sick and infirm has been reported by Bruce White *et al.* (*British Medical Journal*, 1957, 1, 381). In this outbreak six patients developed rising titres of antibody, and the clinical illnesses resembled influenza.

REFERENCES

- Grist, N. R. (1955). *British Medical Journal*, 2, 994.
 — (1957). *Scot. med. J.*, in press.
 — Sommerville, R. G., and Carson, H. G. (1957). *British Medical Journal*, 1, 378.
 Jensen, K. E., Minuse, E., and Ackermann, W. W. (1955). *J. Immunol.*, 75, 71.
 Kuroya, M., Ishida, N., and Shiratori, T. (1953). *Yokohama med. Bull.*, 4, 217.
 Matsuzawa, M., Shiratori, T., and Kikuchi, H. (1954). Quoted by Jensen *et al.* (1955).
 Medical Research Council (1955). *British Medical Journal*, 2, 1139.

AGAMMAGLOBULINAEMIA WITH SPLENOMEGALY

BY

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Agammaglobulinaemia is a biochemical defect characterized by absence of serum gamma-globulin and is usually associated with deficiency of immunoglobulins, resulting in increased susceptibility to infection. The frequent recurrence of infection, which is the principal clinical feature of this condition, has been accentuated by the use of antibacterial drugs which have enabled these subjects to survive a succession of infections to which they might otherwise have succumbed.

Since agammaglobulinaemia associated with recurrent sepsis was first described by Bruton (1952) over 40 cases have been recorded. In these cases the symptoms and signs of the disorder have usually been those of recurrent infections. The purpose of this paper is to report two cases of agammaglobulinaemia in which enlargement of the spleen and liver and generalized enlargement of lymph nodes were also outstanding clinical features.

Case 1

The patient, a man of 33, had suffered from measles and pertussis in childhood, but apart from this had enjoyed good health until 1942, when at the age of 19 he had pneumonia. Enlarged lymph nodes were palpable in the neck and in both axillae, and the chest radiograph showed enlarged lymph nodes at the hilum of the right lung and shadows in the right lung. Respiratory symptoms recurred four months later and septic tonsils were removed. He remained in poor health and in the subsequent 14 years suffered numerous infections. In 1945 he had gingivitis, laryngitis, and pleurisy, and in 1946 seborrhoeic impetigo, herpes zoster, laryngitis, and pneumonia. In 1946 generalized enlargement of lymph nodes was present, enlarged nodes being palpable in the cervical, epitrochlear, axillary, and inguinal regions on both sides. In 1948 he had mumps and a respiratory infection, and in 1949 furunculosis and several respiratory infections.

In 1950 he was admitted to hospital with pleurisy. A firm spleen was palpable 1 in. (2.5 cm.) below the left costal margin, and the liver was palpable 1 in. (2.5 cm.) below the right costal margin. Generalized enlargement of superficial lymph nodes similar to that found in 1946 was noted and the chest radiograph again revealed right hilar node enlargement. Penicillin was given and respiratory symptoms improved, but jaundice occurred later and lasted three weeks. At this time the level of serum globulin was normal and albumin was raised. Total protein was 8.8 g. per 100 ml. (albumin 6.1 g., globulin 2.7 g.). The thymol turbidity was 4 units (normal). The blood count was normal. Biopsy of an enlarged lymph node showed reactive hyperplasia but no other abnormality.

Between 1950 and 1954 he suffered six acute respiratory infections. In 1954 sarcoidosis was suspected because of respiratory symptoms, hilar node enlargement, lymphadenopathy, hepatosplenomegaly, and a negative Mantoux test. Another enlarged lymph node was removed and showed reactive hyperplasia but no evidence of sarcoidosis or any primary reticuloses. The total serum protein was 8 g. per 100 ml. (albumin 6.4 g., globulin 1.6 g.).

In November, 1955, he had measles for the second time. In December the zinc flocculation test was 5 units (normal). In February, 1956, he had pneumonia and was treated with tetracycline, but pneumonia recurred in May and he was again treated with tetracycline. In May the zinc flocculation test showed only 1.5 units, suggesting that the serum gamma-globulin was low. In June the total serum protein was 6 g. per 100 ml. (albumin 4.6 g., globulin 1.4 g.). In July he had another acute respiratory infection which responded to chlortetracycline.

