HYPOGAMMAGLOBULINAEMIA

By A. W. MORRISON (London)

THIS deficiency disease, first described by Bruton in 1952 as Agammaglobulinæmia, is an important cause of recurrent bacterial infections in early childhood due to near absence of γ-globulins, implying a failure of the infant's body mechanisms to form circulating antibodies. By 1956 less than 50 cases had been reported in the world literature (Martin, 1956), but there is now a very lengthy bibliography of hypogammaglobulinæmia syndromes.

The disease is encountered mainly in male infants. Female cases are sufficiently rare to give the following report some interest. The first female case from this country was published in 1957 by Pearce and Perinpanayagam.

Case Report I

T.P., a female infant, aged 22 months, was first seen on March 14th, 1960, with a history of failure to thrive, recurrent attacks of bronchitis, pneumonia, bilateral suppurative otitis media and purulent nasal discharge from 18 months of age, the onset being ascribed to whooping cough. During most of this time the infant had been fretful, difficult and lethargic.

Past History. She was the sixth child and had been a normal delivery at full term, weighing 6 lbs. 12 ozs. (3·06 kilos.). She was breast fed for 5 months, gaining weight, teething at 9 months, walking at 1 year and talking at 18 months. She had been vaccinated against smallpox after birth, with a primary response, and immunized against whooping cough and diphtheria.

Family History. The family tree is shown in Fig. 1, the significant features being an elder brother, aged 9 years, with an identical past history, and a maternal aunt who had died from meningitis at 2 years of age, after an infancy of recurrent ear and chest infections. There were no diseases on the father's side and the parents were unrelated.

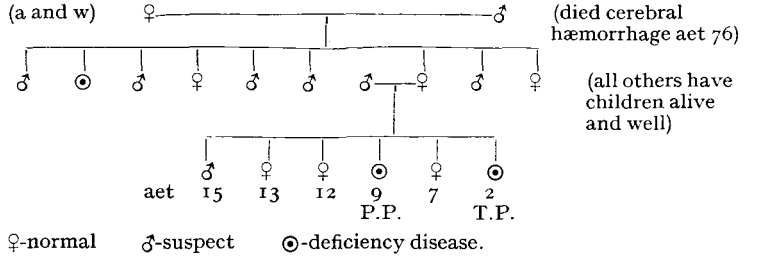


FIG. 1

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

Examination. The infant looked ill. There were scattered moist sounds in both lung bases and the right mid-zone; she had mucopurulent nasal discharge and left acute suppurative otitis media. Lymph glands and spleen were not palpable. Her weight was 20 lbs. (9·07 kilos.). She was admitted for investigation and treatment started with tetracycline 125 mg. 8 hourly.

Investigations

Chest X-ray Patchy shadowing both bases, and more marked right middle lobe indicating partial collapse and incipient bronchiectasis.

Urine No abnormality.

Hb. 70 per cent. (10·4 gms. per 100 ml.)

W.B.C. 23,700 per c. mm. Polymorphs 74 per cent. "shift to the left". Lymphocytes 26 per cent.

Blood film No abnormality.

Swab left ear Coagulase-positive. Staphylococci—penicillin sensitive.

Blood group Group O. Rh. positive (Anti-D.)

Isohæmagglutinins Anti-O—nil. Anti-B—nil. Anti-A—weak in undiluted serum only.

Serum electrophoresis α and β globulins relatively increased. γ-globulin much reduced.

Serum γ-globulin 160 mgm. per 100 ml.

E.U.A. Adenoids normal for age. Bilateral antral lavages—muco-pus both sides. Pus in trachea and right main bronchus. No evidence of bronchial obstruction.

Diagnosis. Hypogammaglobulinæmia with bronchiectasis and recurrent sinusitis and otitis media.

Treatment and Progress. The infant responded to tetracycline therapy, temperature subsiding, chest signs improving, otitis media resolving and the W.B.C. falling to 11,700 per c. mm. one week later. She was discharged from hospital pending supplies of γ-globulin being obtained. In the interval there were numerous infections treated with antibiotics.

