Summary

Two cases of *hæmophilus influenzae* meningitis have been described who showed lack of response to the routine antibiotics. These two cases did not respond to the oral Penbritin because of vomiting and were treated with intramuscular and intrathecal Penbritin with successful results as shown by biochemical and clinical responses. It should be stressed that neither of these preparations of

Penbritin is yet available on the market; both were obtained by special arrangements. We consider that these routes of administration of Penbritin would be useful in the treatment of patients with *hæmophilus influenzae* meningitis.

We would like to thank the Beecham Research Laboratories Ltd., for the generous supplies of both intramuscular and intrathecal Penbritin at very short notice.

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FIBRINOLYSIN THERAPY IN ARTERIAL THROMBO-EMBOLISM

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THE lysis of intravascular clot using thrombolytic substances has been achieved by various workers since Clifton, Grossi and Cannamela (1954) originally demonstrated the effect of fibrinolysin in venous thrombosis in 1954. A vast amount of literature has accumulated on the therapeutic uses of such drugs especially in the United States of America. In this country, thrombolytic therapy using streptokinase has recently been reported (Verastraete, Amery, and Verylan, 1963; and McNicol, Reid, Bail and Douglas, 1963). Our experience with fibrinolysin (Actase) therapy has been limited but favourable. The following cases are particularly significant:—

Case No. 1

A woman (A. H.) aged 64 years was admitted on 8.2.63 with colicky abdominal pain of twenty-four-hours' duration and constipation for two days. Her abdomen was moderately distended in the lower part and a straight X-ray showed some distention of the small intestine (Fig. 1).

A diagnosis of subacute intestinal obstruction was made and was treated on conservative lines with a satisfactory response.

She had had a sub-total thyroidectomy ten years ago. She had a blood pressure of 180/100 mm. Hg. and auricular fibrillation was noted. The chest X-ray and ECG were compatible with the diagnosis of mitral valve disease. She had no previous history of intermittent claudication.

FIG. 1.—Case 1.

On 12.2.63 she suddenly developed loss of sensation of her left foot and toes. On examination, the left foot and toes were extremely pale and cold. There was no

FIG. 2.—Before treatment.

FIG. 3.—After treatment.

palpable pulse in the left limb and no oscillations were recorded on that leg. A diagnosis of left iliac arterial embolism was made, and the patient was prepared for operation. Within the next hour, her right upper limb suddenly became pale and cold and pulseless below the axilla. This was thought to be due to an embolus in the axillary artery and in view of the multiple embolic phenomena, it was decided to treat the patient medically.

One million units of Actase in 250 ml. of 5% dextrose were infused intravenously in two hours and after one hour this was repeated. 10,000 units of Heparin was also given intravenously followed by 5,000 units every four hours for the next twenty-four hours. The infusion of Actase was given for the next two days at a dose of two million units in twenty-four hours. 100 mg. of phenindione was given orally twenty-four hours after the initial Heparin administration and 50 mg. was continued twice daily to keep the prothrombin concentration below 30% of normal.

Twelve hours after the treatment was started, the colour of the right arm and left leg had improved and the right arm felt warm. There was no palpable pulse in the right arm or leg. After twenty-four hours the right arm recovered completely with return of the brachial and radial pulses. After forty-eight hours, the colour of the left foot had returned to normal and the extremity was warm. The sensation in the toes and foot had also returned. There was no pulsation of the femoral or popliteal arteries.

She started having regular bowel actions and the abdominal distension completely subsided in the next few days. Within a week, she was discharged from the hospital on a prophylactic maintenance dose of phenindione. Exercise test on the walking machine showed no indication of claudication.

Case No. 2

Male, aged 49 yrs. (R.R.) was admitted on 30.6.63 with severe cramp-like pain in the right leg and foot of eight hours' duration. He gave a history of cramps in the right calf on and off in the night but no definite intermittent claudication. A week before, he had had an injection of anti-tetanic serum and on the night before admission had had urticarial reactions to it.

On examination the right foot and leg were pale and

cold and there was no arterial pulse palpable except the femoral at the groin. The sensations of the foot were normal but movements of the toes and ankle were painful. An oscillograph recording showed marked diminution of the right side compared to the left (Fig. 2). A diagnosis of acute femoral thrombosis was made. Investigations: ECG and chest X-ray normal. Prothrombin concentration 50%, bleeding time 1½ minutes, clotting time 23 minutes (Wrights method at 37°C.), WBC 10,400/mm., ESR 1 mm./hr.

Treatment was immediately started with Actase and Heparin as described for the previous case. At twenty-four hours the colour of the foot was better and both leg and foot were warm. At forty-eight hours, the posterior tibial pulse had returned and the veins had filled, and at seventy-two hours both posterior tibial and dorsalis pedis were felt in the right limb. The oscillograph recording showed a remarkable improvement (Fig. 3). Exercise test on the walking machine showed that he could walk two miles without claudication. He was discharged on a maintenance dose of phenindione.

Discussion

Case 1 shows the successful medical treatment of multiple arterial embolism. We assume that the intestinal obstruction was also due to an embolism of a mesenteric vessel. It is difficult to draw completely valid conclusions from this case but in our experience anticoagulants alone have not so far produced such dramatic results. Anticoagulant drugs will provide a satisfactory degree of protection against the development and extension of thrombosis (Moser, 1959). These agents, however, have very little influence upon intravascular clot formed already. Fibrinolysis being plasmin itself provides a more direct attack on the fibrin clot. In this it is superior to streptokinase and streptodornase which indirectly activate the patient's available plasminogen (Randolph and Starling, 1961). The simultaneous administration of Heparin is believed to promote synergism and does not alter the effectiveness

(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.,