ANTIBODY DEFICIENCY SYNDROME:
A CASE WITH NORMAL IMMUNOGLOBULIN LEVELS

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SUMMARY

A girl is reported in whom abnormal susceptibility to infections in many sites, involving many types of bacteria and leading to fatal bronchopneumonia, was associated with normal levels of all immunoglobulins, but complete absence of isohaemagglutinins, and failure of antibody response to some bacterial antigens (*Salmonella typhi* O, *Salmonella paratyphi* B, O and H, and pertussis), possible delay in developing antibodies to streptococcal infection, but normal antibody production to other Salmonellae (O and H), staphylococci, diphtheria and tetanus toxoid. Histology of lymphoid tissues, and delayed type hypersensitivity and *in vitro* lymphocyte transformation were normal.

This suggestive evidence of partial antibody deficiency syndrome, with normal concentration of all immunoglobulins, is compared with Aldrich's syndrome, and discussed as a possible instance of partial defect of the final stages of antibody synthesis or release.

INTRODUCTION

Now that the complexity of the immunity deficiency syndrome is gradually being recognized in terms of a wide range of combinations of quantitative and qualitative defects of both humoral and cellular immunity (Peterson, Cooper & Good, 1965; Soothill, 1968), the possibility must also be considered that in some patients defects may occur in immune response, humoral or cellular, to individual types of organisms (viruses, bacteria, etc.), or indeed to individual species, with normal immunity to others. Apart from the experimentally producible phenomenon of specific immune tolerance, and a specific unresponsiveness to

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viral infections described by Fulginiti *et al.* (1966), we are not aware of documentation of such antigen-specific immunity defects, and therefore present details of a patient who had a remarkable series of infections with a fatal outcome, who had defective antibody response to certain bacterial antigens but a normal response to others, no detectable isohaemagglutinins, and quantitatively normal immunoglobulins and normal cellular immunity mechanisms.

Case Report

The patient was born at full term, on 30 October 1964, an apparently normal female child. Birth weight was 2·8 kg. Her parents, unrelated, and one sister are well. At 1 month she had a cyanotic episode with inspiratory stridor while feeding, with spontaneous recovery. At 3 months, shortly after her father had had a respiratory infection, she developed pyrexia, dyspnoea and blood-stained purulent discharge from nose and eyes. An epulis was noted in her left lower alveolar margin. Over the next 14 months she had almost continuous upper and
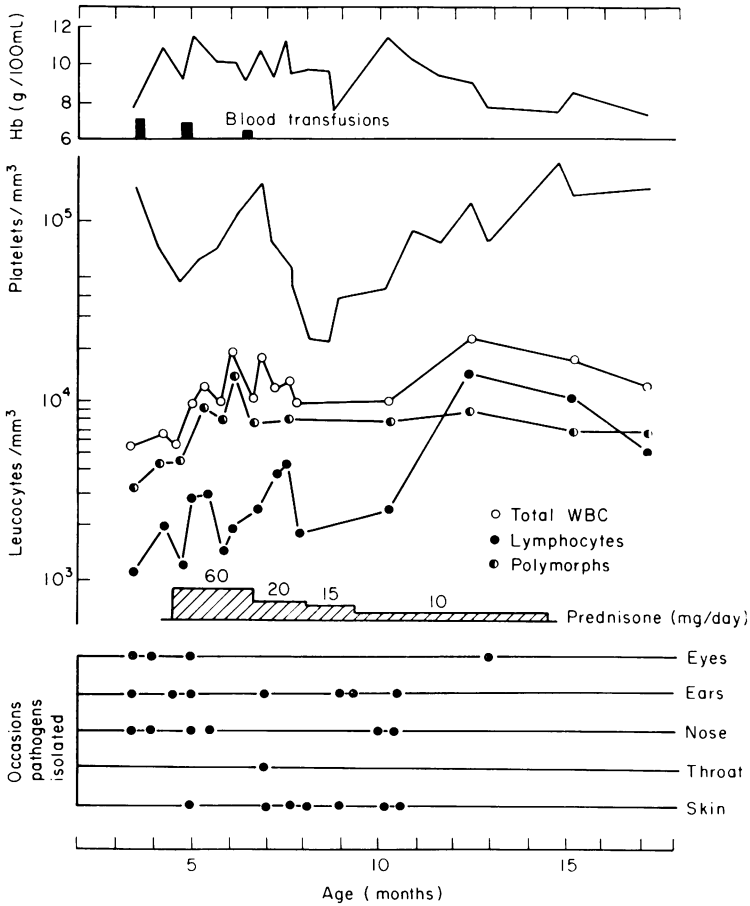