Gamma-globulin treatment. The γ-globulin employed was supplied by the Medical Research Council Working Party on Hypogammaglobulinæmia, being a 10 per cent. solution containing 1: 10,000 merthiolate suitable for intramuscular injection. Treatment was started on May 24th, 1960, when the patient was 24 months old, weighing 20 lbs. (9·07 kilos). *The initial dose* was 0·25 g. per kg. body weight, given by five daily injections of 0·05 g. per kg. *The maintenance dose* was 0·025 g. per kg. body weight per week.

The infant was weighed weekly at the time of injection and the dose of γ-globulin estimated on the above body weight basis. Records were kept of temperature, the nature of any illness since the last injection, antibiotics employed and laboratory investigations. This regime was continued until the child died almost a year later.

The initial response to treatment was satisfactory and for 2 months there was no recurrence of otitis media; cough, though still present, was diminished, and the lung signs became confined clinically and radiologically to the right middle lobe. No febrile episodes were reported, antibiotics were not required

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

and weight increased by 1 lb. By June 6th, 1960, the serum γ-globulin had risen to 280 mg. per 100 ml.

From August, 1960, there was a recurrence of febrile attacks and of bilateral otorrhœa which became chronic on the left. Signs of collapse and consolidation progressively involved both lung bases as well as the right middle lobe and clubbing of the fingers and toes developed. Numerous courses of antibiotics including tetracyclines, various penicillins and two short treatments with chloramphenicol had minimal effects on the symptoms and signs. There was no further gain in weight.

Most of the aural swabs grew penicillin sensitive staphylococci and the sputum cultures showed a mixed flora including *Strep. viridans* and *H. influenzae* The serum γ-globulin level fell to 160 mg. per 100 ml. on September 15th, and although a level of 320 mg. per 100 ml. was recorded on October 24th, this was not associated with an improved clinical state. By January, 1961, the level had fallen again to 160 mg. per 100 ml. All samples of serum throughout were positive for C-reactive protein.

Whereas in the earlier part of the illness there had been a polymorphonuclear leucocytosis in response to febrile attacks, this was not seen after August, 1960, and the W.B.C. remained about the 10,000 per c.mm. level. The Hb. varied from 60 per cent. to 70 per cent.

From the end of January, 1961, consolidation became extensive in both lungs and the infant was weak and dyspnœic with intermittent hæmoptysis. Diarrhœa became a new feature with pale motions three to four times daily. Stools examined for trypsin showed normal digestion of the film. She became progressively more cachectic, failing to respond to antibiotics and died on May 5th, 1961, aged three years, weighing 21 lbs. (9·52 kilos).

Morbid anatomy summary

Respiratory system. There was copious pus in the bronchial tree due to bronchiectasis and suppurative pneumonitis involving most parts of both lungs. The right middle lobe was a series of saccular cavities. No polycystic disease. On microscopic section there was focal bronchopneumonia. In the granulation tissue surrounding bronchiectatic lesions there were occasional pyronin positive cells which could have been partially mature plasma cells or developing reticulum cells. There was no evidence of pneumocystis carinii.

Heart. The heart muscle was softened by toxic change and the right side hypertrophied and dilated.

Liver. This showed swelling and pallor with nutmeg markings. On section there was severe fatty degeneration.

Spleen. This was of normal appearance and on section showed a mild degree of septic spleen.

Sternal bone marrow. The section showed good hæmopoiesis but no plasma cells could be identified.

Lymph glands. Follicles were present but without Fleming centres. A few plasma cells were found but they were very scanty.

Kidneys. Were normal.

Suprarenals. The cortical parts were somewhat wasted. There was no evidence of tuberculosis.

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

Hypogammaglobulinaemia

Case Report II

P.P., the brother of T.P., was seen in May, 1960, aged 9 years, in view of the similarity of his past history.

History. From 10 months of age he had had frequent attacks of bilateral otitis media, recurrent tonsillitis, bronchitis and pneumonia, the latter usually four to five times a year. His tonsils and adenoids had been removed at $2\frac{1}{2}$ years of age and other illnesses had included scarlet fever, measles, whooping cough and ? tuberculous cervical glands.

In 1956, aged 5 years, he was investigated elsewhere and found to be undersized and underweight, with established bilateral basal bronchiectasis and splenomegaly. His γ-globulins were reported normal at this time, and investigations excluded congenital cystic pancreas and pituitary deficiency. He was treated with continuous antibiotics for some years, but his episodes of acute infection did not diminish in frequency until he was over 6 years of age, when he started gaining weight.

