectomized soon after birth. This is in accordance with recent studies in patients with selective IgA deficiency, who showed decreased numbers of E-rosette-forming lymphocytes in their peripheral blood.

The phylogenetically 'young' IgA system is highly developed on mucosal surfaces, and seems to protect them against invasion by microorganisms. It has therefore been called the secretory immunoglobulin system and compared with a mucosal 'antiseptic paint' (Heremans, Crabbé, and Masson, 1966; Tomasi and Bienenstock, 1968). IgA antibodies have no bacteriostatic or bacteriolytic properties but apparently just coat the surface of bacteria and change their properties in such a way that the adhesion to and subsequent invasion of epithelial cells is greatly inhibited. This provides a very effective protection against bacterial invasion (Williams and Gibbons, 1972).

Surprisingly the clinical expression of IgA deficiency is extremely variable, showing a wide spectrum ranging from apparent clinical health to

severe liability to infections. The factors involved are not yet fully understood. However, a good deal is known about the mechanism of IgA secretion. The newly formed IgA molecule released from the submucosal plasma cell is transported to the mucosal surface with the aid of a well characterized molecule, the secretory piece; usually two molecules of IgA are linked together by one secretory piece. In addition, this complex is surrounded by one molecule of J chain. Secretion in the absence of secretory piece seems to be impossible. This apparently occurs if large areas of mucosal surface are destroyed, for instance, during necrotizing enteritis or in coeliac disease. In such cases high IgA levels are usually found in serum: apparently the IgA is synthesized at an increased rate but cannot be secreted onto the mucosal surface; it is therefore deviated 'backwards' into the bloodstream. The apparent paradox that congenital absence of IgA secretion occasionally leads to a similar state of maldigestion and malabsorption is well explained on grounds of the pathogenesis, since these patients are not protected against invasion by microorganisms from the gut lumen.

Some of the gastrointestinal changes seen in alpha-chain disease, which are discussed elsewhere in this symposium by Professor Seligmann, might have the same explanation since the secreted immunoglobulin is incomplete and functionally inefficient.

Individuals with IgA deficiency and no tendency to infection have been shown to secrete large amounts of IgM on to their mucosal surfaces. In some, but not all, of these the same secretory piece is operative. It seems therefore that the phylogenetically oldest immunoglobulin can effectively take over the missing function of the youngest.

IgA deficiency has been discussed extensively because it is the most important example of deficiency of a single immunoglobulin. Severe diminution and increase of all the other immunoglobulin classes have been described, but the associated clinical features are variable and inconstant.

Transient hypogammaglobulinaemia of infancy

Almost 100 years ago clinical observation led to the conclusion that the newborn infant is protected against infections by substances transferred from the mother. The basis of this 'loan immunity' (*Leihimmunität*) was explained when it was shown that IgG is able to cross the placenta and that in the full-term infant the plasma concentration is as high as or even higher than that of the mother. This transplacental transport is highly selective and probably involves partial degradation and subsequent rearrangement of the complicated IgG

molecule. Many studies have shown that this maternal IgG is gradually used up during the first three to six months of life and is slowly replaced by the infant's own immunoglobulins. It has long been known that resistance against infection reaches its lowest point around the third month of life, and this corresponds with the lowest point of a trough in plasma IgG concentration. Exact knowledge of the normal values and their variation is essential for the detection of these infants who need, and will benefit greatly from, gamma globulin injection during this critical phase.

There is a great variation in the plasma IgG values in infants. In premature babies who are born with a considerably smaller supply of maternal IgG the mean value decreases to very low levels. If the standard deviation is calculated in the usual manner, extremely low and physiologically unlikely 'normal' values will be obtained. We have studied the distribution pattern and have found it greatly skewed towards the higher values (fig 1) in both

Fig 1 Distribution pattern of IgG concentrations in premature infants of 30-33 weeks gestational age, and of 4-8 weeks chronological age. Percentiles and arithmetic values.

'normal' premature and full-term infants (Pilgrim *et al.*, 1975). It therefore seems much more logical to plot the deviation in the form of percentile curves instead of standard deviations (fig 2). Since the gestational age which determines the amount of transferred maternal gamma globulin is of crucial importance, we have divided infants into three groups according to gestational age (30-33 weeks, 34-37 weeks and 38 weeks or more) and have studied their postnatal development. The IgG levels are different up to a postnatal age of about 14 weeks by which time the premature infant has made up for its immunological handicap at birth (fig 3).

