tion, or of 10.6 to 24.2% of all normal homozygotes born. Since malarial deaths are likely to follow what must be a considerable proportion of the loss of child life—that in the first month or two—we may surmise that the observed figures would approximate to the lower rather than to the higher of these limits.

These considerations reduce the difficulty mentioned above, of requiring an excessively high malaria death rate to account for the maintenance of sickling rates as high as 39%; we find that no very high malaria death rate need be recorded if the loss of life from other diseases is high, and especially if a large proportion of that loss consists of neonatal deaths. These are the conditions that prevail in Bwamba and many other parts of Africa.

Although, as we have said, we have no mortality statistics for Bwamba, we may compare it with large parts of the Belgian Congo. Duren (1951) reviewed the sources of information on malaria mortality in the Congo, and after taking due account of their inadequacy he concluded that below the age of 3 years deaths directly from malaria amounted to 14 to 22 per 1,000 per annum. Colbourne and Edington (1954) obtained a roughly similar figure, 17 per 1,000 for children under 1 year in Accra, and 10 per 1,000 for children from 1 to 5 years. The mortality in Bwamba is unlikely to be less than these estimates, which amount to a cumulative loss during childhood of about 5 to 10% of children born. This is very close to the figure, 6.9% or more, which we have shown to be required for preserving a state of balanced polymorphism in Bwamba, and we may therefore conclude that malaria could act as an effective selective agent under the primitive conditions of Bwamba, to maintain a sickling rate as high as 39%. It follows from our consideration of the mechanics of balanced polymorphism that the malaria situation in two regions might be the same in the sense that it caused the same loss of life before the age of, say, 3 or 5 years, yet in these two regions it might be the factor in maintaining two entirely different sickling rates. This could come about if the two populations differed in their mortality before the age at which the malaria mortality in each was at its greatest. Hence no simple measure of malaria morbidity or mortality even if it were the malarial mortality in normal homozygotes that could be measured, could enable one to predict accurately the sickling rate that might be maintained. The situation cannot be defined without reference to the whole infant mortality, and its relation in time to the malarial deaths.

Summary

The Baamba, an African tribe showing a high sickling rate (39%) has been examined to determine how this high rate can be maintained.

Of the 623 subjects examined, 227 were sicklers. No genetic variants of normal adult haemoglobin other than haemoglobin S were found. Amongst 191 sickling subjects over the age of 5 no homozygotes were detected; and it is concluded that the survival of sickle-cell homozygotes plays no significant part in maintaining the sickling rate of this tribe at its high level.

If selective death of non-sicklers from malaria was responsible for the maintenance of the 39% sickling rate in Bwamba, 10.6–24.2% of all normal homozygotes (or 6.9–15.7% of the whole child population) would have to die from malaria. Reasons are given for supposing that the actual death rate to be observed would approximate to the lower rather than the higher of the two limits, and that such a death rate from malaria is to be expected in Bwamba.

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FAMILIAL AGAMMAGLOBULINAEMIA

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Absence of serum gammaglobulin causing lowered resistance to infection was discovered by Bruton (1952) in a boy suffering from recurrent septic infections. More cases in boys were described by Janeway, Apt, and Gitlin (1953). The condition as it occurred in boys was thought to be primary, familial, and sex-linked.

The primary disorder was subsequently described in males and females of all ages; of 38 case histories that we have been able to obtain, 18 have been those of boys. Kulneff, Pedersen, and Waldenström (1955) describe the disease in two brothers aged 9 and 7, and in a distant male relative aged 5.

The important features of the disease are repeated septic respiratory and non-respiratory infections, lack of cutaneous responses to antigens, almost complete absence of circulatory antibodies and of gammaglobulin from the blood serum and connective tissues, diminution in the number of plasma cells in the tissues, and failure of lymphatic nodes to respond to antigenic stimuli (Janeway, 1954). In most cases isohaemagglutinins have been entirely absent from the blood. Virus exanthems usually run their normal course, but in some children they recur. Infants suffering from agammaglobulinaemia may die of intractable infections (Keidan, McCarthy, and Haworth 1953; Janeway, 1954; Hutchison, 1955). Most of the female patients have had bronchiectasis, and in most of the adults the spleen has been enlarged.

Patients who have been given repeated injections of gammaglobulin (0.1 g. per kg. body weight per month) have usually responded well. Treatment with antibiotics has been found essential to control acute infections (Janeway, 1954), and has sometimes been given continuously with good effect.