On admission to hospital in July he was seen to be a lean man with a frequent dry cough. The spleen was palpable 8 cm. below the left costal margin and felt firm. The liver was palpable 6 cm. below the right costal margin. Moderately enlarged firm lymph nodes were palpable in the epitrochlear, axillary, and inguinal regions on both sides. Rales were heard at the bases of both lungs.

Investigations

Paper electrophoresis of serum revealed no detectable gamma-globulin. Total serum protein was 6.39 g. per 100 ml. Electrophoretic analysis on the Tiselius apparatus (Professor N. H. Martin) showed: albumin, 62.8% (4.01 g.); globulins—alpha-1 5.4% (0.34 g.), alpha-2 14.4% (0.94 g.), beta 17.5% (1.12 g.), gamma 0.0% (less than 100 mg. per 100 ml.). Gamma-globulin was present in negligible quantities as determined by immunological techniques—approximately 60 mg. per 100 ml. by both red-cell agglutination and precipitation diffusion methods. Zinc flocculation test, 1 unit; thymol turbidity test, 2 units.

Deficiency of circulating antibodies was demonstrated by the following investigations. His red blood cells were group A, but anti-B isoagglutinins were present in the serum in negligible quantities (titre 1 in 2). His serum failed to agglutinate suspensions of *Salm. typhi* or *Salm. paratyphi A* and *B* in spite of previous T.A.B. inoculation. Mumps complement fixation was negative in spite of a previous history of mumps. The antistreptolysin titre was less than 10 units per ml. The Schick and Dick skin tests were positive. No skin reaction occurred with 100 tuberculin units of P.P.D., or with *Candida albicans* antigen, which gives delayed-type reactions in 95% of healthy adults. The *C. albicans* complement-fixation test was negative.

Another axillary lymph node was removed. Examination of sections stained by haematoxylin and eosin showed diffuse hyperplasia of the reticulo-endothelial elements of the stroma of the node. The germinal follicles were numerous, with considerable variation in size, some follicles being large and hyperplastic. The axillary lymph node removed in 1954 had a similar appearance, and that removed in 1950 was also similar except that stromal hyperplasia was not so intense. Reticulin stains revealed well-marked follicular patterns. Examination of sections stained specially for plasma cells with Unna-Pappenheim methyl-green pyronine stain showed that in the node removed in 1956 transitional plasma cells (Fagraeus, 1948) were plentiful in the germinal follicles and along the sinuses. Mature plasma cells were very sparse, however, in contrast to normal nodes, where large numbers of mature plasma cells can usually be found in the sinuses. The appearance of the node removed in 1954 was similar.

The chest radiograph showed bilateral hilar lymph-node enlargement and shadows at the bases of both lungs.

The E.S.R. was persistently low even during infections (1–4 mm. per hour, Westergren). Red-cell and white-cell counts were normal. During infection normal neutrophil leucocytosis occurred.

Soon after admission to hospital he became severely ill with pneumonia, but responded to penicillin and streptomycin. However, only one week after stopping these drugs pneumonia recurred and he was given tetracycline. Gamma-globulin, 0.15 g. per kg. body weight, was administered intramuscularly. This was followed by weekly maintenance doses of 0.05 g. per kg. body weight. The serum gamma-globulin, estimated by paper electrophoresis one day and seven days after the second maintenance dose, was 0.5 g. per 100 ml. and 0.2 g. per 100 ml. respectively. Seven days after the tenth injection serum gamma-globulin was 320 mg. per 100 ml. by the precipitation diffusion method and 270–320 mg. by the red-cell agglutination method. During the three months he has been on the treatment he has had some minor infections, but none of them have been severe or have required antibacterial drugs.

