PAEDIATRICS

SUPPLEMENT

1957

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FOR THE PRACTITIONER

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1957

Under the General Editorship of

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This is the second Supplement to Paediatrics for the Practitioner. New thoughts and work are introduced in original articles and, from time to time in the future, paediatric practice will be surveyed by means of critical papers. Subjects in the main volumes will also be revised when extensive changes in practice have occurred. Subjects in the original articles are fully indexed independently of the Noter-up.

The Noter-up section keeps readers up to date with advances made in paediatrics and will also show where, as a result of more recently acquired knowledge, the practice to be recommended now differs from that in the main volumes. Each year's Noter-up section replaces completely the previous edition.

To make full use of the main work and Noter-up readers should first refer to the main volume in which the particular subject appears. To ascertain whether changes have occurred, they should then refer to the Supplement, turning first to the specific volume number shown at the top of the left hand margin of each page. By reference to the details ranged beneath this, readers can then easily find the Part, page and sub-title referring to the original article in the main volume. In each case, where alteration has occurred or new material has been inserted, the text is placed under the same heading as that which appears in the main work.

August, 1957 *THE PUBLISHERS*

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PART I

ORIGINAL ARTICLES

GAMMA-GLOBULINS AND IMMUNITY

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RESISTANCE to infection depends on many factors; some are inherently protective, such as the integrity of the skin and mucous membranes, the ciliated epithelium of the air passages, acidity of gastric juice and lysozyme in tears; others operate when the tissues become infected, and these may be divided into two types—non-specific and specific.

Non-specific factors

The non-specific factors include local inflammatory changes which serve to bring phagocytes to the threatened area, and the so-called " acute phase reactions " (fever, leucocytosis, increased levels in the plasma of fibrinogen, *alpha*$_2$-globulin and mucoprotein, and the production of C-reactive protein) which precede the development of specific immunological responses.

Also plasma possesses bactericidal properties and the power to inactivate certain viruses. It contains *properdin* (from *perdere*, to destroy), a globulin which provides one type of bactericidal action for, in conjunction with complement and magnesium, properdin provides a system which inactivates certain viruses and participates in the destruction of certain Gram-negative bacteria and protozoa (Pillemer and his colleagues, 1954). Properdin may perhaps be a primordial type of antibody but one without the specificity that true antibodies have acquired during the process of evolution. It has been shown that lipopolysaccharide substances, derived from the cell walls of certain Gram-negative bacteria, injected intravenously into laboratory animals are pyrogenic *and* have the power to heighten the non-specific bactericidal action of plasma (Howard, Rowley, and Wardlaw, 1957). It is also known that the macrophages of the reticulo-endothelial system help to clear bacteria from the circulation.

Specific factors

The specific factors are related to the activity of the plasma cells which produce antibodies, that is *gamma*-globulins, in response to the antigens of bacteria, viruses and other substances, which antigens the cells of the host " recognize " as foreign and against which specific antibodies are produced.

The way in which the different defensive actions support and assist each other is a notable feature of resistance. For example, specific antibody-protein is fixed by the corresponding antigen in the bacterial coverings; this coats the organisms with a layer of sticky protein which serves to anchor them, assisting the phagocytes to engulf and destroy.

Another type of specific reaction depends on past antigenic experience; as a result of such experience the character of the response to an infection is altered when the tissues are again invaded with the same or an antigenically similar organism (sensitization). This process of sensitization may modify out of all recognition the type of illness which results from the subsequent infection. The way in which the reaction to streptococcal infection depends on past streptococcal experience is a good example. Characteristically a newborn infant reacts indolently, with little or no fever, to a first streptococcal infection. This can be contrasted with the acute febrile illness seen in a child aged 3 years with streptococcal tonsillitis, or, again, with the still different response sometimes occurring in older children who may develop acute rheumatism, nephritis, or some other type of post-streptococcal illness.

THE NATURE OF *GAMMA*-GLOBULIN

Gamma-globulin is a heterogeneous protein, consisting of relatively large molecules with molecular weights ranging from 160,000 to 300,000, which can be separated from the rest of the serum proteins by electrophoresis, by various precipitation methods, or by means of the ultra-centrifuge.

