Introduction

Hypoglycaemia is one of the commonest of medical emergencies, mainly due to its high frequency as a complication of insulin therapy of diabetes. It sometimes arises, however, ‘spontaneously’ as a manifestation of other diseases. The present review deals exclusively with hypoglycaemia caused by neoplastic disease.

For a very brief period, between 1927 and 1930, tumours capable of producing hypoglycaemia were thought always to secrete insulin and arise exclusively within the pancreas. In the intervening years it has become increasingly apparent that almost any type of neoplasm can cause hypoglycaemia through a number of different mechanisms (Marks & Rose 1964, Laurent et al. 1971, Daughaday 1989, Fajans & Vinik 1989).

Symptomatology

Hypoglycaemia may be the presenting symptom of a tumour, a terminal epiphenomenon or anything in between, but is always rare. It is usually episodic and provoked by fasting rather than reactive to the ingestion of food. The one notable exception is hypoglycaemia due to pheochromocytoma which may be of either variety (Gorden et al. 1981, Hiramatsu et al. 1987, Paineau et al. 1988, Akiba et al. 1990).

Symptoms of acute neuroglycopenia, characteristically associated with insulin overdose, are unusual in tumour-induced hypoglycaemia. Instead there is a gradual loss of cognitive function associated with diminished motor activity, lethargy, the onset of somnolence and a gradual drift into stupor or coma. Recovery may occur spontaneously at any time but is hastened by the ingestion of carbohydrate by mouth or the injection of glucose or glucagon.

Biochemically, tumour-induced hypoglycaemia is usually associated with hypoketonaemia (<300 µmol/l) unlike that of most other types of ‘spontaneous’ hypoglycaemia apart from insulinoma (Teale et al. 1987). Only rarely are patients desperately ill in between hypoglycaemic episodes except when it is a terminal event in patients with liver metastases.

Classification of hypoglycaemia-producing tumours

Tumours producing hypoglycaemia can, broadly speaking, be divided - on the basis of the mechanism by which they most commonly produce hypoglycaemia - into: (1) insulin-secreting tumours; (2) non-islet cell (insulin-like growth factor-II (IGF-II)-secreting) tumours; (3) myeloma, lymphoma and leukaemia; and (4) metastatic neoplasia.

Hypoglycaemia produced by tumours other than insulinomas is usually referred to as ‘non-islet cell tumour hypoglycaemia’ (NICTH) and has more than one cause.

Pancreatic endocrine tumours

Insulin-secreting tumours are the commonest hormone-producing neoplasms of the gastrointestinal tract. They occur with an incidence of between 0.5 and 1 per million of the population per year (Kavlie & White 1972, Atkinson et al. 1981, Cullen & Ong 1987, Watson et al. 1989). More than 80% are solitary benign adenomas, composed mainly or exclusively of morphologically normal B-cells. About 10% are metastatic, i.e. malignant, whilst a further 10% are multiple but behave as benign.

Women outnumber men in the ratio of 6:4 for benign but not for malignant insulinomas. The highest incidence is in middle aged adults, though both benign and malignant insulinomas have been observed very rarely in children and in the very elderly.

Insulin-secreting tumours

Clinically significant insulinomas are generally between 10 and 20 mm in diameter at the time of diagnosis, although tumours as large as 150 mm or as small as 5 mm in diameter have been found during surgery. Occasionally very small tumours are overlooked at operation and found only after very thorough histopathological examination of the resected pancreas, or not at all.

In fewer than 5% of cases of true hyperinsulinaemic hypoglycaemia can no tumour be found. Whilst some of these may be due to a small tumour being overlooked either at operation or at autopsy others are due to a functional abnormality of the B-cells similar to that
causing persistent hyperinsulinaemic hypoglycaemia of infants (PHHI) which may, or may not, manifest itself histologically as islet hyperplasia (nesidioblastosis). This condition must be distinguished from the nosologically distinct condition of microadenomatosis which can occur either as an isolated histopathological finding or as part of multiple endocrine neoplasia type I (MEN-I) (Diarmuid et al. 1994).

