HYPOGAMMAGLOBULINAEMIA AND TUBERCULOSIS

IMPLICATIONS OF THEIR ASSOCIATION, AND OTHER OBSERVATIONS

BY

RAYMOND PARKES, M.D.

Lately Medical Registrar, Harefield Hospital, Middlesex

Hypogammaglobulinaemia, as an isolated serum-protein deficiency, is of current interest to clinician and immunologist alike. Present-day antimicrobial therapy prevents most patients with this defect from dying of the infections to which they are prone, and so there exists a " provocative experiment of nature "—as Good (1954) has called it—by which problems of immunity and hypersensitivity in man may be uniquely investigated. This is so because γ-globulin carries the majority of conventional serum antibodies measurable by currently available techniques, in addition to isohaemagglutinins.

Deficiency may be classified in this way : (1) Transient or physiological: found in infants aged 4 to 12 months and sometimes not rising to normal levels for 18 months (Gitlin and Janeway, 1956). (2) Congenital: a sex-linked, recessive, genetic inheritance of inadequate production of the protein fraction, affecting only males in the patients so far described, though inheritance allows its rare occurrence in females (Gitlin and Janeway, 1956). (3) Acquired: arising in older children and adults of either sex not previously afflicted by morbid frequency of infection, and, though it *appears* not to be inherited, an inherited defect may be manifesting itself in later life (Gitlin and Janeway, 1956). As γ-globulin (normal value, 600 to 1,200 mg./100 ml.) is not completely absent from the serum, being up to 25 mg./100 ml. in the congenital form and up to 100 mg./100 ml. in the acquired (Gitlin and Janeway, 1956), the term " hypogammaglobulinaemia " is used here rather than " agammaglobulinaemia." Both congenital and acquired forms appear to be permanent, and sometimes other protein fractions may also be deficient (Gitlin *et al.*, 1956).

By the middle of 1957 more than 100 cases of hypogammaglobulinaemia (congenital and acquired almost equally distributed) had been reported in the world medical literature, and among these were three patients with associated tuberculosis. The implications of this association and other incidental features are the subject of this paper, which includes a report of a patient with pulmonary tuberculosis.

Case Report

The patient, an unmarried woman aged 22, was the only child in an average working-class home. There was nothing significant in the family history.

Clinical History.—A forceps delivery, she was healthy until about 4 years of age, when recurrent " colds "—usually with cough—started, obviously being more frequent than in other children. Minor convulsions were also observed, and a year later typical grand-mal epilepsy, with approximately one seizure daily, had developed. From then on she was never free from colds ; yellow nasal discharge and cough with yellow sputum (sometimes subject to acute increase with fever) were almost always present, and sties abnormally common. From the age of 10 grand-mal seizures increased in frequency and severity.

Between 1949 and 1955 she had (apart from almost continuous symptoms of chronic bronchitis) severe streptococcal sore throat, repeated indolent furunculosis, six episodes of lobar or segmental pneumonia associated with undue prostration which resolved with antimicrobial therapy, empyema of the maxillary antra, a heavy infection of mouth and pharynx with *Candida albicans*, appendicectomy for an acutely inflamed appendix (not examined histologically), and a large abscess in the buttock. Most bacterial infections were accompanied by moderate leucocytosis. In 1952, when 17, she was ill with aplastic anaemia (probably due to the anticonvulsant drug troxidone, which was withdrawn) and was treated with multiple blood transfusions and antibiotics for about three months.

In 1954, after haemoptysis, she was found to have pulmonary tuberculosis, with positive sputum, and treatment with streptomycin and isoniazid was instituted. In 1955 she entered Harefield Hospital, when she was febrile and exceptionally lethargic, and antituberculous treatment was continued. Over the next twelve months she had three lower segmental non-tuberculous pneumonias, recurrent indolent furunculosis, non-tuberculous cystitis, offensive vaginal discharge, present for many months, and bilateral middle-ear deafness without evidence of labyrinthine damage. Petit mal occurred frequently daily, though grand-mal seizures showed little change.

