liver was enlarged to 5 cm below the costal margin and was hard and nodular. The eyes were dry and there was loss of transparency of the conjunctivae, with Bitot's spots. The retinae had a yellowish cast, but the fundi were otherwise normal. The serum bilirubin was 19.4 mg/100 ml, and the serum carotene was 10 µg/100 ml. After eight daily injections of vitamin A dark-adaptation was much improved, and within two weeks he was able clearly to distinguish objects in the dusk, and his ability to read print was completely normal.

Comment

Some 3,500 years elapsed between early reports of the successful treatment of night blindness (*Ebers Papyrus*, 1937) and the recognition that this was due to replacement in the diet of the fat-soluble A factor (Bloch, 1924). Dietary deficiency of vitamin A is now virtually unknown in the western world, for requirements are low and body stores high; thus up to two years may be required before volunteers fed on a diet free of vitamin A develop the earliest manifestations of deficiency (Keele and Neil, 1961). Since vitamin A and carotene are both fat soluble, however, deficiency may occur in patients with malabsorption. Ritter (1963) studied a group of patients with various gastrointestinal disorders and found that slight impairment of dark-adaptation may occur after partial gastrectomy in prolonged and severe chronic gastroenteritis, chronic pancreatitis, and in portal cirrhosis. The changes associated with chronic hepatocellular damage he attributed to deficient storage rather than poor absorption. Ritter pointed out the importance of even minor defects in dark-adaptation in relation to professional ability and, in particular, night-driving.

Actual night blindness is extremely rare but has been reported in cystic fibrosis (Petersen, Petersen, and Robb, 1968). The impairment of fat absorption resulting from loss of the emulsifying action of bile can rarely persist for long enough to produce overt evidence of hypovitaminosis A. In the present case obstructive jaundice had been present for 13 months before the first symptoms of night blindness appeared, and even so it is possible that the neoplastic invasion of the liver contributed to produce this relatively early onset of symptoms. The rapid, complete, and lasting response to parenteral vitamin A has provided at least some small solace in the otherwise dismal progress of this patient's prolonged obstructive jaundice.

We are grateful to Mr. J. K. M. Rawlinson, who operated on this patient; to Messrs. Crookes Laboratories, who specially prepared the parenteral vitamin A; and to Dr. P. Robb, of Walton Hospital, and Mr. E. Davies, of Broadgreen Hospital laboratories, for the biochemical investigations.

Requests for reprints should be sent to: Dr. J. M. Wright, 46 Grey Road, Walton. Liverpool L9 1AZ.

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Malignant Argentaffinoma with Carcinoid Syndrome and Hypoglycaemia

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The carcinoid tumours which occasionally produce ectopic hormones—for instance, ACTH—usually derive from tissues having their origin in the embryonic foregut. We describe here a case of a malignant argentaffinoma arising in the ileum, producing a mild but typical carcinoid syndrome, and associated with severe hypoglycaemia due to increased plasma concentrations of immunoreactive insulin (I.R.I.).

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Case Report

IN 1957, at the age of 46, the patient had "a growth the size of a walnut" removed from her small intestine. No further details are available. In 1967 she had occasional facial flushing and hirsutism of the face, arms, and legs. Later mild diarrhoea began. On 28 July 1968 the first attack of hypoglycaemic coma occurred, and these attacks became frequent. At laparotomy no pancreatic tumour was found, but multiple hepatic metastatic nodules were present, and a biopsy specimen from one of these showed a carcinoid tumour. Her symptoms remained. When examined at St. Mary's Hospital a large left supraclavicular lymph node was palpable, and the liver was enlarged 2 in (5 cm) below the right costal margin.

