Clin. exp. Immunol. (1966) **1**, 223–231.

ACQUIRED DYSGAMMAGLOBULINAEMIA IN A YOUNG MAN

R. T. WILLIAMS

Crumpsall Hospital, Manchester

(*Received* 25 *October* 1965; *accepted* 11 *November* 1965)

SUMMARY

A 26-year-old man had been subject to repeated infections since the age of 15. He was found to have complete absence of isohaemagglutinins, even though he was blood group O, and absence of antibodies to any of the common bacterial and viral infections. A full course of typhoid–paratyphoid A and B vaccine produced no antibody response and a large dose of inactivated poliomyelitis vaccine produced only a minimal response. Estimation of the immunoglobulin levels in the serum revealed a normal amount of IgG globulin, increased amounts of IgM globulin and diminished amounts of IgA globulin.

The plasma γ-globulins constitute a group of proteins which are structurally related but differ in molecular weight, antigenicity and electrophoretic mobility. They have in common the property of being carriers of antibody activity and for this reason the term immunoglobulin is preferable to γ-globulin for describing these proteins. There are three main groups of immunoglobulin and the literature on the subject is confusing because of the variety of symbols which have been used to describe the groups. The World Health Organization (Memorandum, 1964) has recommended that new terms are used and these new terms, together with synonyms, are shown in Table 1.

The IgG globulins normally constitute about 70% of the total immunoglobulins and the majority of acquired antibacterial, antitoxin and antiviral antibodies are contained in this group. IgA globulins make up 20–25% of the immunoglobulins and, although their functional role has not been clearly defined, there is no doubt that acquired antibodies may be carried in this fraction (Turner & Rowe, 1964). The skin-sensitizing activity of human allergic sera is also a function of IgA globulin (Heremans & Vaerman, 1962). IgM globulins constitute about 5% of the total immunoglobulins; isohaemagglutinins, cold haemagglutinins, Wassermann antibodies and many of the heterophile antibodies have been identified in this fraction.

In 1952, Bruton first described the condition of congenital agammaglobulinaemia in

Correspondence: Dr Rhys T. Williams, Crumpsall Hospital, Manchester 8.

which there is marked deficiency of total immunoglobulins and liability to recurrent infections; the plasma immunoglobulin concentrations are usually under 100 mg/100 ml as opposed to the normal range of 600–1500 mg/100 ml. This was followed by the recognition of 'acquired' idiopathic agammaglobulinaemia of infancy. With the development of more sensitive techniques it became apparent that immunoglobulins are never entirely absent so the term hypogammaglobulinaemia was introduced. The subject is well reviewed by Soothill & Squire (1963).

The term dysgammaglobulinaemia has been used in more than one sense. As originally used by Giedion & Scheidegger in 1957 the term described a condition in which normal

TABLE 1. Nomenclature of the immunoglobulins

New terms proposed by W.H.O.	IgG	IgA	IgM
Alternative new terms proposed by W.H.O.	γG	γA	γM
Previous terms used	γ	1A	1M
	γ2	$\beta 2^{A}$	$\beta 2^{M}$
	γss		19Sγ
	7Sγ		

concentrations of functionally defective immunoglobulins occurred and where there was no evidence of a primary disease such as myelomatosis. A similar case has been described by Gilbert & Hong (1964). This seems to be the best use of the term dysgammaglobulinaemia but confusion has been caused by applying it to the syndrome of hypogammaglobulinaemia with low levels of IgG but high levels of functionally effective IgM. This syndrome was first recognized by Kekwick *et al.* (1961) but it was Rosen *et al.* (1961) who described it as dysgammaglobulinaemia and the term has subsequently been used to describe several similar cases (Israel-Asselain, Burtin & Chebat, 1960; Burtin, 1961; Hong *et al.*, 1962; Gitlin, Rosen & Janeway, 1962; Rosen & Bougas, 1963; Huntley, Lafferty & Lyerly, 1963; Hinz & Boyer, 1963). These patients are subject to recurring bacterial infections but the antibodies associated with IgM globulins, such as the isohaemagglutinins, are found in normal or increased amounts.

Qualitative defects in immunoglobulins occur in myelomatosis, Waldenstrom's macroglobulinaemia and some lymphomas (Zinneman & Hall, 1954; Lawson *et al.*, 1955; Ossermann & Takatsuki, 1963). Although the abnormal globulins produced in these conditions appear to be devoid of antibody function, there always appears to be some normal immunoglobulin present (Ratcliff, Soothill & Stanworth, 1963). This report concerns a young man in whom a qualitative defect of the immunoglobulins exists but in whom there is no evidence of a primary disease such as myelomatosis or lymphoma.

