Fat-balance studies were made. 50 g. of fat per day was administered for five days in Cases 1 and 2 and for nine days in Case 3, and the fat-excretion in the stools measured. Fat-absorption was normal in all (see Table).

Barium-meal and follow-through examinations did not reveal anything abnormal in any of the three patients.

Gastric mucosa from Case 3, showing atrophy. (H. and E. $\times 120$.) Gastric mucosa obtained from Cases 1 and 2 showed a similar picture.

Response to Vitamin B₁₂ Therapy

Reticulocytosis (see Table), with haematological remission and return of the haemoglobin value to normal, followed the daily administration of 100 μ g. of vitamin B₁₂ by injection. The patients have been maintained in remission by the regular administration of parenteral vitamin B₁₂. In the first patient menstruation began six weeks after the institution of vitamin B₁₂ therapy. The second patient has since become pregnant, and the pregnancy and delivery were uncomplicated.

Discussion

The disease in the three patients does not differ significantly from Addisonian pernicious anaemia in white subjects, and the diagnostic criteria have been satisfied. The occurrence of pernicious anaemia in a younger age-group in Bantu subjects may possibly be a reflection of the age distribution of the population at risk. The significance of these cases lies in the possible confusion of the diagnosis with the much more common megaloblastic anaemia occurring in association with pregnancy—most often after the pregnancy. It is of significance that the second patient has subsequently become pregnant, and it is apparent how easily her pernicious anaemia could be confused with the form associated with pregnancy.

Addisonian pernicious anaemia must be considered in the differential diagnosis of megaloblastic anaemia in young Bantu females. Pernicious anaemia and megaloblastic anaemia occurring after pregnancy can be readily differentiated with the aid of specialized techniques: the serum vitamin B₁₂ is low in pernicious anaemia, while it is normal in post-pregnancy megaloblastic anaemia; the absorption of vitamin B₁₂ is defective in the first group, while normal in the second (Metz *et al.*, 1960b); gastric atrophy is present in pernicious anaemia, but not in the post-pregnancy group (Metz, 1959). These techniques are not available to all, and the most practical method of excluding pernicious anaemia is the augmented histamine test.

Summary

Three young Bantu women were found to be suffering from a condition indistinguishable from true Addisonian pernicious anaemia.

The significance of this finding is discussed with reference to the megaloblastic anaemias found in malnourished populations.

We thank the Director of the South African Institute for Medical Research for facilities to study these patients; Dr. E. Lester-Smith for supplies of radioactive vitamin B₁₂; Lederle Laboratories, New York, for supplies of intrinsic factor; Glaxo Laboratories, Wadeville, for supplies of vitamin B₁₂; Dr. D. L. Mollin for carrying out the vitamin B₁₂ assays; Professor E. Kark and Dr. I. W. Simson for help with the gastric biopsies; and Mr. D. Hart for technical assistance.

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CIRRHOTIC HEART FAILURE

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Some patients with portal cirrhosis have a higher cardiac output than normal (Kowalski and Abelmann, 1953; Murray *et al.*, 1958). Clinically the skin is warm and often dry (because of inability to sweat), the pulse is rapid and full, and the pulse pressure is increased. The cardiac impulse is forceful, with an accentuated mitral first sound, and often there is a systolic ejection murmur maximal internal to the apex; there may even be a short diastolic murmur.

Such a hyperdynamic state can occur in uncomplicated portal cirrhosis and in hepatic failure, the result of both cirrhosis and severe infective hepatitis. It is most frequently observed, however, in patients with extensive portal collateral circulations as a result of liver disease, especially if accompanied by a fall in the serum albumin concentration (Murray *et al.*, 1958).

It is not directly due to the anaemia or vitamin B deficiency, which may complicate portal cirrhosis: It is possible that failure to detoxicate a vasodilator substance (Shorr *et al.*, 1951) may account for the hyperdynamic circulation, or that the increase in cardiac output is secondary to the development of extensive arterio-venous anastomoses as a result of portal hypertension. Portal-systemic communications and spider naevi are well recognized, and there may also be intrahepatic shunts. In addition, anastomoses between the portal

and pulmonary veins have been demonstrated anatomically (Calabresi and Abelmann, 1957), and a proportion of patients with portal cirrhosis have a diminished arterial oxygen saturation (Snell, 1935; Murray *et al.*, 1958). Rydell and Hoffbauer (1956) reported the case of a child with what was thought to be cyanotic congenital heart disease, who was found at necropsy to have cirrhosis with extensive arteriovenous communications in the lungs. A similar case has been seen by one of us.

In adults, cardiac failure as a result of portal cirrhosis appears to be rare, and Murray and his colleagues could find no reports in the literature. Sherlock (1958) states, however, that "the occasional patient may proceed to frank congestion" (see Case 1, Murray *et al.*, 1958). Three such patients have been seen recently in the space of a month.

Case 1

A 71-year-old retired labourer was admitted to hospital with a history of increasing shortness of breath and ankle-swelling over the past few months. He had been subject to winter bronchitis and exertional dyspnoea for five years. He had also been troubled by piles. Alcohol intake was moderate.

