of familial pattern in the understanding of this disease. A positive family history of peptic ulcer is an important feature and is one of the basic characteristics of a duodenal ulcer in children.

**Summary**

The families of 37 children with the established diagnosis of duodenal ulcer were studied to assess the incidence of peptic ulcer in the relatives of these children. 23 children had a positive family history of peptic ulcer: 19 children had one or other parent or sibling affected with the disease. Positive family history is an important characteristic of duodenal ulcer in children.

**References**


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**Combined immunodeficiency with hyper-γ-globulinaemia**

Infants with major defects in cell-mediated immunity and hypo-γ-globulinaemia (severe combined immunodeficiency) usually die in the first few years of life from infections unless they receive a successful bone marrow transplant. Nezelof et al. (1964) described an infant with a major defect in cell-mediated immunity and normal serum immunoglobulin levels who died at 16 months from a lung infection. This paper describes a similar infant with absent cell-mediated immunity and hyper-γ-globulinaemia in whom we were unable to show any functional antibody.

**Case report**

A male was born at term, of normal delivery, birthweight 3·6 kg, after an uneventful first pregnancy. At 10 weeks he presented with failure to thrive (weight 4·5 kg), loose stools, and intermittent cough soon followed by bronchopneumonia. There was lymphopenia, neutropenia, and eosinophilia (lymphocytes 208/mm³, neutrophils 1440/mm³, eosinophils 800/mm³). Serum immunoglobulins were: IgG 200, IgA 20, IgM 35 mg/100 ml. Pneumonia responded slowly to antibiotics but lymphopenia persisted (lymphocytes 70 to 399/mm³). Tonsils and lymph nodes were not clinically detectable and the thymus was not visible on chest x-ray. At 4 months he was readmitted with fever, loose stools, and continued poor weight gain. Stool culture grew *Pseudomonas aeruginosa*. Sweat sodium was 11 mmol/l and chloride 12 mmol/l. Jejunal biopsy was normal and contained plasma cells. Tests for malabsorption were negative.

Over the next 8 months he developed several upper respiratory infections, pneumococcal pneumonia, and an intractable oral *Candida* infection. At 12 months he weighed 8·3 kg and at 14 months was admitted to Northwick Park Hospital for further investigations of his immune status. On examination he was wasted, height and weight being below the 3rd centile. Lateral x-ray of the nasopharynx did not show the adenoidal pad. No other significant abnormalities were found.

**Initial laboratory investigations.** Haemoglobin 11·7 g/dl, neutrophils 7300/mm³, lymphocytes 291/mm³, eosinophils 1168/mm³. Examination of the bone marrow was normal apart from absence of iron stores. Serum immunoglobulins in mg/100 ml with 95% normal adult range in parentheses: IgG 400 (646-1484), IgA 41 (73-552), IgM 114 (50-261), IgD 5 units/ml (5-50), IgE 3 units/ml (25-373). Blood group O, no isohaemagglutinins detected. There were no 'natural' serum haemagglutinating antibodies to a pooled polysaccharide antigen prepared from six common commensal serotypes of *Esch. coli*. Serum precipitins to *Haemophilus influenzae*, pneumococcus, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella sp.*, and *Candida albicans* were not detected. He was immunized with 1·2 ml TAB vaccine (Burroughs Wellcome) and 0·5 ml tetanus toxoid (Lister Institute), with a booster after 8 weeks. No antibodies were detected to either immunization up to 2 months later (Widal <1:10, H and O, tetanus antitoxin <1:10 IU/ml). Intradermal injection of 0·1 ml 1% *C. albicans* (Bencard) failed to produce a reaction within 72 hours. Contact sensitivity to dimethoatoxybenzene (5% in acetone sensitizing dose and challenge with 0·1% after 3 weeks) was negative. An area on the
left thigh was painted with 2% picryl chloride and a draining lymph node was removed 5 days later from the groin. Histological examination of this node showed marked depletion of lymphocytes in all areas; there were no lymphoid follicles or germinal centres. Peripheral blood lymphocytes were incubated for 3 days with purified phytohaemagglutinin (PHA, Burroughs Wellcome) and the degree of lymphoblast transformation measured by incorporation of radioactive \textsuperscript{14}C thymidine. There was no increase in isotope uptake in the stimulated cultures (unstimulated 317 counts/min per $5 \times 10^8$ cells; PHA stimulated 294 counts/min per $5 \times 10^8$ cells). There was also no response with pokeweed and concanavalin A mitogens.