The natural history of insulinomas (Marks 1991) suggests that apart from their propensity for causing hypoglycaemia - from which death is fortunately very rare - they produce no adverse effects. Specifically they appear not to cause obstruction to the hepatic or pancreatic ducts or to undergo malignant transformation. There are many reports, especially in the older literature, of symptoms attributable to hypoglycaemia due to insulinoma extending over a period of 25 years or more before its true cause was identified and removed (Fonseca et al. 1989).

The average time between onset of symptoms and diagnosis of its cause as due to insulinoma is now about 1 year. Delay, when it does occur, is almost always the consequence of reluctance by the patient to seek help, or failure of the practitioner to suspect hypoglycaemia. Once suspected, diagnosis of insulinoma seldom presents any real difficulty (Marks & Rose 1981, Marks 1991, Marks & Teale 1996, Marks 1997, Nauck et al. 1997).

Insulinomas are distributed evenly throughout the pancreas and only very rarely ectopically (2%). In this respect, as in the relative infrequency of their malignancy, insulinomas differ from other hormone-producing tumours of the gastrointestinal tract.

The commonest ectopic sites are the duodenum and the immediate vicinity of the pancreas, but less than 1% of the 677 insulinomas collected from the literature by Laurent and co-workers prior to 1971 were located outside the pancreas. Only a tiny number of ectopic tumours have been reported in recent years (Yoshikawa & Wakasa 1980, Miyazaki et al. 1986).

**Insulinoma histology** Many insulinomas are composed entirely of seemingly normal B-cells. More thorough examination, especially by electron microscopy and immunocytochemistry, usually reveals a small but variable number of other pancreatic endocrine cell types, of which somatostatin-containing D-cells are the commonest.

Insulinomas show variable and unpredictable staining with traditional as well as with immunohistological reagents, including synaptophycin, neuron-specific enolase and chromogranin, which have been used as general markers of neuroendocrine tumours or tumours of amine precursor uptake and decarboxylation cells (APUDomas). Some stain very poorly or not at all even with anti-insulin antisera.

Attempts to classify insulinomas into prognostically useful histopathological categories have been made for 60 years or more with little success (Graeme-Cook et al. 1990). It became apparent soon after their initial identification that classical morphological and histological criteria were of little value for distinguishing malignant from benign tumours. Only the presence of metastases, or their subsequent appearance, could be relied upon to make the distinction.

Creutzfeldt and co-workers (1973) classified insulinomas into four types on the basis of their histological, ultramicroscopic and immunocytochemical appearances.

Type 1 is the commonest and accounts for almost half of the cases. In this type, virtually every cell contains typical \( \beta \)-granules.

Type 2, the second commonest, accounts for 25% of the cases. Most of the cells contain a number of atypical granules - demonstrably different from those of normal A, B, D or PP cells - in addition to typical \( \beta \)-granules. The atypical granules resemble the coated \( \beta \)-granules that are found in small numbers in normal B-cells and within which proinsulin is believed to be converted into insulin and C-peptide (Orci et al. 1988).

Type 3 tumours consist solely of cells containing atypical \( \beta \)-granules. None contains typical ones. Though not specifically identified as such, these probably correspond to predominantly, or exclusively, proinsulin-secreting tumours (proinsulinomas).

Type 4 tumours included the only two metastatic carcinomas in the Creutzfeldt series. None of the four tumours so classified had any of the characteristic histological features of an insulinoma. All gave negative reactions with classical histological and immunocytochemical stains. They all showed ultramicroscopic signs of high functional activity. Tumours of this type would possibly, in former times, have been classified as carcinomas of unknown origin or carcinoids rather than ‘insulinomas’, even in experienced histopathological laboratories.

Berger and co-workers (1983) classified hypoglycaemia producing tumours of the pancreas on their functional rather than histological characteristics.

Group A tumours were characterised by the almost complete suppressibility of insulin and proinsulin secretion by both diazoxide and somatostatin. Histologically they were characterised by an abundance of well-granulated B-cells in a trabecular arrangement.

Group B tumours resisted the suppressant effects of diazoxide and somatostatin and their cells were arranged in a ‘medullary pattern’ and contained fewer less well granulated \( \beta \)-granules.