Although it is established that the bulk of the circulating antibody-protein is found in the *gamma*-globulin fraction, a small amount of antibody material has been identified among the *beta*-globulins. The heterogeneous character of the protein molecules in the *gamma*-globulin fraction is not surprising in view of the multiplicity of specific antibodies which it contains. It has, moreover, been found that the antibody-containing globulins can be subdivided into $gamma_1$-globulins and $gamma_2$-globulins, and these two types of *gamma*-globulin have a slightly different amino-acid constitution.

ELECTROPHORETIC ANALYSIS OF SERUM PROTEIN FRACTIONS

Originally, the separation of the serum proteins into *serum albumin* and *serum globulins* was done by " salting-out " techniques which depend on the different solubilities in aqueous saline solution of these proteins. Later, it was found that it could be done by the ultra-centrifuge. Then came a turning point with the description by Tiselius, in 1937, of a still more precise separation of the plasma protein components by *boundary electrophoresis*—a method in which the separation was effected by the passage of a weak current through a buffered solution of proteins contained in a specially shaped U-tube. This technique depends on the fact that under the influence of an electrical field the particles in such a solution will move according to their electrical charge, which is related to their size. The molecules of albumin, being the smallest, move farthest, next come the *alpha*-globulins, then the *beta*-globulins, and finally the *gamma*-globulins, which move least.

Electrophoresis by the Tiselius method is accurate and quantitatively reliable. Its drawbacks are that it is slow, requires a large sample of serum and expensive optical apparatus, and could never have wide use in routine clinical chemistry.

In 1950, several workers, including Tiselius, described a new electrophoretic method, *zone-electrophoresis*, using filter paper as a matrix; this placed the investigation within the reach of most hospital laboratories.

The serum (or other protein solution to be analysed) is absorbed on a strip of filter paper which is exposed to a weak electrophoretic current. A number of strips can be processed together, dried and then stained. On each stained electrophoretic strip a pattern is seen and by means of photo-electric scanning the pattern can be recorded in graphic form. This roughly approximates to the pattern obtained by Tiselius' original method, often referred to as the *Schlierin* diagram. The electrophoretic pattern of the serum of a normal child, aged 7 years, is shown in Fig. 1. Zone-electrophoresis on filter paper has not the quantitative accuracy

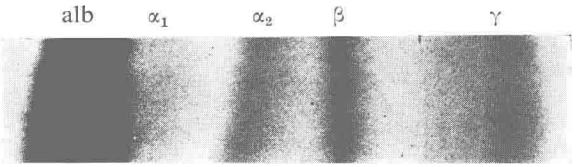

Fig. 1.—Electrophoresis on filter paper; serum of a healthy child aged 7 years. Normal pattern.

of the original method and the results are not reproducible unless the details of the technique are carefully standardized; nevertheless, it shows the amounts of the various proteins in a roughly quantitative way and demonstrates any important deviation from the normal.

ELECTROPHORETIC APPLICATIONS

Electrophoretic analysis has been used for the study of many problems. In physiology it has made a contribution to protein chemistry and in the case of plasma protein has revealed new fractions; in consequence the *alpha*-globulins, *beta*-globulins, and *gamma*-globulins have each been divided into subfractions. Combined chemical, immunological and electrophoretic methods are now being used in order to give greater precision.

As an instrument of clinical research electrophoresis has been used to demonstrate alterations in the protein constitution of body fluids in disease (for example, in nephrosis and myelomatosis) and it has made the recognition of certain new clinical conditions possible (for example, agammaglobulinaemia and hypogammaglobulinaemia). It also enables the different types of haemoglobin (such as those responsible for sickle-cell anaemia and thalassaemia) to be readily differentiated. Thus, it has considerable value in routine clinical biochemistry.

PREPARATION OF *GAMMA*-GLOBULIN FOR CLINICAL USE

Gamma-globulin consists, for the most part, of specific antibody-proteins, and can be thought of as a mixture of these proteins, but since every person has a different antigenic experience, and since each will react in a slightly different manner to antigenic stimulation, the antibody pattern will be special to the individual subject. Such differences will, however, be lost when sera are pooled for the purpose of preparing *gamma*-globulin in bulk; in other words, specimens of pooled serum reflect only an average antibody spectrum. Methods of preparation and storage of *gamma*-globulin may possibly modify its final antibody content.