**Progress** (Fig. 1). In view of his failure to respond to immunization he was regarded as having a qualitative defect in immunoglobulin production as well as defective cell-mediated immunity, and accordingly was treated with human $\gamma$-globulin (25 mg/kg body weight per week). During the subsequent 6 months he remained free from serious infections, gained a little weight but suffered from recurrent cough and oral thrush. At 20 months he developed a cough with fever which failed to respond to antibiotics. He gradually deteriorated and a month later was diagnosed as suffering from *Pneumocystis carinii* pneumonia in view of the characteristic radiological signs of bilateral perihilar consolidation. He was treated with pentamidine isethionate and sulphadiazine, but died 4 days later.

Transfer factor prepared from 6 pints of blood obtained from healthy adult donors was injected subcutaneously 3 days before death. Lymphocytes obtained from the peripheral blood on the day of death again failed to transform to PHA. The lymphocytes were also tested for the presence of surface immunoglobulins using fluoresceinated sheep antihuman immunoglobulin serum (Burroughs Wellcome). The percentage staining with specific class antisera was as follows: IgG 80\%, IgA 10\%, and IgM 2\%. Serum immunoglobulin concentrations from blood taken on the day of death were: IgG 705 mg/100 ml, IgM 900 mg/100 ml, and IgA 1445 mg/100 ml. The high serum IgA and IgM could not be explained by monoclonal increases since there was no 'M' band on cellulose acetate protein electrophoresis and $\kappa$ and $\lambda$ light chains were present on serum immunoelectrophoresis.

**Necropsy**

**Respiratory system.** Both lungs were almost completely solid and airless. Sections of the lung showed an interstitial pneumonitis, with alveolar walls greatly thickened and infiltrated by plasma cells and histiocytes (Fig. 2a). In the alveoli there was an extensive exudate with much granular eosinophilic material infiltrated by plasma cells and histiocytes. Grocott staining showed the presence of a moderate number of silverpositive bodies with the characteristic form of *Pn. carinii* in the granular material. Electron microscopy of lung showed the presence of many large cells with abundant cytoplasm and extensive dendritic processes. These cells, which were unquestionably macrophages, also showed an extensively developed rough endoplasmic reticulum; the cisternae of which were often dilated.

**Lymphoid system.** The thymus was not seen macroscopically, but rudimentary thymic tissue was found in sections of tissue lying in front of the tracheal bifurcation. The gland contained clumps of spindle cells intermingled with loose connective tissue (Fig. 2b). There was no corticomedullary differentiation and virtually no small lymphocytes. Several clearly defined Hassall's corpuscles were seen, some showing central cystic degeneration. Small lymph nodes (up to 3 mm in diameter) were found in the mesentery and in the abdominal para-aortic area. These nodes were markedly hypoplastic (Fig. 2c); no primary follicles were seen and the glands appeared almost empty of cells other than the basic background of spindle cells separated by sinuses. Scanty plasma cells and histiocytes were found in the sinuses.

Lymph nodes from the deep cervical chain and mediastinum showed a marked contrast to the abdominal nodes. They were enlarged up to 1 cm in diameter with a firm and homogeneous cut surface. There were no germinal centres and no classical primary follicles of small lymphocytes, but there were ill-defined aggregates of small lymphocytes interspersed with plasma cells in the cortex. The most notable features of these lymph nodes were the infiltration with plasma cells and histiocytes (Fig. 2d). Many histiocytes showed haemophagocytosis.

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**Fig. 1.** Relation between serum immunoglobulins and clinical events.
The spleen weighed 12 g and was unusually firm. There was almost complete absence of lymphocytic aggregates about the splenic arterioles and elsewhere. The trabecular framework of the red pulp showed marked fibrosis.

The tonsils and adenoids were not seen in multiple blocks taken through the area. Bone marrow showed active haemopoiesis with plasma cells being present in large numbers.

Gastrointestinal system. No lymphoid aggregates were found in the small or large gut. The appendix contained no lymphoid follicles, but there were a moderate number of lymphocytic cells and a few eosinophils in the lamina propria. Some plasma cells were identified in the lamina propria of the small gut and colon. All other organ systems were essentially normal. In particular, three normal parathyroid glands were identified histologically.

Discussion

The clinical course, normal serum immunoglobulin levels, gross deficiency in cell-mediated immunity, and the presence of enlarged mediastinal lymph nodes containing plasma cells parallels the case described by Nezelof et al. (1964). The WHO Committee on Primary Immunodeficiency (Fudenberg et al., 1971) have classified such cases as part of the spectrum of severe combined immunodeficiency (SCID). However, it has recently been suggested by Lawlor et al. (1974) that this condition warrants a separate classification.