Case report

The patient is a 26-year-old man who works as a loom fitter in a cotton mill. As a child he had not shown any undue susceptibility to infections and measles was the only common childhood illness from which he suffered. At the age of 15 he developed pneumonia and from that time suffered repeated infections. He bears the scars of numerous boils and carbuncles and in 1960 a groin abscess and a perinephric abscess required drainage. It was noted at the time of

that hospital admission that the spleen was palpable 2 in. below the costal margin. Sternal marrow examination showed very hyperplastic red and white cell series. Later that year he first consulted a dermatologist about widespread leukoderma which had been present for 2 years. He had developed patches of eczema in the leukodermic areas and over the following years he was treated with a variety of applications, including antibiotics and adrenocorticosteroid ointments, and with adrenocorticosteroids in small doses by mouth. In 1962 and again in 1963 he developed left-sided pneumonia. In 1963 he was also admitted to hospital for the treatment of an exacerbation of eczema. From August 1963 he was given repeated courses of chloramphenicol because of persistent cough with purulent sputum. He was admitted to Manchester Royal Infirmary at the end of February 1964 with a further attack of left-sided pneumonia.

At the time of admission he was febrile and distressed with signs of left lower lobe pneumonia. Leukoderma affected all areas of the skin but the eczema had almost completely disappeared and there were only a few small patches. Scars of herpes zoster lesions were visible over the left scapular region. The spleen was grossly enlarged and firm, extending 2 in. below the umbilicus. The liver was palpable 1 in. below the costal margin. There were no palpable lymph nodes.

LABORATORY RESULTS

Haematology

Repeated blood counts have shown persistent depression of all the formed elements of the blood and it is interesting that the greatest depression of the polymorphonuclear leucocytes always occurred at the height of an infective episode. Thus, on first admission, the white cell count was 3150/mm^3, 13·5% polymorphonuclear leucocytes, 72·5% lymphocytes, 14·0% monocytes. Fourteen days later the white cell count was 5400/mm^3, 78% polymorphonuclear leucocytes, 7% lymphocytes, 2% eosinophils and 13% monocytes. Over the succeeding months, during which he had further infective episodes, the total white cell count ranged from 2700 to 6000/mm^3, often with granulopenia. The haemoglobin level ranged between 8·7 and 11·7 g/100 ml with a reticulocyte count up to 2·5%. Sternal marrow examination was normal apart from a mild degree of erythroid hyperplasia. The platelet count was usually in the range 60 000–100 000/mm^3.

Splenic puncture (Dr M. C. G. Israëls)

No cytological abnormality was discovered in the smear obtained by splenic puncture.

Blood group

Blood group O Rh positive (R_1R_1). Secretor of H substance. No anti A, anti B or other blood group antibodies detected in serum (Dr F. Stratton). It was the difficulty experienced in attempting to group and cross-match blood that first pointed to the antibody defect.

Serum proteins

Albumin 4·0 g/100 ml, globulin 2·3 g/100 ml. Normal electrophoretic pattern.

Immunoglobulin studies

Estimation of the immunoglobulins was performed by Dr J. F. Soothill using the gel diffusion precipitin technique (Soothill, 1962).

The results were as follows:

IgG globulin	560 mg/100 ml
IgA globulin	0·8% reference normal serum
1gM globulin	600% reference normal serum

Antibody studies

Response to T.A.B. vaccine. The response to Typhoid, Paratyphoid A and B vaccine was estimated. 'Wellcome' brand Typhoid–Paratyphoid A and B vaccine (Wellcome Research Laboratories, Beckenham, England) was used. The vaccine contained 10^9 heat-killed *Salmonella typhi* organisms per ml. Three subcutaneous injections of vaccine were given at 28-day intervals; the first injection was of 0·5 ml and the next two of 1·0 ml each. Following each injection he suffered a moderately severe reaction with fever and rigors. Blood was drawn for assay of agglutinins at monthly intervals up to 1 month after the last injection. The assay of agglutinins was performed by the routine tube-dilution technique. The titres as measured before the course of injections and at intervals after each injection remained unaltered and were as follows:

Salmonella typhi 'H'	Negative 1/20
Salmonella paratyphi A 'H'	Negative 1/20
Salmonella paratyphi B 'H'	Negative 1/20
Composite *Salmonella* 'H' non-specific	Negative 1/20
Salmonella typhi 'O'	Negative 1/20
Salmonella paratyphi B 'O'	Negative 1/20
Brucella abortus	Negative 1/20

Response to inactivated poliomyelitis vaccine. The response to a large dose of inactivated poliomyelitis vaccine was estimated. The vaccine (Glaxo Laboratories Ltd, Greenford, England) contained at least 30 million TCD_{50} for Poliovirus types I and III and at least 10 million TCD_{50} for type II. Two injections of 5 ml of vaccine were given on successive days and the antibody response was estimated on blood drawn 12 days after the second injection. Standard neutralization tests were carried out in 2°C monkey kidney cultures using 100 TCD_{50} of virus (Polio II, II and III) and determining the end-point from the cytopathic effect. The neutralization test titres before and after the injection of vaccine were:

	Before	After
Polio I	1/2	1/10
Polio II	1/2	1/20
Polio III	1/2	1/5

Other antibody studies which were performed are listed in the table below:

Anti-streptolysin	< 50 todd units
Anti-staphylolysin	Negative
Viral complement fixation tests to Influenza A, B, and C, Psittacosis, Q Fever, Adenovirus, Parainfluenza 1, 2 and 3, Mumps S and V, L.C.M. virus	Negative 1 in 8

Herpes simplex	50% inhibition at 1 in 40
Cold agglutinins	Negative
Cold haemolysins	Negative
Paul Bunnell	Agglutination to 1 in 8
Sheep-cell agglutination	Negative <4
Thyroid auto-precipitin test	Negative
Thyrotoxic (anti-microsomal) C.F. test	Negative at 1 in 5
Tanned cell agglutinating antithyroglobulin test	Negative at 1 in 10

The Heaf tuberculin test was negative.
No L.E. cells were found and antinuclear factor was not detected.

Red cell survival (Dr E. J. Watson-Williams)

The uncorrected half-life of the patient's own red blood cells was 20·5 days (normal values 24–34 days). This slight reduction from normal could have been due to repeated venesections for other purposes during the estimation of the red cell survival.

The survival of labelled group B cells was also estimated. In a normal person the survival of red cells of another blood group is so short as to make the estimation of the half-life impossible; Cutbush & Mollison (1958) showed that 3 min after the injection the amount of ^{51}Cr in the red cells was only 1–3% of the amount injected. In this patient (who was group O) the half-life of labelled group B cells was 12 hr.

Cytogenetic study

Cytogenetic studies were carried out using peripheral blood lymphoctyes cultured by the method of Hungerford *et al.* (1959). The results are shown in the table:

Chromosome count distribution (%)						
<44	44	45	46	47	48	>48
0	0	4	84	12	0	0

No. of cells counted, twenty-five.

The modal number was forty-six but there were a number of cells with forty-seven chromosomes (12%). The additional chromosome in each of these cells (see Fig. 1) was an abnormal, long, submetacentric autosome (Type 11 of Elves & Israels, 1963).

Other laboratory investigations

Blood urea, serum electrolytes and plasma bicarbonate, normal. Serum iron 60 μg/ 100 ml. Serum cholesterol 125 mg/100 ml. Serum calcium 10·2 mg/100 ml. Serum inorganic phosphorus 4·4 mg/100 ml. Serum alkaline phosphatase 25–36 King Armstrong units per 100 ml. Serum B_{12} 301 μμg/ml. Schilling test B_{12} excretion 12·1%. Folate activity 4·0 mμg/ml. Faecal fat excretion, average 6·0 g/day. Faecal stercobilinogen, average 48 mg/100 g. Urine—no protein. Twenty-four-hour urine coproporphyrin, no gross increase. Sodium content of sweat, 36 mEq/l.

Family history

The patient's mother and father were healthy and neither had shown undue susceptibility to infections. There was no history of consanguinity in the marriage. The father was blood group A Rh positive (D). The serum proteins were albumin 4·9 g/100 ml, globulin 3·1 g/100 ml and γ-globulin 1·1 g/100 ml. Electrophoresis showed a normal globulin pattern.