The cases here described are those of two brothers who are suffering from familial agammaglobulinaemia in its classical form.

Case 1

This patient was born in November, 1945. He had bronchopneumonia at two months. Left chronic otitis media began in 1948 and persisted until 1951, when tonsillectomy was performed; both antra were washed out, with the production of mucopus. The ear dried up, but mucopurulent discharge started again within three months.

1952.—Left cortical mastoidectomy was performed. Pus and soft granulation tissue were present in the mastoid cavity. The operation wound became septic and took five months to heal. March: Shortly after the mastoidectomy chest *x*-ray examination showed patchy infiltration in the right lower lobe, with enlargement of the hilar glands. April: He was Mantoux 1/100 negative; six weeks later Mantoux 1/100 positive. Guinea-pig inoculation of gastric washings showed generalized tuberculosis at necropsy. E.S.R. was 10/200 mm./hr.; white cell count, 14,200 per c.mm. (neutrophil polymorphs 75%, lymphocytes 18%, monocytes 7%). Intramuscular streptomycin was given for one month. July: Chest *x*-ray film showed a primary focus in the right lower lobe, with a small pleural effusion; the bronchogram was normal. His ear was still discharging and there was mucopurulent discharge from his antra. A further month of streptomycin with P.A.S. was given.

1953.—Right cortical mastoidectomy was performed. A further course of intramuscular streptomycin was given. Soon after, he developed a right upper lobe pneumonia. White cells, 5,900 per c.mm. (polymorphonuclear leucocytes 33%, lymphocytes 61%, mononuclear leucocytes 2%, eosinophil leucocytes 3%, monocytes 1%, basophils 1%). September: Chest *x*-ray film showed a little enlargement of the right hilar shadow only.

1954.—February and April: He had further attacks of right upper lobe pneumonia. July: Mantoux 1/10,000 positive; given intramuscular streptomycin, oral P.A.S., and oral isoniazid for one month. August: E.S.R. 5 mm.; chest *x*-ray film showed pleural thickening right side. October: Appeared to be well; ears dry, E.S.R. 4/200 mm. hr. Shick-positive. Bronchogram showed a small saccular dilatation of a right lower lobe segmental bronchus, but there was no other abnormality. One dose T.A.F. was given.

1955.—He had right lower lobe pneumonia in February, and bronchitis and right otitis media in March. He was seen at Edmonton Chest Clinic on June 7 suffering from right lower lobe pneumonia, and was admitted to the North Middlesex Hospital. This was his twelfth hospital admission and seventh hospital. *X*-ray examination showed both antra to be infected. Because of the history of recurrent infections, agammaglobulinaemia was suspected, and confirmed by paper electrophoresis of the serum proteins.

Investigations.—Paper electrophoresis: The serum was subjected to electrophoresis on paper—the paper strips were dried and stained with bromocresol green, and the protein fractions were cut out. The dye was eluted with a solution of equal parts of methanol and 10% sodium carbonate, and measured by absorptiometry. No correction was made for any difference in the dye-binding of different protein fractions. Electrophoretic pattern: Albumin, 3.71 g./100 ml.; α1-globulin 0.67, α2-globulin 0.84, β-globulin 0.80, γ-globulin 0.05 (normal 0.8–1.4). Re-examination of the serum in November gave a similar pattern. Zinc turbidity, 0.5 unit. Blood group A (no β-isohaemagglutinins present). Schick-positive. Mantoux 1/10,000 positive. Chest *x*-ray examination on August 10 showed that the pneumonia had resolved. He was discharged on August 12, taking oxytetracycline, 100 mg. four times a day. When seen on December 29 he had completed a term at school without interruption for the first time, and was well.

Case 2

This patient, the only sibling of Case 1, was born in March, 1951. He appeared to be healthy in infancy apart from an attack of gastro-enteritis at 8 months. At 10 months he was inoculated against whooping-cough and diphtheria. He had had measles (age unknown). At 15 months he was inoculated with B.C.G. Two months later he was Mantoux 1/100 positive, and was again positive a year later (strength unknown).