It is likely that the rise in serum immunoglobulins was related to the Pn. carinii infection, and intense antigenic stimulation from the lungs probably accounts for the plasma cell infiltrate of the mediastinal lymph nodes. The hyper-γ-globulinaemia, particularly the rise in IgA, was clearly out of proportion to that seen in normal individuals after infection. Gelfand et al. (1973) described an infant with SCID who developed a grossly raised serum IgM, which they suggested was related to transfer factor therapy. This case shows that such increases can occur spontaneously since it is inconceivable that the transfer factor given in this case caused the extreme rise of serum IgA within 2 days. Furthermore, similar infants have been described with very high levels of serum IgE (Kikkawa et al., 1973) and IgD (Rubenstein, Speck, and Jeannet, 1971).

The normal limitation of antibody production may depend upon the presence of special lymphocytes which suppress the response. Experiments in mice have shown that such suppressor lymphocytes occur after cell mediated (Zembala and Asherson, 1973) and humoral immune reactions (Gershon and Kondo, 1971). Furthermore, mice thymectomized at birth may develop markedly raised levels of serum IgA (Humphrey, Parrott, and East, 1964). It is therefore possible that the excessive production of IgA in our patient was related to the absence of suppressor T lymphocytes.

It has been suggested that SCID is due to a lymphoid stem cell defect, but this is unlikely in our patient in view of the presence of lymphocytes bearing surface immunoglobulin (B cells) and plasma cells. However, it is conceivable that these B cells were of maternal origin and that the eosinophilia and failure to thrive were manifestations of a chronic graft versus host reaction.

The recognition of this subgroup of SCID is important since we may be able to learn more about the regulation of the immune response from such cases. Clinically, it is useful to underline that the presence of normal or raised serum immunoglobulins does not rule out a severe and lethal immunodeficiency. The accepted treatment for SCID is a bone marrow graft, preferably from a histocompatible and mixed lymphocyte reaction negative sib. The treatment of choice in this rare subgroup is not clear, but it would seem rational to attempt a thymus graft initially, followed by a bone-marrow graft if this is unsuccessful.

Summary

An infant is described with absence of cell mediated immunity and apparent failure to produce functional antibody despite raised serum immunoglobulin concentrations. A marked rise in serum IgA occurred during the terminal phase of his illness. We draw attention to this subgroup of severe combined immunodeficiency where there is a tendency to spontaneously develop hyper-γ-globulinaemia.

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References


Fig. 2.—(a) Lung shows interstitial infiltrate with many plasma cells. There is an alveolar exudate of granular material in association with many desquamated cells (H and E. × 157). (b) Rudimentary thymus gland composed of spindle cells with occasional degenerate Hassall's corpuscles (H and E. × 59). (c) Pelvic lymph node showing a lack of follicles. A basic anlage of spindle cells is separated by sinusoids containing scanty lymphocytes (H and E. × 157). (d) Mediastinal lymph node. Cords of plasma cells are seen, separated by sinusoids containing many active macrophages (H and E. × 157).


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**Trial of artificial diet in treatment of cystic fibrosis of pancreas**

The major clinical features of cystic fibrosis (CF) of the pancreas include, with rare exceptions, malabsorption, malnutrition, and growth failure. Standard treatment of this disease includes the use of a high calorie, high protein diet and pancreatic enzyme supplements to improve intestinal absorption. Even with such treatment nutrition and growth may be impaired, and undernutrition may further predispose to respiratory infections.

Darby and Seakins (1971) described the use of a dietary amino acid supplement in treatment of CF but noted no benefit to their patients. More recently, Allen, Mason, and Moss (1973) have reported encouraging results from the use of an artificial diet in the treatment of CF, with evidence of improvement in growth and clinical status.

We report our experience with the use of an artificial diet in a group of patients with CF.

**Patients and methods**

Twelve patients with CF, whose ages ranged from 4 months to 12 years and who had all been previously treated with normal diet plus pancreatic enzyme supplements, were started on an artificial diet similar to that described by Allen et al. (1973). This consisted of Albumaid (a beef protein hydrolysate) and Caloreen (a glucose polymer), prescribed in sufficient quantities to provide 100% of the patient's protein and calorie requirements. It was given in water, flavoured to taste with tomato or fruit juice, or in the case of infants dissolved in sufficient water to provide the total daily fluid intake. Additional eating was discouraged, but additional fluids were permitted. All patients were given daily 10 ml medium chain triglyceride oil, Ketovite tablets, and liquid, and a standard mineral supplement. Pancreatic enzymes were only given when any normal food was taken. Normal treatment, including physiotherapy and antibiotics in the presence of chest infection, was continued throughout the period of the trial. The trial period was for a full year in each case. If the patients found difficulty in keeping to the diet, the follow-up and observations described below were continued for a full year and advice and encouragement to continue with the diet were offered at each visit.

At the beginning of the trial patients were examined clinically and classified into grades 1 or 2 using the criteria similar to those recently described by Mearns (1972) for assessing respiratory status. Patients without

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