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INSULINOMAS IN NORTHERN IRELAND BETWEEN 1960 AND 1980

A Review of 16 Cases

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INSULIN secreting tumours producing inappropriate hyperinsulinism are rare. Wilder, Allen, Power and Robertson, in 1927 described the first patient in whom hypoglycaemia was shown to be related to carcinoma of the pancreatic islets, which were presumed to be secreting insulin. The majority of insulinomas are small benign tumours amenable to surgical removal. They cause severe metabolic and/or behavioural upset and are not always correctly diagnosed. Successful treatment depends upon clinical awareness, accurate biochemical diagnosis, radiological localization and precise surgical removal. Some tumours are malignant [1], [2] and these tend to metastasize to regional lymph nodes and the liver. Like other polypeptide-secreting carcinomas they are usually relatively slow growing, the hypoglycaemia tending to be more devastating than the catabolic effects of the metastases.

We report the experience of insulin secreting islet cell tumours at the Royal Victoria Hospital, Belfast. Sixteen cases have been treated between 1960 and 1980, 3 of which were malignant. These were, we believe, the only insulinomas associated with hypoglycaemia diagnosed in Northern Ireland (population 1.5 million) during the past 20 years so that the incidence was approximately 0.5 per million per year. The aim of this paper is to demonstrate the changes in diagnostic techniques which have evolved during the past 20 years, and to assess their value.

CLINICAL FEATURES

Ten patients were male and six female, with ages ranging from 18 to 74 years. Their symptoms at the time of presentation were varied and often bizarre with neurological and behavioural disorders predominating. Nine patients developed unusual behaviour patterns with psychological disturbances; 13 patients reported neurological symptoms including loss of consciousness, transient hemiparesis, epileptiform attacks, double vision, dizziness, staggering and/or numbness. Other complaints were of headaches and attacks of sweating, hunger or vomiting.

Perhaps the most spectacular complaint was from a patient (MR) who stated that she "woke up unconscious". This was her way of stating that people had difficulty rousing her each morning. Another patient (ET) lost consciousness in a golf bunker after numerous energetic attempts to remove his ball. One young man (HS) habitually went to his work as a labourer after eating a minimal breakfast — on a number of occasions while cycling home for lunch he collapsed and lost consciousness at the roadside. One adult man (JH) had been admitted to a mental hospital because of bizarre and inappropriate behaviour, culminating in an episode of "indecent exposure" when he went to the front door to collect the milk bottles on a Sunday morning before breakfast, without his trousers.

Two patients presented with weight loss (one of these was subsequently shown to have a malignant tumour); in contrast many of the others had gained weight. This may have been as a result of the anabolic effect of insulin or, alternatively, because the patients discovered that repeated carbohydrate intake modified their symptoms. Another patient, (LM) a diabetic on insulin treatment, had been found to require less and less insulin and was finally able to stop his insulin therapy entirely, before laparotomy for symptoms of intestinal obstruction revealed an insulin secreting pancreatic islet-cell tumour.

DIAGNOSIS

The initial suspicion that symptoms may be due to hypoglycaemia is the essential part of the diagnostic process, and was made by doctors from various disciplines. The suspicion was raised for six patients by a neurologist, in one by a psychiatrist, in two by general physicians and in the remainder by their family doctors. In all instances the triad was demonstrated of (1) symptoms compatible with hypoglycaemia, (2) a demonstrably low blood sugar, and (3) relief of the symptoms by taking glucose.

Confirmation of the suspicion requires biochemical and radiological investigation. Diagnostic tests during the past 20 years have included early morning fasting estimations of plasma glucose, prolonged fasting, an extended 50G oral glucose tolerance test and a 1.OG tolbutamide tolerance test. In twelve cases measurement of fasting plasma insulin by radioimmunoassay [4] was possible (normal fasting range 5-15 mU/1). The results of these tests are summarized in Tables I and II.

Early morning fasting plasma glucose was 2.2 mmol/1 (40 mg/100 ml) or less in 13 of the 16 patients: in 10 of the 11 cases where plasma insulin measurements were possible it was above 15 mU/1, and even the figure of 13 mU/1 in Case 15 is inappropriately high for the very low blood sugar of 1.5 mmol/1.

