Progress report

Diagnosis of insulinoma

Insulinoma is a term used by clinicians and biochemists to describe the (usually) small tumours composed of islet cell tissue that develop in the pancreas and ectopic sites, and which manifest themselves almost exclusively by their ability to secrete insulin and produce 'spontaneous' hypoglycaemia. Though often described as β-cell tumours, insulinomas only rarely consist exclusively of one islet cell type. Their histological heterogeneity may account for the unpredictable way in which they respond to various stimuli to insulin secretion (see below).

Most insulinomas occur as solitary tumours, but in upwards of 10% of cases there are two or more; in a somewhat smaller proportion of cases an insulinoma represents the pancreatic element of the pluriglandular syndrome. For this reason it is advisable to investigate all patients in whom a diagnosis of insulinoma is made to exclude coexisting, but asymptomatic, parathyroid and pituitary neoplasms. This is especially important in patients with diffuse adenomatous involvement of the islets, in those harbouring multiple insulinomas, and in those who develop the disease during the first two decades of their life.

A diagnosis of malignant insulinoma may be difficult to establish preoperatively but is increasingly likely the shorter the history and more intense the hypoglycaemia. The histological criteria of malignancy in endocrine tumours in general, and insulinomas in particular, are notoriously unreliable and a diagnosis of malignant insulinoma should only be made with confidence when there is evidence of metastatic spread beyond the pancreas. It is often stated, on the basis of large series of cases collected from the literature, that about 10% of insulinomas are malignant but this is probably an underestimate. About 2% of insulinomas arise in ectopic sites outside the pancreas.

Tumours that produce hormones in addition to insulin are increasingly frequently recognized. An association with ectopic ACTH and MSH secretion is especially common but production of glucagon, gastrin, and serotonin by insulinomas, singly or collectively, is also well documented. Most, if not all pancreatic tumours secreting more than one hormone that have so far been reported, were malignant or derived from patients with the pluriglandular syndrome. It is, however, likely that more thorough preoperative investigation of patients with simple tumours will reveal some with polyendocrinopathy which is in keeping with their multifarious histopathology.

Coexistence of insulinoma with other real or potential causes of hypoglycaemia such as non-islet cell tumours, partial gastrectomy, cirrhosis, and insulin-treated diabetes has been observed on several occasions.

Apart from their development as part of the pluriglandular syndrome,
comparatively little is known about the aetiology of insulinomas. The possibility that at least some represent a compensatory reaction to a genetic defect of insulin secretion which is characteristic of diabetes mellitus warrants further consideration.41–48

The necessity for distinguishing between hypoglycaemia—which can be defined as an arterial (or in the fasting subject, a venous or capillary) blood glucose concentration of less than 40 mg per 100 ml—and which may or may not be symptomatic—and the signs and symptoms of neuroglycopenia that it causes, is insufficiently appreciated. Nevertheless increasing awareness of the protean nature of neuroglycopenia, a heightened suspicion index, and the ready availability of reliable blood glucose measurements contributes to the increasing frequency with which insulinomas are recognized and treated. Insulinoma can no longer be looked upon as a rare tumour but as one which every physician and surgeon engaged in hospital practice is likely to encounter at least once every 10 years and probably more often.19

**Aetiology of Hypoglycaemia in Insulinoma**

Inappropriate, rather than excessive, secretion of insulin is the major cause of hypoglycaemia from insulinoma.4,5,35,44 Hypoglycaemia is normally a potent inhibitor of insulin secretion.35,45 Continuous secretion of insulin by an insulinoma even in the face of hypoglycaemia leads to inhibition of hepatic glucose release (both by direct action of insulin on the liver and indirectly by depressing glucagon release from the α-cells of the pancreas46) with worsening of hypoglycaemia until it reaches such severity that it causes cerebral symptoms and mobilization of counterregulatory glucose homeostatic mechanisms. The failure of insulin secretion to suppress adequately in response to hypoglycaemia, which is the most characteristic and virtually pathognomonic biochemical feature of insulinoma, is readily demonstrated by simultaneous measurement of plasma insulin and blood glucose concentrations.2,3,5,35,47

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The famous triad of a (fasting) blood glucose concentration below 40 mg per 100 ml associated with symptoms which can be provoked by fasting and relieved by glucose, first enunciated by Whipple,48 and subsequently modified to accommodate the more specific blood* glucose methods now available, remains the keystone for diagnosis of insulinoma. The importance of using accurate, precise and specific, blood glucose methods for detecting hypoglycaemia cannot be overemphasized.49