Investigation of the Family.—The patient's parents, sister, and five brothers were all well and not unduly susceptible to infection. The father, mother, and sister all had high levels of serum gamma-globulin. Total protein was determined by the Van Slyke method, using tyrosine standard and Folin-Ciocalteu reagent. The globulin fractions were determined by paper electrophoresis. In healthy subjects the total serum globulin was 2.4 g. per 100 ml. (standard deviation 0.30) and the gamma-globulin 0.99 g. per 100 ml. (standard deviation 0.18) by these techniques. The levels (in g. per 100 ml.) were: father—albumin 3.4, globulin 3.8, gamma-globulin 1.9; mother—albumin 3.7, globulin 3.4, gamma-globulin 1.6; sister—albumin 4.3, globulin 3.2, gamma-globulin 1.7. The serum proteins of three brothers and the patient's two sons were normal.

Case 2

This patient was born in 1940, one month prematurely; her birth weight was 5 lb. (2,270 g.). She was well until the age of 2 years, when measles was followed by recurrent bilateral otorrhoea. After whooping-cough at 3 years she had persistent cough and failed to thrive. She first attended hospital in 1951, aged 11 years, with bilateral mucopurulent otorrhoea.

At 12 years she was admitted to hospital with an acute febrile respiratory infection. She was physically underdeveloped, underweight, partially deaf and mentally dull. The spleen was grossly enlarged, its edge being palpable below the umbilicus. The liver edge was palpable 5 cm. below the right costal margin, and lymph nodes were palpable in the neck. The chest radiograph showed shadows at the bases of both lungs. In spite of this acute febrile respiratory infection there was no leucocytosis, the total leucocyte count being 5,000 per c.mm. (neutrophils 53%, lymphocytes 41%). There was no anaemia, and iliac crest bone marrow was reported as normal. The infection responded to penicillin. Thereafter, apart from cough, she remained without symptoms until the age of 14 years, when she was again admitted to hospital with another acute respiratory infection. The spleen was even larger, its edge being palpable in the left iliac fossa. The chest radiograph showed shadows in the lingula and left lower lobe. There was no leucocytosis; total count 6,000 (neutrophils 60%, lymphocytes 36%). The pulmonary infection was controlled with antibiotics, but persistence of cough, sputum, and some radiological shadows suggested the presence of bronchiectasis.

Because of its large size the spleen was removed, although the cause of the splenomegaly was obscure. At laparotomy the liver was slightly enlarged, but of normal consistency, and a biopsy was taken. About the splenic and hepatic vessels there were several enlarged lymph nodes, which were removed.

In a microscopical section of the spleen there was a relative increase in the amount of splenic pulp with reduction in the number of Malpighian bodies. In the pulp most of the sinuses were widely dilated and lined by cells which were more pleomorphic than is usually seen in a normal spleen. Germinal follicles were sparse and of varying size. No cells of the plasma-cell series, either mature or tran-

sitional, were demonstrated by Unna-Pappenheim stains. The lymph node from the splenic hilum consisted chiefly of diffuse sheets of lymphocytes with only an occasional germinal follicle, which again varied considerably in size. There was diffuse hyperplasia of the reticulo-endothelial elements of the stroma. Reticulin stains confirmed the sparseness of germinal follicles. No cells of the plasma-cell series were demonstrated by Unna-Pappenheim stains. There was no significant change in the liver cells.

After the operation, paper electrophoresis of the serum showed absence of gamma-globulin. Total serum protein was 5.4 g. per 100 ml. (albumin 4.2 g., globulin 1.2 g.).

Eighteen months after splenectomy the patient developed severe pneumococcal meningitis. A leucocytosis was now present; total leucocytes, 40,000 (neutrophils 88%, lymphocytes 8%). She responded well to antibacterial therapy. Paper electrophoresis of serum again showed no gamma-globulin. Two months later the patient developed another respiratory infection, which responded poorly to penicillin.

In 1955 (aged 15 years) she was admitted to Brompton Hospital. The liver edge was palpable 5 cm. below the right costal margin, and moderately enlarged firm lymph nodes were palpable in neck and axillae. Total serum protein was 5.7 g. per 100 ml. (albumin 4.2 g., globulin 1.5 g.). No gamma-globulin was detected by paper electrophoresis of serum. Thymol turbidity and zinc flocculation tests showed only 1 unit.