Only 20% of circulating total immunoreactive insulin (IRI) was proinsulin and proinsulin-like components in group A patients, which is not very dissimilar to that of
normal subjects. In group B patients on the other hand they accounted for 50% or more of total IRI. The difference reflects the smaller proportion of coated to uncoated β-granules in the group A patients.

Despite their sophistication compared with previous classifications, neither the Creutzfeldt nor Berger classifications enables a prognostically important distinction to be made between malignant and non-malignant tumours. Nor, for that matter (Graeme-Cooke et al. 1990), does the observation that malignant, but not benign, insulinomas express - and sometimes secrete - the subunits of human chorionic gonadotrophin which had originally appeared to offer this possibility.

Confusion between malignant insulinomas masquerading as metastatic carcinoids may, and sometimes does, occur. This is less likely to occur if immunostaining with insulin antisera is carried out routinely on all pancreatic carcinoids since symptoms from hypoglycaemia are not inevitable until quite late in the course of the disease (Marks 1995).

**Amyloid** A substance with the histological appearance of amyloid was recognised as being deposited in varying amounts in insulinomas whether benign or metastatic long before it was isolated and characterised chemically (McIntyre 1989, Porte & Kahn 1989, O'Brien before it was isolated and characterised chemically amounts in insulinomas whether benign or metastatic long before it was isolated and characterised chemically (McIntyre 1989, Porte & Kahn 1989, O'Brien before it was isolated and characterised chemically)

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Islet amyloid polypeptide (also known as amylin) is a 37 amino acid polypeptide which is co-secreted with insulin from both normal and diseased B-cells. It may be co-deposited with the pentomeric amyloid protein (pentraxin) common to all varieties of amyloid in the islets of patients with non-insulin-dependent diabetes mellitus (NIDDM) as well as in patients with pancreatic endocrine tumours (Crowley et al. 1996), though it is rare in all except insulinomas.

It has been suggested that amylin might be of pathogenic importance in the aetiology of NIDDM. It is now known, however, to be co-produced and co-secreted with insulin by normal as well as by insulinoma B-cells and those of patients with NIDDM. It is still unknown, however, why islet amyloid polypeptide should be deposited in large amounts in some insulinomas but not in others, nor whether it has any prognostic significance. It does not occur in children with (familial) PHHI (Rother et al. 1995), which, in its nosology at least, resembles insulinoma.

**Mixed cell tumours and carcinoid**

While most benign insulinomas contain isolated D and/or A cells, their presence in greater numbers is usually associated with malignancy, i.e. metastasising tumours. Metastatic islet cell tumours often resemble carcinoids histologically and may be reported as such unless special staining techniques are used. They may be associated with no evidence of endocrinological disturbance until quite late in life and long after the initial histological diagnosis has been made.

Functional transformation from a pancreatic endocrine tumour manifesting features of a ‘glucagonoma’ into an ‘insulinoma’ and vice versa has been described. So too have manifestations of ectopic hormone production which are more often seen with other types of pancreatic endocrine tumour most of which are malignant. Among the most common syndromes associated with ectopic hormone production by insulin-secreting carcinomas of the pancreas are Cushing’s syndrome, Zollinger-Ellison syndrome, hyperparathyroidism, acromegaly, carcinoidosis, and goitre and hypercalcitoninaemia (Laurent et al. 1971, Wright et al. 1980, Marks & Rose 1981, Bugalho et al. 1994).

Metastatic insulinomas and mixed islet cell tumours vary in their aggressiveness (Ericksson et al. 1989). Progression, from the first appearance of symptoms to death from inexorable hypoglycaemia can occur in 6 months or less unless effective antihypoglycaemic treatment with diazoxide plus chlorothiazide, surgical ablation (debulking), chemotherapy, hepatic artery embolisation, or cryotherapy either alone or in combination, can be achieved (Valette & Souquet 1989, Wells et al. 1990, Krentz et al. 1996).

Providing hypoglycaemia can be prevented, good quality-of-life with survival (for 10 years or more) can occur since these tumours, though malignant, are often very slow growing and do not produce the typical features of metastatic disease such as anorexia, nausea and loss of body weight until late in the course of the disease.

