Hormone-secreting tumours of the pancreas

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THE discovery of the islet cells of the pancreas and of their physiology and pathology is a fascinating story (Table 1). In 1924 (2 years after the discovery of insulin) Harris postulated that excessive secretion of insulin might sometimes cause spontaneous hypoglycaemia. In 1927 W. J. Mayo explored the

TABLE 1

Landmarks in the history of the islets of Langerhans

1869	First description of pancreatic islets by Langerhans
1902	First tumour of the islets described by Nicholls
1922	Discovery of insulin by Banting and Best
1923	Discovery of glucagon by Murlin and colleagues
1924	Harris postulates the possibility of insulinoma
1927	Wilder extracts insulin from a malignant pancreatic tumour explored by W. J. Mayo
1929	First successful operation for insulinoma by R. Graham
1938	Whipple's diagnostic triad
1950	Del Castillo reports first case of carcinoma of pancreas with Cushing's syndrome
1955	Zollinger and Ellison report two cases of pancreatic islet-cell tumour with primary jejunal ulceration
1957	Recognition of watery diarrhoea syndrome with pancreatic islet-cell tumour by Priest and Alexander
1960	Gregory extracts gastrin-like substance from Zollinger-Elison tumour
1960	Stammers removes islet-cell adenoma as primary definitive treatment of Zollinger-Elison syndrome
1966	McCavran reports case of glucagon-secreting tumour of islet cells

abdomen of a patient who had been studied by Wilder and found an islet-cell carcinoma with metastases in the liver. An extract of the tumour contained a hypoglycaemic factor indistinguishable from insulin. Two years later Graham removed a benign adenoma from a patient studied by Howland and cured the organic hyperinsulinism. Since then hundreds of such insulinomas have been recognized and treated. The first case of a glucagon-secreting tumour of the islet cells was reported in 1966.

In 1955 Zollinger and Ellison described a syndrome of fulminating peptic ulceration, gastric hypersecretion and an islet-cell tumour of the pancreas not composed of β -cells. By 1960 many other examples of the syndrome had been recognized and Gregory had extracted from one tumour a substance indistinguishable from the antral hormone gastrin.

This finding was surprising since, while insulin and glucagon are normal secretions of islet cells, gastrin is not. It is now apparent, though, that many tumours in various parts of the body are capable of secreting substances, usually polypeptides, with hormone-like activity and that some tumours secrete more than one. Most of these tumours are derived from cells which are related embryologically to that part of the alimentary tract concerned with the secretion of general, alimentary or tissue hormones. An oat-cell carcinoma of the bronchus, in particular, may secrete substances indistinguishable from corticotrophin, antidiuretic hormone, melanocyte-stimulating hormone, parathormone, insulin and give rise to the appropriate clinical syndromes. Some bronchial tumours secrete derivatives of the amino-acid tryptophan which cause a syndrome similar to that of argentaftinomatosis. Still other tumours, including neuroblastomas, medullary carcinoma of the thyroid and islet-cell tumours, may cause diarrhoea, whose cause is not yet known but which may prove to be an abnormal polypeptide.

Carcinoma of the pancreas has been associated on several occasions with Cushing's syndrome and assay of the tumour has yielded a potent corticotropic substance.

The hormone-secreting tumours of the endocrine and of the exocrine pancreas must, therefore, be considered as special examples of a general phenomenon of tumour pathology which has come to light in recent years.

Pathology

Islet-cell tumours can be found, if looked for carefully, in 1–2% of routine autopsies (Gibson & Welbourn, 1960). Most of these are silent and hypersecretion occurs in only a very small minority.

About two-thirds of all islet-cell tumours are found in the body or tail of the pancreas (Sieracki, Marshall & Horn, 1960) (see Fig. 1). This distribution corresponds with that of normal pancreatic islets. About one-tenth of the secreting tumours are found in ectopic sites, especially at the hilum of the spleen or close to the duodenum or pyloric

FIG. 1. Sites of islet cell tumours.

antrum. In about one-third of the patients the tumours are multiple. In one-third of those with hyperinsulinism and one-half of those with gastrointestinal disturbances the tumours are histologically malignant. The malignancy, however, is of low grade and long-term survival is not uncommon, even in patients with proved metastases (Kernan & Poletti, 1965). Few of the tumours are large and one in seven escapes attention even when the pancreas is mobilized and palpated carefully. In a few patients the hyperfunctioning lesions are not discrete tumours, but hyperplasia of the islets or generalized adenomatosis. In some cases islet-cell tumours form part of the disease of *multiple endocrine adenopathy*, with hyperplasia or tumour of the anterior pituitary, the parathyroids, the adrenal cortex and, on occasion, the thyroid (Wermer, 1963).