Several methods are available for the preparation of plasma protein fractions in bulk. At the Lister Institute in the United Kingdom the ether fractionation method of Kekwick and MacKay is used. One pint of whole blood yields 120 millilitres of serum, and from this quantity 750 milligrams of *gamma*-globulin can be prepared. (For further details *see* page 15).

PHYSIOLOGY OF *GAMMA*-GLOBULIN

The amount of *gamma*-globulin in the intravascular and extravascular fluid spaces (called the *gamma*-globulin pool) depends on a balance between production and expenditure.

Synthesis

In so far as *gamma*-globulin consists largely of antibody-protein it can be said that the site of its formation is the site of antibody formation, and the evidence points to the plasma cells in the lymph nodes and other portions of the reticulo-endothelial system. On antigenic stimulation the lymph nodes of a normal child proliferate, their germinal follicles enlarge and secondary follicles appear, with many plasma cells forming in the periphery of the follicles and in the medullary cords. By a fluorescein staining technique, devised by Coons and his colleagues (1955), it is possible to see conjugated antibody-material in the plasma cells and tissues under the fluorescence microscope by virtue of a brilliant yellow-green label. In children suffering from agammaglobulinaemia (*antibody deficiency syndrome*) antigenic stimulation is followed by the same follicular proliferation in the lymph nodes, but secondary follicles do not form, nor is there plasmocytosis, and antibody-protein is not identifiable by Coons' method, despite the fact that antigen can be proved to reach and to stimulate the follicles. Furthermore, plasma cells are virtually absent from the bone marrow and from inflammatory exudates in patients with the antibody deficiency syndrome. These points lend strong support for the view that plasma cells are concerned in the production of antibodies. Lymphocytes may be concerned in some other way, perhaps in the transport of antibody. Little is known about the production of *gamma*-globulin in the liver, although there is an increase of *gamma*-globulin in some hepatic disorders and plasma cells form in the portal connective tissue in certain circumstances. (*see also* page 15).

It is probable that *gamma*-globulin is built up out of amino acids which in the living state are continually being formed into different kinds of protein and broken down again. Recent work, employing isotope-labelled *gamma*-globulin, has shown that injected antibody-protein behaves as a foreign substance, not participating in the continual renewal of protein structures but being soon eliminated like other foreign protein. In contrast, autogenous antibody-protein behaves like tissue protein, participating in the constant exchanges of amino acids. Like the other plasma proteins, it is distributed almost equally between the plasma and the extravascular tissue spaces, being also found in skin and muscle.

Expenditure

It is not known how the size of the *gamma*-globulin pool is regulated in health, but the amounts used and destroyed are balanced by production so that the pool remains more or less constant. No doubt some of the *gamma*-globulin is utilized by combination with antigen but much is destroyed like the rest of the plasma protein, isotopic methods suggesting that it has a half-life or turnover time of approximately 20 days.

Fig. 2 has been constructed to illustrate the kinetics of the *gamma*-globulin pool in the case of an adult weighing 70 kilograms (11 stone). The calculations are based on an isotopically ascertained half-life of 20 days. It shows that about 15 grammes of *gamma*-globulin may be expected to leave the interstitial tissue

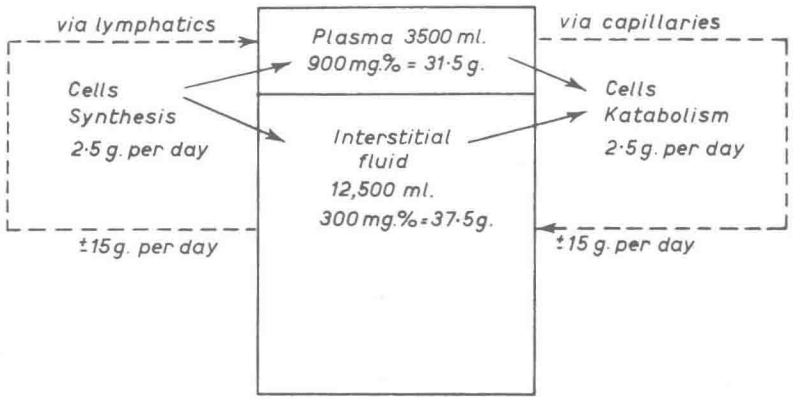

Fig. 2.—*Gamma*-globulin metabolism calculated for a man weighing 70 kilograms. Body pool = 1 gramme per kilogram. (*After Janeway, C. A., and Gitlin, D.*, 1957.)

spaces each day, later returning by the lymphatics into the plasma. An approximately equal amount reaches the tissue spaces from the plasma. About 2·5 grammes are expended and replaced daily. The figures for a child would be different, and can be calculated according to weight and age (*see* Fig. 3).

