Delayed hypersensitivity to dinitrochlorobenzene (DNCB) was induced at the age of 13 months by applying 2 mg in acetone to a 1 cm² area of the forearm. No delayed reaction followed, and no reaction was provoked by the application of a further dose of 0.02 mg 2 weeks later; but a third dose of 0.04 mg at the age of 14 months produced a normal delayed hypersensitivity reaction, with a wheal and vesicles. He was still positive at the age of 4½ years with a 0.05 mg dose, when a weak delayed reaction to candida 0.1% was also shown.

Antibody was not detected to herpes simplex, cytomegalovirus, or rubella at the age of 14 months. One month after measles inoculation the titre of measles antibody was 1/64, at 26 months of age.

Comment

This boy clearly has the Wilm's-aniridia syndrome together with a temporary state of delayed development of immunoglobulins. A clinical picture of eczema, allergy, and tendency to recurrent infection associated with low IgG, low normal IgA, and normal IgM in the early months of life, which spontaneously improves, is characteristic of a relatively common disorder of the immune response, transient hypo-γ-globulinaemia of infancy. In our experience children with this disorder may develop eczema, vomiting, diarrhoea, and failure to thrive which recover spontaneously as the child's immunoglobulins rise to normal. We are not aware of any other children with the syndrome who have developed malignant disease. Frommel and Good (1971) postulate that the syndrome is due to relative inability to produce a normal primary response of macroglobulin type (21S) and consequent failure to convert to 7S (IgG and IgA) antibody production. The syndrome may be familial.

In 1968, Fraumeni and Glass summarized 22 cases of Wilm's tumour associated with aniridia, and since then further reports of at least 5 other cases have appeared (Surugue, 1967; Mackintosh *et al.*, 1968; Woodard and Levine, 1969; Haicken and Miller, 1971). Another case has been personally reported to us in Manchester by Dr. P. M. Jones. This brings the total number of recorded cases to at least 29. No mention of immunoglobulin levels or predisposition to allergy or infection have been recorded, but this does not exclude the possibility that other cases may have had low levels of IgG at some time before the diagnosis of Wilm's tumour.

We suggest that serum immunoglobulins be monitored in the early months of life in future cases of congenital aniridia. Other cases may be found; and further cases of transient hypo-γ-globulinaemia with the Wilm's-aniridia syndrome would be most interesting, both from the general point of view, as illustrating further the relation between immune

deficiency and malignancy, and as an indicator, perhaps specific, of the premalignant state in the individual case.

Summary

A case of Wilm's-aniridia syndrome is presented. Initial management of aniridia was complicated by infection and asthma, and low IgG was discovered. Immunological status subsequently developed normally, with normal immunoglobulins, normal antibody levels, and normal delayed hypersensitivity tests. Wilm's tumour was diagnosed at 32 months. Immunological studies should be made in other cases of congenital aniridia.

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Immunoglobulins in normal infant born of severe hypo-γ-globulinaemic mother

Immunological maturation in normal infants born of normal mothers is well known (Berg, 1969). But there are few reports dealing with infants of mothers with immunoglobulin deficiencies. Bridges *et al.* (1959) and Zak and Good (1959) have reported a rise

in serum γ -globulins between 35 and 42 days and between 20 and 28 days in two infants born to the same α - γ -globulinaemic mother. Holland and Holland (1966) described the early onset of IgG, IgA, and IgM production by an infant of an α - γ -globulinaemic mother having had γ -globulin treatment during pregnancy.

We have had the rare opportunity of studying the immunological maturation in another infant born of a severely hypo- γ -globulinaemic mother.

Case report

A boy was born on 15 December 1971, the first child of a 25-year-old woman with severe hypo- γ -globulinaemia. There was no history of recurrent infections in the mother's family, nor in the father and his family. The mother's disease is assumed to be acquired, with symptoms beginning when she was 3 years old. She has suffered from recurrent pulmonary infections which had led to pulmonary fibrosis, and in 1958 a bronchiectatic left lower lobe was removed.

The otherwise normal pregnancy was complicated by several episodes of pulmonary infections in spite of continuous treatment with ampicillin. The mother had not been on regular treatment with γ -globulin earlier, and did not receive γ -globulin at all during pregnancy. One month before delivery the mother's serum immunoglobulins were IgG <1 mg/100 ml, IgA 2 mg/100 ml, and IgM 10.7 mg/100 ml. At delivery, all three serum immunoglobulins were <1 mg/100 ml.

The baby, who weighed 3600 g at birth, was immediately transferred to an isolation room in the paediatric department and placed in an incubator. He remained in good health without infections until he was just over 3½ months old when he had varicella with a normal uncomplicated course. When he was nearly 4½ months old he had an upper respiratory infection without any complications, and after that he was placed in the public ward. On 15 May 1972 he was discharged in good health weighing 7900 g. He has since been observed as an outpatient and has been found to be a healthy, normally developing boy.