While fasting under supervision, all patients became hypoglycaemic. Only 4 patients required to fast more than 12 hours, the one who persisted up to 36 hours before demonstrating hypoglycaemia had the smallest adenoma in this series

TABLE I

Plasma Glucose and Insulin Data during fasting

Case		Age	Sex	Year of operation	Lowest early morning values of plasma glucose and corresponding plasma insulin: Glucose (mmol/l)	Insulin (mu/l)	Lowest plasma glucose during prolonged fast and corresponding plasma insulin: Glucose (mmol/l)	Insulin (mu/l)	time of fasting (hr)
1	M.O'N	38	M	1960	4.0	—	1.8	—	8.0
2	H.P.	39	F	1964	2.0	—	1.1	—	15.5
3	W.B.	66	M	1964	0.8	41*	1.4	41*	12.0
4	R.McC	41	F	1965	1.3	—	1.5	—	—
5	H.S.	43	M	1966	1.4	—	1.5	—	7.0
6	L.I'A	45	M	1967	1.1	240	1.1	240	12.0
7	M.R.	74	F	1969	2.2	75	2.2	75	14.0
8	J.H.	51	M	1972	1.1	20	1.8	29	10.6
9	J.M.	35	M	1972	1.5	36	1.4	36	10.5
10	M.S.	57	F	1973	2.2	18	1.9	21	6.0
11	E.T.	19	M	1975	2.2	16	1.5	23	6.0
12	J.D.	68	M	1975	3.3	100	2.0	23	24.0
13	A.S.	31	M	1976	2.8	125	1.1	—	36.0
14	L.M.	49	M	1976	1.2	116	3.1	165	10.5
15	L.McL	18	F	1978	1.5	13	2.5	64	10.0
16	S.McG	57	F	1978	0.8	41	1.3	30	10.2

Footnote :

* plasma insulin measured by Dr. C. N. Hales, Cambridge, by an early radio-immunoassay and reported to be "elevated".

(case 13). At least 4 patients became spontaneously hypoglycaemic during the night, and formal fasting was unnecessary — the problem was more one of clinical management with intravenous glucose infusions prior to surgery.

Fifteen of the patients were studied during an oral GTT, which was extended beyond 2 hours in 9 instances. The shape of the glucose curve was not informative: plasma glucose values were usually low throughout, with a very minor rise after the 50G glucose load. Two patients showed plasma glucose well into the diabetic range — case 7 was not known to be diabetic and had normal blood glucose values post-operatively. Case 14 was an insulin requiring diabetic before developing his islet cell carcinoma and has been recorded elsewhere [6]. The time of onset of hypoglycaemia after the peak of the curve was variable (up to 9 hours) and some patients were not followed sufficiently long to achieve hypoglycaemia. Only

TABLE II

Plasma Glucose and Insulin Data during Oral Glucose Tolerance Test, and I/V Tolbutamide Test.

Case		Age	Sex	Year of operation	Lowest plasma glucose following the peak of 50 g OGIT and corresponding plasma insulin			Lowest plasma glucose following 1.0 g tolbutamide I/V and corresponding plasma insulin		
					Glucose (mmol/l)	Insulin (mu/l)	time from Oral Glucose (hr)	Glucose (mmol/l)	Insulin (mu/l)	time from I/V tolbutamide (hr)
1	M.O'N	38	M	1960	1.4	—	9.0	—	—	—
2	H.P.	39	F	1964	1.6	—	3.0	1.1	—	0.25
3	W.B.	66	M	1964	1.8	—	4.5	1.1	—	2.0
4	R.McC	41	F	1965	1.6	—	3.5	1.5	—	0.5
5	H.S.	43	M	1966	6.7	—	2.0	—	—	—
6	L.I'A	45	M	1967	1.1	195	4.0	—	—	—
7	M.R.	74	F	1969	11.2	—	2.0	1.9	200	0.5
8	J.H.	51	M	1972	1.9	32	3.5	—	—	—
9	J.M.	35	M	1972	—	—	—	—	—	—
10	M.S.	57	F	1973	1.9	27	4.0	1.4	28	0.5
11	E.T.	19	M	1975	4.5	—	2.0	—	—	—
12	J.D.	68	M	1975	1.9*	46*	2.5	—	—	—
13	A.S.	31	M	1976	1.2	99	0.5	1.4	—	0.5
14	L.M.	49	M	1976	8.2	210	2.0	—	—	—
15	L.McL	18	F	1978	2.2	33	2.0	—	—	—
16	S.McG	57	F	1978	2.0	76	5.5	—	—	—

Footnote :

* glucose and insulin values observed following a mixed meal, rather than standard OGTT.

four patients, including the two diabetics, did not produce a plasma glucose of 2.2 mmol/1 or less during this test. In all cases where plasma insulin was measured it was clearly inappropriately elevated.