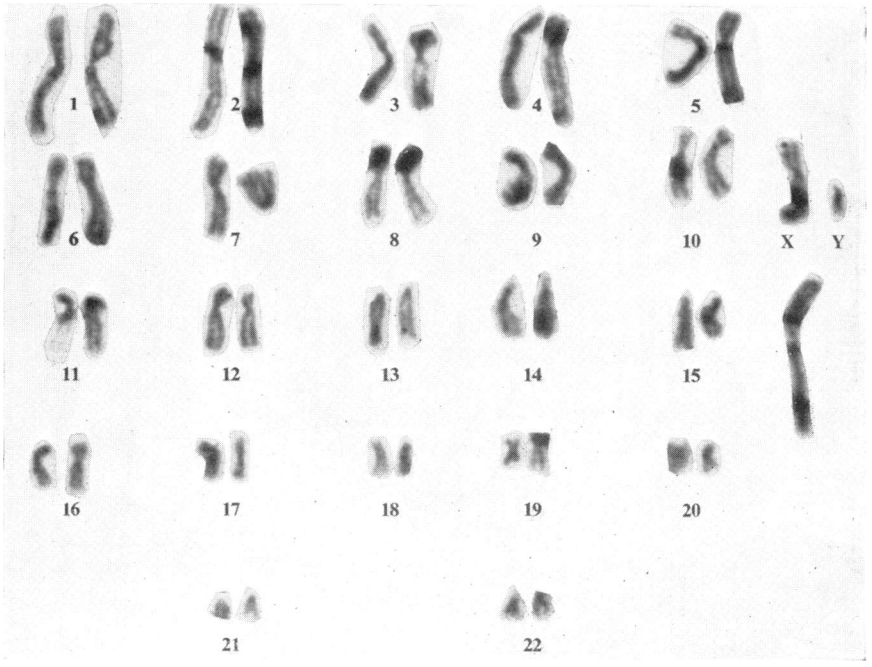

FIG. 1. Additional, long, submetacentric autosome occurring in 12% of cells.

The mother was blood group B Rh positive (D). The serum proteins were albumin 4·2 g/100 ml, globulin 3·1 g/100 ml and γ-globulin 1·3 g/100 ml. Electrophoresis showed a normal globulin pattern. Both the father and the mother had normal haemoglobin levels and normal white cell counts and both had negative sheep cell agglutination tests. The patient had been their only child.

Progress

The attack of pneumonia was treated with penicillin and streptomycin and later with tetracycline. Shortly after discontinuing the tetracycline, and while still in hospital, he developed an upper respiratory infection with temperature rising to 104°F. He was accordingly maintained on prophylactic antibodies until treatment with pooled γ-globulin was started. He was given an initial loading dose of 0·05 g pooled γ-globulin per kg body weight each day for 5 days followed by weekly injections of 0·025 g/kg body weight. Ten days after starting on the γ-globulin injections he was again admitted to hospital with

left lower lobe pneumonia and, after treatment with antibiotics, was again discharged with the weekly γ-globulin injections as the only treatment. When he developed a further attack of pneumonia in less than a month it became apparent that the γ-globulin injections alone were not providing sufficient protection and he has therefore been given tetracycline 250 mg q.i.d. in addition since then. On the combined antibiotic and γ-globulin treatment he has remained well and has had no further attacks of pneumonia.

DISCUSSION

Routine estimation and electrophoresis of serum proteins had given no indication of a γ-globulin abnormality and it was not until it was found that there was absence of isohaemagglutinins was the antibody deficiency state suspected. Further studies then revealed absence of antibodies to any of the common bacteria or viruses apart from a slightly raised titre to herpes simplex; the serum inhibited the formation of pocks by herpes simplex virus on the chorio-allantoic membrane of 11-day-old chick embryos to a dilution of 1 in 40. Although non-specific inhibitors to herpes simplex virus do occur, their titre is usually less than 1 in 20. It was also possible to demonstrate a low titre of heterophile antibody; this antibody is found in the IgM globulin fraction, which showed a marked increase in concentration in the patient's serum. Administration of a full course of Typhoid–Paratyphoid A and B vaccine did not produce any detectable antibody response. However, a large dose of inactivated Poliomyelitis vaccine did produce a minimal normal antibody response. Labelled red blood cells for group B introduced into his circulation had a half-life of 12 hr. Although this is considerably reduced compared with normal values of 24–34 days for homologous cells, it does demonstrate a gross departure from normal; in the presence of isohaemagglutinins the half-life of group B cells in a person of group O would have been so short as to be unmeasurable (Cutbush & Mollison, 1958).