Examination. He was a small boy for 9 years. There was gross scarring of both tympanic membranes and some clubbing of the fingers due to bilateral basal bronchiectasis. Productive cough was minimal. There was no lymphadenopathy or splenomegaly.

Investigations

Hb. 76 per cent. (11·2 g. per 100 ml.)
Blood film. No abnormality.
W.B.C. and differential counts. Normal.
Blood Group. Group O. Rh. positive (Anti-D.)
Isohæmagglutinins. Anti-A present in titre of 1 in 8.
Anti-B present in titre of 1 in 4.
Electrophoresis. Increased α_2 globulin, slightly reduced γ-globulin.
Serum γ-globulin. 800 mg. per 100 ml.

In June, 1962, he had an isolated attack of pneumonia and pleurisy which responded to antibiotics. Serum γ-globulin was repeated and found to be 640 mg. per 100 ml., with the γ macroglobulin (β_{2m}-iota) 50 per cent. of standard "normal" serum.

He was last seen in January, 1963, thriving well, gaining weight and having had no further illnesses. At that time his serum γ-globulin had risen to 800 mg. per 100 ml. but the γ-macroglobulin was still relatively low.

Diagnosis. From the history, the somewhat low levels of serum γ-globulin and the low titres of Anti-A and Anti-B, the diagnosis of hypogammaglobulinæmia is suggested. By the time the boy was investigated at 5 years of age he may already have started forming antibodies, and certainly his clinical improvement dated from about this time.

Discussion

Classification of the causes of hypogammaglobulinæmia is not easy on account of the great variety of syndromes so far described, but the one outlined in the *Lancet* in 1961 has the advantage of simplicity:

1. Congenital hypogammaglobulinæmia.

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

2. Primary acquired hypogammaglobulinæmia.
3. Secondary acquired hypogammaglobulinæmia.

To this might be added two further categories:

4. Physiological hypogammaglobulinæmia.
5. Hypogammaglobulinæmia associated with other protein abnormalities.

1. Congenital Deficiency

As postulated by Janeway *et al.* and later established by the observations of Porter and others, the common variety of congenital hypogammaglobulinæmia is found in male infants and is inherited, like hæmophilia, as a recessive sex-linked Mendelian trait. As pointed out in the *Lancet* (1958), this would not exclude occasional cases in females. These infants have greatly diminished faculty for synthesis of gamma globulin antibodies and are, in consequence, susceptible to recurrent bacterial infections. Bruton *et al.* have shown that these proteins are not destroyed at an unusually rapid rate.

From a few months of age the clinical picture is one of recurrent suppurative otitis media, sinusitis, bronchitis, pyoderma, urinary infections and possibly septicæmia, lung abscess and meningitis. Diarrhœa and steatorrhœa are common in both the congenital and primary acquired forms (Cook and Melrose, and Hutchison). Before the days of antibiotics many of these infants died, but now that more of them are surviving the earlier infections, the diagnosis of this deficiency syndrome is becoming commoner. Children who survive frequently have bronchiectasis. They also appear to have increased susceptibility to protozoal and possibly fungal infections. Cases of pneumocystis carinii are reported by Hutchison, Bird and Thomson, McKay and Richardson, and Burke *et al.* Kala-azar of unusual duration is reported by Wright. Ramón Guerra *et al.* describe severe generalized moniliasis in the antibody deficiency syndrome.

Following upon virus infections or after virus immunizations, including smallpox, herpes simplex, influenza, polio viruses, adenoviruses and mumps, virus antibodies are almost never found in the serum of these children (Good and Zak, and MacCallum) but despite this they usually have a normal clinical response to virus infections. Squire, however, considers there may be an increased susceptibility to infective hepatitis. Somers, Galloway and MacBean, and others have reported deaths from generalized vaccinia, but Gitlin (1955 and 1956) suggested that vaccinia gangrenosa causing death in young infants was due to exaggerated physiological hypogammaglobulinæmia in the early weeks of life when maternal γ-globulin is gradually lost from the infant's circulation.