The tumours associated with Cushing's syndrome are often highly malignant. Their origin is uncertain, but most or all of those which are well documented seem to arise from the endocrine portion of the pancreas.

Microscopy and staining properties

Microscopically, the best differentiated islet-cell lesions (both hormone-secreting and non-secreting) are composed of small cells arranged in sheets, cords and ribbons with little connective tissue amongst them. Special stains designed to demonstrate β -granules in normal pancreatic islet-cells frequently yield positive results with well-differentiated insulin-producing tumours. Similarly, α -granules can be demonstrated in some well-differentiated ulcerogenic tumours (Gibson & Welbourn, 1960). Poorly differentiated tumours have no special staining properties and are commonly referred to as 'non- β ' islet-cell tumours of the pancreas.

Organic hyperinsulinism

Hyperinsulinism associated with a lesion of the islet-cells is well-known but rare. It is commonest in

middle age, but has been found in infants and the aged. The sexes are equally affected. Occasionally there is a family history of diabetes.

Clinical features

Clinical features are caused by attacks of hypoglycaemia, which occur particularly during periods of fasting. They are therefore commonest in the early morning and in the late afternoon. They are aggravated by exercise and relieved by consumption of sugar. Because they are taking little exercise and receiving regular meals, some patients may remain entirely symptom-free while in hospital.

Symptoms are mild and infrequent in the early stages and become severe and frequent later. The disease usually runs a course of several years but occasionally it is fulminating in onset and rapidly fatal. The symptoms and signs are very variable and may be considered under the following headings:

- (a) Those related to the nervous system:
 - (1) Mental disturbance.
 - (2) Sympathetic stimulation.
 - (3) Organic nervous disease.
- (b) Hunger and epigastric discomfort.

The mental features range from mild neurotic symptoms, such as tiredness, anxiety, restlessness, confusion and emotional instability, to those of frank psychosis. Sympathetic stimulation may be caused in part by reflex release of adrenaline in response to hypoglycaemia. The features are similar to those of phaeochromocytoma and include flushing, sweating, pallor, tremor, palpitation and transient hypertension. Signs of organic nervous disease include disturbance of speech and vision, vertigo, convulsions (especially in infants) hemiparesis, loss of consciousness and coma. In the final stages irreversible anoxic changes occur in the cerebral cortex, basal ganglia and cerebellum, and the patient passes into a state of decerebrate rigidity and dies.

The hunger and epigastric discomfort, which are common symptoms, may lead patients to eat excessively and to put on weight. They may discover for themselves that sugar brings relief and may develop a craving for it.

Diagnosis

The diagnosis of organic hyperinsulinism is often delayed for a long time because of the variety of the symptoms and the rarity of the condition. The following list shows the early, incorrect diagnoses, written by consultants into the case sheets of ten patients, eventually discovered to be suffering from organic hyperinsulinism.

Organic nervous disease:

- Subdural haematoma.
- Encephalitis.
- Cerebral arteriosclerosis.

Functional nervous disease:

- Epilepsy (five patients).
- Narcolepsy.
- Cataplexy.

Mental disorder:

- Hysteria.
- Emotional disturbance.
- Depressive psychosis (mental hospital).

Once the presence of hypoglycaemia has been established, all its possible causes must be considered. The more important are as follows:

- (1) Idiopathic (? functional hyperinsulinism):
 - (a) Functional.
 - (b) After gastric surgery.
 - (c) Infantile.
- (2) Hypersensitivity to insulin (absence of insulin antagonists):
 - (a) Adrenocortical failure.
 - (b) Anterior pituitary failure.
- (3) Excess of insulin:
 - (a) Exogenous-overdosage in diabetics or in others with access to insulin.
 - (b) Endogenous-organic hyperinsulinism.
- (4) Disturbance of glycogen storage in liver:
 - (a) von Gierke's disease.
 - (b) Cirrhosis, acute yellow atrophy, etc.
- (5) Unknown:
 - (a) Mesothelioma of abdomen or thorax.
 - (b) Hepatoma.
 - (c) Adrenocortical tumour.
 - (d) Pseudomyxoma peritonei.