From these observations it is clear that the patient's immunoglobulins are qualitatively defective. It is possible that he may be suffering from a neoplastic process involving the cells which produce the immunoglobulins. If this is so then it would be reasonable to suppose that the grossly enlarged spleen was the main organ involved; however, splenic puncture did not show any cytological abnormality. There was no evidence of involvement of any other part of the lympho-reticular system.

Cytogenetic studies showed an abnormal cell line containing an additional long submetacentric autosome, similar to those seen in some cases of Waldenström's macroglobulinaemia (Gowans, Gesner & McGregor, 1961; Benirschke, Brownhill & Ebaugh, 1962; Elves & Israëls, 1963). Similar abnormal lymphoid cell lines have, however, also been observed in normal subjects (Elves & Israëls, 1963) and it may therefore be suggested that this genetic abnormality precedes the biochemical defect. Thus the presence of abnormal amounts of macroglobulin may be the result of the stimulation of the abnormal cells, which are normally dormant, to produce immunoglobulin. The origin of the chromosome abnormality is at present not clear.

Splenomegaly has been described in the 'acquired' form of hypogammaglobulinaemia and the enlargement has on occasion been sufficiently great to warrant splenectomy for mechanical reasons (Citron, 1957). The occurrence of neutropenia, particularly at the height of an infection, is also well recognized as a feature of hypogammaglobulinaemia

(Good *et al.*, 1960). In the patient described there was gross enlargement of the spleen and pancytopenia; acute infections were usually accompanied by a further fall in the leucocyte count.

This patient resembles those described by Giedion & Scheidegger (1957) and Gilbert & Hong (1964) in that immunoglobulins present in normal or increased amounts are functionally ineffective. Giedion & Scheidegger reported a 4-year-old boy who had quantitatively normal IgG globulin but a deficiency of IgA and IgM globulins. Gilbert & Hong described an adult negro woman with a marked deficiency in IgM and IgA globulins but only a moderate decrease in IgG globulins. Immunological studies in both these patients showed absence of normal antibody activity and failure to respond normally to stimulation with various antigens. The isohaemagglutinins were absent in the patient described by Giedion & Scheidegger but present in the patient described by Gilbert & Hong. Furthermore, in the latter patient, although the onset of susceptibility to infections was relatively late in life, multiple immunoglobulin alterations in the family suggested an inherited disorder.

ACKNOWLEDGMENTS

I wish to thank Professor D. A. K. Black for permission to publish this case report. I should also like to thank Dr J. F. Soothill for his advice and help, and Dr Michael W. Elves for the cytogenetic studies.

REFERENCES

BENIRSCHKE, K., BROWNHILL, L. & EBAUGH, F.G. (1962) Chromosomal abnormalities in Waldenström's Macroglobulinaemia. *Lancet*, **i**, 594.

BRUTON, O.C. (1952) Agammaglobulinaemia. *Pediatrics*, **9**, 722.

BURTIN P. (1961) An example of a typical agammaglobulinaemia (a case of severe hypogammaglobulinaemia with increase of the β-2 macroglobulin). *Rev. franç. Étud. clin. biol.* **6**, 286.

CITRON, K.M. (1957) Agammaglobulinaemia with splenomegaly. *Brit. med. J.* **i**, 1148.

CUTBUSH, M. & MOLLISON, P.L. (1958) Relations between characteristics of blood-group antibodies *in vitro* and associated patterns of red-cell destruction *in vivo*. *Brit. J. Haemat.* **4**, 115.

ELVES, M.W. & ISRAËLS, M.C.G. (1963) Chromosomes and serum proteins: a linked abnormality. *Brit. med. J.* **ii**, 1024.

GIEDION, A. & SCHEIDEGGER, J.J. (1957) Congenital immunological paresis in the absence of specific β2-globulin and normal quantities of γ-globulin. *Helv. paediat. Acta* (*Basel*), **12**, 241.

GILBERT, C. & HONG, R. (1964) Qualitative and quantitative immunoglobulin deficiency. *Amer. J. Med.* **37**, 602.

GITLIN, D., ROSEN, F.S. & JANEWAY, C.A. (1962) Undue susceptibility to infection. *Pediat. Clin. N. Amer.* **9**, 405.

GOOD, R.A., ZAK, S.J., CONDIE, R.M. & BRIDGES, R.A. (1960) Clinical investigation of patients with agammaglobulinaemia and hypogammaglobulinaemia. *Pediat. Clin. N. Amer.* **7**, 397.