These infants also appear to have a normal clinical response to tuberculous infection (Parkes), though Squire reports tubercle in 5 per cent. of these patients. Garvie and Kendall emphasize this contrast of a normal

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

acquired immune reaction to the tubercle bacillus. Whereas the Mantoux reaction becomes positive after infection or inoculation, after diphtheria immunization the Schick test fails to convert from positive to negative. It is well known that in tuberculous infections there is a rise in α_2 and β globulins, while in bacterial and viral diseases there is an initial rise in α_2 globulin followed by a later rise in γ-globulin associated with the production of specific antibodies. It would therefore appear that in tuberculous infections and possibly in virus diseases, the antibody forming mechanisms and/or cells might differ from those involved in protection against the commoner bacteria.

The plasma cells are accepted as being the main site of antibody formation and γ-globulin synthesis. Certainly in congenital and primary acquired hypogammaglobulinæmia plasma cells are absent or very scanty in inflammatory exudates, in the bone marrow, and in lymph glands and the latter may remain 'fœtal' in type with almost no follicular pattern (Sundburg, and Martin, 1955). In the acquired type of deficiency there are several reports of enlargement of lymph nodes and spleen. (Grant *et al.*, and Citron).

The fundamental deficiency in this disease would therefore appear to be of a factor responsible for the development or maturation of plasma cells or their precursors (Martin, 1962).

In a suspected case of congenital hypogammaglobulinæmia the diagnosis is confirmed by demonstrating the near absence of γ-globulin in the infant's serum, assuming that other causes of lowered γ-globulin have been excluded. The commonest of these is the *physiological* drop in circulating γ-globulins after birth. At birth the γ-globulin level in the serum lies between 750-1,000 mg. per 100 ml., falling by about one third to 250-330 mg. per 100 ml. at 1 month, starting to rise again at 3 months, reaching 500-750 mg. per 100 ml. between 1 and 2 years of age, and thereafter rising to the adult level of 800-1,100 mg. per 100 ml. (Orlandini *et al.*, Longsworth *et al.*, and Moore *et al.*).

The methods for estimating serum γ-globulin, namely free electrophoresis, the inhibition of antiglobulin antiserum and the gel diffusion precipitin methods are described and compared by Kekwick *et al.* For the ordinary laboratory the electrophoretic method is the one of choice though it is not as sensitive as the others, nor is it precisely quantitative.

The Working Party on Hypogammaglobulinæmia of the M.R.C. require a serum γ-globulin content of less than 100 mg. per 100 ml. in infants under 6 months, or less than 200 mg. per 100 ml. in older children or adults before inclusion in the trial. These levels make a useful, if rather stringent, criterion for the diagnosis of the deficiency syndrome.

The inability to form antibodies is also demonstrable by the absence, or very low titres, of circulating isoagglutinins, whatever the blood group of the patient. This knowledge makes a simple and useful test to exclude

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

or enhance the suspicion of hypogammaglobulinæmia, but it must be remembered that isoagglutinins are absent, or almost absent at birth, that they start to be formed between 3 and 6 months of age, that they reach their maximum titres between 5 and 10 years of age (average at 8 years: Anti-A titre of 1-380, Anti-B titre of 1-160) and thereafter fall during adolescence and adult life. (Average Anti-A titre of 1-32 to 1-64, Anti-B titre of 1-16 to 1-32).

Gitlin *et al.* have shown by immuno-electrophoresis that in hypogammaglobulinæmia the globulins which are low or absent are gamma (7s) globulin, β_{2m} (19s) globulin (which is γ macroglobulin) and β_{2a} globulin. It is interesting to note that Anti-A and Anti-B are found in either the (19s) or (7s) globulins.

Soothill points out that in the deficiency syndrome if the macroglobulin is low, isoagglutinin activity is always abnormal, but if the macroglobulin is normal or high, isoagglutinin activity may be high, normal or absent.

C-reactive protein is an alpha globulin (Perlman *et al.*) and appears to be a non-specific antibody. It is not normally present in serum but appears in response to a variety of inflammatory conditions and after tissue necrosis. The C-reactive protein test, like the E.S.R., is non-specific but has the advantages of not being affected by anæmia or dysproteinæmia and it is either positive or negative whereas the E.S.R. result can be equivocal (Dawson). It also appears to be a more critical indication of disease activity.