Examination revealed a large dyspnoeic individual, but there was no cyanosis or jaundice. The peripheries were warm and there was a marked tachycardia. The internal jugular veins could be seen pulsating at the angle of the jaw, and there was marked oedema of the legs up to the thighs. The blood-pressure was 140/70. No murmurs could be heard, though the chest was grossly emphysematous. There were rhonchi throughout the lungs, and the abdomen was distended and tympanitic. Rectal examination revealed prolapsed piles.

A provisional diagnosis of cor pulmonale was made, though the absence of cyanosis was thought unusual, and he was treated with tetracycline, mersalyl, oral diuretics, and a low-salt diet. The chest x-ray film showed nothing of note, and the electrocardiogram (E.C.G.) was of low voltage. Blood urea was normal, but the haemoglobin was reduced (7 g./100 ml.) and there was evidence of deficiency of iron. Liver-function tests were not carried out. Although the chest symptoms improved there was little change in the signs of cardiac failure, and iron was given parenterally for the anaemia. The patient complained increasingly of abdominal distension, and, because it was thought that this might be due to ascites, abdominal paracentesis was carried out. Three litres of clear yellow fluid was removed, following which he rapidly deteriorated, dying in coma three weeks after admission.

Necropsy revealed a classical portal cirrhosis, the liver being about two-thirds the normal size and nodular. The heart was normal in size, though there was moderate atheroma of the coronary arteries. The other organs were generally congested.

Case 2

A 64-year-old housewife had complained of progressive shortness of breath on exertion and swelling of the ankles during the eight weeks prior to admission. She stated that she had had jaundice 10 years previously after a course of injections.

She was obese and dyspnoeic, and oedema was present up to the mid-thorax. Ascites was also present. The pulse was rapid, the peripheries were warm and dry. The jugular venous pressure was raised 2 in. (5 cm.) and the blood-pressure was 140/80. The mitral first sound was loud and there was a harsh systolic and a short diastolic murmur, best heard internal to the apex. A provisional diagnosis of mitral-valve disease was made.

She was treated with a low-salt diet, digitalis, and mercurial diuretics. Chest x-ray examination showed a little

cardiac enlargement, but rather surprisingly no pleural effusion. The E.C.G. showed left axis deviation. Blood count, blood urea, and electrolytes were all normal, and the Wassermann reaction was negative.

A few days after admission she was observed to be jaundiced. The serum bilirubin was 5.3 mg., thymol turbidity 10 units, alkaline phosphatase 13.3 K.-A. units, and serum albumin 3.1 g. and globulin 2.9 g./100 ml. There was little response to treatment, and because of the gross oedema Southey tubes were inserted into the legs. Three litres of fluid was removed, but there was a steady deterioration and she developed signs of liver failure. In spite of protein restriction, neomycin, and "parentrovite," she died in coma 10 days after admission.

Necropsy revealed a small nodular liver, about half the normal size. The heart was slightly enlarged, but there was no significant coronary or valvular disease. The organs were congested, and there was some bleeding from ulceration of the upper gastro-intestinal tract.

Case 3

A 65-year-old housewife was admitted to hospital because of swelling of the ankles, shortness of breath on exertion, and scanty micturition for about a year. Her past history was interesting. Four years previously she had had a haemoptysis, the cause of which could not be established by investigations which included bronchoscopy. During the next 18 months she had three episodes of haematemesis, the cause being obscure until a firm liver-edge was felt and the radiologist raised the possibility of oesophageal varices. Liver-function tests were normal and she remained in reasonable health for the next year.

She was obese and mildly icteric, with a few spider naevi on the face. There was no clinical evidence of liver failure. The skin was dry and hot, the pulse full, and blood-pressure 160/100. The jugular venous pressure was at the angle of the jaw, and there was gross oedema up to the thighs, with blistering of the overlying skin. A moderately loud apical systolic murmur was present. The abdomen was distended with fluid and no organs could be palpated.

Liver-function tests showed a serum bilirubin of 5.3 mg., thymol turbidity 14 units, alkaline phosphatase 23.3 K.-A. units, albumin 3 g., globulin 4.1 g./100 ml., with an increase in gamma-globulin on electrophoresis. The chest film x-ray showed moderate cardiac enlargement. The E.C.G. showed left axis deviation with some right ventricular strain; a barium swallow revealed oesophageal varices. The blood count was normal, but the blood urea was moderately raised and the prothrombin time reduced.

She was treated with a low-salt diet, mersalyl, parentrovite, and later with oral diuretics. There was no improvement, however, and it was decided to insert Southey tubes into her legs. This produced an initial dramatic improvement, and about 7 litres of fluid was drained over several days. This was soon followed by the signs of hepatic failure, which progressed rapidly to coma and death 18 days after admission.

Necropsy revealed a very small nodular liver. The heart was only slightly enlarged and was free from serious disease. There was evidence of generalized venous congestion, and of diffuse bleeding into the stomach and oesophagus.