The I/V tolbutamide test was used prior to the introduction of insulin radioimmunoassay but only occasionally after 1965. Hypoglycaemia was certainly demonstrated rapidly in all six patients, but the levels of plasma glucose were not markedly lower than those achieved by simple fasting, and the test is not used routinely at present.

RADIOLOGY

Arteriography

Comparison of the arteriographic, operative and histological findings is made in Table III. Except in one patient (case 6) radiology was performed by the same radiologist (E McI). The main investigation used to localize the tumour was coeliac axis angiography by retrograde femoral artery catheterization. The examination was carried out under local anaesthesia with mild pre-medication. Hyoscine-N-butylbromide was used to prevent movement of bowel gas between the series. A standard 7-gauge polyethylene catheter, pre-curved for injection, was used. The technique required a rapid film-changer. Initially the coeliac axis was examined by hand injection of 15-20 mls Triosil 440. Films were taken for 15 seconds with emphasis on films in the capillary phase. These films were inspected and decision made on further views (either lateral or oblique with caudal or cephalad angulation, or superior mesenteric injection for super-selective catheterisation). Subtraction techniques were used for the examination of films.

Ultrasound Examination

A Picker Echoview with a 2.5 MH long focus transducer was used. Scans were obtained in longitudinal, transverse and oblique projections.

Computerized Axial Tomography

This was performed at 1.5 cm intervals through the pancreas. The equipment used was an EMI 5005/2085 scanner with a field of thirteen inches and a scanning time of 25 seconds. Scans were also obtained after enhancement with 50 mls Urografin 370. A further series of scans was then obtained during simultaneous enhancement with 25 mls Urografin 370 injected at 1 ml per second during each scan cycle.

The results of the radiological findings and their correlation with the surgical findings are listed in Table III. The only case of false-negative arteriography, (case 6) was investigated elsewhere; in all the remaining cases arteriography was useful in predicting tumour site. Benign insulinomas varied in size from one to several centimetres in diameter. They were well demarcated and showed a dense capillary blush. In contrast, the malignant tumours were poorly demarcated, had poor capillary blush and showed end-arterial distortion and neovascularity.

Ultrasonic examination demonstrated only tumours in excess of 3 cm. in diameter. It proved much more valuable in the head than in the body or tail of the pancreas. Computerized axial tomography appears promising particularly when simultaneous enhancement was employed.

These methods are illustrated in the figure.

SURGERY

Wide exposure of the whole pancreas was usually achieved by a long transverse epigastric incision. In six patients the tumour was in the head of the pancreas; these were locally resected without mortality but with considerable short-term

TABLE III

Radiological and Operative Findings

(All cases were islet cell adenomas except 6, 14 and 16 which were carcinomas).

Case	Coeliac Angiogram	Operative Findings
1	Not done	1.0 cm diameter tumour at junction of head/ neck of pancreas
2	Not done	1.0 cm diameter tumour at head of pancreas
3	Not done	1.0 cm diameter tumour
4	Not done	1.2 cm diameter tumour at junction of head and uncinate process
5	Not done	2.0 cm diameter tumour at junction of head and uncinate process
6	Normal (radiology elsewhere)	Two large modules in pancreas
7	Not done	1.0 cm diameter tumour at head of pancreas
8	Increased vascularity of head of pancreas	Large tumour upper/lateral area of head of pancreas
9	2 cm tumour in body	Tumour deep in upper part of head of pancreas
10	Capillary blush probably in head of pancreas	1.0 cm diameter tumour to left of neck of pancreas
11	Single tumour in extreme tail of pancreas	2.0 cm diameter tumour in tail of pancreas
12	4.0 cm diameter tumour in head of pancreas	Spherical tumour in head of pancreas
13	Small tumour to left of coeliac axis	No macroscopic tumour. Microscopic adenoma found after subtotal distal pancreatectomy
14	Large tumour extending from spine to splenic pedicle — 8 x 7 cm	Tumour of body/tail of pancreas 9 x 9 cm
15	3 tumours. upper head, high neck and extreme end of tail of pancreas (C.A.T. Scan: Abnormal thickening junction of body and tail of pancreas	3 tumours. 0.7 cm in neck 2.0 cm mid-body 2.0 cm extreme tail
16	Single large tumour in upper quadrant of head: ? another in neck of pancreas (C.A.T. Scan: Single tumour in head of pancreas	Massive tumour in head of pancreas. and multiple hepatic metastases