In January, 1954, he had synpneumonic empyema of staphylococcal origin; a subsequent staphylococcal infection of the nose was treated with chloramphenicol. All the polymorphs disappeared from his blood, but eventually he made a satisfactory recovery. In June he was reinoculated with B.C.G. following a negative tuberculin test (multiple puncture). In July he was examined again on receipt of the information that his brother was suffering from agammaglobulinaemia. He had had bronchitis a week before, treated by oral penicillin. On examination his general appearance was healthy, but crepitations were heard at the left base. An eschar was present at the site of inoculation, and the glands in the left axilla were enlarged. Chest *x*-ray examination showed nothing abnormal.

A fortnight later his nose and eyes were sticky, but there were no signs of bronchitis. Chest *x*-ray showed pneumonitis at left base.

Investigations.—Serum electrophoretic pattern (method as in Case 1): Albumin, 3.6 g./100 ml.; α1-globulin 0.7, α2-globulin 0.85, β-globulin 0.80, γ-globulin 0.15. Re-examination of the serum in November gave a similar pattern. Zinc turbidity, 0.5 unit. Blood group, A (no β-isohaemagglutinins present). Schick-negative.

By the middle of August he had developed a more severe cough and crepitations had returned. Chest *x*-ray films showed no change. The eschar was healing and the axillary glands were no longer palpable. The tuberculin test (multiple puncture) was positive. Oxytetracycline (100 mg., four times daily) was given. Apart from occasional slight attacks of diarrhoea he remained well and free of cough. He attended infant school during the autumn term.

In December he had left basal pneumonia treated by increasing dose of oxytetracycline. E.S.R. was 5/200 mm. in one hour; tuberculin jelly test positive. He was discharged well, taking oral penicillin. A fortnight later he was still well.

Investigation of Relatives

The maternal grandfather was Lithuanian. A maternal uncle was constantly ill until the age of 16 years. At the time of writing he was in good health.

Blood samples obtained from the father and mother showed a perfectly normal electrophoretic pattern and normal zinc turbidity. Samples were also obtained from the father's brother and his three sisters, and parents, and from the mother's sister and three brothers. All showed normal gammaglobulin as judged from normal zinc turbidity, and sera from the maternal relatives showed normal electrophoretic patterns.

Complete genotypes of the family were made by Dr. Dorothy Parkin, of the Lister Institute. There is no constant genetic feature in the blood groups of the family which can be related to the appearance of agammaglobulinaemia.

Discussion

The occurrence of tuberculosis in Case 1 and the behaviour of the Mantoux reaction is of interest. The disease, which developed after the symptoms of agammaglobulinaemia were established, ran its normal course, complicated by septic infections, and was cut short by the usual chemotherapy and antibiotic treatment. The boy's Mantoux reaction remained positive. The second child was first vaccinated with B.C.G. before there were any symptoms suggestive of agammaglobulinaemia and the Mantoux reaction became transiently positive. On re-vaccination the Mantoux became positive, and it has persisted for eight months. The axillary lymph node glands became enlarged, a normal consequence of B.C.G. inoculation. The patients of Kulneff *et al.* (1955) were also vaccinated with B.C.G.; the first in infancy before symptoms of agammaglobulin-

aemia had developed, his Mantoux remaining positive; the second, after symptoms had appeared, his Mantoux also remaining positive. The third patient was apparently vaccinated after discovery of agammaglobulinaemia. His Mantoux test did not convert.

Only one other case with a positive tuberculin reaction has been recorded, that of an adult male, Mantoux 1/1.000 positive (Lang, Schettler, and Wildhack, 1954).

Good (1955) states that he attempted to sensitize three patients with tuberculin and failed. It seems that gammaglobulin is not essential tb the development of a positive skin reaction to tuberculin or for its maintenance, but it may facilitate conversion.

We should not have inoculated our patient with B.C.G. had we known at the time he was suffering from agammaglobulinaemia, although the inoculation in this case was successful. Infections of little account in normal children may have disastrous consequences in these unfortunates. Keidan *et al.* (1953) record the death of an infant from generalized vaccinia. Sanford, Favour, and Tribeman (1954) vaccinated an adult who already had a normal vaccinia scar. The patient developed an enormous ulcer. Corbeel, Lahey, and Guest (1954) record the case of a 4-year-old boy who suffered from varicella for 60 days.

The explanation of the persistently low E.S.R. reading in our two cases, a phenomenon also noticed by Jacobsen (1954) and by Prasada and Koza (1954), is not obvious. One is tempted to attribute the low reading to the agammaglobulinaemia, but further investigation is needed to elucidate this problem.

