(Carrol, 1959). It is well recognized that the percentage of failures is always higher in lower femoral and popliteal embolisms even after early surgery. Case 2 illustrates the success of medical treatment in such a situation. Although intra-arterial perfusion therapy at or near the site of obstruction is to be preferred (Cliffton 1960) intravenous administration may be used with success if treatment is started early. For maximum benefit it should be given within 72 hours (Popkin 1961).

Summary

Patients who have multiple recent emboli or those who are not fit for a laparotomy and embolotomy may be successfully treated medically with fibrinolysin. Fibrinolysin therapy may be preferred to surgical treatment in the lower femoral and popliteal embolisms and acute thrombosis. Anticoagulants may be administered simultaneously as their action is known to be complementary.

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IDIOPATHIC ACQUIRED HYPOGAMMAGLOBULINAEMIA WITH MELANOSIS, ASSOCIATED WITH SIBSHIP IMMUNOGLOBULIN ABNORMALITIES AND ANKYLOSING SPONDYLITIS

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THERE is increasing evidence that a genetic factor plays a role in idiopathic acquired hypogammaglobulinaemia (Citron, 1957; Wollheim, 1961). Recently, quantitative abnormalities of the serum immunoglobulins have been found in the families of cases of idiopathic acquired hypogammaglobulinaemia (Fudenberg, Franklin, German and Kunkel, 1962). A significantly higher than normal incidence of rheumatoid factor and of frank rheumatoid arthritis has also been found in these families (Fudenberg and others, 1962; Good, Kelly, Rotstein and Varco, 1962).

The following case of idiopathic acquired hypogammaglobulinaemia demonstrates familial abnormalities of the immunoglobulins. There are, in addition, two previously unrecorded features. In the first place, a brother who has abnormal immunoglobulins, has ankylosing spondylitis. This occurrence is of interest in view of the high frequency of rheumatoid arthritis in the families of Fudenberg and others (1962), and the controversial relationship of the two forms of arthritis. In the second place, the patient had marked diffuse melanosis and vitiligo.

Case Report

A Jewish medical practitioner was well until 1950,

when, at the age of 36, he developed cough and sputum. He had, from that time, repeated febrile episodes associated with purulent sputum and occasional haemoptysis, which responded to bed rest and antibiotics.

In 1958, he was admitted to another hospital with an exacerbation of his chest symptoms of eleven weeks duration. He was found to have partial collapse of the lower lobes of the lungs, with bilateral hilar lymphadenopathy and hepatosplenomegaly. He was thought at this time to be slightly hyper-pigmented. Routine investigations were non-contributory, although serum protein electrophoresis showed a marked reduction of the gamma-globulin level. The patient refused any biopsy procedure, and a presumed diagnosis of Hodgkin's Disease was made. The chest infection responded to routine treatment. Radiotherapy was given to the mediastinum, with a subsequent reduction in the size of the hilar glands.

Acute chest infections continued to recur several times a year, with increasing exertional dyspnoea. He received antibiotics and various cytotoxic drugs in view of the presumed diagnosis of a lymphoma.

He was admitted to University College Hospital in 1961, with a history of increasing cough, muco-purulent sputum, dyspnoea and ankle oedema for three months. He also gave a history of increasing generalized pigmentation and vitiligo for at least four years. There was no history of joint pain or swelling, backache, gastrointestinal upset, arsenic medication or of skin eruptions.

Examination showed a well-nourished man in severe congestive cardiac failure. His temperature was 99.4°F.,

FIG. 1.—Bilateral sacro-iliitis in a man, aged 44, with immunoglobulin abnormalities (brother of patient with idiopathic acquired hypogammaglobulinemia).

blood pressure 90/70, and pulse rate 114/min. and regular. There was marked clubbing of the fingers, and unequivocal generalized brown pigmentation, with vitiligo of the right hand and abdominal wall. There was no buccal pigmentation. There were bilateral basal rales. The liver and spleen were palpable 5 and 10 cm., respectively, below the costal margin. There was no significant superficial lymphadenopathy, and the skeletal and central nervous systems were clinically normal.

Investigations

Hæmoglobin 12.1 g./100 ml. White blood-cells 10,000/cu. mm. (neutrophils 77%), erythrocyte sedimentation rate 22 mm./hr. Plasma electrolytes (mEq/l):—sodium 131, potassium 3.3, chloride 92, CO_2 capacity 27.2. Blood urea 28 mg./100 ml., routine urinalysis normal. Urinary excretion (mg./24 hr.) 17-ketosteroids 6.8, 17-ketogenic steroids 21.2. Sputum culture yielded *Pseudomonas pyocyanea*, sensitive to chloramphenicol.

Total serum protein was 4.4 g./100 ml., with electrophoresis showing a small reduction of the albumin, a small increase of the α_1 globulin, and a virtual absence of the gamma globulin levels. Gel-diffusion precipitin estimation (Gell, 1957) confirmed the severe hypogammaglobulinemia, with a level of 2.5 mg./100 ml., the β_2 M (19Sy) level being 100% of a standard 'normal' serum. The patient was blood group O, but without detectable anti-A or anti-B iso-hæmagglutinins. Chest x-ray showed cardiomegaly and bilateral basal collapse. The electrocardiogram showed marked right ventricular hypertrophy.