Hypogammaglobulinaemia was diagnosed in May, 1956, and in August therapeutic replacement of γ-globulin was begun.

Clinical Examination (in Harefield Hospital).—The tuberculous upper-lobe consolidation in the right lung which was present on admission resolved over a period of six months. At no time were lymph nodes, liver, or spleen enlarged.

Investigations. — (1) *Plasma Proteins :* — April, 1956: γ-globulins absent on paper electrophoresis and Kunkel's zinc sulphate turbidity test : fractional precipitation values between 60 and 120 mg./100 ml. December: 320–340 mg./100 ml. February, 1957: 320 mg./100 ml. by precipitin diffusion method. Albumin, α_1,α_2, and β globulins, normal values. Fibrinogen, 0.18 g./100 ml. (normal, 0.2 to 0.4 g./100 ml.). (2) *Haematology :*—Morphology and numerical values of peripheral blood cells always normal, except for moderate neutrophil leucocytosis during bacterial infections. Group A1, Rh positive, R1 R1 (CDe/CDe). Isohaemagglutinins absent. A and H secretor substances in saliva. (3) *Vaginal discharge* revealed occasional *Staph. aureus* but no monilia or *Trichomonas vaginalis*. No plasma cells. (4) *Sputum* was usually purulent, and contained many neutrophil leucocytes but no plasma cells. *H. influenzae* grown on a few occasions. In December, 1955, and March, 1956, two cultures were tubercle-positive ; 28 cultures negative thereafter. (5) *Tuberculin Tests :*—April, 1956, K.O.T. 1 : 1,000 positive (induration, 2 cm. ; erythema, 3.5 cm.). September, K.O.T. 1 : 100 positive (induration, 1.5 cm. ; oedema, 3 cm. ; erythema, 6 cm.). (6) *Schick and Dick Tests* were negative on two separate testings (the patient was never immunized against diphtheria). (7) *Electroencephalograms*:—August, 1956, pronounced epileptic pattern with generalized high-voltage discharges.

Chest *x*-ray films in 1949 to 1956 showed various transient middle and lower lobar consolidations. Right upper lobe tuberculous consolidation and collapse (1954) cleared slowly, though without proper re-expansion. No hilar node enlargement ever seen. Bronchograms in December, 1956, showed moderately severe " saccular " bronchiectasis of anterior and apical segments of the right upper lobe. *Otherwise the bronchial tree appeared entirely normal.*

Treatment.—Streptomycin, 1 g. daily, with isoniazid, 300 mg., for 14 months, and various other antimicrobial agents for non-tuberculous infections were often required for periods of many weeks. Intramuscular administration of γ-globulin was started in August, 1956 (almost two years after tuberculosis was diagnosed), the dosage schedule (according to a Medical Research Council therapeutic trial in which this patient was included) being 0.5 g./kg. body weight in one week as a loading dose ; followed by 0.025 g./kg./week for four months ; and from December, 1956, 0.5 g./kg./

week for another four-months period. It was convenient to spread injections over five days in the week. Methoin and phenobarbitone were given in small daily doses as anticonvulsants.

Diagnostic Criteria and Treatment

Acquired hypogammaglobulinaemia was diagnosed on the grounds of the history (continued bacterial infection probably starting when the patient was about 5, and nine episodes of bacterial pneumonia in six years), γ-globulin deficiency on paper electrophoresis, zinc sulphate turbidity tests, and fractional precipitation; and the absence of isohaemagglutinins. The criteria for active pulmonary tuberculosis, which developed some years after the estimated onset of hypogammaglobulinaemia, were development under observation, haemoptysis, two sputum cultures positive for tubercle bacilli, and normal resolution with anti-tuberculous drug therapy.

Treatment of patients with hypogammaglobulinaemia involves antimicrobial agents and the permanent replacement of γ-globulin, the usual dose being 0.1 g./kg./month. Prolonged antibiotic prophylaxis (for example, with tetracycline) has been recommended (Mazzitello and Good, 1956). The antimicrobial agents given for non-tuberculous infections in this patient invariably succeeded, but, before γ-globulin therapy, more slowly than in normal individuals. After six months' replacement of γ-globulin its serum level had increased more than threefold; though little change was observed on paper electrophoresis.