The low white cell count observed during acute infections in both cases is of interest. Janeway (1954) states that in about one-third of all episodes of respiratory sepsis in these children the white count is lowered. He attributes this to the severity of septic infections of children whose defences are impaired.

Almost all the boys described have had normal bronchograms. The bronchogram of our first case showed a normal bronchial tree except for a small cavernous dilatation of a bronchus in the right lower lobe. This was probably the site of a primary infected tuberculous gland which caseated and ruptured into the bronchus.

The case of the younger child was probably discovered in the earliest stage of the evolution of the disease so far demonstrated. He had had only one severe episode of respiratory infection, 18 months before agammaglobulinaemia was diagnosed, since when he had been well. The only antibiotic treatment he had received was chloramphenicol for the first infection and several short courses of oral penicillin shortly before the diagnosis of agammaglobulinaemia was made. We have not yet been able to make a complete investigation of his antibodies.

The diagnosis of agammaglobulinaemia is not difficult in a person with such a prolonged history as Case 1. However, such a history is not always due to a lack of gammaglobulin in the serum. A girl aged 3½ years, a patient of one of us (I. G. W.), developed otitis media in the first week of her life and has had 20 to 30 attacks since then; in addition, she contracted tuberculosis from her grandmother in the first year of life and has since developed bronchiectasis in the right middle lobe. It is interesting that until recently her tuberculin reaction has only been very weakly positive (jelly negative, Mantoux 1/100 positive), but electrophoresis of her serum proteins in 1953, 1955, and 1956 showed a normal pattern on each occasion. Conversely, agammaglobulinaemia is sometimes found by chance in adults who have not suffered unduly from infections.

The disease has so far been recorded only in persons of European extraction living in America, Northern Europe, the United Kingdom, and New Zealand. It has not been recorded from Southern Europe or the Latin American countries. It is possible that it is a disease of Northern European stock.

Summary

Two brothers are described who are suffering from familial agammaglobulinaemia. The younger boy's case was discovered very early in the evolution of the disease. His serum still contained a very little gammaglobulin.

One brother had had tuberculosis; the other had been inoculated with B.C.G. The significance of this in relation to the Mantoux reaction is discussed.

The serum of all available members of the family has been examined by the zinc turbidity test or by electrophoresis. No further case of agammaglobulinaemia has been found. Complete genotyping was performed, but no constant feature was discovered which could be related to the appearance of agammaglobulinaemia in the two brothers.

The significance of the finding of a low erythrocyte sedimentation rate requires further investigation.

We wish to thank Dr. Dorothy Parkin, of the Blood Group Reference Laboratory, Lister Institute, for blood-grouping the relatives; Dr. P. M. Gilbert, of the North Middlesex Hospital, and Mrs. B. N. Hands, formerly health visitor, Middlesex County Council, for their assistance.

[ADDENDUM.—The elder boy has now been included in the M.R.C. clinical trial of gammaglobulin in the treatment of hypogammaglobulinaemia which has just begun. He has received 8 weekly intramuscular injections of 0.85 g. pooled gammaglobulin (0.025 g./kg. body weight/week). None of the very frequent electrophoretic patterns of the serum proteins taken up to the present time has shown any appreciable increase in the circulating gammaglobulin.]

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The United Kingdom tobacco manufacturing industry announces the formation of a standing committee, composed of representatives of the Federation of Home and Export Tobacco Manufacturers, the British-American Tobacco Co. Ltd., and the Imperial Tobacco Co. (of Great Britain and Ireland) Ltd., to give formal status to their co-operation in research. In 1954 the industry gave £250,000 to the Medical Research Council for investigations into the causes of lung cancer. Sir ALEXANDER H. MAXWELL, tobacco adviser to the Board of Trade and chairman of the British India Tobacco Corporation, is chairman of the committee. Sir ALFRED EGERTON, F.R.S., and Sir RONALD FISHER, F.R.S., have consented to act as scientific consultants to the committee in the fields of physical chemistry and statistics respectively, and it is intended to invite eminent authorities on other subjects to serve in a consultative capacity. The offices of the committee will be at 6–10, Bruton Street, London, W.1. Commenting on the formation of the committee, Sir Alexander Maxwell said: "The committee will aid and supplement existing sources of research and information on questions relating to smoking and health."