On several occasions his bacterial flora in the nose, eyes, skin, anus, faeces, and urine was normal. *Esch. coli* was isolated from the throat on 11 January, and three times after that in the next three months.

His cell-mediated immunity was considered normal from mixed lymphocyte culture reaction and from the stimulation of the patient's lymphocytes by phytohaemagglutinin. HL-A typing performed with highly selected lymphocytotoxic antibodies tested against the patient's lymphocytes showed no evidence of abnormal lymphocytes.*

His serum immunoglobulins have been followed from birth (Fig.). They were determined by rocket electrophoresis (Laurell, 1966). Antisera were made by Dakopatts, Copenhagen, Denmark, and the method was standardized against Standard Human Serum (570)

FIG.—Development of serum immunoglobulins during the first 6 months of life in a boy born of a severely hypo- γ -globulinaemic mother.

Behringwerke, Germany. In the cord blood there was <1 mg/100 ml each of IgG, IgA, and IgM. A spontaneous increase in the immunoglobulins was observed during the first month and continued during the following months.

Discussion

In this boy born of a severely hypo- γ -globulinaemic mother we observed the spontaneous increase in the immunoglobulins during the first 6 months of life. Neither the mother nor the child received immunoglobulin therapy. γ -Globulin treatment of the boy was considered but withheld, partly for diagnostic reasons, and partly because we were uncertain if treatment with γ -globulin in this patient might give a small risk of antibody production against the Gm subtypes of IgG. On the other hand, we found it

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necessary to keep the boy isolated to protect him from infections. The period of isolation was prolonged because of the varicella and the upper respiratory infection. There were remarkable fluctuations of the immunoglobulin values from time to time, probably partly due to the infections. We consider these immunoglobulin reactions as a sign of normal capability of immunoglobulin production. This case thus showed the development of immunoglobulins by the infant itself, uninfluenced by passively transferred maternal immunoglobulins.

Summary

The immunoglobulin production in a normal boy born of a severely hypo- γ -globulinaemic mother was followed during the first 6 months of life. As the mother did not receive γ -globulin treatment during pregnancy, the development of immunoglobulins by the infant was uninfluenced by passively transferred maternal immunoglobulins. In the cord blood there was >1 mg/100 ml each of IgA, IgG, and IgM. A spontaneous increase in the immunoglobulins was observed during the first month and continued during the following months.

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Dietary requirement of phenylalanine in infants with hyperphenylalaninaemia

Hyperphenylalaninaemia has been variously defined and named (Carpenter, Auerbach, and DiGeorge, 1968; Jervis, 1967; Scriver, 1967). We

define it as the condition in which plasma phenylalanine is above 5 mg/100 ml but usually below 20 mg/100 ml on a normal diet. Originally we, like many others, treated children with this condition, but now they are maintained on a normal diet and brain damage is not evident. Our belief in the safety of not treating these children has been strengthened by the discovery of a family containing 3 hyperphenylalaninaemic children when the youngest was detected by routine Guthrie tests. The two older sibs had phenylalanine levels consistently between 10 and 20 mg/100 ml and were mentally normal.

In 1967, Hsia and O'Flynn stated that the phenylalanine intake tolerated by hyperphenylalaninaemic individuals (90–100 mg/kg per day) was higher than that of classical phenylketonuria (30–40 mg/kg per day). This suggests that dietary management of these individuals could be much less restrictive, and therefore a low phenylalanine diet would be worth while, even though the risk of brain damage in this condition appears minimal. The purpose of this study was to see if hyperphenylalaninaemic children could have their plasma phenylalanine levels maintained at a desirable level on a less restricted diet than classical phenylketonuric patients.

Patients and treatment

Four hyperphenylalaninaemic children were initially treated with low phenylalanine diets until the age of 9 months with the aim of keeping their serum phenylalanine levels below 10 mg/100 ml. These children were all detected by routine Guthrie test (Guthrie and Susi, 1963) in the 6 years before June 1969. In the same period 5 children with classical phenylketonuria were similarly detected and were randomly assigned to a treatment group in which the aim was to keep the plasma phenylalanine level between 5.5 and 10 mg/100 ml. Accurate dietary records of these children were kept and their plasma phenylalanine levels were measured at roughly weekly intervals. Plasma phenylalanine was measured by the fluorometric method of McCaman and Robins (1962) as modified by Wong, O'Flynn, and Inouye (1964).

All the children designated phenylketonuric had phenylalanine loads performed in the first year of life which confirmed the diagnosis of classical phenylketonuria. The 4 children with hyperphenylalaninaemia are now off diet with raised plasma phenylalanine levels and normal intelligence.

Results

The Table shows the plasma phenylalanine level and phenylalanine intake (expressed as mg/kg body weight per day) of the 4 hyperphenylalaninaemic