Progress

A diagnosis of hypogammaglobulinemia, with bronchiectasis and cor pulmonale, was made. There was little clinical improvement despite treatment of the heart failure and the chest infection, including intramuscular gamma globulin in full doses. He died suddenly, two weeks after admission.

Autopsy Findings

There was a recent pulmonary embolus, together with

an organizing pulmonary embolus (thrombus) of several weeks duration. There was severe, bilateral basal bronchiectasis, and dense pleural adhesions. The heart showed marked right ventricular hypertrophy. The liver was enlarged (2,600 g.) with congestive changes, while the spleen was greatly enlarged (1,350 g.), with loss of the normal architecture on cut surface. The only enlarged lymph glands were a few in the mediastinum.

The genito-urinary tract, the endocrine glands including the adrenals, and the alimentary system were normal. Permission to examine the brain was withheld.

Special stains of the skin sections excluded causes of pigmentation, other than melanin. Histology of the spleen and lymph glands showed replacement of the normal architecture by large pale reticulum cells. The liver showed 'nutmeg' changes only. In all the tissues examined, there was a complete absence of plasma cells. The histological findings thus confirmed the diagnosis of idiopathic acquired hypogammaglobulinemia (Martin, 1962).

Family History

There is no family history of an increased tendency to infections, abnormalities of pigmentation, or rheumatoid arthritis. The patient's father died, aged 52, of chronic osteomyelitis, septicæmia and chronic nephritis. The patient's mother had diabetes mellitus, and died, aged 77, of a cerebrovascular accident. The patient himself had no offspring.

The patient's brother is a medical practitioner, born in 1909. He complained of backache in 1953 at the age of 44. An x-ray showed bilateral sacro-iliitis (Fig. 1). The diagnosis of early ankylosing spondylitis was made, and a course of radiotherapy to his back relieved the symptoms. He has never had evidence of peripheral arthritis, symptoms of conjunctivitis, urethritis or colitis.

The patient's sister was born in 1907, and is alive and well. Each of the patient's siblings has two children in their late teens, without significant past or present medical history.

Family Investigations

Blood was obtained from the brother and sister of the

patient. Hæmoglobin, white-cell count and differential, erythrocyte sedimentation rate, total serum proteins and paper electrophoresis were all normal, as were the Rose-Waaler and Latex Fixation tests. Immunoelectrophoresis, however, showed the following abnormalities: (a) Brother (with ankylosing spondylitis); marked reduction of the β_2A , reduction of the β_2M , and slight reduction of the γ globulin levels.

(b) Sister; marked reduction of the β_1A , slight reduction of the β_2A and γ , reduction of the β_2M , and an increase of an α_2 globulin, possibly an haptoglobin.

Discussion

Fudenberg and Franklin (1963) have reviewed the genetics of the hereditary human gamma globulin types. The immunoglobulin abnormalities, found in the first-degree relatives of patients with idiopathic acquired hypogammaglobulinæmia, are assumed to depend on aberrations of production, in the heterozygous state, of particular immunoglobulin structural sub-units. They believe the high incidence of rheumatoid factor in these relatives is an associated feature of the gene defect. The high incidence of frank rheumatoid arthritis in these relatives (Fudenberg and others, 1962) is presumably also explained in this way.

The consensus of opinion, certainly in this country, is that ankylosing spondylitis and rheumatoid arthritis are different diseases (Short, Bauer and Reynolds, 1957). If, however, the incidence of ankylosing spondylitis in the families of cases of idiopathic acquired hypogammaglobulinæmia proves to be raised, similarly to that of rheumatoid arthritis in these circumstances, it would be highly suggestive of a common ætiological factor, presumably genetic, between the two forms of arthritis.

There was no evidence, in this case, of an endocrine cause of melanosis. There was also no evidence

of steatorrhœa, which is a known complication of hypogammaglobulinæmia (Cooke, Weiner and Shinton, 1957) and in which melanosis is well recognized (Wells, 1962). Antimitotic drug administration may have contributed to the severity of the melanosis (*Brit. med. J.*, 1963), but the skin changes were undoubtedly present before such therapy was first instituted.

Little is known of the ætiology of non-endocrine melanosis, associated with systemic diseases. A large proportion of these diseases, such as kala-azar, Gaucher's Disease, Felty's Syndrome, Hodgkin's Disease and others (Sutton, 1956), have in common marked reticulo-endothelial involvement and hyperplasia. By analogy, it seems possible that the melanosis of the patient reported here was, in some as yet inexplicable way, related to his marked reticulum cell hyperplasia.

Summary

A case of idiopathic acquired hypogammaglobulinæmia is reported. Siblings of the patient have quantitative abnormalities of their immunoglobulins. One of these siblings has ankylosing spondylitis, which is of interest in view of recent reports of a high incidence of rheumatoid arthritis in the relatives of cases of idiopathic acquired hypogammaglobulinæmia. The patient himself had marked melanosis which, it is tentatively suggested, was related to his reticulum cell hyperplasia.

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