Deficiency of normal circulating antibodies was shown by deficiency of beta-agglutinins in her group A blood (the anti-B titre varied between 0 and 1 in 8). Her serum failed to agglutinate suspensions of *Salm. typhi*, *Salm. paratyphi A* and *B*, *Br. abortus*, and *Br. melitensis*. The Schick reaction was positive in spite of previous diphtheria toxoid. The Dick test was positive. The reaction to 100 tuberculin units was negative. *C. albicans* reaction was also negative.

Leucocytes were 26,000 per c.mm. (neutrophils 71%, lymphocytes 19%). Cultures of sputum yielded pneumococci, haemolytic streptococci, and coagulase-positive staphylococci. Penicillin improved respiratory symptoms and cleared pathogens from the sputum, but prompt clinical and bacteriological relapse occurred on stopping penicillin. The patient developed a fulminating *H. influenzae* meningitis, which, in spite of the administration of gamma-globulin and antibiotics, proved fatal. Post-mortem examination was refused.

Investigation of the Family.—Her parents and sister were well and were not unduly susceptible to infection. Her mother's serum globulin was raised—albumin 3.3 g., globulin 3.2 g. per 100 ml. The increase of globulin was distributed evenly throughout the alpha-2, beta, and gamma fractions. The serum protein of her father and sister showed no abnormality.

Discussion

Agammaglobulinaemia may occur as an isolated defect of the serum, the other electrophoretic components of globulin and albumin being present in normal quantity. This abnormality may be associated with a variety of clinical features on the basis of which cases may be divided into two broad groups, congenital and acquired.

In congenital agammaglobulinaemia increased susceptibility to infection occurs in infancy or childhood, exclusively in males; and its occasional occurrence in brothers and other males in the family suggests that the defect is genetically determined and probably transmitted as a sex-linked recessive trait (Janeway *et al.*, 1953). In this condition the deficiency of gamma-globulin is permanent, and it should be distinguished from cases of agammaglobulinaemia of limited duration occurring in infants of either sex in whom it is thought that the passively transferred gamma-globulin from the mother is not replaced by the infant's own gamma-globulin owing to a delay in the assumption of normal gamma-globulin synthesis (Good and Mazzitello, 1956).

Acquired agammaglobulinaemia may occur in either sex at any age. It may be secondary to disorders of the

reticulo-endothelial system, and has been found in association with malignant lymphoma (Arends *et al.*, 1954), chronic lymphatic leukaemia (Brem and Morton, 1953; Jim and Reinhard, 1956), myelomatosis (Zinneman *et al.*, 1954), and histoplasmosis (Seltzer *et al.*, 1955). There are other cases in which the disease is acquired but no cause for the gamma-globulin deficiency can be found, and these are referred to as the acquired idiopathic type (Good and Mazzitello, 1956).

Agammaglobulinaemia may occur not as an isolated defect, but in association with a general hypoproteinaemia, such as occurs in a variety of conditions, including nephrosis.

The term agammaglobulinaemia implies absence of gamma-globulin as detected by electrophoresis of serum. However, the use of more delicate immunological techniques for the detection of gamma-globulin may reveal small quantities of gamma-globulin where electrophoresis fails to demonstrate any. Strictly speaking, therefore, these are cases of hypogammaglobulinaemia. Moreover, immunoglobulins may occasionally occur in serum which is apparently deficient in gamma-globulin, and, probably because of this, agammaglobulinaemia is not always associated with increased susceptibility to infection (Martin, 1954).

The two cases described here have the features of the acquired idiopathic type of agammaglobulinaemia, in that there was good health before onset of symptoms of recurrent infection and also absence of any primary disorder to which the development of agammaglobulinaemia might be attributed. Moreover, in Case 1 the normal zinc flocculation, thymol turbidity, and total globulin levels in the early stages of the disease are strong circumstantial evidence that gamma-globulin was present in appreciable quantities at the time, so that the agammaglobulinaemia must have developed later.