It is the author's belief that the continued use of inaccurate, imprecise blood sugar methods which are adequate for use in the diabetic clinic, but unsuitable for use in the hypoglycaemic range, is one of the commonest causes of delay in the diagnosis of insulinoma. In our experience, more than 90% of all patients eventually proved to be suffering from insulinoma can be shown to have hypoglycaemia after a 12 to 14-hour 'overnight' fast, providing that the test is made on three or more occasions, and a specific blood glucose method is used.

*Glucose measurements are increasingly frequently made on serum or plasma, and are on average 14% higher than the corresponding blood glucose level.
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The hypoglycaemia produced by an overnight fast is often relatively slight and may be insufficient to cause symptoms, especially in subjects who have become habituated to low blood glucose concentrations. In such individuals a more prolonged period of fasting—up to 72 hours or more accompanied by moderate exercise—may be necessary before neuroglycopenic symptoms supervene. Even under these stringent conditions some patients (probably less than 2%) fail to exhibit either hypoglycaemia or neuroglycopenia. Conversely some individuals who do not have an insulinoma, but suffer from obesity and mild diabetes mellitus, develop symptomatic hypoglycaemia during fasting.

Interpretation of the prolonged fast test may be difficult and asymptomatic hypoglycaemia, with blood glucose values as low as 25 mg per 100 ml, is not uncommon, even among normal subjects. In these individuals, however, insulin secretion is not inappropriate and plasma IRI levels are depressed. Neuroglycopenic symptoms do not occur and the EEG remains normal.

Because of dissatisfaction with the prolonged (72-hour) fast test for insulinoma, many different procedures aimed at increasing diagnostic specificity and precision have been introduced during the past two decades. Except in a small minority of cases, few of these tests offer any real advantage over repeated ‘overnight’ or 24-hour fasts, during which blood glucose and plasma insulin levels are assayed. Some of them are frankly misleading and will not be discussed further.

Intravenous Tolbutamide Test

Originally introduced as a diagnostic procedure for diabetes mellitus, the intravenous tolbutamide test rapidly gained widespread popularity as a test for insulinoma, especially when serial plasma insulin as well as blood glucose measurements could be made. Characteristically, in patients with insulinoma, the intravenous injection of 1 g tolbutamide causes, within 30 minutes, a normal or exaggerated fall in blood glucose concentration and this is sustained for at least a further 150 minutes; plasma insulin rises excessively, to over 150 mU/ml, within five minutes and returns to fasting levels more slowly than normal.

More extensive experience with the intravenous tolbutamide tests has shown that it is less specific for insulinoma than was originally thought, especially if glucose alone is measured. Patients suffering from any of the diseases causing fasting hypoglycaemia may demonstrate the abnormal glucose response to tolbutamide, though they seldom, if ever, have the exaggerated insulin response typical of insulinoma.

Approximately 20% of patients with proven insulinomas are ‘tolbutamide negative’, both with respect to the glucose and plasma insulin response. The failure of patients with insulinoma to respond to tolbutamide with an exaggerated insulinaemic response is particularly common in children.

An exaggerated insulin response to intravenous tolbutamide is not pathognomonic of insulinoma, but is a common finding in patients suffering from such diverse conditions as hepatic cirrhosis, Cushing’s syndrome, acromegaly, lipodystrophy, and simple obesity, but in these conditions the fall in blood glucose concentration is diminished and delayed.

The intravenous tolbutamide test is not without danger and may even cause death. Its use should, therefore, be restricted to patients in whom a
diagnosis of insulinoma, though possible, is unlikely. It should never be performed when hypoglycaemia is already present (the results of a fasting blood glucose analysis should always be known before the test is commenced) as this not only increases the hazard, but rarely yields clinically useful additional information.

Steinke and Soeldner\(^6\) advocate the use of intravenous tolbutamide as a means of reducing the time necessary to produce symptomatic fasting hypoglycaemia in patients with insulinoma. According to these authors any patient suffering from an insulinoma will develop symptomatic hypoglycaemia within 24 hours without food when given 1 g of sodium tolbutamide intravenously after an overnight fast, whereas up to 72 hours may be necessary if tolbutamide is not given.