Special investigations

Thirty years ago Whipple (1938) described a triad of features which is of the greatest help in establishing the diagnosis of organic hyperinsulinism. First, there are attacks of nervous or gastrointestinal disturbances coming on in the fasting state. Secondly, if the blood sugar is measured at this time it is found to be below 50 mg/100 ml. (The true blood *glucose*, which is now measured in most laboratories, is usually below 30 mg/100 ml.) Thirdly, all the features are relieved immediately by the ingestion or intravenous injection of glucose.

Unfortunately we are often unable to observe a patient during a hypoglycaemic attack and must therefore use special tests. These depend on the measurement of the blood glucose and the plasma insulin (Samols & Marks, 1963) during fasting or after provocation of hypoglycaemia by glucose, glucagon, L-leucine or tolbutamide (Fajans *et al.*, 1961). All these agents tend to stimulate the overproduction of insulin by the tumour. Two of the tests are of particular value; the prolonged fast and the tolbutamide test.

In the fasting test the patient is kept as active as possible and nothing is allowed by mouth except water, salt, and tea or coffee without milk or sugar.

He is observed closely and the blood glucose is measured every 3 hr. When hypoglycaemic symptoms appear a final blood sample is taken and 50 g of glucose are given by mouth or intravenously. At the Mayo Clinic, where this test has been used extensively in a very large series, 75% of the patients gave a positive response within 24 hr and 98% did so within 48 hr (ReMine, Scholtz & Priestley, 1960).

The tolbutamide test depends on the fact that this substance releases insulin from insulinomas as well as from normal islet cells. When 1 g of sodium tolbutamide is injected intravenously it causes an exaggerated fall in the blood glucose and rise in plasma insulin within 30 min. The test is less of an ordeal for the patient than the prolonged fast, but it has not yet been shown to be so reliable.

Electroencephalography reveals characteristic changes during an attack of hypoglycaemia, but it is useless for diagnosis at other times.

It should be noted that mesotheliomas may be indistinguishable from insulinomas by these tests if the blood glucose only is measured. Mesotheliomas are, however, usually palpable or demonstrable by X-rays (Welbourn, 1965) and do not cause a rise in the plasma insulin levels.

Management

When the diagnosis of hyperinsulinism has been made, or in the very rare instances when it cannot be excluded by laboratory tests, laparotomy and partial pancreatectomy are essential. Since pre-operative fasting may provoke hypoglycaemia an intravenous glucose drip should be set up before operation and continued in the theatre. It is important to remember that the tumours are often multiple and that they may be very difficult or impossible to locate at operation. In every case the whole of the pancreas must be mobilized, inspected and palpated from the front and from the back. Any suspicious nodule should be excised and examined at once by frozen section. Whether or not a tumour is found the body and tail of the pancreas, together with the spleen, should be removed, because this region contains two-thirds of all tumours and because, if there is hyperplasia of the islet cells, the mass of secreting tissue will be reduced. Ninety per cent of the pancreas can be removed without interfering seriously with its function. A tumour in the head, neck or uncinate process should be excised, not simply enucleated, because of the possibility of malignancy. A large tumour in the head may demand formal pancreatoduodenectomy, but this should be avoided if possible because of its dangers and because of the difficulty of long-term postoperative management.

The early results of surgery are excellent, provided all the tumours are found and removed. Three-

quarters of the patients are cured by one operation, but there are many cases on record of the necessity of repeated operations to find even one insulinoma. The only long-term results which have been published are those of six patients reported originally by Whipple & Frantz (1935). Twenty-five years after operation only one could be regarded as thoroughly well (Markowitz, Slanetz & Franz, 1961).

Hypoglycaemia presents a difficult problem in patients with inoperable islet-cell carcinoma. They should take protein and fat at all meals, to prolong the post-cibal rise in the blood glucose, and eat sugar when an attack is imminent. The drawback of this regimen is that it causes obesity. Cortisone, which raises the blood glucose by promoting gluconeogenesis, is helpful in some patients but is liable to cause complications; and glucagon, which is effective, demands intramuscular injections. The cytotoxic drug cyclophosphamide and the diabetogenic agent diazoxide are both undergoing trial.

Zollinger-Ellison syndrome

The Zollinger-Ellison syndrome consists of: (1) gastric hypersecretion; (2) peptic ulceration; and (3) a non- β islet-cell lesion of the pancreas.

Details from 260 cases have been collected and reviewed recently by Ellison & Wilson (1964). There is a slight preponderance of males (3:2); most patients are middle-aged (30-50) years) but the condition occurs in childhood (twelve of the 260 were below the age of 15).