Gross enlargement of the spleen was a striking clinical feature of both cases. In Case 2 enlargement of the spleen was present before severe infections had occurred, and the spleen was observed to increase in size during the next three years until splenectomy. In Case 1 enlargement of the spleen was noted eight years after the onset of the disease with symptoms of infection and enlarged lymph nodes, and the spleen increased in size over the next six years. The liver was enlarged in both patients. Generalized enlargement of lymph nodes was present in both patients, including hilar nodes in Case 1 and intra-abdominal nodes in Case 2.

Among 45 cases of agammaglobulinaemia reported in the literature there are six cases in which the spleen was enlarged (Rohn *et al.*, 1954; Grant and Wallace, 1954; Rosecan *et al.*, 1955; Collins and Dudley, 1955; Young *et al.*, 1955; Good and Mazzitello, 1956). All six were of the acquired idiopathic type; three were in males and three in females, their ages ranging between 17 and 53 years.

In these cases the microscopical appearance of the reticulo-endothelial tissue showed similar features to those described here. Of four cases in which the spleen was examined there was reticulum-cell hyperplasia of variable degree in all four. Germinal follicles were sparse in two. Lymph nodes were examined in two and showed reticulum-cell hyperplasia in both. In the present cases there was diffuse hyperplasia of the reticulo-endothelial elements of the stroma of all lymph nodes examined, and also of the spleen in Case 2. Germinal follicles were sparse in the lymph node and spleen in Case 2, in contrast to Case 1, in which the numbers of germinal follicles were consistently within normal limits in three separate biopsies taken over the course of six years.

The most striking variation from normal, present uniformly in all histological material from both Case 1 and Case 2, was the virtual absence of mature plasma cells. Absence of plasma cells has been noted previously in cases of agammaglobulinaemia (Good and Mazzitello, 1956). Plasma cells are known to be concerned with the production of gamma-globulin and circulating antibodies (Sundberg, 1955), and agammaglobulinaemia has been attributed to absence of these cells. Although there was severe deficiency of

mature plasma cells in both cases, they differed in that transitional plasma cells were plentiful in the germinal follicles and sinuses of Case 1, whilst in Case 2 no cells of the plasma-cell series were present in the sparse germinal follicles or in the sinuses. It may be, therefore, that the deficiency of mature plasma cells present in both cases resulted from a disturbance acting at different stages of development of the plasma cells.

Among the relations of these patients deficient in gamma-globulin there were healthy individuals of both sexes with hypergammaglobulinaemia. Abnormally high serum gamma-globulin occurred in the father, mother, and sister of Case 1, and the mother of Case 2 had a raised total globulin level. Similar findings were reported by Young *et al.* (1955), who found hypergammaglobulinaemia in the healthy mother and brother of an adult male patient with acquired idiopathic agammaglobulinaemia. This evidence suggests that the abnormalities of globulin production in these families might depend upon genetic factors and that some cases of acquired idiopathic agammaglobulinaemia are genetically determined like the congenital variety, but differ from it in the late onset of symptoms and the occurrence in females as well as males.

No neutrophil leucocytosis occurred in response to infection in Case 2 until after splenectomy, when neutrophils increased readily in infection. Among the six cases of agammaglobulinaemia with splenomegaly detailed above, three had neutropenia and neutrophilia did not occur in infections. Three cases had an acquired haemolytic anaemia, in two of which the spleen was removed, with relief of the anaemia in both. The relief of haemolytic anaemia and neutropenia by splenectomy suggests that these disturbances were due to destruction of erythrocytes or leucocytes by the enlarged spleen and not to an immunological mechanism, since circulating antibodies were deficient or absent in these patients.

The E.S.R. determined in Case 1 on 11 separate occasions, usually during infection, was 5 mm. per hour or less (Westergren), except on one occasion. In Case 2 the E.S.R. was moderately raised during infection except in the last few weeks before death, when in spite of much pulmonary infection the E.S.R. was 3 mm. per hour or less. Persistently low E.S.R. readings during infection have been noted in some other cases of agammaglobulinaemia (Elphinstone *et al.*, 1956).