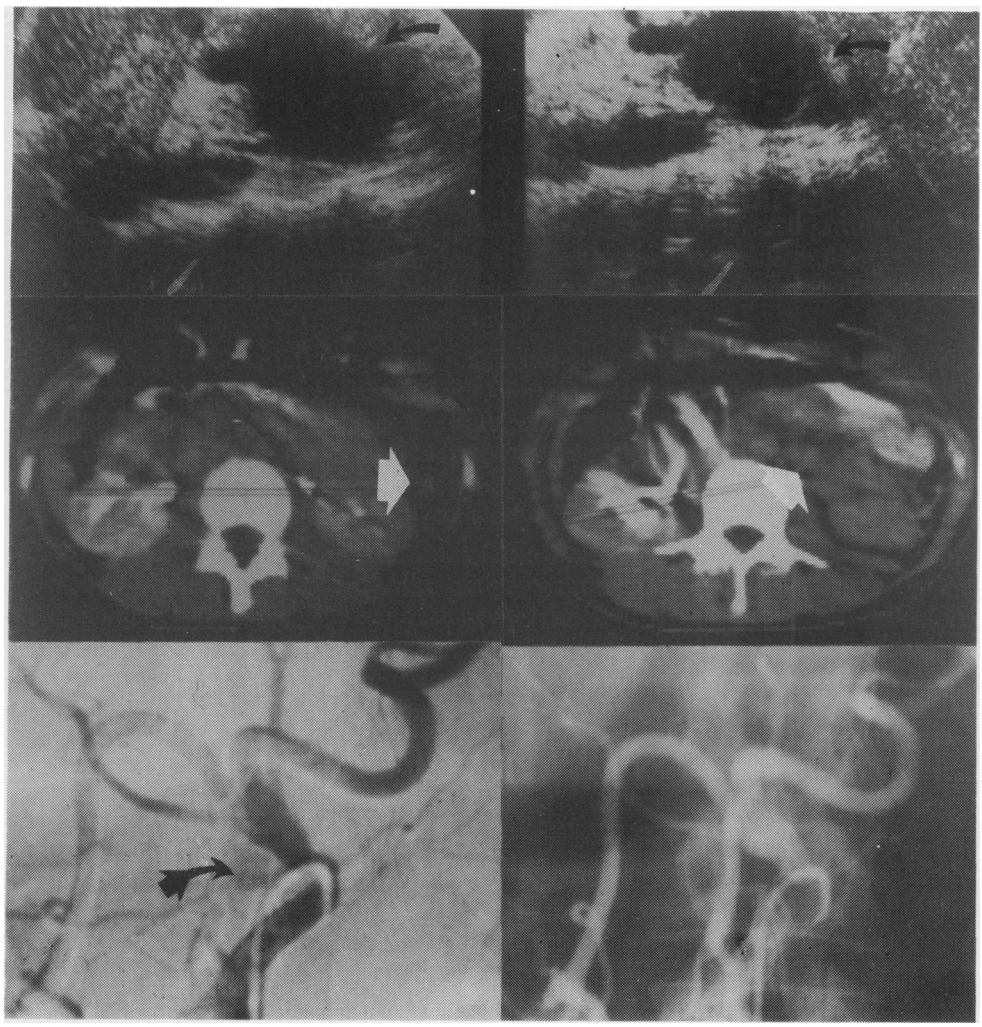

FIG. 1.

ULTRASOUND

The upper two sections show a large (3 cm.) insulinoma in the head of the pancreas — demonstrated by ultrasound.

C.A.T. SCAN

The centre sections show a single insulinoma in the tail (left), and another in the body of the pancreas (right) — following contrast enhancement of the C.T. scan.