Pathogenesis (see Fig. 2)

On more than a dozen occasions, a potent gastric secretagogue has been extracted from a pancreatic

lesion (Gregory *et al.*, 1960). These extracts, when given subcutaneously or intravenously to dogs with gastric pouches, induced a secretory response identical with that to the antral hormone gastrin (Gregory & Tracy, 1964). This gastrin-like substance, therefore, is assumed to be responsible for the gastric hypersecretion; and the hypersecretion, in turn, for most of the clinical manifestations of this disease.

Peptic ulcers

Until recently a fulminating ulcer diathesis, often with multiple ulcers at unusual sites, was regarded as an essential feature of this disease. However, in three-quarters of the 260 patients reviewed by Ellison & Wilson (1964), the primary ulcer was single and situated in the first part of the duodenum. Furthermore, in a large proportion of patients the onset of the disease was insidious: 80% had had peptic ulcer symptoms for 1 year, 20% for 5 years and 8% for 10 years or longer.

Disorders closely related to Zollinger-Ellison syndrome

Three conditions—pancreatic tumours with watery diarrhoea, multiple endocrine adenopathy and islet-cell tumours with multiple hormone production—are closely allied to the Zollinger-Ellison syndrome.

Pancreatic tumours and diarrhoea. In the Zollinger-Ellison syndrome large volumes of highly acid gastric juice enter the duodenum and small bowel. In about half of all patients diarrhoea, sometimes with steatorrhoea, results. Continuous aspiration of gastric juice through a naso-gastric tube relieves this diarrhoea temporarily, while excision of the pancreatic tumour or total gastrectomy cures it (Summerskill, 1959).

Pancreatic tumours which are indistinguishable histologically may be associated with an entirely different type of diarrhoea (Telling & Smiddy, 1961; Matsumoto *et al.*, 1966). This diarrhoea is watery and rich in electrolytes, and dominates the clinical picture. The condition is aptly described as 'pancreatic cholera'; severe hypokalaemia may develop and may be fatal. Gastric hypersecretion and peptic ulceration are usually absent.

The most remarkable feature of these patients is that they have normal parietal cells but are often achlorhydric. A possible explanation for this phenomenon, suggested by Sircus (1965), is that a polypeptide analogue of gastrin displaces the natural substance from its parietal cell receptors and blocks the action of the hormone on secretion. The watery diarrhoea stops immediately after excision of the pancreatic tumour. In one inoperable case there was a good response to steroid (Smith, 1965).

There is a whole range of syndromes between

FIG. 2. Mechanism of Zollinger-Ellison syndrome.

these two extremes of gross gastric hypersecretion with steatorrhoea and achlorhydria with watery diarrhoea. For instance, moderate gastric hypersecretion may be present with 'non-specific' diarrhoea and late development of peptic ulceration.

Multiple endocrine adenopathy is familial and is inherited as an autosomal dominant characteristic with variable clinical expressions. Apart from having multiple functioning and non-functioning endocrine adenomata, families with this disease suffer from a strikingly high incidence of peptic ulceration, sometimes refractory to the usual forms of treatment (Wermer, 1963; Ballard, Frame & Hartssock, 1964).

Patients with the Zollinger-Ellison syndrome, on the other hand, are commonly discovered to have tumours of the endocrine glands other than the pancreas (incidence variously estimated to be between 3 and 40%). In every patient therefore, a search should be made for endocrine lesions before operation: a glucose tolerance curve should be obtained, the pituitary fossa X-rayed, the serum calcium and phosphorus levels measured, the urinary tract X-rayed and adrenal steroid excretion estimated. Examination of close relatives for possible endocrine disease is also advisable.

Multiple hormone production by one pancreatic tumour. Clinical features suggestive of hyperfunction by several endocrine glands usually indicate multiple endocrine adenopathy. There is, however, another form of polyhormonal disease in which several hormones are produced at a single site. About ten such cases with pancreatic non- β islet-cell tumours have been described (Hallwright, North & Reid, 1964; Law *et al.*, 1965). In addition to fulminating peptic ulceration these patients had clinical features of Cushing's syndrome or other endocrine disease.

Diagnosis of Zollinger-Ellison syndrome

The Zollinger-Ellison syndrome should be suspected in any patient who has:

1. Peptic ulceration in childhood.
2. Diarrhoea with peptic ulceration.
3. Primary ulcers, which are multiple or in unusual sites, especially in the lower duodenum or jejunum.
4. Gross gastric hypersecretion, especially high basal (resting) secretion.
5. Fulminating peptic ulcers which recur rapidly after normally adequate surgery.