**Aetiology of pancreatic endocrine tumours**

Most insulinomas occur sporadically, a further 5-10% as part of the MEN-I syndrome (Diarmuid et al. 1994, Thakker 1997). An association with NIDDM has been suggested on the basis of a small number of family studies but a link has not been established (Service et al. 1976).

A relative insensitivity to exogenous insulin is often observed in patients harbouring insulinomas and generally attributed to, though far from established as due to, ‘down regulation’ of insulin receptors (Nankervis et al. 1985, McGee et al. 1987, de Kreutzenberg et al. 1994). It has long been known to persist after successful removal of the tumour and abolition of hypoglycaemia, and in a minority of cases insulin manifests itself as impaired glucose tolerance or even frank diabetes. While this may be secondary to damage done to the pancreas during resection of the tumour (Dunn 1971) it may also be due to persistence of a primary defect in peripheral insulin sensitivity (de Kreutzenberg et al. 1994) similar to that seen in patients with NIDDM.

It is probably no coincidence that no example of a benign insulinoma developing in a patient with type I
diabetes (insulin-dependent diabetes mellitus (IDDM)) has ever been reported, in contrast to patients with type II diabetes (NIDDM) in whom it occurs with possibly an even greater frequency than in the general population (Heik et al. 1988, Grunberger 1993). A contrary view has been expressed by Kane et al. (1993) who found pre-existing diabetes in only 1 of their series of 313 patients with insulinoma, making it a very rare occurrence indeed.

A case of malignant insulinoma has, however, recently been reported in a patient with incontrovertible type I diabetes (Swartberg et al. 1996).

MEN-I
Insulinomas are the commonest manifestation of MEN-I after parathyroid and pituitary adenomas. They do not occur in the other varieties of multiple endocrine adenomatosis, i.e. MEN-IIa and -IIb. The familial occurrence of seemingly solitary insulinomas (Maioli et al. 1992) has been reported on several occasions, but whether this represents a forme-fruste of MEN-I (Diarmuid et al. 1994) or a specific abnormality awaits gene analysis of affected individuals (Larsson et al. 1988).

Hyperinsulinaemic hypoglycaemia in children and young adults is particularly likely to be due to either MEN-I or to the persistent functional hyperinsulimism of infancy, formerly referred to as nesidioblastosis (Mathew et al. 1988, Losada et al. 1995). In children below the age of 4 years the histopathological features of solitary insulinomas removed at operation resemble those of ‘nesidioblastosis’ more closely than those of solitary benign insulinomas in adults.

Chemical pathology
Insulin Spontaneous hypoglycaemia was believed from the time of its first description as a clinical entity, until the introduction of radioimmunoassays for insulin in blood, to result from overproduction of insulin by an insulin-secreting tumour similar to that of thyroxine in thyrotoxicosis rather than, as is now quite apparent, from its inappropriate rather than excessive secretion (Samols & Marks 1963).

Normal glucose homeostasis depends, in large part, upon the ability of the very modest fall in blood glucose concentration produced by fasting to below a predetermined ‘set’ to suppress endogenous insulin secretion. The suppression is not ordinarily complete, however; (unlike in IDDM) so that although peripheral glucose-dependent tissues no longer abstract glucose from the glucose pool, lipolysis in adipose tissue and glycogenolysis in the liver is not sufficiently disinhibited as to permit rampant ketosis and hyperglycaemia. Instead plasma ketones (and non-esterified fatty acid (NEFA) levels) rise only modestly and net glucose production by the liver (appearance) is constrained to match utilisation by the brain and other obligatory glucose using tissues (Marks & Rose 1981).

It is the inability of insulin-secreting tumours of the pancreas to shut down their insulin secretion in response to hypoglycaemia, whether induced by fasting or exogenous insulin, that is their biochemical hallmark. This anomaly occurs only very rarely in other disorders, most notably PHHI or ‘nesidioblastosis’ and sulphonylurea overdose (Teale et al. 1989).