ANGIOGRAPHY

The lower two sections demonstrate the requirement for subtraction technique to be applied to angiography in the unsubtracted Glms. The insulinoma is totally obscured by the spinal bone density on the standard engiographic view (right), whereas it is clearly indicated by subtraction (left).

morbidity. One tumour was intimately related to the common bile dust which was damaged during exploration; this was not recognized and lead to a subhepatic collection of bile requiring drainage subsequently. In two other cases a pancreatic duct was probably damaged, leading to fistula formation in one and a pseudocyst in the other. To minimise complications we now routinely use a hand lens to inspect the tumour bed for leakage of pancreatic juice: this leakage can be made more obvious by injection of secretin. When the tumour was located in the neck, body or tail, surgery was easier; a distal pancreatectomy was performed in seven patients and a microscopic adenoma was found. One patient with multiple endocrine adenomatosis had three macroscopic tumours in the body and tail, and three further tumours were identified microscopically. A "blind" distal pancreatectomy was performed in only one patient in whom a microscopic adenoma was found.

MEDICAL MANAGEMENT

Streptozotocin was given to two of the patients with malignant tumours (Cases 6 and 14), who have been reported elsewhere [5], [6]. One patient was an insulin-dependent diabetic who developed hypoglycaemia which persisted even after withdrawal of insulin therapy. He had an islet cell carcinoma with hepatic metastases. After intravenous streptozotocin he became hyperglycaemic and again required insulin. He relapsed after one year despite intensive streptozotocin therapy. Plasma gastrin was also initially elevated at 290-500 ng/l (normal 0-150 ng/l) with associated acid hypersecretion, and these values also fell to normal after streptozotocin. The other patient survived for four years, eventually dying from cachexia and renal tubular acidosis, which was most probably caused by the drug. A short course of diazoxide has been successful in maintaining a normal plasma glucose in case 16, where a large hepatic metastasis remained in situ: It is uncertain whether this lesion is still truly functioning and both glucose and insulin values have now remained normal for over a year without further therapy.

Only one patient (Case 15) could be considered to have multiple endocrine adenomatosis, on the basis of multiple islet cell adenomas and hyperparathyroidism. Cells within the islet cell adenoma stained positively for pancreatic polypeptide. Her father had both a pituitary chromophobe adenoma and a parathyroid adenoma, and a paternal uncle is known to be panhypopituitary.

Follow-up has varied from one to 18 years. Four patients have died. Case 3, W.B., died 6 years post-operatively from a cerebrovascular accident. Case 6, L.I'A., and Case 14, L.M., died 4 and one years respectively after their diagnostic laparotomies from malignant tumour metastases, although hypoglycaemia had been effectively treated and the cause of death was ultimate cachexia. Case 7, M.R., died of heart failure 7 years post-operatively.

In 11 patients a recent value of plasma glucose and insulin was available at review in 1979. Plasma glucose (random, mid-afternoon) varied from 4.1 to 9.0 mmol/l, and plasma insulin from 2.0 to 32.5 mu/l.

DISCUSSION

Insulinomas are uncommon and present in widely differing ways [3], [7], [8], [9]. The present series is typical of experience elsewhere in the high proportion of cases presenting with neurological and psychiatric symptoms. Stefanini et al [8] in a world-wide literature review of 1067 cases which included 9 of this series, reported neuropsychiatric complaints in 92 per cent of cases. Other presentations include gastroenterological symptoms and the generalised features of malignancy.

Since symptoms are intermittent and presenting complaints variable, long delays can occur before the correct diagnosis is made [7], [9]. The present study clearly indicates that awareness of the modes of presentation by doctors in widely differing fields is the vital step in diagnosis. Subsequent proof of diagnosis has become easier now that plasma insulin measurements are readily available. This has simplified many of the tests which were previously advocated [7], [10]. The present series shows that the plasma glucose and insulin results obtained in early morning specimens (at least 3), and if necessary during a relatively short further fast, allowed the diagnosis to be made biochemically in all cases where this combination was used. The prolonged glucose tolerance test was also useful in our series but others have pointed out the unreliability of the test [9], [11]. Currently, we investigate by collecting a series of early morning fasting plasma glucose and insulin specimens, the last of which is followed by a prolonged glucose tolerance test over 6 hours. On the next day, if hypoglycaemia has not been demonstrated, a prolonged fast is commenced with blood samples being taken every 6 hours for insulin and glucose measurements. The fast should be stopped after 2 days. During similar procedures each of our patients had, at some stage, unequivocal hypoglycaemia with a clearly raised plasma insulin; these findings agree closely with those reported in the series of Service et al [9], Scholz et al [12] and Clark et al [13].