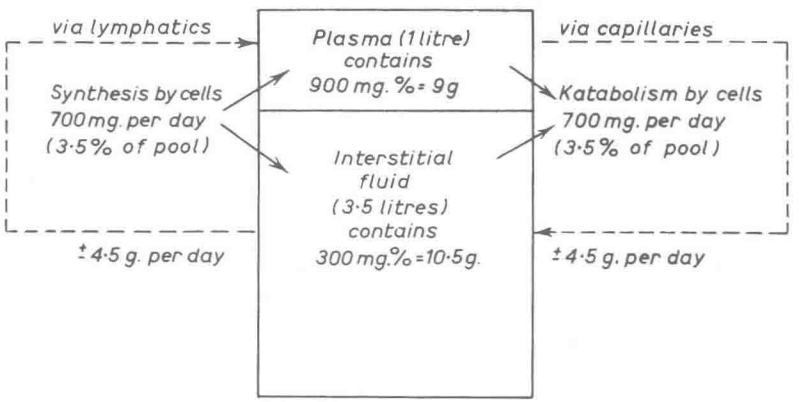

Fig. 3.—*Gamma*-globulin metabolism calculated for a child weighing 20 kilograms. Body pool = 20 grammes (approx.). (*After Janeway, C. A., and Gitlin, D.*, 1957.)

Quantitative variations

The size of the pool is changed by physiological factors and by disease, the variations being reflected by alterations in the plasma level.

Physiological Factors

Influence of age

In the human foetus the serum *gamma*-globulin increases steadily from a zero level to reach a peak at term. This peak, which is higher than at any time during infancy, approximates the maternal level, for the *gamma*-globulin reaches the foetus across the placenta. After birth the infant loses his maternally transmitted *gamma*-globulin; the serum level falls rapidly in the first week and then more slowly to reach a minimal level at about 1 month, when it is approximately one-third of the peak at birth. There is no evidence that the plasma level of *gamma*-globulin in early infancy is influenced by feeding with colostrum and breast milk. The available evidence indicates that practically no *gamma*-globulin is produced during the first 4 weeks of life, but that subsequently immune bodies are formed under antigenic stimulation. From the age of about 3 months the *gamma*-globulin level of the infant is rising slowly but does not reach adult level until the age of 2 years or later (Orlandini and his colleagues, 1955) (*see* Fig. 4). Thus, the

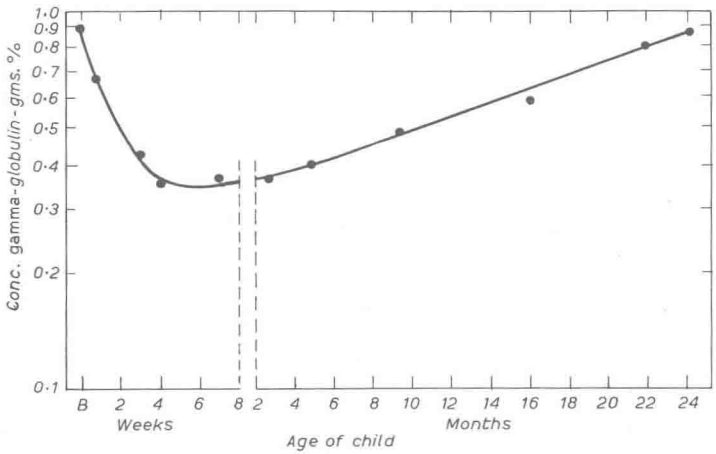

Fig. 4.—Variation of average serum concentration of *gamma*-globulin with age; note that this is a semi-logarithmic plot and that there is a change in units in the abscissa. (*After Janeway, C. A., and Gitlin, D.* (1957), *Advances in Paediatrics; and by courtesy of Year Book Publishers.*)

finding of low *gamma*-globulin values during early infancy—well below the values for older children and adults—should not be interpreted as evidence of a *gamma*-globulin deficiency. Occasionally, however, an infant seems incapable of forming *gamma*-globulin until some months have passed, and then hypogammaglobulinaemia is to be regarded as a pathological condition (*see* page 10).