Fig 2 Development of IgG concentrations in premature infants of 30-33 weeks gestational age. Percentiles and arithmetic mean with standard deviation.

Gestational age groups: a = 30-33 wks.; b = 34-37 wks.; c = >38 wks.

Fig 3 Development of IgG concentrations in premature infants of different gestational age. Gestational age groups: a = 30-33 weeks; b = 34-37 weeks; c = > 38 weeks.

Primary immune deficiency syndrome with ataxia telangiectatica

In this very peculiar progressive neurological disease with autosomal recessive inheritance, there are striking telangiectases of the conjunctivae, other mucosae and skin, together with a liability to recurrent respiratory infections; IgA levels are reduced. At necropsy the thymus shows abnormalities similar to those described in patients with severe combined immune deficiency. The usually accepted assumption of a T lymphocyte abnormality, however, fails to give a fully satisfactory explanation for all the clinical observations. The disease becomes manifest at school age and gets progressively worse. There is an associated high incidence of malignant tumours.

Immune deficiency syndrome with thrombocytopenia and eczema (Wiskott-Aldrich syndrome)

This clinically well delineated syndrome with sex-linked inheritance is associated with very severe infections which usually kill the patient within the first years of life. However, no consistent or really severe defects of the functions of B and T cells have been found, despite extensive studies. At present an abnormality of the macrophages is suspected (Cooper, Chase, Lowman, Krivit, and Good, 1968) but this question is still wide open.

ACQUIRED AND TRANSIENT IMMUNE DEFICIENCY DISORDERS

Acquired deficiencies of both the B and T cell systems are much more frequent than the congenital forms. Table III exemplifies some typical situations, but is far from being comprehensive. The laboratory procedures used for the evaluation of the immunological potential of such patients are the same as those outlined earlier. One example is the transient depression of cell-mediated immune functions occurring during some virus infections; even in Von Pirquet's time it was known that the cutaneous tuberculin reaction is abolished for several weeks after an attack of measles, during which time there may be a very rapid exudative spread of a tuberculous infection. It seems likely that the virus alters the membrane surface of lymphocytes in such a way that the normal triggering by specific antigens is not possible.

Condition	Deficient System			
	B	T	Granulocytes	Macrophages
Newborn infant	+			
Virus infection		+		
Neutropenia			+	
Splenectomy				+
Malignant lymphomas				
Chronic lymphatic leukaemia	+			
Hodgkin's disease		+		
Mucocutaneous candidiasis		+		
Endocrine disorders	+	+		+
Uraemia		+		(+)
Diseases with protein loss	+			
Diseases with lymph loss		+		

Table III *Acquired and transient immune deficiencies*

Therapeutic Approaches (Hitzig, 1971)

CONVENTIONAL TREATMENT

Patients with constitutional immune deficiencies suffer from recurrent infections or are chronically ill. In some of them symptomatic treatment is

effective: congenital sex-linked agammaglobulin-aemia can usually be kept under control by regular injections of human gamma globulin (0.3 ml/kg each week or 1.0 ml/kg every three weeks). This replacement treatment has been reviewed extensively. Table IV shows the preparations available and table V the indications for treatment and dose schedules. However, such treatment does not solve all problems. Disadvantages are that the usual intramuscular injections are painful for the patient and that intravenous injections may lead to very severe reactions. At all stages of acute or chronic infection the usual antimicrobial treatment is given but this will not be discussed here.

Preparation	Immunoglobulin Contained	Route of Administration	Approximate Physiological Half-life
Plasma (blood)	IgG, IgA, IgM	iv	1 to 3 weeks
Standard γ globulin	IgG	im	3 weeks
Special γ -globulin preparations for iv administration	IgG	iv	$\frac{1}{2}$ to 2 weeks
Special multiclass γ globulin preparations	IgG, IgA, IgM	im	? $\frac{1}{2}$ to ? 3 weeks

Table IV *Therapy with immunoglobulins*

The real problems arise with cellular immunodeficiencies which are invariably fatal if untreated. To help these patients, exceptional and even heroic therapeutic approaches are necessary.

BONE MARROW TRANSPLANTATION

On the assumption of a stem cell deficiency a considerable number of patients with severe combined immune deficiency have received bone marrow transplants. Last year 25 patients were known to have had replacements and this number has steadily increased since. The greatest danger is graft-versus-host reaction which is still difficult to treat. The principles of the procedure are well outlined in a protocol set up by the Society for Experimental Haematology. In the majority of cases, however, no compatible donor is available. It is now evident that in such cases no attempt should be made to transplant incompatible bone marrow. The above-mentioned protocol in these cases recommends the use of fetal tissues.