After three months' γ-globulin therapy the patient was animated and cheerful, when previously she had been dull and lethargic; and both she and her parents said she had never been so well. Respiratory infections and frequent inexplicable low-grade fevers no longer occurred. Nasal discharge and purulent sputum practically ceased, but indolent skin infections still gave trouble despite antibiotics.

Hypogammaglobulinaemia and Epilepsy

After some months of γ-globulin therapy fewer grand-mal seizures occurred and petit-mal episodes were rarely observed; electroencephalograms were impressively better, though no change in anticonvulsant drugs had been made for more than 18 months. In spite of this striking improvement there is no apparent connexion in this patient between hypogammaglobulinaemia and epilepsy.

Reticulo-endothelial System and Hypogammaglobulinaemia

Plasma cells are the chief source of γ-globulin and bacterial antibodies (Craig *et al.*, 1954; Coons *et al.*, 1955; Good and Varco, 1955), though the role of lymphocytes has not been fully clarified (Sundberg, 1955). In congenital and acquired hypogammaglobulinaemia plasma cells are absent or extremely sparse in pus, lymph nodes, and bone marrow, and were not found in inflammatory products of this patient. In addition, abnormal enlargement of lymph nodes, liver, and spleen, separately or together, have been reported in some cases of the acquired deficiency only (Rohn *et al.*, 1955; Good and Mazzitello, 1956; Citron, 1957); and, occasionally, a thymoma has been discovered (Good and Varco, 1955; Martin *et al.*, 1956; MacLean *et al.*, 1956; Ramos, 1956), removal of which did not alter the serum γ-globulin level in one patient (MacLean *et al.*, 1956). Such abnormalities were not present in my patient, but they have been found associated with granuloma or tumour involvement of the reticulo-endothelial system in some patients—sarcoidosis (Zinneman *et al.*, 1954), malignant lymphoma (Arends *et al.*, 1954), chronic lymphatic leukaemia (Prasad and Koza, 1954; Jim and Reinhard, 1956), as well as generalized amyloidosis (Gras *et al.*, 1954)—and it may well be that such involvement directly impairs plasma-cell function and therefore antibody formation. It is probable that acquired hypogammaglobulinaemia is more commonly due to immaturity of plasma cells, as instanced by Citron (1957), and this may be genetically determined.

The immediate question is: Can tuberculosis cause hypogammaglobulinaemia by widespread involvement of the reticulo-endothelial system? At present no evidence supports this, and the frequency of tuberculosis in hypogammaglobulinaemic patients has, to date, been similar to that in the general population. The association of the two conditions is probably coincidental. My patient's history suggested the presence of hypogammaglobulinaemia some years (five at least) before pulmonary tuberculosis developed.

Neutropenia or lymphopenia, which may reflect reticulo-endothelial dysfunction, is found in some patients (Good and Varco, 1955), but was not found in mine. Perhaps such findings are sometimes due to heavy infection depressing blood-cell formation.

Bacterial Infections other than Tuberculosis

Hypogammaglobulinaemia is apt to reduce bacterial immune response, and abnormally frequent, and often severe, infections at any site with both Gram-positive and negative organisms occur (Mazzitello and Good, 1956). Pneumonia, bronchiectasis (a common finding), and infection of the gastro-intestinal tract simulating ulcerative colitis or steatorrhoea are found more often in the acquired form (Gitlin and Janeway, 1956), but this patient had no bronchographic evidence of bronchiectasis other than in the right upper lobe, which was not unexpected after its long-standing collapse. It may be that acquired hypogammaglobulinaemia will be found in a few bronchitic patients, and this is even more likely in young patients with bronchiectasis. Steatorrhoea was not observed in my patient, and although it has been described with acquired hypogammaglobulinaemia (Sanford *et al.*, 1954; Rohn *et al.*, 1955; Rosecan *et al.*, 1955; Zinneman and Hall, 1956; Cooke *et al.*, 1957), it is more likely that bacterial infection of the bowel, rather than an intrinsic anomaly of fat absorption, explains the symptoms.

