from the liver. Kho (1957) found aplasia of the bone-marrow, affecting especially the erythropoietic system, associated with a normochromic normocytic anaemia at one time or the other in cases of kwashiorkor. He attributed it to chronic protein deficiency superimposed by chronic infections. Walt *et al.* (1962) described the development of erythroid hypoplasia during recovery (Foy *et al.*, 1961, see above) despite routine treatment with riboflavine.

Summary and Conclusion

The present study of 22 children suffering from prolonged calorie and protein malnutrition revealed a normocytic orthochromic anaemia with normoblastic erythropoiesis, most of them showing marked reduction in cellularity, affecting especially the red-cell precursors. The anaemia was associated with a fatty liver and low serum proteins. On a regime of dietary treatment with no haematinics there was marked improvement in the clinical condition, reduction or disappearance of fat from the liver, a rise in serum proteins, and a significant rise of 2.03 g./100 ml. in the mean value of haemoglobin. The most likely cause of anaemia in kwashiorkor is perhaps chronic protein malnutrition.

We are grateful to Major K. N. Rao for a grant from the State Medical Research Committee; to Principal Ansari and Superintendent Mr. G. Subba Rao for the facilities given; and to Drs. K. Subba Rao and Chudamani for help in the radiological studies.

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DEVELOPMENT OF DIABETES MELLITUS AFTER PORTACAVAL ANASTOMOSIS

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Disturbances of carbohydrate tolerance may accompany portal cirrhosis. These are thought to be due to inability of the liver to maintain a normal output of glucose, though alterations in peripheral uptake may also contribute (Paton, unpublished observations). Hypoglycaemia is extremely rare (Zimmerman *et al.*, 1953), and hyperglycaemia with a mildly diabetic glucose tolerance is the more usual finding. The significance of the association of diabetes mellitus with portal cirrhosis is, however, disputed. Two large series (Reinberg and Lipson, 1950; MacDonald and Mallory, 1958) showed an incidence of approximately 5%, which was not significantly different from that in controls. Bloodworth (1961), on the basis of a survey of 27,050 consecutive necropsies, has questioned the validity of this conclusion. His evidence shows quite clearly that the association has become more frequent in recent years, and is now double the incidence in the general population. He suggests that this is due to the increased life expectancy both of patients with portal cirrhosis and of those with diabetes mellitus.

We have encountered two patients with portal cirrhosis who developed diabetes mellitus after successful portacaval anastomosis. So far as we are aware only Hunt (1958) has previously commented on such an association.

Case 1

A 32-year-old housewife was admitted to hospital in 1954 and 1956 with haematemesis. There was no history of jaundice, dyspepsia, or alcoholism. She was slightly pigmented and the spleen was easily palpable. Leucopenia and mild thrombocytopenia were present, though liver-function tests were normal. A barium swallow, however, showed extensive oesophageal varices. Fasting blood sugar was 98 mg./100 ml. She was referred to Professor Milnes Walker, who carried out an end-to-side portacaval anastomosis in February, 1957. Liver biopsy

showed an increase in fibrous tissue and the portal pressure at operation was 27 mm. Hg. She had two episodes of hepatic failure during the month following operation, but subsequently made a satisfactory recovery.

She remained reasonably well until September, 1958, when intense thirst and polyuria suddenly developed, accompanied by menstrual irregularities. She was readmitted in diabetic precoma with a blood sugar of 506 mg./100 ml. and moderate amounts of acetone in the urine. The diabetes proved extremely difficult to control, and frequent episodes of hypoglycaemia alternating with attacks of portal-systemic encephalopathy occurred. She was finally stabilized on soluble insulin 40:30 units and has remained reasonably well since, apart from a tendency to anaemia.

Investigations at the time of her admission with diabetes were as follows: Hb 14.6 g./100 ml.; W.B.C. 4,300/c.mm.; serum bilirubin, 2.8 mg./100 ml.; alkaline phosphatase, 16.3 King-Armstrong (K.A.) units; thymol turbidity, 3 units; serum albumin, 3.9 g./100 ml.; serum globulin 1.1 g./100 ml.; blood urea, 31 mg./100 ml.; serum iron, 69 µg./100 ml.; total iron-binding capacity (T.I.B.C.), 380 µg./100 ml. Marrow and skin biopsies showed no excess iron. A test of insulin sensitivity resulted in a maximum fall of 100 mg. in the blood sugar from a fasting level of 325 mg./100 ml.

Case 2

A 48-year-old single toolmaker, a heavy drinker, was admitted to hospital on three occasions between January and August, 1961, with severe haematemesis. He was found to have several spider naevi and moderate hepatosplenomegaly. Liver-function tests were normal apart from some increase in gamma-globulin, but a liver biopsy revealed portal cirrhosis and a barium swallow oesophageal varices. After splenic venography an end-to-side portacaval anastomosis was performed by Mr. P. G. Bevan. Portal pressure at operation was 42 mm. Hg.