2. Primary Acquired Hypogammaglobulinæmia (Idiopathic)

There is little difference between this syndrome and the clinical picture and laboratory findings in the congenital form, excepting that the primary acquired disease is found in both male and female children and in adults, some of whom have a history of recurrent infections dating from childhood. Adults with a short history, not secondary to other diseases, may form a separate group.

Woolheim recently reported three female cases, one the child of a first cousin marriage, and the other two with a common pedigree, some four generations before. He suggested that primary acquired hypogammaglobulinæmia was also hereditary being due to an autosomal recessive Mendelian inheritance. Both the brother and sister reported here could come into this category, two out of six siblings being approximately the expected incidence assuming both parents to be heterozygous carriers. Keidan *et al.* also report a female case, the child of a first cousin marriage and Bernheim records hypogammaglobulinæmia in two heterozygous twins of different sex.

When we consider that probably less than fifteen female cases have been recorded in the world literature and that six of these would be in

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

keeping with a recessive autosomal inheritance, it adds weight to Woolheim's suggestion.

Finally, mention must be made of the interest aroused by successful skin homografts to patients with congenital hypogammaglobulinæmia reported by Good and others; and also of the report by Martin *et al.* (1957) of antibody protein synthesis by lymph nodes homotransplantable to a hypogammaglobulinæmic adult.

3. Incidence and Prognosis of Infantile Hypogammaglobulinæmia

In December, 1961, the Section of Experimental Medicine and Therapeutics of the Royal Society of Medicine discussed hypogammaglobulinæmia. Squire gave an interim report on the findings of the Working Party's experience of 82 cases having gammaglobulin treatment between 1956 and 1961. In Great Britain the average incidence in boys was 13 per million and in girls 3 per million, but he emphasized that these were probably underestimates. The overall mortality for children and adults was 21 per cent., the mortality for boys being 15 per cent. and for girls 56 per cent. The prognosis was decidedly better in children gaining weight and nearing their standards for age and sex, most of the survivors being in fairly good health and some fully recovered. The outlook was worse in female cases and when steatorrhœa developed.

Now that more of these infants are surviving, the opportunity has arisen to assess the results of γ-globulin replacement therapy, and the final results of the M.R.C. trial will be invaluable to clinicians.

4. Secondary Acquired Hypogammaglobulinæmia

Failure of synthesis of γ-globulin has been encountered in a variety of Reticuloses mainly in adults of either sex. It is reported in malignant lymphoma by Arends *et al.*, in chronic lymphatic leukæmia by Prasad, Hudson and Wilson, and Fairley and Scott, in lymphosarcoma of the spleen by O'Brien and Walsh, in multiple myeloma by Porges and in thymoma by Gafni *et al.* Sarcoidosis has been suspected of depressing antibody synthesis (Zinneman *et al.*).

Secondary hypogammaglobulinæmia has also been reported in association with certain autoimmune diseases such as systemic lupus erythematosis (Leonhardt, and Weinstock and Lee), autoimmune hæmolytic disease (Fudenburg and Solomon) and rheumatoid arthritis (Good *et al.*, and Robertson).

5. Hypogammaglobulinæmia with other Protein Abnormalities

In this group of patients the low γ-globulins are usually associated with lowered serum proteins as in nutritional hypoproteinæmia (Krebs), idiopathic hypoproteinæmia (Bound and Hackett) and in the nephrotic

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

syndrome (Schick and Greenbaum). Here the clinical picture is likely to include generalized œdema, hypoproteinæmia and proteinuria. There is not necessarily an increased susceptibility to infection. Reductions in serum γ-globulin are also seen in the familial dysproteinæmia of Homburger characterized by œdema and ulceration of the legs (Firkin and Blackburn), and occasionally in liver disease (Czyzyk and Poirier).

Summary

The case history, laboratory and post-mortem findings of a female infant with hypogammaglobulinæmia are presented. The girl's brother may have had the same deficiency disease.

Since the advent of antibiotics more of these children are surviving and the disease is probably not so rare.