Fig. 1. Chart showing, from above downwards: Haemoglobin values; transfusions of packed cells (170 ml, 130 ml and 70 ml); platelet counts; total leucocyte counts, absolute neutrophil counts and absolute lymphocyte counts; prednisone therapy, and the occasions on which pathogenic organisms were cultured from various sites, throughout the patient's life.

lower respiratory tract infections, skin infections, conjunctivitis, oral ulceration, paronychiae, and finally confluent bronchopneumonia. The lower part of Fig. 1 illustrates the frequency with which pathogenic organisms were isolated from accessible sites. The patient was on almost continuous antibiotic therapy: Albamycin, Chloramphenicol, Celbenin, Erythromycin, Kanomycin, Colomycin, Streptomycin, Sulphonamide, Ampicillin, Lincocin and Neomycin were used, usually singly and Chloramphenicol only once (dose 100 mg/day for 4 days from 16 February 1965). Prednisone therapy is shown in Fig. 1.

Besides the infection, anaemia was a persistent clinical problem. Repeated blood transfusions were required (see Fig. 1) and there was a period of thrombocytopenia. Lymphocyte counts were low early in the illness, but at no time was there neutropenia, and both lymphocytes and platelets rose to normal levels later in the illness. The blood film showed both hypochromia and evidence of haemolysis. There was a reticulocytosis of 3·5–8·7%; serum haptoglobin was undetectable, and ^{51}chromium-tagged red cell survival $T_{\frac{1}{2}}$ was 18 days. Platelet antibodies were not detected by direct agglutination, complement fixation or antiglobulin consumption techniques (Dr N. F. W. Brueton). Tibial bone marrow (27 July 1965) showed marked reduction of megakaryocytes; the few present were small with normal nuclear lobulation but virtually agranular faintly basophilic cytoplasm with no evidence of platelet formation or cytoplasmic vaculation. Erythropoeisis and myelopoesis were normal. Lymphocytes and plasma cells were present in normal numbers.

Buccal smears were chromatin positive and chromosome cultures revealed a normal female karyotype (Dr A. B. Raper).

At the ages of 4, 8 and 12 months blood urea, serum electrolytes and bicarbonate and full urinalysis were found to be normal.

Immunity testing

Immunoglobulins. Results of gel diffusion precipitin estimations of serum immunoglobulins IgG, IgA and IgM are given in Table 1. These values are normal for the age. IgD was not

TABLE 1. Serum immunoglobulins

	27 August 1965 (10 months)	21 October 1965 (12 months)	17 December 1965 (13½ months)	15 February 1966 (15½ months)	23 March 1966 (16½ months)
IgG (mg/100 ml)	750	750	700	720	800
IgA (mg/100 ml)	25	34	25	65	55
IgM (mg/100 ml)	65	45	75	92	90
IgD (% of reference serum)		<10		<10	<10

detectable in the three sera studied; this is frequently so in healthy individuals. Immunoelectrophoresis (Fig. 2) showed initially a double arc of IgG reacting proteins on two occasions at 10 months and 12 months. At 14 months the IgG band was normal.