Though insulinoma B-cells may be functionally abnormal in other ways, none is as uniformly present as failure to suppress insulin secretion in response to hypoglycaemia. Most respond poorly, if at all, to the insulinotrophic effects of hyperglycaemia per se (produced by intravenous glucose for example) and do not exhibit a first phase insulin response to intravenous glucose.

They do, on the other hand, generally respond normally or excessively to glucagon and other insulinotropic enteric hormones (gastric inhibitory peptide and glucagon-like peptide-I (GLP-I)) that are released into the blood following ingestion of a meal. This may account for the rare examples of insulinoma that present with a history of reactive rather than of fasting hypoglycaemia.

The insulinotropic amino acid L-arginine generally produces a normal insulinemic response in insulinoma patients. This is in contrast to L-leucine which - whether given orally or intravenously - often provokes excessive insulin secretion and precipitates hypoglycaemia. A similar response is observed only in patients with the leucine-sensitive variety of PHHI and normal subjects pretreated with sulphonylureas.

Insulinomas may respond to hypercalcaemia by secreting insulin in amounts sufficient to produce hypoglycaemia. Advantage has been taken of this fact -like that of other insulin secretagogues, such as tolbutamide and glucagon - in the diagnosis of insulin-secreting tumours. All such tests are of limited diagnostic use because of their low predictive value. They are most useful (Doppman et al. 1995) when employed in conjunction with percutaneous trans-hepatic catheterisation for pre-operative localisation, should this be considered necessary, of insulinomas already diagnosed by more reliable methods.

Proinsulin Proinsulin ordinarily constitutes a higher proportion of circulating total IRI in patients with insulinomas than in healthy people, especially in patients harbouring malignant tumours (Samols 1965, Hayashi et al. 1977, Cohen et al. 1986, Cohen & Camus 1988, Hampton et al. 1988, Hale et al. 1991, Marks et al. 1992, Tasaka et al. 1993, Gorden et al. 1995). It is still unclear whether this is a consequence of the neoplastic process or a factor in its aetiology, as it might be if the propensity to develop an insulinoma is greater in people with a predisposition to NIDDM.
Rarely, benign tumours have been found that secrete proinsulin as their main (Alsever et al. 1975) or even sole insulin-like product, leading to the suggestion that they should be called ‘proinsulinomas’ (Cohen & Camus 1988).

In one such case, recently studied by us, all of the very small amount of circulating insulin appeared to derive from the normal islets and it responded to insulinotrophic stimulation with glucose, glucagon etc. and to suppression by octreotide, whereas the proinsulinoma itself did not.

**Non-pancreatic tumours**

In 1929 Nadler and Wolfer published a case of hypoglycaemia associated with primary carcinoma of the liver. One year later Doege described a patient with episodes of glycaemia associated with primary carcinoma of the liver. In 1929 Nadler and Wolfer published a case of hypoglycaemia when they recurred and were shown to be of hypoglycaemic origin (Marks & Rose 1964, Laurent et al. 1971).

More cases of hypoglycaemia occurring in association with hepatic and other types of carcinoma, or with mesenchymal tumours, were described over the years, in which it was the presenting or dominant feature of the patient’s illness. In others it occurred only as a terminal event.

Hypoglycaemia of both types is referred to, throughout the rest of this article, as NICTH and has many causes.

**Types of tumour**

The association that has attracted most interest has been that between hypoglycaemia and large fibrosarcomas, usually of low or moderate malignancy, arising in the thorax or retroperitoneal space. Hypoglycaemia is, however, rare even in them. In one large series of cases (England et al. 1989) only 3% with benign and 11% with malignant fibrous tumours developed hypoglycaemia at any time in their evolution. Apart from hepatomas the proportion of epithelial tumours manifesting hypoglycaemia is even smaller, probably less than 0.1%.

The true incidence of tumour-induced hypoglycaemia is, however, difficult to ascertain and no population study comparable with those for insulinoma has been published. In our own experience of cases of hypoglycaemia referred for diagnosis from all over Britain, NICTH is about one-quarter (25%) as common as insulinoma but this is probably an underestimate. Many cases undoubtedly go unrecognised especially in patients with metastatic disease.