**Glucagon Tests**

The ability of glucagon to stimulate insulin secretion from neoplastic islet tissue is the basis of diagnostic tests for insulinoma.\(^4,18\) When given intramuscularly (1 mg) glucagon causes a modest rise in arterial, and to a lesser extent, venous, blood glucose concentration, which is followed, in most insulinoma patients, by an exaggerated and usually symptomatic reactive hypoglycaemia within two hours.

In the intravenous test 1 mg glucagon is given by rapid intravenous injection and the plasma insulin and blood glucose response measured. More than 70% of patients with insulinoma show an exaggerated rise in plasma insulin within five or 10 minutes of the injection, often with delayed return to basal values. The rise in venous blood glucose concentration is often subnormal.\(^4\)

Although the intravenous glucagon test is just as nonspecific as the intravenous tolbutamide test it is safer. The main indication for its use is in the differential diagnosis of spontaneous fasting hypoglycaemia, for whereas intravenous glucagon may cause hyperinsulinaemia in many conditions, especially those associated with insulin resistance such as obesity, acromegaly, and Cushing’s syndrome, in most varieties of spontaneous hypoglycaemia which might be confused clinically with insulinoma, the insulinaemic response to intravenous glucagon is normal or more commonly subnormal.\(^4\) The glucose response alone is seldom helpful except in the diagnosis of glycogen storage disease.

**L-leucine Test**

Whilst l-arginine is the most potent of the many amino acids capable of stimulating insulin secretion in normal subjects,\(^67\) in patients with insulinoma it is l-leucine that has this property. Advantage has been taken of this fact to produce a test for insulinoma which, though less sensitive than intravenous tolbutamide, is more specific.\(^68,69,70\) In approximately 50% of patients with insulinoma, l-leucine given orally produces a profound fall in blood glucose and excessive rise in plasma insulin. This combination is seen in no other condition apart from 'idiopathic hypoglycaemia of childhood'\(^71\) and sulphonylurea pretreated individuals.\(^72\) Unlike l-leucine, l-arginine provokes no larger a rise in plasma insulin in patients with insulinoma than in normal subjects and does not cause a fall in blood glucose concentration.\(^73,74\)
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Oral Glucose Tolerance Test

The oral glucose tolerance test, like its intravenous counterpart, has been discredited as a test for insulinoma. Every type of response from an almost perfectly flat 'curve' to a typical diabetic curve (save for the pretest fasting values which are characteristically low rather than high) has been seen in patients with insulinoma, and been described as 'typical' of this condition. For this reason many authors have suggested abandoning oral glucose tolerance tests as an aid to diagnosis or differential diagnosis of insulinoma, as in most cases it provides little more information than can be obtained from an overnight fasting blood glucose measurement, especially as the plasma insulin response to oral glucose may be normal, exaggerated, or impaired. Nevertheless, in a tiny majority of cases—of which there is only one example so far recorded—oral glucose may produce such severe symptomatic reactive hypoglycaemia that further investigation may be indicated. Under these conditions, fasting hyperinsulinaemia, inappropriate insulin secretion, and exaggerated insulinaemic responses to other stimuli may be revealed, even though fasting for as long as 72 hours may fail to cause either neuroglycopenic symptoms or demonstrable hypoglycaemia.

Insulin in Blood

Plasma insulin measurements have proved valuable in the differential diagnosis of spontaneous hypoglycaemia although they have found no place in its initial recognition. The fasting plasma IRI is usually raised in patients with insulinoma and if due regard is paid to the normal depression of plasma insulin concentration by hypoglycaemia a condition of 'relative fasting hyperinsulinaemia', due to inappropriate insulin secretion, is demonstrable in more than 95% of cases. In any individual subject multiple sampling on different days increases the likelihood of demonstrating relative or absolute hyperinsulinaemia. Nevertheless, for reasons that are far from clear, babies and young children harbouring insulinomata—and they are not as rare as was once believed—may fail to show even relative fasting hyperinsulinaemia. They may also have remarkable resistance to the insulinotropic effect of some, if not all, of the normal stimuli to insulin secretion and their sole biochemical abnormality demonstrable by current techniques may be fasting hypoglycaemia—and (possibly) the failure of plasma insulin levels to fall to undetectable levels as a result.