Otitis media, common in these patients but unrecognized in the present one, appeared to have caused her bilateral middle-ear deafness.

Fungus and Virus Infections

Hypogammaglobulinaemia does not seem to cause undue susceptibility to fungus infection, but administration of certain antibiotics may lead, as in normal individuals, to development of monilial infection (Mathias and Rees, 1956); and this is the most likely explanation of the *Candida albicans* infection of mouth and pharynx in this patient. There is, however, some evidence that γ-globulin deficiency (either transient or congenital) may be aetiologically related to *Pneumocystis carinii* pneumonia in early childhood (Hutchison, 1955; Bird and Thomson, 1957), and further study of this will be of interest.

Virus infections are no more frequent in hypogammaglobulinaemic patients than in normal individuals, and they follow an expected course. Virus antibodies are not found in these patients' serum, nor is it possible to produce them with virus antigens (Good and Varco, 1955). Immune response to virus infection, therefore, unlike that to bacterial infections, may be either wholly or partly independent of γ-globulin, or may be mediated through minute quantities of it, through the α-globulin fraction of plasma proteins, or through some purely cellular mechanism (Raffel, 1956).

Tuberculosis

The reported cases of tuberculosis associated with hypogammaglobulinaemia are one of tuberculous lymphadenitis (Veterans Administration, 1955); one of inactive pulmonary tuberculosis with acute tuberculous lymphadenitis and apparent steatorrhoea (Zinneman and Hall, 1956); one of primary pulmonary tuberculosis with tubercle bacilli in gastric washings (Elphinstone *et al.*, 1956); and one of primary tuberculosis in a child (cited by Zinneman and Hall, 1956), which has not been authenticated (Zinneman,

personal communication, 1957). The first two had the acquired deficiency, the second two the congenital. My patient appears to be the second recorded with active pulmonary tuberculosis.

As almost all the earlier described cases of hypogammaglobulinaemia were tuberculin-negative, it was originally thought that all such patients would *not* possess delayed tuberculin hypersensitivity as shown by positive skin tests with old tuberculin or P.P.D. (Young *et al.*, 1955), though not all those reported have been tested. Nevertheless, a skin test has been found to be *positive* in at least three patients (Lang *et al.*, 1954; Elphinstone *et al.*, 1956; Zinneman and Hall, 1956), and is clearly demonstrated in my patient. Furthermore, B.C.G. can induce delayed tuberculin sensitivity in patients with hypogammaglobulinaemia (Kulneff *et al.*, 1955; Porter, 1955).

Since Chase (1945, 1946) demonstrated that the delayed type of specific cutaneous sensitivity to tuberculin can be transferred to *insensitive* guinea-pig recipients by injections of leucocytes drawn from *sensitive* donor guinea-pigs, others —notably Lawrence (1949, 1955), Urbach *et al.* (1952), Good and Varco (1955), and Porter (1955)—have transferred delayed tuberculin sensitivity from sensitive human donors by intradermal injections of their *washed* leucocytes into insensitive human recipients. And Good *et al.* (1957) have, by the same method, conveyed such sensitivity (which has persisted so far for two years) from sensitive donors to insensitive recipients; while, even more strikingly, Porter (1955) has transmitted tuberculin sensitivity from a child with congenital hypogammaglobulinaemia, in whom it was produced by B.C.G., to a normal insensitive subject. Although leucocytes employed in these transfer techniques are injected intradermally, Schlange (1954) has claimed that delayed tuberculin sensitivity was induced in a tuberculin-negative (insensitive) infant (with erythroblastosis foetalis) by whole blood transfusion.

It is not known how an injection of a few sensitized donor leucocytes causes human recipients to respond to specific test substances in the same manner as did the donor following natural infection (Lawrence, 1956); and the chemical nature of the "transfer factor" is unknown (Lawrence, 1956), though it can survive certain enzyme action (Lawrence, 1955) and be set free from sensitized leucocytes by interaction with specific antigen (Lawrence and Pappenheimer, 1956, 1957). It should be added that production of delayed hypersensitivity to tuberculin and other bacterial antigens in a previously insensitive hypogammaglobulinaemic patient has been achieved by subcutaneous homograft of lymph nodes from a sensitized human donor (Martin *et al.*, 1957).