In premature infants the level of *gamma*-globulin is lower at birth than in full-term infants and these low levels may persist until the third month or later.

The interpretation of the electrophoretic patterns obtained in infants and young children is thus much affected by the age factor; therefore, electrophoretic results are probably best interpreted by comparison with standard patterns known to be normal for the age.

PATHOLOGICAL CONDITIONS

GAMMA-GLOBULIN DEPLETION

When there is defective production of *gamma*-globulin the size of the pool shrinks, for there is little evidence that *gamma*-globulin can be conserved. The fall in available *gamma*-globulin is reflected by a fall in the plasma level and this can be shown easily by electrophoresis. The concentration of *gamma*-globulin in plasma (mean value 900 mg. per 100 ml.) can vary more widely than any other plasma protein, yet this variation causes no significant change in the distribution of body water because of the very small osmotic influence of *gamma*-globulin, and oedema is not associated with hypogammaglobulinaemia. This contrasts with the much higher osmotic activity of serum albumin, loss of which is a potent cause of oedema.

Hypogammaglobulinaemia manifesting as part of a general disorder of plasma protein

(1) Protein malnutrition is probably the commonest cause of hypoproteinaemia. Kwashiorkor rarely causes hypogammaglobulinaemia even when the serum albumin is much reduced; indeed, there is frequently either concurrent infection or parasitization leading to hypergammaglobulinaemia (*see also* Vol. 1, page 447).

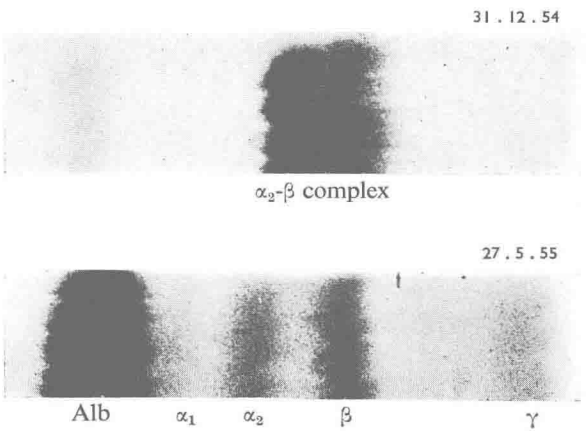

Fig. 5.—The upper electrophoretic strip shows the features occurring in an active phase of nephrosis (child aged 11 years): greatly reduced albumin and *gamma*-globulin fractions; the *alpha*$_2$ and *beta*-globulins form a complex poorly differentiated one from the other. The lower strip, from the same patient, shows a normal electrophoretic pattern after remission.

In the so-called *nutritional recovery syndrome* an increase in the serum *gamma*-globulin is said to be an early change, and it subsequently falls to a normal level (*see* Supplement, 1956, page 108). Chronic diarrhoeal states may also result in hypoproteinaemia.

(2) Except in countries where protein malnutrition is common, hypoproteinaemia is more likely to be due to loss of protein than to defective synthesis. This loss occurs in the *nephrotic syndrome* and mainly affects the serum albumin (*see* Vol. 2, page 437) but, in addition, hypogammaglobulinaemia is an almost constant feature of this syndrome, the other globulin fractions being less affected. Thus, serum electrophoresis shows a characteristically disturbed pattern which returns to normal if a good remission takes place. This sequence of changes is illustrated in Fig. 5 by two electrophoretic strips—the first made during an active phase of the disease, the second when a remission had been obtained by steroid treatment (*see* page 150).

Loss of serum protein, especially albumin, may also result when there is excessive exudation from mucous membranes or skin surfaces, as in severe chronic ulcerative colitis, extensive burns or eczema, and in conditions associated with long-standing blood loss.