IMPLANTATION OF FETAL TISSUES

In late embryonic and early fetal life the haemopoietic stem cells differentiate and proliferate in the liver. Before the 18th gestational week these stem cells have no immunological competence. First attempts at implantation of fetal liver resulted in a considerable increase in the number of lymphoid

<i>Prophylaxis and Therapy</i>	<i>Protective Value</i>	<i>Time of Application</i>	<i>Dose (ml/kg)</i>
<i>Immunoglobulin, normal human (16%, im)</i>			
Measles			
Full protection	++	First 4 days after exposure	0.2
Mitigation	+	First 4 days after exposure	0.02-0.04
Mitigation	++ to (+)	From 5th day after exposure to appearance of Koplik spots	0.02-0.2
Rubella			
Mitigation	?	First 8 days after exposure	0.2
In pregnancy	?	First 8 days after exposure	1.0-2.0
Varicella			
	+ ? - ?	As early as possible	0.4-1.0
Viral hepatitis	++	First 2 weeks after exposure	0.01-0.1
Poliomyelitis	+	Before or early after exposure (in unvaccinated persons)	0.3-0.5
Antibody deficiency syndrome	+	Every 3-4 weeks	1.0-2.0
Infants with severe infections	+	First day, if necessary, same dose on 3rd day	1.0
Sepsis, resistance to antibiotics, severe burns	+	First day, if necessary, same dose on 3rd day	1.0
<i>Immunoglobulin, human antitetanus</i>			
Prophylaxis	++	Early; at same time active immunization	250-500 IU im
Therapy	+	Immediately	500-5000 IU
<i>Immunoglobulin, human antivaccinia</i>			
Late primary vaccination	+	Simultaneously with active vaccination	0.01-0.05 ml/kg
Relative contraindication for revaccination	+ ?	Simultaneously with active vaccination	0.2 ml/kg
Mitigation of variola	++ to -	Early after exposure	0.2-0.6 ml/kg
Complications of vaccination	+		} 0.2-2.5 ml/kg
Generalized vaccinia	+ or -		
<i>Immunoglobulin, human antipertussis</i>			
Complications in infants (up to 2 years)	+ ?	Early	0.2-0.5 ml/kg
<i>Immunoglobulin, human antiparotitis</i>			
Prophylaxis of orchitis	+ ?	Early	0.05-0.1 ml/kg
<i>Immunoglobulin, human anti-D</i>			
Prophylaxis of Rh-sensitization	++	After birth, if 0.1 ml fetal Hb-containing erythrocytes is present in the maternal circulation	0.1-0.5 ml/kg

Table V *Therapy with immunoglobulins*

cells, but not in functional reconstitution of the patient. The excellent results of bone marrow transplants discouraged further work in this direction for several years. However, recent experience in patients for whom no matched bone marrow donor was available seems to be more encouraging. We know of three successful transplants. One of them is our patient with ADA deficiency who received 10^8 liver cells from a fetus aged 14 gestational weeks. She subsequently showed a dramatic clinical improvement, and also the ADA activity increased to low normal values. After a transient drop, the level of enzyme activity is now in the subnormal range found in the heterozygous but immunologically healthy parents of our patient.

TRANSFER FACTOR

There is still great controversy over the value of Lawrence's dialysable transfer factor, presumably a product of sensitized lymphocytes. It has the unique advantage of not being antigenic and not producing graft-versus-host reactions. We recently reviewed work on transfer factor (Hitzig and Grob, 1974), and, owing to the lack of standardization both of the preparation and of the clinical application, we found it very difficult to make a final judgment. It seems that in the Wiskott-Aldrich syndrome it is

helpful in about half the patients treated. The most dramatic success has been obtained in patients with chronic mucocutaneous candidiasis, especially the granulomatous form, but even in this condition some failures have been recorded.

Therapeutic trials on patients with congenital immune deficiency have contributed to the basic understanding of physiological immune mechanisms and to the treatment of acquired diseases as well. In particular the knowledge gained from bone marrow transplantation in severe combined immune deficiency has opened the way to similar treatment of patients with leukaemia and aplastic anaemia and may become quite important in the future.

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