Antibodies. 1. Isohaemagglutinins: The patient was blood group B (Rh positive). Her neat serum taken at 16 months of age did not agglutinate group A1 cells (including Bromelin-treated cells) after 2 hr incubation at room temperature, and 2 hr and 16 hr incubation at 10°C. 1·3 ml of ^{51}chromium-labelled adult group A1 red blood cells (Cutbush & Mollison, 1958) were administered. The decay of radioactivity is plotted in Fig. 3. After an initial fairly rapid fall, about one-half of the radioactivity survived at 6 days; this possibly represents a double exponential as reported by Chaplin (1950) in hypogammaglobulinaemia. It is possible that a very small amount of isohaemagglutinin was responsible for this initial fall, but it is impossible to exclude heterogeneity of the cells used. Serum taken 1 month after this procedure (23 March

1966) still showed no evidence of complete or incomplete isohaemagglutinin activity in spite of the possibility of immunization by the administered group A cells.

2. Antibacterial antibodies: Antibody studies are shown in Table 2. The patient had suffered several infections caused by *Staphylococcus aureus*, and β-haemolytic streptococci were cultured from the infected eczema of the neck on 24 May 1965.
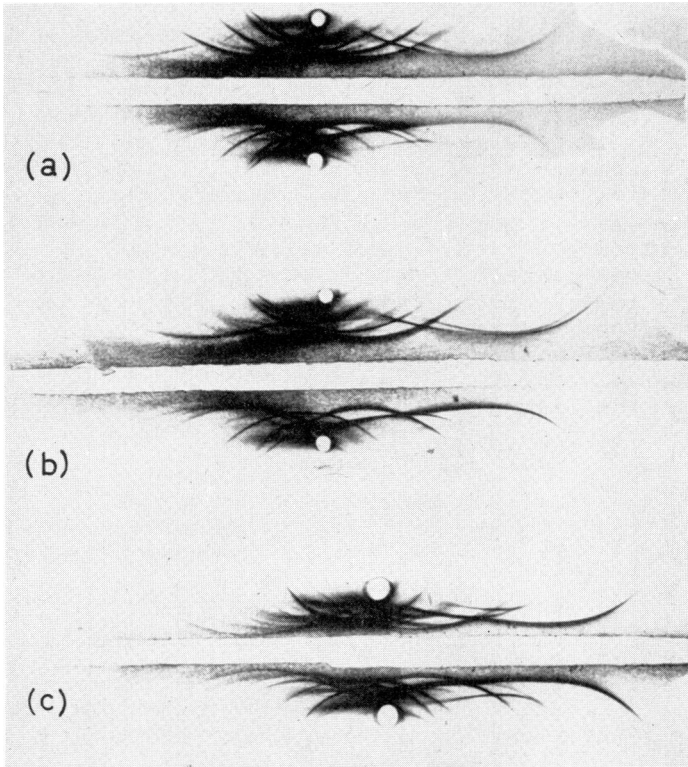

FIG. 2. Immunoelectrophoretic patterns of the patient's serum (above the troughs) at: (a) 10, (b) 12, and (c) 14 months of age. In each case a normal serum has been run below the trough.
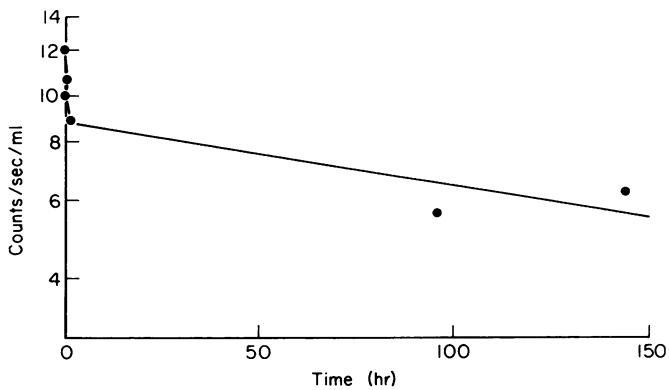

FIG. 3. Survival of ^{51}Cr-labelled normal group A_1 red cells in the circulation of the patient (group B); radioactivity of packed RBC expressed as counts/sec/ml.