The post-operative course was entirely uneventful and the patient was discharged with advice to abstain from alcohol and

to take a low-protein high-carbohydrate diet. Five months later he suddenly developed thirst, tiredness, visual disturbances, and balanitis. He was admitted in diabetic precoma with large amounts of ketones in the urine and a blood sugar of 314 mg./100 ml. There was nothing on clinical examination to suggest haemochromatosis, and staining of the original liver biopsy showed no excess of iron.

The results of serial glucose-tolerance tests are shown in the Chart. Liver-function tests were as follows: serum bilirubin, 1 mg./100 ml.; alkaline phosphatase, 10 K.A. units; thymol turbidity, 11 units; serum albumin, 3.7 g./100 ml.; globulin, 3.0 g./100 ml., with an increase in gamma-globulin. The Hb was 14.2 g.; serum iron, 64 µg./100 ml.; T.I.B.C., 282 µg./100 ml. Barium swallow showed only a trace of the former varices.

Case 2. Results of successive oral glucose-tolerance tests.

The diabetes proved easy to stabilize with insulin, and with adjustment in the diet it has subsequently been possible to keep the urine sugar-free without insulin.

Comment

The development of acute diabetes mellitus in these two patients was unexpected. Both had had numerous routine urine tests for glycosuria with negative results, and one had had a normal fasting blood-sugar level before operation. Both denied knowledge of any relative with the disease.

The question of haemochromatosis was considered (Tuttle *et al.*, 1959; Schaefer *et al.*, 1962), but the evidence is strongly against such a diagnosis. Neither showed the classical pigmentation, and the woman was still menstruating; the iron-binding capacity of the serum was not saturated. A search for excessive iron deposits in Case 1 proved negative. The acuteness of the diabetic syndrome is quite unlike that normally occurring in haemochromatosis.

The literature on portacaval anastomosis does not mention diabetes mellitus as a recognized complication, and Professor Milnes Walker (personal communication) in a series of nearly 200 patients has seen only one other who developed mild diabetes seven years after operation. Hunt (1958), however, refers briefly to three instances and stresses the practical difficulties of management.

These were exemplified by the first patient. During control of the diabetes she had frequent attacks of hypoglycaemia alternating with episodes of portal-systemic encephalopathy. The encephalopathy was finally controlled by restriction of protein intake to 20 g. daily and by daily enemata and aperients, while the hypoglycaemic attacks were prevented by generous administration of carbohydrate together with cautious doses of insulin. It may be that the tendency to hypoglycaemia was aggravated by the

necessary restriction of protein, and it would be interesting to know whether a causal association between hypoglycaemia and portal-systemic encephalopathy has been observed.

Assuming that the association is more than coincidental, a number of possible explanations may be considered. The first is that the diabetes is merely a manifestation of the increased incidence in cirrhosis. This seems unlikely in view of the fact that hyperglycaemia in cirrhosis is commonly mild and insulin-insensitive. Secondly, the process which caused the cirrhosis may also have led to pancreatic fibrosis—a common accompaniment of certain types of chronic liver disease—or that during the operation the blood supply of the pancreas was disturbed. In this connexion Hunt found thrombosis of the portal vein in two of his patients, but this was certainly not present at operation in our own patients, and there is no reason to suspect that thrombosis has occurred subsequently.

A third explanation, which could be subjected to experimental testing, is that diversion of portal-venous blood into the systemic circulation causes episodes of hyperglycaemia, which result in pancreatic exhaustion through overstimulation of insulin production. The passage of glucose from the intestines into the systemic veins, by-passing the liver, would cause postprandial hyperglycaemia, and this would be encouraged by the common instruction to such patients to take a high-carbohydrate low-protein diet after portacaval anastomosis. If this is the case the oral glucose-tolerance test after portacaval anastomosis should be of the lag type, provided the patient has been taking a high-carbohydrate diet.

Lastly, there is the possibility that shunting of blood from the liver may affect insulin action. Samaan *et al.* (1962) have shown that the level of "typical" insulin-like activity in the serum, which corresponds to pancreatic insulin, is higher in patients with liver disease than in healthy subjects, while the level of "atypical" insulin-like activity, which they believe to be insulin modified by passage through the liver, is considerably reduced. These abnormalities were accentuated by portacaval anastomosis in two patients, and in one who was mildly diabetic before operation glucose tolerance was further impaired by the anastomosis.

Summary

Two cases are described in which a successful portacaval anastomosis for portal cirrhosis was followed after an interval by the acute onset of diabetes mellitus.

While such a sequence may be coincidental there are a number of possible mechanisms which might account for such an association.

Further studies are needed to determine whether patients with cirrhosis who have undergone portacaval anastomosis develop disturbances of carbohydrate tolerance.

We wish to thank Professor R. Milnes Walker and Mr. P. Gilroy Bevan for their help, and Mr. W. B. Yeoman and his staff for biochemical assistance.

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