The induction of hypoglycaemia by intravenous infusions of alcohol after 36 hours without food has been advocated as a method for demonstrating inappropriate insulin secretion in patients harbouring insulinomas but experience with this procedure is still too limited to warrant drawing conclusions about its clinical usefulness.

Several explanations have been put forward to account for the failure in some cases of insulinoma to demonstrate 'hyperinsulinaemia' in peripheral blood. One possible cause is increased efficiency of abstraction of insulin from portal venous blood by the liver; another is incorrect timing of the collection of blood for insulin assay as there is evidence that insulin secretion by insulinomas is episodic rather than constant. Since the half-life of insulin in the circulation is very short—probably less than seven minutes—periods of normo- or even hypoinsulinaemia may alternate with periods of
marked hyperinsulinaemia whose respective intensity and duration varies from tumour to tumour and possibly their size and stage of development.

The demonstration, first by Samols and subsequently by others, that some particularly malignant insulinomata secrete insulin that differs immunologically from native insulin is explicable on the basis of increased liberation of proinsulin by these tumours. On current evidence it is not unlikely that in yet other tumours—notably those of non-pancreatic origin—a biologically active material, which is nevertheless devoid of insulin immunoreactivity, may be secreted and be responsible for producing hypoglycaemia.

**Differential Diagnosis of Insulinoma**

Inappropriate insulin secretion, i.e., the presence of normal or high plasma insulin levels in the presence of hypoglycaemia, is the hallmark of insulinomata. It occurs in no other condition, of which the reviewer is aware, apart from an exceedingly small proportion of nonpancreatic tumours producing hypoglycaemia and some cases of 'idiopathic hypoglycaemia of childhood'. Most neoplasms that produce hypoglycaemia, apart from insulinomas, do not produce insulin and plasma IRI levels are almost invariably low, both in the fasting state and in response to insulinotropic agents. Plasma IRI levels are also usually low in other types of spontaneous hypoglycaemia, including those due to endocrinopathy, drugs and ethanol, starvation, and liver disease.

**Radiographic Localization**

Even the most competent surgeon may, from time to time, experience difficulty in locating at operation an insulinoma that had been confidently diagnosed by biochemical investigation preoperatively. Some help may be provided by coeliac axis arteriography, which depends upon the intense vascularity of insulinomas rather than their space occupancy, and has proved useful in locating the tumour in about a quarter to a half of the cases investigated. Higher detection rates have been claimed for this procedure by some authors, but these represent series of isolated observations collected from the literature, and may well reflect a bias for reporting successes rather than failures.

Coeliac-axis arteriography is virtually harmless when performed by an experienced radiologist. It would seem to be indicated preoperatively, therefore, in all patients in whom a firm diagnosis of insulinoma has been made and where the necessary radiological facilities exist. Whilst positive location can help the surgeon to identify the tumour at laparotomy with a minimum of delay, a negative result has no diagnostic significance. Because of their almost invariable small size, other radiological manoeuvres, such as contrast radiography and tomography, play no part in the diagnosis and localization of insulinomases. Pancreatic scintiscans with isotopic selenium have so far been equally unrewarding.

**Summary**

A diagnosis of insulinoma is usually easy once the condition has been suspected. Measurement of blood glucose by a reliable method after an
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overnight fast on three or more occasions reveals fasting hypoglycaemia in the majority of cases. The simultaneous demonstration of absolute or relative hyperinsulinaemia is almost pathognomonic for insulinoma; no further investigation apart from coeliac-axis-arteriography to locate the tumour, and tests to eliminate the possibility of a coexisting pluriglandular syndrome is indicated on clinical grounds except in children, under the age of 10, in whom idiopathic hypoglycaemia of childhood must always be considered. An infallible method of distinguishing between the last named condition and insulinoma has still not been devised; indeed it seems not unlikely that some children diagnosed and treated for idiopathic hypoglycaemia of childhood are harbouring small insulin-secreting tumours.

In about 10% of cases of insulinoma there are good grounds for suspicion but simple tests such as overnight fasting blood glucose measurements yield negative or inconclusive results. Under these circumstances one or more of the dynamic procedures such as the glucagon, leucine, prolonged fast, alcohol infusion, oral glucose tolerance, or intravenous tolbutamide test may be indicated. The latter should be reserved for use in cases where the diagnosis of insulinoma is unlikely. Coeliac-axis arteriography is helpful in about 30% of the cases in locating the tumour before operation.

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