TABLE 2. Antibody studies (where none was detected, titre of lowest dilution used is given, e.g. <1)

	21 October 1965 (12 months)	12 November 1965 (12½ months)	17 December 1965 (13½ months)	15 February 1965 (15¾ months)	23 March 1966 (16½ months)	4 April 1966 (17 months)
Staphylococcus α-haemolysin (u./ml)	—	—	—	0·025–0·05	0·25–0·5	0·5–1·0
Anti-streptolysin O (u./ml)	1	—	<50	<1	>400	>400
Diphtheria antitoxin (u./ml)	—	—	—	0·01–0·02	0·01–0·02	0·5–1·0
Tetanus antitoxin	—	—	—	0·1–0·2	0·1–0·2	0·5–1·0
Pertussis agglutinin	—	—	—	<1	<1	<1
Iso-agglutinins (anti-A)	<1	—	—	—	<1	—
Salm. typhi O agglutinins		<20	—	—	—	—
Salm. typhi H agglutinins		5120				
Salm. paratyphi AH agglutinins	—	2580				
Salm. paratyphi BO agglutinins		<20				
Salm. paratyphi BH agglutinins		<20				
Non-specific Salmonellae		<20				

The following immunization regimes were given:

Typhoid–paratyphoid (TAB)	27 October 1965	(0·2 ml S.C.I.)
	4 November 1965	(0·4 ml S.C.I.)
Diphtheria–pertussis–tetanus	15 February 1966	(0·5 ml I.M.I.)
	23 March 1966	(0·5 ml I.M.I.)

Staphylococcal antibodies were normal (Dr D. Gall, Wellcome Research Laboratories) but the first three sera studied for streptococcal antibodies were negative in spite of known previous streptococcal infection. Response to diphtheria and tetanus toxoids were normal, but pertussis agglutinins were not detected before or after the immunization procedure. Eight days after the second TAB injection the patient's serum gave a very high titre of antibodies to *Salmonella typhi* H (1/5120) and paratyphi A, H (1/2580) were detected, but no antibodies to *Salmonella paratyphi* B, H or O, *Salmonella typhi* O, or non-specific *Salmonella* antibody were detected (lowest dilution of serum used was 1 in 20).

Cellular immunity

(a) Capacity to develop delayed-type skin hypersensitivity was tested by the method of Uhr, Dancis & Neumann (1960) using 2-4-dinitro-fluorobenzene (DNFB). Sensitizing dose: 0·02 ml of 10% DNFB on 14 December 1965, which led to a primary erythematous reaction with some desquamation 2 days later. Three weeks later (4 January 1966) 0·01 M DNFB was applied by patch test. No immediate reaction was seen, but on 6 January 1966 there was a strong reaction.

TABLE 3. Percentages of transformed 'blast' cells in stimulated lymphocyte cultures of the patient and three adult controls

Additive	Patient	Control 1	Control 2	Control 3
Phytohaemagglutinin	61	44	40	49
Staphylococcal filtrate	65	20	2·6	41
Streptolysin O	6·6	0·2	0·8	1·2
Saline control	1·0	0·2	0·2	—

(b) *In vitro* cultures of blood lymphocytes (Moorhead *et al.*, 1960) were performed on 25 February 1966. The patient's cells showed normal blast-cell transformation responses to the non-specific stimulants phytohaemagglutinin and staphylococcal filtrate (Table 3). Streptolysin O caused a significant degree of blast-cell transformation of the patient's cells but not of those of the three controls.

Histology

1. The biopsy of the epulis taken on 4 May 1965 showed non-specific chronic inflammatory changes including moderate numbers of plasma cells.

2. Biopsy of supraclavicular lymph gland (12 April 1966) showed a reduced number of follicles (Fig. 4), but normal numbers of lymphocytes and mature pyroninophilic plasma cells.

3. Autopsy (53 hr after death) (Dr J. Andrews)

(a) *Macroscopic.* Both lungs showed extensive bronchopneumonic consolidation with pleurisy and pleural effusions. Thymus (4 g) and spleen were normal. Soft enlarged lymph nodes were present in the neck. Pharyngeal tonsils were normal. The brain showed marked internal hydrocephalus, apparently due to fibrous adhesions obstructing the foramina of Lushka and Magendie.