It is concluded that agammaglobulinaemia of the acquired idiopathic type may be associated with generalized hyperplasia of the reticulo-endothelial system and should be considered in the diagnosis of enlargement of the spleen and lymph nodes of obscure origin, particularly in the presence of recurrent infection.

Summary

Attention is drawn to the association of acquired idiopathic agammaglobulinaemia with enlargement of the spleen and lymph nodes. Two cases are described and six similar ones in the literature are reviewed. The principal histological features are diffuse reticulo-endothelial hyperplasia and deficiency of plasma cells. Haemolytic anaemia and neutropenia may occur. In some cases increase in the serum globulin of healthy relatives has been found.

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ADDENDUM.—Since this paper was submitted another patient with hypogammaglobulinaemia, whose mother had increased serum gamma-globulin, has been investigated. The patient was a girl of 14 years who during the past

year had suffered from 14 attacks of acute pulmonary infection. Previously she had been well. Her serum gamma-globulin was only 0.2–0.3 g. per 100 ml. Her mother was quite well, but had a marked increase in serum gamma-globulin (2 g. per 100 ml.). The serum proteins of the patient's father and sister were normal. This observation adds further support to the suggestion that in some cases of acquired idiopathic agammaglobulinaemia (hypogammaglobulinaemia) the abnormality of gamma-globulin production is genetically determined.

REFERENCES

- Arends, T., Conrad, E. V., and Rundles, R. W. (1954). *Amer. J. Med.*, 16, 833.
 Brem, T. H., and Morton, M. E. (1953). Cited by Zinneman *et al.* (1954).
 Bruton, O. C. (1952). *Pediatrics*, 9, 722.
 Collins, H. D., and Dudley, H. R. (1955). *New Engl. J. Med.*, 252, 255.
 Elphinstone, R. H., Wickes, I. G., and Anderson, A. B. (1956). *British Medical Journal*, 2, 336.
 Fagraeus, A. (1948). *Acta med. scand.*, 130, Suppl. 204, p. 9.
 Good, R. A., and Mazzitello, W. F. (1956). *Dis. Chest*, 29, 9.
 Grant, G. H., and Wallace, W. D. (1954). *Lancet*, 2, 671.
 Janeway, C. A., Apt, L., and Gitlin, D. (1953). *Trans. Ass. Amer. Phys.*, 66, 200.
 Jim, R. T. S., and Reinhard, E. H. (1956). *Ann. Intern. Med.*, 44, 790.
 Martin, N. H. (1954). *Lancet*, 2, 1094.
 Rohn, R. J., Behnke, R. H., and Bond, W. H. (1954). *J. Lab. clin. Med.*, 44, 918.
 Rosecan, M., Trobaugh, F. E., and Danforth, W. H. (1955). *Amer. J. Med.*, 19, 303.
 Seltzer, G., Barron, S., and Toporek, M. (1955). *New Engl. J. Med.*, 252, 252.
 Sundberg, R. D. (1955). *Ann. N.Y. Acad. Sci.*, 59, 671.
 Young, I. I., Wolfson, W. Q., and Cohn, C. (1955). *Amer. J. Med.*, 19, 222.
 Zinneman, H. H., Hall, W. H., and Heller, B. I. (1954). *J. Amer. med. Ass.*, 156, 1390.

AGAMMAGLOBULINAEMIA

REPORT OF TWO ADULT CASES

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The clinical and laboratory findings in patients with deficiencies or absence of gamma-globulin in their serum have been described only in the past few years. Most of the cases have been in children (Bruton, 1952; Fried and Henley, 1954; Elphinstone *et al.*, 1956), but a number of examples of the condition have been recorded where the deficiency has not appeared until adult life (Grant and Wallace, 1954; Wall and Saslaw, 1955).

The purpose of this paper is to record the findings in two further adult female patients in whom this deficiency was present.