Intravenous administration of adrenaline 2 µg and noradrenaline 10 µg caused flushing, during which the concentration of bradykinin in the arterial blood (Allwood and Lewis, 1964) did not rise. Urinary 5-hydroxyindole acetic acid (5 HIAA) excretion was 270 mg/24 hours. Paper chromatography of the urine showed an increase in 5-HIAA only. No 5-hydroxytryptamine (5-HT) or 5-hydroxytryptophan (5-HTP) spots were present. The effect of a prolonged fast on the plasma glucose and plasma I.R.I. (Samols and Bilkos, 1964) is shown in the Chart. After 28 hours of fasting a hypoglycaemic attack occurred (plasma glucose 16 mg/100 ml), which was effectively reversed by intravenous glucose.

Thirty minutes after oral leucine (150 mg/kg body weight) plasma I.R.I. rose from 45 µU/ml to a peak level of 85 µU/ml. Intravenous tolbutamide, glucagon, and glucose did not cause an increase in plasma I.R.I., nor did oral glucose. Low plasma glucose levels (25 mg/100 ml) were often associated with inappropriately high plasma I.R.I. concentrations. Other investigations aimed at discovering any ectopic hormone production were negative, and no gross evidence was found for excessive production of growth hormone, ACTH, TSH, ADH, or parathyroid hormone. There was no overall increase in the urinary excretion of adrenal androgens. The hirsutism was not investigated further.

The hypoglycaemic attacks became more difficult to control and diazoxide 500 mg, frusemide 40 mg, and bendrofluazide 40 mg daily with prednisone 5 mg thrice daily had little effect on their frequency. During one attack cardiac arrest occurred.

Necropsy—Near the ileocaecal valve there was a mass consisting of coiled and adherent loops of small intestine. Microscopy showed infiltration by nests and cords of carcinoid cells typically uniform with scanty to moderate cytoplasm. The nuclei were small and uniform with fine nucleoli. Some mitotic figures were present. The liver contained multiple yellowish tumour nodules with haemorrhagic areas. Both ovaries were completely replaced by tumour.

Plasma glucose and immunoreactive insulin concentrations during a prolonged fast.

Tumour seedlings were present on the peritoneum. The pancreas was macroscopically and microscopically normal. The Gomori-aldehyde-fuchsin stain did not show β -cell granules. Enlarged tracheobronchial lymph nodes contained carcinoid tumour, and microscopically tumour was present beneath the pleura of both lungs and in the left supraclavicular lymph node. There was no evidence of carcinoid heart disease. The argentaffin reaction on postmortem material showed scanty positive granules. The diazonium reaction on the liver biopsy specimen at operation was strongly positive. The tumour contained 138 μ g 5-HT/g tissue, and paper chromatography of an extract showed only 5-HT. No

5-HTP or 5-HIAA was detected in the tumour. Assay of I.R.I. showed normal liver tissue to contain 4.5 μ U/g and tumour tissue 14.5 μ U/g.

Comment

It is most probable that the primary tumour in this case was an ileal argentaffinoma, incompletely removed in 1957. The presence of an excess of 5-HIAA in the urine, the absence of major amounts of 5-HTP and 5-HT from the urine, the absence of 5-HTP in the tumour, and the presence of large amounts of 5-HT in the tumour are also typical of an ileal carcinoid tumour. Though at necropsy, perhaps because of autolysis, the argentaffin stain showed only scanty positive granules the diazonium stain on the biopsy specimen at operating showed many positively staining cells.

The hypoglycaemia was due to increased levels of circulation I.R.I., the source of which cannot be stated with absolute certainty. The studies done showed that the secretion of insulin, from whatever source, was not responsive to normal controlling mechanisms. The problem, which cannot be definitely resolved on our data, is whether this argentaffinoma was producing the insulin or a substance which was stimulating the pancreas to produce insulin. We are inclined to the view that the tumour was producing insulin and it would therefore seem that ileal argentaffin cells can be added to the list of tissues which when they become cancerous may undergo non-random functional dedifferentiation and produce unexpected hormones (Williams, 1969).

Requests for reprints should be addressed to Dr D. G. Grahame-Smith.

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