Just as tuberculin sensitivity apparently behaves normally in patients with hypogammaglobulinaemia, so the acquired immune response to tuberculous infection (judged by the clinical course) appears no different in these patients from that in normal individuals: at least, in my patient (in whom tuberculosis was known to have existed for two years before γ-globulin therapy began) and those reported to date. Indeed, such infection has followed a normal pattern of behaviour without tendency to fulminate or spread; and, so far, B.C.G. injections have caused no evidence of tuberculous disease (Kulneff *et al.*, 1955; Porter, 1955; Elphinstone *et al.*, 1956), and are possibly without danger.

Baldwin and Iland (1953) demonstrated an increase in serum γ-globulin in normal subjects with active tuberculosis, and, although it contained complement-fixing antibodies in advanced disease, they could find no antibody to the tubercle bacillus in the increased fraction; but Pescetti and Orlandi (1956), using a modified technique, produced contrary evidence indicating that γ-globulin may carry tuberculous antibodies. This discrepancy may be due to experimental method. But the fact remains that *clinically* the immune response to tuberculosis can function normally in the presence of isolated γ-globulin deficiency; and Raffel (1955) states that, experimentally, a cellular mechanism may be responsible for acquired immunity rather than the acquisition of antibodies, as measured by present techniques. It is not known what place natural non-antibody protective substances found in the serum, such as properdin (Pillemer *et al.*, 1954), may have; but in one patient with tuberculosis and hypogammaglobulinaemia (Veterans Administration, 1955) this substance was absent: it is uncertain whether it is linked to γ-globulin.

Sensitivity to Diphtheria and Streptococcal Antigens

Schick and Dick tests have invariably been found positive in patients with hypogammaglobulinaemia, and attempts to produce antibodies to diphtheria and streptococcal toxins in such patients have failed (Good and Varco, 1955). There is abnormal susceptibility to infection with these organisms. Using the leucocyte transfer technique, Lawrence (1952, 1955) and Lawrence and Pappenheimer (1956) have transferred delayed skin sensitivity to diphtheria toxin and streptococcal antigens from sensitized normal human donors to unsensitized normal human recipients. But they were unable to detect any serum antibody of conventional type to diphtheria toxin (Lawrence and Pappenheimer, 1956). It seems likely that, although leucocytes may normally play some part in the development of delayed hypersensitivity, the serum antibody response to these two infections is mediated chiefly by γ-globulins, as it may be to all bacterial infections other than tuberculosis.

Atypically, in this patient both Schick and Dick tests were *negative* (although she had never had diphtheria immunization) and indicated the presence of delayed sensitivity to the appropriate antigens. A possible explanation is that this was induced by cell transfer in the blood transfusions she received four years previously—a process that might be predicted from the observations already quoted, but is not proved.

Conclusions

Hypogammaglobulinaemia in man offers a remarkable natural experiment for the study of delayed hypersensitivity and serum antibody response to tuberculosis. Both appear to function normally in patients suffering this deficiency, so that in normal individuals the two phenomena may be independent of γ-globulin and may be to a large extent related to cellular mechanisms. This theory is reinforced, in the case of hypersensitivity, by leucocyte transfer experiments, and Pappenheimer (1955) has made the interesting suggestion that sensitized leucocytes may, in the presence of antigen, liberate "transfer factor," which is then ingested by non-sensitized leucocytes, and so set up a "biological chain reaction" maintaining hypersensitivity.

An α-globulin fraction analogous to that discovered in guinea-pigs by Cole and Favour (1955), and shown to transfer delayed tuberculin sensitivity in these animals, may exist in man, but has not yet been demonstrated. Hence, this fraction or one or more of the other fractions may yet be shown to possess antibody activity to antigens of the tubercle bacillus in man.

