patients with α_1 -antitrypsin deficiency reported to date (Ishak *et al.*, 1972; Berg and Eriksson, 1972; Cohen *et al.*, 1973; Campra *et al.*, 1973; Palmer *et al.*, 1973) and the fact that in most of them liver disease was unsuspected or discovered fortuitously, unlike our patient, imply that it is a rare cause of symptomatic cirrhosis in adults. Nevertheless, α_1 -antitrypsin deficiency should be considered in adult cirrhotic patients with unusual pathological features and when there is no other obvious aetiology. Suspicion should also be raised when there is a history of hepatic disease in infancy or childhood, as seen in our patient and the case reported by Ishak (1972), even though it is apparently very rare for such children to survive into adult life. Homozygous or heterozygous deficiency of α_1 -antitrypsin will be common among close relatives of such patients, as shown by our family study. Recognition of these subjects in affected families is probably important, since avoidance of contributory causes of obstructive airways disease, such as smoking, may prevent or halt the progress of the condition. This may also apply to alcohol with respect to the liver, but at present the prognosis of hepatic disease in adults is unknown and it is only

by identification and follow up of these patients that further knowledge will be obtained.

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Cure of Insulin-dependent Diabetes Mellitus by Removal of a Glucagonoma

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Exogenous glucagon can cause diabetes mellitus in some animals (Salter *et al.*, 1969; Frey *et al.*, 1972) but this has never been satisfactorily shown in man. Pancreatic glucagonomas have previously been reported in association with diabetes mellitus (McGavren *et al.*, 1966; Yoshinaga *et al.*, 1966) but these cases had extensive pancreatic involvement and resection of the tumour proved impossible. Thus it is still unknown whether diabetes in man can be caused by raised plasma glucagon levels.

We report on a patient who presented with insulin-dependent diabetes mellitus and a dermatosis which appeared to be specifically associated with islet-cell tumours. The resection of a glucagonoma together with three-quarters of her pancreas resulted in the disappearance of the rash and the return to near-normal of her glucose tolerance.

Case Report

A 50-year-old housewife presented in 1969 with perineal irritation. There was no family history of diabetes mellitus and glycosuria was not found. A candida infection was successfully treated but returned in 1970 together with perineal intertrigo. Glycosuria was detected and a 50-g oral glucose tolerance test was performed. The results were found to be normal and it was noticed that she had a low renal threshold for glucose.

Her rash became rapidly worse and spread to her fingers and shins, where the red, scaly eruption proved refractory to treatment. The dermatosis followed a relapsing course and in January 1973 the patient began to lose weight. She then presented with extensive intertrigo of the groin, perineum, and buttocks, together with exfoliating lesions of the palms and fingers and papules over the elbows and shins. She also complained that her tongue felt sore, and on examination it was seen to be smooth and shiny and vermilion.

The patient again had glycosuria, and a random blood sugar was 230 mg/100 ml. The haemoglobin was 11.4 g/100 ml with normal indices, E.S.R. 18 mm in the first hour, and the alkaline phosphatase, bilirubin, SGOT, vitamin B₁₂, and folic acid were all normal. Chlorpropamide did not control her diabetes mellitus and she was put on soluble insulin 40 units/day in divided doses. This dose had to be rapidly increased during the next two months (table I), during which time she had frequent fasting blood sugars above 200 mg/100 ml. At no time was any ketonuria detected.

TABLE I—Antidiabetic Therapy

Date	Drug	Route	Diet
12/1/73	Chlorpropamide 250 mg every morning	Oral	140 g carbohydrate orally
16/1/73	Chlorpropamide 500 mg every morning	Oral	"
20/1/73	Sol. insulin 40 U/day	Subcutaneous	"
18/2/73	Sol. insulin 48 U/day	Subcutaneous	"
3/3/73	Sol. insulin 68 U/day	Subcutaneous	"
6/3/73	Operation		
6/3/73	Sol. insulin 36 U/day	Intravenous infusion	125 g carbohydrate as i.v. dextrose
7/3/73	Sol. insulin 24 U/day	Intravenous infusion	"
11/3/73	Sol. insulin 16 U/day	Intravenous infusion	"
12/3/73	Sol. insulin 18 U/day	Subcutaneous	130 g carbohydrate orally
16/3/73	Glibenclamide 15 mg/day	Oral	"
22/3/73	Glibenclamide 10 mg/day	Oral	"
28/3/73	Glibenclamide 5 mg/day	Oral	"
30/3/73	None		

A tentative diagnosis of a pancreatic tumour was made, based on the similarity of this case to three previously-described cases of pancreatic tumour, which were associated with a red raw tongue, an intractable rash, and diabetes mellitus of recent onset (Becker *et al.*, 1972; Church and Crane, 1967; Wilkinson, 1971). Investigation of her exocrine pancreatic function was performed by an intravenous

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infusion of secretin plus pancreozymin. This showed a greatly reduced bicarbonate output and an even more strikingly diminished total volume of 102 ml in 1 hr.