A more frequent problem is encountered where indefinite symptoms might possibly be due to hypoglycaemia, but where a low plasma glucose has never been clearly demonstrated. We have not found any patient with an insulinoma who did not show unequivocal hypoglycaemia during early morning sampling, a prolonged oral GTT or during prolonged fasting up to 36 hours. The patient with the smallest lesion (case 13) clearly demonstrated inappropriate hyperinsulinism on early morning fasting measurements, but required up to 36 hours continuous fasting to produce symptomatic hypoglycaemia. More complex tests to provoke insulin secretion are unnecessary to exclude true insulin-secreting adenomas.

After the biochemical diagnosis had been established selective arteriography was impressive in localization of the tumour. Before this technique was introduced and adopted by Olsson [14] in 1963, tumours were found only by observation or palpation of the pancreas at operation. In our series a tumour as small as 2 cm in diameter has been visualized; others have claimed to see tumours as small as 0.5 cm [8]. There has been one false negative and one false positive arteriogram (86% success rate). Others have reported rather more false negatives, particularly when the lesion is in the tail of the pancreas [8], [15-18]. Our detailed technique has been given, as we feel that it is of considerable importance in enhancing the usefulness of the test; without subtraction tumours occurring in areas overlain by gas or over the spine or ribs may easily be missed.

Successful surgery requires accurate localization and adequate exposure. Even after reliable localization it is advisable to explore the whole pancreas in every case as the tumour may be multiple or the localization faulty. Though a vertical incision may be adequate, we have generally preferred a long transverse epigastric incision. When the tumour is in the head of the pancreas, local excision is safer than pancreatico-duodenectomy [8]; local resection was performed in 7 cases without the mortality reported elsewhere [8] but with considerable short-term morbidity. When the tumour was located in the neck, body or tail, distal pancreatectomy was performed in 7 patients. (One early patient underwent a blind distal pancreatectomy, a procedure which we no longer advocate). In circumstances such as these where no tumour is seen at laparotomy, distal pancreatectomy removes only about one third of insulinomas [8], [19]. In these circumstances intraoperative catheterization of the splenic and portal veins may be indicated in an attempt to localize the site of insulin secretion [20], [21].

In the present series, we have seen no recurrences after removal of a benign tumour. The incidence of malignancy (13%) is in keeping with that described elsewhere [8], [9]. In a number of cases local invasion was reported histologically, but these cases have not developed either recurrent hypoglycaemia or other sequelae of malignant disease. When metastases were present streptozotocin therapy was of considerable short-term help, although vomiting was a major problem and one patient (5) developed severe renal tubular acidosis after 4 years therapy, a complication which has also been reported by other workers [22], [23], [24].

We conclude that the basic methods of diagnosis of insulinoma have not changed since radioimmunoassays for insulin became available, and remain based on the simple demonstration of hypoglycaemia with inappropriate hyperinsulinism. A team approach to management in a specialized centre is strongly advocated; we have shown that arteriography is helpful in localization while skilled surgery by one team reduces morbidity and mortality. Although the outcome for patients with metastases was poor, in cases with histologically benign insulinomas only one recurrence of hypoglycaemia was seen.

We are grateful to Dr. J. S. Logan for his permission to report Case 5. The other patients were all at some time under the care of the Metabolic Unit. We are grateful to numerous colleagues for referring patients and for help and consultation during their management.

ADDENDUM

1. J.D. Case 12 died in 1980 from intestinal obstruction associated with recurrent hypoglycaemia. Autopsy at another hospital did not reveal any evidence of residual islet cell tumour in the pancreas or elsewhere, but the available biochemical evidence suggests that there must have been some recurrence.
   J.H. Case 8 has developed recurrent hypoglycaemia with inappropriate hyper-

insulinism in 1981, and liver scans show multiple hepatic secondaries. Review of the original histology in both cases 8 and 12 does not give any indication that either might originally have been recognisable as potentially metastatic.

2. Since writing this paper a further patient with an islet cell tumour in the head of the pancreas has been diagnosed and the lesion successfully removed.

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