(b) *Microscopic.* The cervical lymph nodes showed many lymphoid follicles with very active germinal centres, in which reticulum cells were prominent, but peripheral lymphocytes scanty; increased numbers of polymorphs were present in the sinusoids. Splenic and tonsillar lymphoid follicles were also rather hyperplastic. The thymus showed increased histiocytic elements but was otherwise normal (Fig. 5).
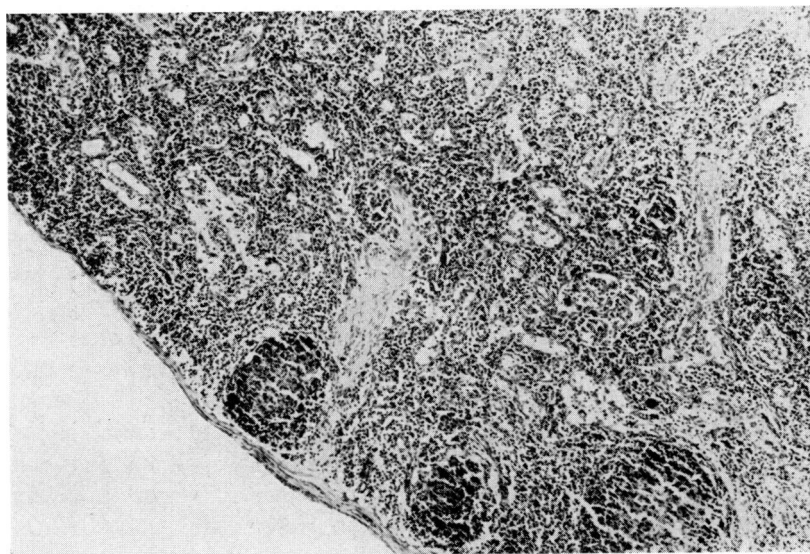
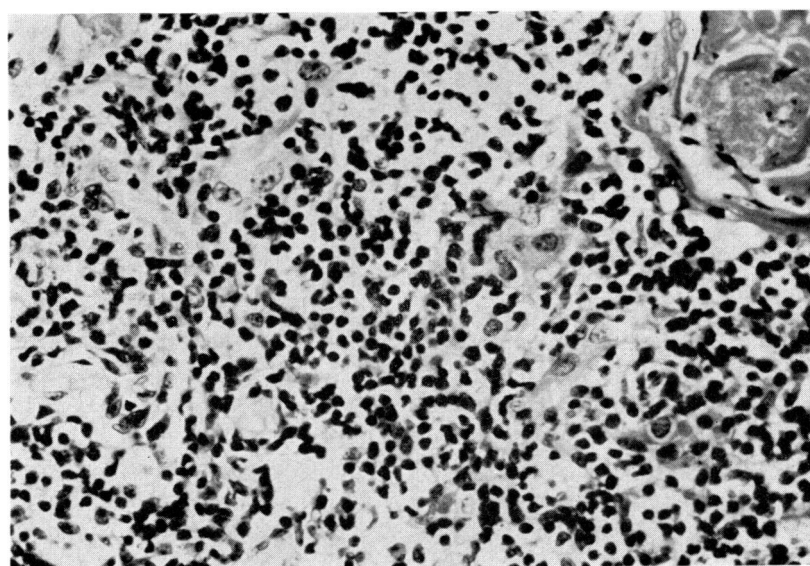FIG. 4. Supraclavicular lymph gland (H & E, × 70). Biopsy.

FIG. 5. Thymus (H & E, × 140). Post-mortem.