Discussion

It may be argued that these three patients were suffering from fluid retention as a direct result of portal cirrhosis. Indeed, Paul Wood (1950) stated that if hepatic disease is unrecognized "the situation may lead to embarrassing diagnostic error, the raised venous pressure, oedema and enlargement of the liver being readily attributed to heart failure." However, the presentation with dyspnoea and peripheral oedema suggests that the final illness was in fact due to cardiac failure. This is strengthened by the clinical picture of a high output state and by the finding of generalized venous congestion at necropsy. There is

ample published evidence that severe liver disease can lead to haemodynamic changes, and the occasional occurrence of cardiac failure is to be expected.

Sources of error are likely to arise from attributing the cardiac failure to cor pulmonale, especially in men, to valvular disease, or to congenital heart disease in children. Constrictive pericarditis may also be considered in view of the gross oedema, but the quiet cardiac impulse and the low output state should serve to distinguish it. Jaundice may be slight or absent, and if present is attributed to venous congestion. Other evidence of liver disease is masked by the anasarca. A careful search may reveal signs of liver failure such as fetor hepaticus and a coarse tremor, though the latter is by no means specific and may occur in other forms of cardiac failure (Conn, 1958). It is debatable whether liver failure ever results from "cardiac cirrhosis" (Sherlock, 1951), though if it does it is likely to be the end-result of chronic rheumatic heart disease and therefore not a source of confusion.

Treatment in the above cases was unsatisfactory. The standard regime of bed rest, salt restriction, and diuretics had little influence on the oedema. It is possible that attempts to improve the body proteins (provided there is no clinical evidence of liver failure) might prove successful, or that other methods of promoting diuresis, such as the use of steroids or spironolactones and osmotic diuretics (Shaldon *et al.*, 1960), would be justified. This presupposes a correct diagnosis of the cause of the cardiac failure. One fact that emerges is the disastrous effect of removal of oedema fluid by mechanical means. It is well known that abdominal paracentesis is poorly tolerated by patients with portal cirrhosis and is best avoided; the same obviously applies to the use of Southey tubes. The reason almost certainly is that these procedures cause marked alterations in electrolyte and water distribution. There is, however, need for a detailed study of their effect in cirrhotics, similar to that of Vere and King (1960) in patients with the nephrotic syndrome.

Summary

Three cases of cardiac failure believed to be secondary to portal cirrhosis are described.

Treatment was unsuccessful and the removal of oedema fluid appeared to hasten death.

Prompt recognition of the cause of the cardiac failure might lead to more effective therapeutic measures.

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Preliminary Communications

Biological Method for Detection of Parathyroid Hormone

Previous methods for the biological detection of parathyroid hormone depend on changes in serum calcium values in the intact animal (Collip and Clark, 1925; Bliss and Rose, 1940; Biering, 1950), in the parathyroidectomized animal after injection of parathyroid extract (Davies, Gordon, and Mussett, 1954; Munson, 1955), or on the determination of urinary phosphate in normal or parathyroidectomized rats after administration of parathyroid hormone (Tepperman, L'Heureux, and Wilhelmi, 1947; Davies and Gordon, 1953; Kenny, Vine, and Munson, 1954; Davies, Gordon, Mussett, 1955); the smallest amount of hormone detectable by these methods is 2.5 U.S.P. units (Davies *et al.*, 1955). A technique for the detection of smaller quantities of parathyroid hormone is presented in this paper. It is based on increase in serum alkaline phosphatase activity after "parathormone" injections into parathyroidectomized rats. No such increase occurs in non-parathyroidectomized rats.

METHODS

Two-weeks-old female rats of the hooded Norwegian variety, maintained before and after operation on a standard cube diet (No. 41, Bruce and Parkes, 1949) and weighing approximately 20 g., were used in all the experiments.

Parathyroidectomy.—The rats were anaesthetized with ether and a midline incision was made in the neck extending slightly beyond the cephalic border of the submaxillary glands, which were freed in the midline by blunt dissection and retracted laterally. The sternohyoid muscle fibres were split in the midline and retracted laterally by a special retractor. The lateral lobes of the thyroid gland were exposed and gently displaced upwards and medially; care was taken to avoid damage to the recurrent laryngeal nerves. The parathyroid glands were removed with small adjacent portions of thyroid. All excised tissue was examined histologically to confirm that parathyroidectomy had been effectively carried out. When incomplete parathyroidectomy was confirmed (this occurred in 8% of animals), the animals concerned were excluded from further study. Fifty rats died immediately after, or within a few hours of, parathyroidectomy, in most cases from haemorrhage or anaesthesia, but the operative mortality decreased with experience. Tetany was not observed in any animals.

Blood Samples.—Blood was withdrawn under light ether anaesthesia from the internal jugular vein (Mouzas and Weiss, 1960) and transferred to siliconed tubes. The serum was separated within one hour of withdrawal: approximately 1 ml. of unhaemolysed serum was obtained for determination of alkaline phosphatase by the Folin-Ciocalteu reagent method of King and Armstrong (1934) and phosphorus by the method of King and Wootton (1956).

Parathyroid Hormone.—Parathormone was used in all experiments: dilutions were made in physiological saline, and final injection volumes in all cases were 2 ml.