Treatment and prognosis

There is no effective medical treatment for the Zollinger-Ellison syndrome; to prevent serious complications early surgery is essential. In an inoperable case or pending surgery an anticholinergic drug, such as poldine methylsulphate (14 mg q.i.d.)

may be tried and may cause some reduction in gastric secretion (Cook & Lennard-Jones, 1966). For a single adenoma local excision or partial pancreatectomy may be sufficient (Smith, 1965). However, after such limited surgery patients have to be followed up very carefully and their gastric acid measured frequently. Even in the initially successful cases a gradual return to gastric hypersecretion is common (Sircus, 1965).

The complete removal of tumour tissue is often impossible because of widespread adenomatosis or of functioning metastases (Block *et al.*, 1962). The immediate danger in these patients stems more from the complications of peptic ulceration than from the tumour itself. Surgery, therefore, must be directed towards the prevention of ulceration. Only complete gastrectomy can achieve this and any lesser procedure courts disaster (Fig. 3).

FIG. 3. Treatment of Zollinger-Ellison syndrome: influence of gastric resection on survival (after Ellison & Wilson, 1964).

Partial pancreatectomy should be added to total gastrectomy where the main part of the tumour is in the body or tail of the pancreas. A 'blind partial pancreatectomy' and regional lymph node biopsy is recommended where no tumour can be found anywhere but the diagnosis of Zollinger-Ellison disease is, nevertheless, strongly suspected.

The exact prognosis after total gastrectomy is not yet known. A few patients, some with metastases, have survived for many years after total gastrectomy. Wilson & Ellison (1966) recently reviewed seventy-eight patients who underwent total gastrectomy for Zollinger-Ellison syndrome. The time of follow-up varied from 6 months to 11 years. There were nineteen deaths, twelve of them postoperative and only four attributable to tumour or cachexia. These occurred 10 months, 1, 2 and 6

years after total gastrectomy. On several occasions other endocrine (especially parathyroid) adenomata have required excision some years after total gastrectomy.

ACTH-secreting pancreatic tumours

In at least ten patients, a pancreatic carcinoma has been found in association with bilateral adrenocortical hyperplasia and Cushing's syndrome (Liddle *et al.*, 1964). In three of these a substance indistinguishable from ACTH of pituitary origin has been extracted from the tumour. Not surprisingly, low levels of ACTH have been found in the pituitary in such patients. Carcinomas of the bronchus, the thymus and of other organs may behave in a similar manner (Ross, 1965).

The presenting symptoms of this disease are lassitude, loss of weight, thirst, ankle oedema and muscle wasting (Geokas *et al.*, 1965). The typical physical stigmata of Cushing's syndrome are often absent, owing perhaps to the extremely rapid onset of the disease. Other endocrine syndromes may be present as well as a result of the production of other polypeptides. Melanocyte-stimulating hormone production is especially common and a brown pigmentation of the skin may be helpful in diagnosis.

Severe hypokalaemic alkalosis and a glucose tolerance test of the diabetic type are almost invariably present. The plasma cortisol levels are extremely high, often higher than in Cushing's syndrome of pituitary or adrenal origin. The urinary 17-oxosteroids and 17-hydroxysteroids are also elevated. The adrenocortical hyperfunction, which these measurements reflect, cannot be suppressed by dexamethasone, indicating that the tumour secretes autonomously.

Surgery has, on occasion, been directed towards the hyperplastic adrenals. If the disease could be detected early it might be cured by excision of the pancreatic tumour, but most cases reported to date have been far advanced and have had a fatal outcome.

Glucagon-secreting tumour of the pancreas

A single case of glucagon secreting α -cell carcinoma of the pancreas was reported recently (McCavran *et al.*, 1966). The patient presented with mild diabetes and dermatitis. It is noteworthy that many patients with the Zollinger-Ellison syndrome have had some impairment of glucose tolerance. It may be that these tumours secrete glucagon in addition to other substances, but this matter awaits further inquiry.

Acknowledgments

We are grateful to Miss S. Barker for Fig. 3 and to Miss M. M. Scott for secretarial assistance. Acknowledgment is made to the authors of Ellison & Wilson (1964) and to J. B. Lippincott Co., publishers of *Annals of Surgery*, for permission to reproduce our Fig. 3.

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