Hypogammaglobulinaemia as an isolated disturbance of serum protein

This type of hypogammaglobulinaemia is seen in several aetiologically different conditions in which diminished resistance to bacterial infection is a feature in common. The children affected respond poorly or not at all to antigenic stimulation; thus, little or no specific antibody is formed and the history is that of repeated bacterial infection (*antibody deficiency syndrome*).

Transient hypogammaglobulinaemia of infancy

During the first 4 weeks of life there is little power to make antibodies, and any specific immunity at this period depends on maternally transmitted *gamma*-globulin: as this disappears, autogenous production comes into play and it would seem to be the physiological ideal for an infant to encounter and respond to antigens *while still partly protected by maternal antibodies.*

Usually by 3 or 4 months of age antibodies are being produced in fair quantity and the *gamma*-globulin level rises steadily, but in certain infants the physiological hypogammaglobulinaemia persists after the fourth month and there may be an increased liability to infection on account of continued failure to produce antibodies. This disorder usually disappears by the sixth month of life. Perhaps it is a factor in certain cases of sudden and unexpected death in infants from bacteriaemia or pneumonia.

Congenital agammaglobulinaemia

Congenital agammaglobulinaemia was first recognized by Bruton in 1952; he reported that a boy suffering from recurrent bacterial infections possessed no *gamma*-globulin peak on serum electrophoresis. Bruton and, later, Janeway and his colleagues (1953) defined this type of agammaglobulinaemia as an isolated disturbance of protein metabolism—a defect due to failure of antibody synthesis and not to increased destruction of *gamma*-globulin. As the disease was described after the advent of chemotherapy the behaviour of such patients in the past is not known, but it is likely that without such treatment many must have died from fulminating bacterial infections.

The disease shows a sex-linked inheritance, being transmitted to males by females, as in haemophilia. Frequent and severe *bacterial* infections occur from infancy or early childhood onwards, affecting in particular the respiratory tract, skin, conjunctivae, intestines, meninges and joints. Yet the patients show a surprising ability to overcome most virus infections in spite of their immunological handicap. Attacks of measles, rubella, chicken-pox, the common cold, acute respiratory disease, mumps and poliomyelitis follow their usual course and do not show an increased incidence of recurrence. This suggests that the immunological mechanisms for resisting bacteria and viruses are quantitatively different, only small amounts of antibody being needed to prevent virus particles from gaining entry to cells.

Since it would appear that congenital agammaglobulinaemia is due to an inborn error of metabolism which interferes with the differentiation of plasma cells and the synthesis of antibodies, other haemopoietic disturbances are of interest. During acute bacterial infections the leucocyte count shows a response

varying from neutropenia to marked polymorphonuclear leucocytosis. Cyclical neutropenia has been observed independently of infection. The ordinary " acute phase reactions " are not inhibited, and the sedimentation rate rises in the usual manner when infection occurs.