DISCUSSION

A case is presented in whom abnormal susceptibility to infections was suggested clinically by almost continuous infections in many systems by numerous different bacteria leading to fatal bronchopneumonia at the age of 17 months, in spite of frequent administration of antibiotics and almost continuous hospitalization. No cause of this susceptibility to infection was detected other than a possible defect of immune mechanisms. Immunoglobulins were present at normal concentration for the age, though a transient doubling of the IgG on immunoelectrophoresis was detected. It is also worth noting that IgG and IgM were not at the high levels expected after such repeated infections. Antibodies to certain bacterial antigens (*Salmonella typhi* H and *paratyphi* A, H, C. diphtheriae, Tetanus toxoid and staphylococcal antihaemolysin) were normal. Initially, antistreptolysin O antibodies were at very low titre at an age approaching a year when β-haemolytic streptococcal infection was known to have occurred and the patient was known to have a normal concentration of immunoglobulins. Subsequently, however, high titres developed. But isohaemagglutinins were completely undetectable and no antibodies were developed to pertussis and to *Salmonella typhi* O and *paratyphi* B, O and H. The distribution of pyroninophilic plasma cells in lymphoid tissue was normal and cellular immunity, as indicated by both cutaneous delayed type hypersensitivity and lymphocyte transformation, were normal.

The association of multiple infections with a period of thrombocytopenia and eczema presents a picture similar to Aldrich's syndrome (Aldrich, Steinberg & Campbell, 1954). In this familial syndrome affecting boys, there are also varying measurable defects of immunity which are perhaps less than would fully explain the great susceptibility to infection, and which include a conspicuous isolated deficiency of isohaemagglutinins. In this syndrome Dalloz *et al.* (1965) have reported an odd immunoelectrophoretic abnormality of IgG, not dissimilar to the phenomenon we demonstrate here. The possibility that this child represents a female counterpart of this syndrome cannot be excluded. It is unlikely that the short course of chloramphenicol, other antibiotics or prednisone could have accounted for the thrombocytopenia and abnormality of immune response (Schwartz & André, 1962).

Various combinations of quantitative and qualitative defects of different humoral immunity mechanisms have been described (reviewed by Good *et al.*, 1962, and Hobbs, 1966), but we are not aware of previous reports of established defects of capacity to produce antibodies with normal concentration of all the immunoglobulins. Cases of 'antikorpermangelsyndrom', profound deficiency of antibody production, with normal levels of IgG have been associated with deficiency of IgA, IgM or both (Giedion & Scheidegger, 1957; West, Hong & Holland, 1962; Palmgren & Lindberg, 1963). The patchy defects in our case also seem different from the failure to respond to viruses reported by Fulginiti *et al.* (1966). Transient hypogammaglobulinaemia, the abnormal prolongation of the physiological trough of IgG, is apparently due to delay in the development of the immunological competence, and is associated with a deficiency of all antibodies. It is possible, in view of the subsequent development of anti-streptolysin in our patient, that her defect might conceivably have been a similarly transient one, though its antigen-selective, qualitative nature makes it obviously different.

The basis of the transient immunoelectrophoretic abnormality of IgG is not clear, and it is unfortunate that its spontaneous disappearance prevented us from investigating it

further. The appearance—rather like a myeloma protein—suggests a concentration of IgG of circumscribed electrophoretic mobility, and perhaps of single light chain type. It is probable that individual antibody activity can favour different allotypes of IgG, and IgG of differing electrophoretic mobility. It is possible that maturation of clones of plasma cells whose resulting IgG differed in these ways, proceeded irregularly in this child, and this was the basis of the heterogeneity of antigen response.

Immunological competence depends on cellular recognition of foreign material (possibly a function of macrophages), and transference of information to reacting cells, both lymphocytes for the delayed type hypersensitivity reaction, and plasma cells for antibody production (see Peterson *et al.*, 1965). The significance of structure and physical form of antigens in relation to recognition and processing at the macrophage stage is still incompletely understood. It seems unlikely that the defect in our patient was associated with a failure at this stage, in view of the profound difference of response to paratyphi A(H) and paratyphi B(H) and to the response by lymphocyte transformation to streptolysin O at a time when antibodies to it were not detectable. These points, and the transient quantitative abnormality of IgG point to a partial defect of the later stages of antibody production and/or release, which may have been improving spontaneously.

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