The hypogammaglobulinæmia syndromes are briefly described with an attempt at classification. Congenital hypogammaglobulinæmia is found in male infants and has a sex-linked recessive inheritance; the primary acquired form is found in infants of either sex and in adults and may be inherited as an autosomal recessive disease. The diagnosis should be suspected in infants who fail to thrive and have recurrent otitis media, sinusitis, pyoderma, bronchitis and pneumonia. These children are likely to be seen, at some stage, by otorhinolaryngologists.

Demonstrating absent or greatly diminished titres of isoagglutinins is a simple preliminary investigation, to be followed when indicated by quantitative estimations of serum globulin fractions.

Very few female cases have been reported and the prognosis is worse in this group. At present the best form of treatment is parenteral gammaglobulin therapy plus antibiotics.

The possibility of Turner's syndrome (sex chromosomes XO) has been excluded in the female case, T.P., by demonstrating "Chromatin positive" staining in the infant's cell nuclei.

Acknowledgements

I am indebted to Dr. J. F. Soothill of the Department of Experimental Pathology, Birmingham, for the quantitative estimations of gammaglobulin, and to Dr. H. Bunje and Dr. J. Carlton of the Medical Research Council, for their encouragement, and assistance with the bibliography. The Lister Institute of Preventive Medicine supplied the gammaglobulin. For pathology reports and observations I am greatly obliged to Professor Keith Simpson, Professor J. R. Squire, Dr. C. Raeburn, Dr. W. W. Walther and Dr. A. J. E. Brafield.

REFERENCES

Arends, T., Coonrad, E. V., and Rundles, R. W. (1954) *Amer. J. Med.*, **16,** 833.

Bernheim, M., Creyssel, R., Gilly, R., and Fournier, P. (1959) *Pediatrie*, **14,** 881.

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

BIRD, T., and THOMSON, J. (1957) *Lancet*, **1**, 59.
BOUND, J. P. and HACKETT, W. R. (1953) *Arch. Dis. Childh.*, **28**, 104.
BRUTON, O. C. (1952) *Pediatrics*, **9**, 722.
——— ,APT, L., GITLIN, D., and JANEWAY, C. A. (1952) *Amer. J. Dis. Child.*, **84**, 632.
BURKE, E. C., BROWN, A. L., JR., and WEED, L. A. (1962) *Proc. Mayo Clin.*, **37**, 129.
CITRON, K. M. (1957) *Brit. med. J.*, **1**, 1148.
COOK, I. A. and MELROSE, A. G. (1958) *Scot. med. J.*, **3**, 135.
CZYZYK, A., and POIRIER, A. (1961) *Sem. Hôp. Paris*, **37**, 1884.
DAWSON, S. F. (1957) *Arch. Dis. Childh.*, **32**, 454.
FAIRLEY, G. H. and SCOTT, R. B., (1961) *Brit. med. J.*, **2**, 920.
FIRKIN, B. G. and BLACKBURN, C. R. B. (1958) *Quart. J. Med.*, **27**, 187.
FUDENBERG, H. and SOLOMON, A. (1961) *Vox Sang.*, **6**, 68.
GAFNI, J., MICHAELI, D., and HELLER, H. (1960) *New Engl. J. Med.*, **263**, 536.
GALLOWAY, W. H. and MACBEAN, L. M. (1958) *Brit. med. J.*, **2**, 490.
GARVIE, J. M. and KENDALL, A. C., (1961) *Ibid.* **1**, 548.
GITLIN, D. (1955-56) *In* YEAR BOOK OF PEDIATRICS, CHICAGO.
——— ., HITZIG, W. H. and JANEWAY, C. A. (1956) *J. clin. Invest.*, **35**, 1199.
GOOD, R. A., (1955) *Amer. J. Dis. Child.*, **90**, 577.
——— , ROTSTEIN, J., and MAZZITELLO, W. F. (1957) *J. Lab. clin. Med.*, **49**, 343.
——— , and ZAK, S. J. (1956) *Pediatrics*, **18**, 109.
GRANT, G. H. and WALLACE, W. D. (1954) *Lancet*, **2**, 671.
HUDSON, R. P. and WILSON, S. J. (1960) *Cancer, (Philad.)* **13**, 200.
HUTCHISON, J. H. (1955a) *Lancet*, **2**, 844.
——— (1955b) *Lancet*, **2**, 1196.
JANEWAY, C. A., APT, L., and GITLIN, D. (1953) *Trans. Ass. Amer. Phycns*, **66**, 200.
KEIDAN, S. E., MCCARTHY, K., and HAWORTH, J. C. (1953) *Arch. Dis. Childh.*, **28**, 110.
KEKWICK, R. A., VALLET, L., CUTBUSH, M., MOLLISON, P. L., THOMAS, A. R., GELL, P. G. H., and SOOTHILL, J. F. (1961) *J. clin. Path.*, **14**, 470.
KREBS, E. G. (1946) *J. Lab. clin. Med.*, **31**, 85.
LANCET, Leading Article (1958) *Lancet*, **1**, 1317.
——— (1961) *Lancet*, **1**, 151.
LEONHARDT, T. (1957) *Lancet*, **2**, 1200.
LONGSWORTH, L. G., CURTIS, R. M., and PEMBROKE, R. H., Jr. (1945) *J. clin. Invest.*, **24**, 46.
MARTIN, C. M., WAITE, J. B., and MCCULLOUGH, N. B. (1957) *J. clin. Invest.*, **36**, 405.
MARTIN, N. H. (1955-56) *Lect. sci. Basis Med.*, **5**, 165.
——— (1956) *Triangle*, **2**, 297.
——— (1962) *Proc. roy. Soc. Med.*, **55**, 398.
MEDICAL RESEARCH COUNCIL: Working Party on Hypogammaglobulinæmia (1957) *Brit. med. J.*, **2**, 1318.
MOORE, D. H., MARTIN DU PAN, R., and BUXTON, C. L. (1949) *Amer. J. Obstet. Gynec.*, **57**, 312.
MACCALLUM, F. O. (1962) *Proc. roy. Soc. Med.*, **55**, 397.
MCKAY, E. and RICHARDSON, J. (1959) *Lancet*, **2**, 713.
O'BRIEN, J. S. and WALSH, J. R. (1961) *Amer. J. Med.*, **30**, 813.
ORLANDINI, T. O., SASS-KORTSAK, A., and EBBS, J. H. (1955) *Pediatrics*, **16**, 575.
PARKES, R. (1958) *Brit. med. J.*, **1**, 973.
PEARCE, K. M. and PERINPANAYAGAM, M. S. (1957) *Arch. Dis. Childh.*, **32**, 422.
PERLMAN, E., BULLOWA, J. G. M., and GOODKIND, R. (1943) *J. exp. Med.*, **77**, 97.