The cause of NICTH was, from the time of its discovery until comparatively recently, the subject of intense speculation (Field et al. 1963, Laurent et al. 1971, Marks & Rose 1981). It is now recognised that in most cases it is a consequence of overproduction of an aberrant form of IGF-II (Megyesi et al. 1974, 1975, Gorden et al. 1981, Axelrod & Ron 1988, Ron et al. 1989, Lowe et al. 1989, Shapiro et al. 1990, Teale & Marks 1990, Daughaday & Trivedi 1992). Other, even rarer causes, are sometimes encountered, however, and these will be discussed later.

**Histological classification**

Though fibromas and fibrosarcomas are probably the best known example of tumour-producing NICTH, no histological type of tumour is exempt. Hypoglycaemia, once manifest, is usually both profound and relentless. It may, however, respond to surgical ablation or debulking of the tumour - at least temporarily. Surprisingly hypoglycaemia does not always reappear even if the tumour recurs and grows to its former size.

In patients who present with NICTH the anamnesis is similar to that of insulinoma. Differentiation is, however, easily made on the basis of plasma hormone assays (Marks & Teale 1996). Unlike insulinoma, in which hypoglycaemia is always the presenting symptom, in NICTH the diagnosis of neoplasia may already have been made by the time hypoglycaemia appears.

NICTH is not necessarily an indicator of size or invasiveness of the tumour, though fibromas and fibrosarcomas are invariably large or very large by the time they manifest it. Only very rarely do such tumours weigh less than 500 g and most weigh between 2 and 4 kg. The largest so far recorded weighed over 20 kg. Most are in the thorax or in the retroperitoneal space and may, despite their large size, have been clinically silent.

Other tumours of a special interest because of their association with hypoglycaemia are hepatomas, haemangiopericytomas, pheochromocytomas, adrenocortical adenomas and carcinomas, myelomas, lymphomas and leukaemias. Even tumours of the meninges have been described as causing NICTH (Ferguson & Flinn 1995, Phuphanich et al. 1995) and it would appear reasonable to assume that no type of tumour is exempt (Table 1).

Cranioopharyngiomas, pituitary adenomas and tumours of the brain that have been treated by irradiation may cause hypoglycaemia secondary to hypopituitarism - usually as a late phenomenon but occasionally as the presenting symptom. They will not be considered here.

**Chemical pathology of NICTH**

Despite a few early reports of dubious authenticity in which insulin was claimed to be the causative agent (Pavelic & Popovic 1981, Baltic et al. 1985) NICTH is now known not to be caused by insulin. Indeed, doubt has been expressed as to whether ectopic insulin production has ever been demonstrated in a tumour that was not of

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Marks and Teale: Tumours producing hypoglycaemia

The few cases of ectopic insulin production extant in the literature have usually either been metastatic APUDomas (Sasaki et al. 1980) possibly of pancreatic origin, or are insufficiently well documented to substantiate the claim that they were insulin or proinsulin producing. A very recent case of cervical cancer investigated by us is a possible exception since it produced insulin, C-peptide and proinsulin in prodigious amounts. In an otherwise typical case of NICTH described by Lyall et al. (1975) plasma insulin levels were both absolutely and inappropriately high during hypoglycaemia prior to removal of a 680 g thoracic neurofibrosarcoma but returned to normal post-operatively with restoration of normoglycaemia. The tumour contained no secretory granules and extracts of it contained no insulin. The possibility that the tumour secreted an insulinotrophic substance cannot be dismissed.

The controversy as to whether NICTH is due to overproduction of one or other of the two IGFs (IGF-I and IGF-II) or to some other substance with insulin-like properties was largely a consequence of difficulties with assay technology (Baxter 1990). These have now been partially resolved but still account for some of the difficulties experienced by authors using poorly validated assay techniques.

The commonest cause of NICTH is undoubtedly the overproduction of an aberrant form of IGF-II (Daughaday 1997). Most, if not all of the other biochemical effects that are observed, such as suppression of insulin, glucagon, growth hormone (GH) secretion and depression of circulating NEFA and ketone levels, stem from this.