On the other hand, in individuals with hypogammaglobulinaemia, delayed hypersensitivity to diphtheria and streptococcal antigens does not develop naturally, though it can be evoked by leucocyte transfer; and immune response is absent, or very feeble, and cannot be induced experimentally. From the clinical and immunological evidence provided by hypogammaglobulinaemic patients, all bacterial infections (other than tuberculosis) appear to behave similarly.

Immunologically tuberculosis appears to stand alone among bacterial infections, though leprosy may show similar behaviour; for, from preliminary observations, there seems to be no correlation between serum γ-globulin levels (electrophoretically determined) and activity of conventional serum antibody in patients with lepromatous disease (Mayama, 1954).

The foregoing is likely to be oversimplified, for improved analysis may reveal new protein fractions and functions. Hypersensitivity and immune response to tuberculosis may then be found to be shared by leucocytes (and other body cells) and some serum protein fraction other than γ-globulin. In short, there may be some combined function of leucocytes and serum proteins.

The door is open to a more comprehensive conception of the immunology of tuberculosis.

Summary

A case of acquired hypogammaglobulinaemia, active pulmonary tuberculosis, and epilepsy is reported, and reference is made to the other recorded cases of hypogammaglobulinaemia associated with tuberculosis.

It is submitted that the association of hypogammaglobulinaemia and tuberculosis is coincidental, and that they bear no aetiological relationship one to the other.

The natural course of tuberculous disease appears to be unaffected by hypogammaglobulinaemia, and delayed hypersensitivity and immune response are normal in patients observed to date.

It is suggested that delayed hypersensitivity and serum antibody response to tuberculosis function independently of γ-globulin, and may rely on a cellular mechanism (leucocytes and other body cells), though the possibility of an unidentified serum protein fraction sharing such immunological powers is not excluded.

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ADDENDUM.—Since this paper was completed I have encountered another patient, similar to mine, at Bellevue Hospital, New York City. A man of 28, with a history of recurrent pneumonia and other infections since the age of 6 months, had bronchiectasis and recently developing pulmonary tuberculosis. Sputum grew tubercle bacilli on four different occasions, and P.P.D. skin tests (second strength) were positive (with induration) on three occasions. No enlargement of lymph nodes, liver, or spleen was ever apparent. Chest *x*-ray films showed bilateral but not extensive upper-lobe disease. Hypogammaglobulinaemia was revealed by serum electrophoresis and fractional precipitation. Tuberculosis followed the expected satisfactory course on antituberculous drugs. He did not receive γ-globulin replacement therapy.

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CLINICAL STUDIES ON THE ACTION OF BEMEGRIDE IN BARBITURATE OVERDOSAGE*

BY

THOMAS J. THOMSON, M.B., F.R.F.P.S. M.R.C.P.

Senior Medical Registrar, University Medical Unit, Stobhill General Hospital, Glasgow, and Department of Materia Medica and Therapeutics, University of Glasgow

Since bemegride (ββ-methylethylglutarimide) was introduced by Shaw *et al.* in 1954, there has been much discussion on whether this drug is a specific antagonist to the barbiturates or a non-specific central analeptic. Many papers have described the stimulating effect of bemegride in barbiturate coma (Shulman *et al.*, 1955; Clemmesen, 1956), but more recent reports have suggested that it appears to have a restorative action in coma due to non-barbiturate sedatives, such as primidone (Dotevall and Herner, 1957) and glutethimide (Rowell, 1957). The factors which influence the outcome in patients suffering from sedative poisoning are so varied that it is impossible to assess the specificity of action of bemegride in such circumstances.

The use of thiopentone in general anaesthesia, however, might appear to provide a suitable background for the study of the action of bemegride in man. Harris (1955), Canbäck *et al.* (1955), and Bentel *et al.* (1956) have reported that 50–100 mg. of bemegride injected intravenously could rapidly terminate anaesthesia induced by 0.5 g. of thiopentone. In these studies the premedication drugs varied, as did the duration of administration of the anaesthetic; no control observations were made.

The pilot study reported here reveals some of the difficulties in demonstrating the antibarbiturate activity

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