Laparotomy was performed on 6 March 1973. A spherical tumour 4 cm in diameter was found overlying the mesenteric vessels and medial to the arrival of the inferior mesenteric vein. This was removed together with the tail, neck, and about one-third of the head of the pancreas. No obvious secondary deposits could be seen anywhere in her peritoneal cavity.

Postoperatively the patient did very well and there was an immediate noticeable decrease in her insulin requirements (table I). Her skin lesions had rapidly improved even after two days, and at one week her tongue, hands, and groin were almost normal.

On 4 April, 29 days postoperatively and seven days after her last dose of glibenclamide, a 100-g glucose tolerance test still showed diabetes, but at 11 weeks had returned to near normal levels (table II).

TABLE II—Results of 100-g Oral Glucose Tolerance Tests expressed as mg/100 ml Blood Glucose

Time after Oral Loads (min):	0	30	60	90	120	180
Four weeks after operation	85	150	200	240	210	140
Eleven weeks after operation	75	125	135	140	135	75

Histology.—The tumour was made up by sheets and trabeculae of pleomorphic cells, with large open nuclei and single large nucleoli. The appearance was that of a malignant islet-cell tumour.

Glucagon Assay.—Pancreatic glucagon was measured by specific radioimmunoassay (Bloom, 1971). The level in fasting plasma kept deep frozen from before operation was 3,500 pg/ml, whereas the postoperative fasting level was 130 pg/ml (normal range 40 to 120 pg/ml). The tumour was extracted by a method of Kenny (1955) and found to contain 22.5 µg/g wet weight. On gel filtration this glucagon was found to elute in the same position as pure porcine pancreatic glucagon (Novo).

Comment

Pancreatic tumours associated with diabetes mellitus of recent onset, an intractable rash, and a red raw tongue have previously been found only at necropsy (Becker *et al.*, 1942; Church and Crane, 1967) or at an inoperable stage in the development of the carcinoma (Wilkinson, 1971; C. Mallinson, personal communication, 1973). In our patient this triad of symptoms disappeared very rapidly after resection of the tumour, suggesting that humoral agents related to the tumour could be responsible. The agents responsible for the cutaneous manifestations are not clear. The presence of an autoantibody as in pemphigus, and the catabolic effect of glucagon are two possible factors. The rapid resolution of the raw tongue and rash, with a preoperative normal serum folic acid and vitamin B₁₂, makes vitamin deficiency from any malabsorption an unlikely factor.

The diabetes mellitus can, however, be closely connected with the glucagon produced by the tumour. Though glucagon has been shown not to produce peripheral insulin resistance

(Cherrington *et al.*, 1972) it does cause a chronic increase in gluconeogenesis secondary to enzyme induction and activation (Park and Exton, 1972). This might be expected to stress the pancreatic beta-cells enough to produce overt diabetes mellitus.

McGavren *et al.*, (1966) and Yoshinaga *et al.*, (1966) reported proved glucagonomas associated with diabetes mellitus, but in both cases the tumour was extensive and inoperable. Thus it is impossible to tell whether the diabetes was caused solely by destruction of pancreatic beta-cells by tumour tissue or whether it was exacerbated by raised levels of circulating glucagon. In this patient it was possible to resect the tumour, however, and though over three-quarters of the pancreas was removed at the same time the diabetes mellitus rapidly regressed postoperatively. This was associated with a drop in plasma glucagon to normal levels, and suggests that the diabetes was caused by the high glucagon levels.

It is thus apparent that glucagon is capable of being a major factor in the production of diabetes mellitus. This raises questions about a possible role for glucagon in common diabetes. Unger *et al.* (1963) reported a relative hyperglucagonaemia in patients with diabetes mellitus, together with a loss of normal glucagon suppression after glucose loading, and an increased response of glucagon output after arginine stimulation. Whether this is due to a primary lesion of the alpha-cells or is secondary to insulin lack is not known. They also found high levels of glucagon in some ketoacidotic patients and commented that this could have contributed to the insulin resistance that these patients displayed.

In conclusion it has been shown for the first time that glucagon can cause diabetes mellitus in man. With modern immunological techniques for its measurement, and an increasing awareness of its powerful gluconeogenic action, more work can be expected on its role in states of disturbed carbohydrate metabolism.

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