Case 1

A single woman, born in 1907, was perfectly well until 1933, when she had a chronic cough for a few months. In 1937 she had her first attack of pneumonia, two more attacks following in 1943. She was admitted to hospital in 1949 for investigation of diarrhoea of one year's duration, and was found to have a mild degree of steatorrhoea (4–8 g. of faecal fat on a 50-g. daily fat intake). Her blood count showed: red cells, 4,460,000 per c.mm.; haemoglobin, 9.9 g. per 100 ml.; M.C.V., 96 cubic microns; M.C.H.C., 25%; white cells, 7,400 per c.mm., with normal differential; and serum proteins: albumin, 4 g. per 100 ml.; globulin, 1.2 g., with gamma-globulin 0.04 g. (alcohol precipitation method—G. Thomas, 1954, unpublished observation). The serum

bilirubin, alkaline phosphatase, cholesterol, empirical tests of liver function, and pancreatic enzymes were normal. Chest radiographs showed no abnormality.

Over the next two years she had pneumonia on four further occasions and her diarrhoea increased. In 1951 she complained of severe attacks of abdominal pain, on account of which an exploratory laparotomy was performed by Mr. B. N. Brooke. A swollen pink pancreas was seen, but no other abnormality.

For the next three years she continued to have recurrent attacks of pneumonia and constant diarrhoea of up to 10 stools a day, and in 1954 she was readmitted to hospital. Estimations of faecal fat then showed an excretion of 10–20 g. a day. The serum amylase fluctuated between 183 and 370 units per 100 ml., with one period of a week during which it rose steadily to 670 units per 100 ml. On admission serum electrolytes showed: sodium 146 mEq, potassium 2.9 mEq, chloride 106 mEq per 100 ml. The blood count, serum proteins, bilirubin, alkaline phosphatase, cholesterol, and empirical tests of liver function showed no significant change from 1949. Gamma-globulin was estimated at 0.05 g. per 100 ml. by alcohol precipitation method and 0.1 g. per 100 ml. by paper electrophoresis (Dr. Hardwick), but none was shown by the Tiselius method (Dr. Kekwick). Serum tested by the immunochemical method (Gell, 1955) for gamma-globulin showed that some was present in amounts approximating to 10% of that in the normal control serum. A routine blood grouping at this time showed absence of iso-agglutinins. She was treated with a high-protein and low-fat diet and pancreatin, 12 g. daily with meals. Her diarrhoea improved on this regime, though she continued to excrete 10–20 g. of fat daily. She was discharged relatively well after two months in hospital.

During the past 18 months the patient has had one further attack of acute bronchitis, which subsided within a week in response to antibiotic therapy. In order to raise her gamma-globulin level before the winter 1 litre of fresh plasma was transfused in October, 1955. The last estimation of gamma-globulin, in July, 1956, by paper electrophoresis, showed it to be 0.3 g. per 100 ml.

Case 2

A single woman born in 1916 was well until the age of 20, when she began to suffer with severe nasal catarrh and repeated "colds" each winter. In 1947, at the age of 31, she had her first attack of pneumonia, followed by further attacks in 1948 and 1949, when she was admitted to hospital for drainage of an empyema. In 1950 and 1951 she had further attacks of pneumonia, and in 1952 she was admitted to another hospital, where she underwent a resection of her right middle lobe for bronchiectasis. This, however, did not prevent her from having a further attack of pneumonia in 1953. In 1954 she had another attack, and later in that year (October) was admitted to hospital for investigation and treatment of her chronic nasal catarrh by Mr. Stirk Adams. A routine blood grouping disclosed at this stage an abnormality in her iso-agglutinins which suggested an absence of gamma-globulin.

Examination of the serum proteins showed albumin 4.1 g. and globulin 1 g. per 100 ml. No gamma-globulin was revealed by the alcohol precipitation method, but paper electrophoresis showed 0.3 g. per 100 ml. The immunochemical method showed the presence of gamma-globulin in quantities below that present in normal control serum. Blood counts, serum bilirubin, alkaline phosphatase, and empirical tests of liver function were within normal limits. Shortly before her intended discharge she again developed pneumonia, which responded to penicillin, but two days after discontinuation of the therapy she had a second attack and, whilst convalescing, a third.

During this period the white blood cells rose from a normal level of 7,000 to 19,000 per c.mm., with 12,000 polymorphs per c.mm. No alterations in the levels of the serum proteins were detected. As no gamma-globulin was available at this