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press

PORGES, R. F. (1956) *J. Lab. clin. Med.*, **47,** 960.
PORTER, H. (1955) *Amer. J. Dis. Child.*, **90,** 617.
PRASAD, A. (1958) *Amer. J. med. Sci.*, **236,** 610.
RAMÓN GUERRA, A. U., APRATTO, J. L., FOSSATTI, C., FERREIRA APOLO, A., PASEYRE, P., MACKINNON, J. E., and ARTAGAVEYTIA-ALLENDE, R. C., (1957) *Rev. colomb. Pediat.*, **16,** 102.
ROBERTSON, D. M. (1960) *Canad. med. Ass. J.*, **82,** 81.
SCHICK, B. and GREENBAUM, J. W. (1945) *J. Pediat.*, **27,** 241.
SOMERS, K. (1957) *Arch. Dis. Childh.*, **32,** 220.
SOOTHILL, J. F. (1962) *Proc. roy. Soc. Med.*, **55,** 395.
SQUIRE, J. R. (1962) *Proc. roy. Soc. Med.*, **55,** 393.
SUNDBERG, R. D. (1955) *Ann. N. Y. Acad. Sci.*, **59,** 671.
WEINSTOCK, I. and LEE, S. L. (1960) *Amer. J. Dis. Child.*, **99,** 242.
WOLLHEIM, F. (1961) *Lancet,* **1,** 316.
WRIGHT, M. I. (1959) *Brit. med. J.*, **1,** 1218.
ZINNEMAN, H. H., HALL, W. H., and HELLER, B. I. (1954) *J. Amer. med. Ass.*, **156,** 1390.

Whipps Cross Hospital,
London, E.11

https://doi.org/10.1017/S0022215100061521 Published online by Cambridge University Press