GOWANS, J.L., GESNER, B.M. & MCGREGOR, D.D. (1961) In: *The Biological Activity of the Leucocyte* (Ed. by G. E. W. Wolstenholme and M. O'Connor), CIBA Foundation Study Group No. 10, p. 32. Churchill, London.

HEREMANS, J.F. & VAERMAN, J.P. (1962) β-2A-globulin as a possible carrier of allergic reaginic activity. *Nature* (*Lond.*), **193**, 1091.

HINZ, C.F., JR. & BOYER, J.T. (1963) Dysgammaglobulinaemia in the adult manifested as autoimmune haemolytic anaemia; serologic and immunochemical characterization of an antibody of unusual specificity. *New Engl. J. Med.* **269**, 1329.

HONG, R., SCHUBERT, W.K., PERRIN, E.V. & WEST, C.D. (1962) Antibody deficiency syndrome associated with beta-2 macroglobulinaemia. *J. Pediat.* **61,** 831.

HUNGERFORD, D.A., DONNELLY, A.J., NOWELL, P.C. & BECK, S. (1959) The chromosome constitution of a human phenotypic intersex. *Amer. J. hum. Genet.* **11,** 215.

HUNTLEY, C.C., LAFFERTY, J.W. & LYERLY, A. (1963) Antibody deficiency syndrome with increased gamma 1 M (B2 M) globulins and absent gamma 1 A (B2 A) globulins and gamma 2 (G) globulins. *Pediatrics,* **32,** 407.

ISRAEL-ASSELAIN, R., BURTIN, P. & CHEBAT, J. (1960) A new biological disorder: agammaglobulinaemia with 2-macroglobulinaemia (a case). *Bull. Soc. med. Hôp. Paris,* **76,** 519.

KEKWICK, R.A., VALLET, L., CUTBUSH, M., MOLLISON, P.L., THOMAS, A.R., GELL, P.G.H. & SOOTHILL, J.F. (1961) Estimation of gamma globulin in the serum of patients with hypogammaglobulinaemia. *J. clin. Path.* **14,** 470.

LAWSON, H.A., STUARD, C.A., PAULL, A.M., PHILLIPS, A.M. & PHILLIPS, R.W. (1955) Observations on antibody content of blood in patients with multiple myeloma. *New Engl. J. Med.* **252,** 13.

MEMORANDUM (1964) Nomenclature for human immunoglobulins. *Bull. Wld Hlth Org.* **30,** 447.

OSSERMAN, E.F. & TAKATSUKI, K. (1963) Plasma cell myeloma: gamma globulin synthesis and structure. A review of biochemical and clinical data, with the description of a newly-recognized and related syndrome, 'H-gamma-2-chain (Franklin's) disease'. *Medicine (Baltimore),* **42,** 357.

RATCLIFF, P., SOOTHILL, J.F. & STANWORTH, D.R. (1963) Physico-chemical and immunological studies of pathological serum macroglobulins. *Clin. chim. Acta,* **8,** 91.

ROSEN, F.S. & BOUGAS, J.A. (1963) Acquired dysgammaglobulinaemia: elevation of the 19S gamma globulin and deficiency of the 7S gamma globulin in a woman with chronic progressive bronchiectasis. *New Engl. J. Med.* **269,** 1336.

ROSEN, F.S., KEVY, S.V., MERLER, E., JANEWAY, C.A. & GITLIN, D. (1961) Recurrent bacterial infections and dysgamma-globulinaemia: deficiency of 7S gamma-globulins in the presence of elevated 19S gamma-globulins. Report of two cases. *Pediatrics,* **28,** 182.

SOOTHILL, J.F. (1962) Estimation of eight serum proteins by a gel diffusion precipitin technique. *J. Lab. clin. Med.* **59,** 859.

SOOTHILL, J.F. & SQUIRE, J.R. (1963) The antibody deficiency syndrome. In: *Clinical Aspects of Immunology* (Ed. by P. G. H. Gell and R. R. A. Coombs). Blackwell Scientific Publications, Oxford.

TURNER, M.W. & ROWE, D.S. (1964) Characterization of human antibodies to *Salmonella typhi* by gel-filtration and antigenic analysis. *Immunology,* **7,** 639.

ZINNEMAN, H.H. & HALL, W.H. (1954) Recurrent pneumonia in multiple myeloma and some observations on immunologic response. *Ann. intern. Med.* **41,** 1152.