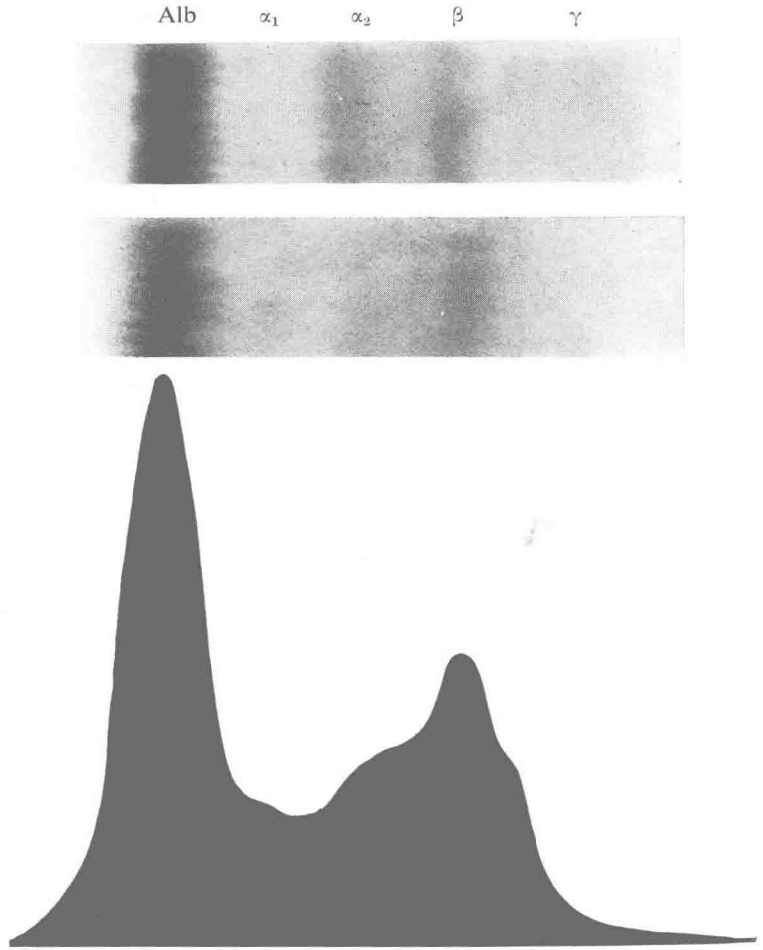

Fig. 6.—Congenital agammaglobulinaemia in a boy aged 3 years presenting with arthritis. The lower electrophoretic strip is compared with the normal for the age, shown above. The abnormal strip is represented at the bottom in the form of a graph plotted by means of a scanner.

Diagnosis

The diagnosis is most easily confirmed by demonstrating the absence of *gamma*-globulin by electrophoresis (Fig. 6), but when this method is not available the following screening tests are useful:

(1) Reduced level of serum globulin.
(2) Lack of antibody response on antigenic stimulation.
(3) Histological changes in the lymph nodes and bone marrow.

(1) The reduction of serum globulin level can be shown by estimating the total

serum protein together with the albumin-globulin ratio. Absence of serum *gamma*-globulin can be demonstrated by Kunkel's zinc turbidity test. Patients with agammaglobulinaemia may show less than one unit (normal 3–12 units). A low *gamma*-globulin level in boys presenting with chronic or recurrent infection is almost diagnostic.

(2) Normal persons have relatively high titres of antibody against erythrocytes of heterologous groups. In congenital agammaglobulinaemia it is easy to show that these antibody titres are of insignificant strength. A positive Schick test persists after administration of diphtheria toxoid.

(3) Bone-marrow smears show virtual absence of plasma cells, the lymph nodes are hypoplastic and a radiograph of the nasopharynx shows almost complete absence of adenoid tissue.

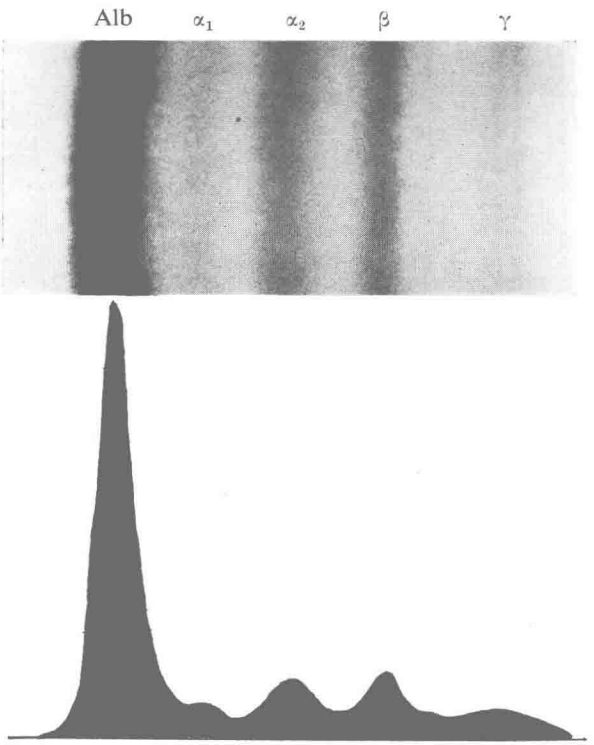

Fig. 7.—Electrophoresis showing hypogammaglobulinaemia of the acquired type in a girl of 3 years with a history of recurrent sepris.

Treatment

General management

Children with congenital agammaglobulinaemia should be protected from infection as far as possible. Prophylactic immunization against bacteria (for example, typhoid and paratyphoid) and toxins (diphtheria, tetanus) is impracticable.

The possibility of vaccination against viruses is being studied. Smallpox vaccination may or may not take, and there have been a few reports of *vaccinia gangrenosa*