A primigravida aged 18 had a termination of pregnancy by suction curettage at 11 weeks. The preoperation blood sample was found to contain specific anti-D detected by Löw's papain technique only, and not by the use of papainized cells. A history of concealed pregnancy or of previous blood transfusions has been carefully excluded, and the laboratory findings have been repeatedly checked on the original specimen and in specimens obtained since operation. The antibody appears to be a *non-immune* type of anti-D evident only after the serum had been "activated" with papain.

Discussion

There is no dispute over the two patients in whom antibodies were found by the indirect Coombs test and these represent an incidence of isoimmunization after abortion of 2%, similar to that suggested by Freda *et al.* (1970). The significance of anti-D detected only by enzyme techniques is, however, still a matter of dispute. Some evidence showing that active 'enzyme' Rh antibodies are of ominous significance for future pregnancies has been presented (Murray, 1971) and we consider that the antibodies to papainized cells reported here after abortion should be taken seriously. Such antibodies probably precede overt immunization, but only experience in following these patients through a subsequent pregnancy will prove whether such antibodies, like those following term pregnancy, will cause haemolytic disease of the newborn.

Including the "enzyme" Rh antibodies, we report in this series an incidence of primary Rh immunization of 9·4%, and because of this evidence we now recommend that Rh-negative women not already immunized should be eligible for prophylaxis with anti-D immunoglobulin. The current dose administered for the prevention of Rh isoimmunization (200 μg) is greater than necessary for the size of transplacental haemorrhage likely to occur after abortion.

Transplacental haemorrhage, as detected by the Kleihauer test, was found in only 29% of patients in this series and, as can be seen in Table III, seemed to be of no value in predicting the development of anti-D. At best, this assessment of transplacental haemorrhage is an inexact measurement and we think that there is no justification for using the time-consuming Kleihauer test as a screening procedure in all cases of abortion eligible for prophylaxis. Only nine cases had a transplacental haemorrhage of 0·1 ml or more of fetal blood. The largest transplacental haemorrhage we recorded in either this or our previous series (Murray *et al.*, 1970) was one of 2·9 ml of fetal blood in a patient terminated at 16 weeks by intra-amniotic saline. The dose of immunoglobulin required to protect against 1 ml of fetal blood has been estimated to be under 75 μg (Mollison *et al.*, 1969) and less than this might be an appropriate dose for cases of abortion.

We have already referred to the practical difficulties of testing and following up women subjected to therapeutic abortion, and some safeguard will be necessary to ensure that anti-D immunoglobulin is given only to women who are Rh-negative without antibodies. Results of such a prevention programme may prove extremely difficult to assess.

Dr. J. C. M. Smith, our research assistant, undertook the hard work of following up these patients, and we are grateful to the medical and nursing staff of the Newcastle hospitals who so willingly co-operated with us in this study. We gratefully acknowledge the technical help of the staff of the Regional Transfusion Centre and the clerical assistance of Mrs. M. Jackson. This work was carried out with the aid of a research grant given jointly by the United Newcastle Hospitals and the Newcastle Regional Hospital Board.

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MEDICAL MEMORANDA

Vitamin A for Night-blindness in Prolonged Jaundice

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British Medical Journal, 1971, **3**, 92–93

Though still a leading cause of blindness in many parts of the world, dietary deficiency of vitamin A is rarely encountered in Britain. Sherlock (1968) mentioned failure of dark-adaptation as a possible consequence of the malabsorption resulting from prolonged cholestasis, but we have been unable to find any reports of night blindness as a result of prolonged biliary obstruction. We therefore feel prompted to report this complication since this at least of the many distressing symptoms of prolonged obstructive jaundice is very readily treated.

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Case Report

The patient, a man aged 67, presented with jaundice in May 1969. After initial fluctuation the pattern became clearly obstructive, with heavy biliuria and bulky acholic stools. Laparotomy on 24 June showed an adenocarcinoma involving the cystic and common bile ducts and extending up into the portal fissure in such a way that neither resection nor bypass procedure could be carried out. Deterioration was slow, with anorexia, pruritus, and gradually deepening jaundice over the year following laparotomy.

In July 1970 he first complained of visual symptoms. In the half-light of the evening he found increasing difficulty in distinguishing objects in his room. If he rose from his bed at night he found he was completely blind, whereas light from the street would previously have been sufficient to allow him to move about the room. When the lighting was good his vision was satisfactory, with the exception that he was unable to read newsprint. He was deeply jaundiced at this stage and emaciated, with a dry scaly skin. The

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.

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Malignant Argentaffinoma with Carcinoid Syndrome and Hypoglycaemia

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British Medical Journal, 1971, **3**, 93–94

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.