There are, however, other rare causes of NICTH such as autoantibodies to the insulin receptor, overwhelming metastatic destruction of the liver and the production of tumour necrosis factor (TNF) and other hypoglycaemic cytokines, and these are considered later.

**Table 1** Histological classification of 68 consecutive tumours producing NICTH through overproduction of IGF-II investigated in Guildford.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number</th>
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<tbody>
<tr>
<td>Carcinoma</td>
<td>31</td>
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<tr>
<td>Lung</td>
<td>7</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6</td>
</tr>
<tr>
<td>Stomach</td>
<td>5</td>
</tr>
<tr>
<td>Undifferentiated</td>
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<tr>
<td>Adrenal</td>
<td>2</td>
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<tr>
<td>Kidney</td>
<td>2</td>
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<tr>
<td>Oesophagus</td>
<td>2</td>
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<tr>
<td>Ovary</td>
<td>1</td>
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<td>Prostate</td>
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<td>Breast</td>
<td>1</td>
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<tr>
<td>Larynx</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoma/fibroma</td>
<td>23</td>
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<tr>
<td>Fibrosarcoma</td>
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<tr>
<td>Haemangioendocrineoma</td>
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<tr>
<td>Neurofibroma</td>
<td>1</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
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</tr>
<tr>
<td>Sarcoma of kidney</td>
<td>1</td>
</tr>
<tr>
<td>Hepatoma</td>
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<tr>
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**IGF-I and IGF-II** Description of the IGFs, their isolation, nomenclature and full range of biological properties is beyond the scope of this review (Froesch et al. 1963, Jacob et al. 1968, Froesch & Zapf 1985, Clemmons 1989). So too is discussion of the IGF-binding proteins (IGFBPs) (Baxter & Martin 1989, Baxter et al. 1995, Baxter 1996) of which at least six types have been identified in plasma and possibly a seventh.

The IGFBPs were identified by their ability to mimic the effects of insulin upon isolated tissues in vitro in the presence of neutralising anti-insulin antibodies. Together, the two IGFBs account for most of the biological activity described in the older literature as non-suppressible insulin-like activity.

Both IGF-I and IGF-II are structurally similar to proinsulin. Immunologically they differ both from it and from one another. Immunoassays have been developed for each of the IGFBPs with little or no cross-reactivity between them and none at all with proinsulin. Clear separation of the three chemical species was, however, not possible with earlier bio- and radioreceptor assays and this may explain some of the confusion found in the older literature surrounding investigations into the aetiology of NICTH.

Both IGF-I and IGF-II circulate almost completely (>90%) bound to specific IGFBPs. This in complete contrast to insulin and proinsulin for which there are no specific binding proteins.

The two IGFBs bind with more or less equal avidity to each of the IGFBPs. The complex formed associates with an acid-labile subunit (ALS) to make a ternary complex. This has a molecular mass in the region of 150 kDa, which virtually confines it to the intravascular compartment. In normal healthy subjects the total concentration of IGF is, in molar terms, equal to or slightly less than that of the combined IGFBPs.

Production of the IGFBPs and their release into the circulation is determined by a variety of factors. Production of the most plentiful (IGFBP-3) is linked, in some poorly understood way, to the production of IGF-I itself. This, in turn, is linked to GH action on the liver.
Though many, if not all, tissues, are capable of producing it, IGF-I in the circulation derives almost entirely from the liver. The liver is also the main, if not sole, source of the IGFBPs. The origin of circulating IGF-II is seemingly not exclusively the liver.

The normal molar ratio of IGF-II:IGF-I in plasma varies but is usually about 3:1. Their concentration, whether expressed in molar or mass units, is many hundreds of times that of insulin (Table 2). They do not ordinarily exert an insulin-like effect, however, either on blood glucose or NEFA levels because they are virtually excluded from contact with insulin and IGF receptors on tissues due to their incorporation into the IGFBP/ALS/IGF ternary complex. This may explain why, despite their normal concentration in patients with uncontrolled IDDM, IGFs exert no hypoglycaemic or antilipolytic effect.

**Big IGF-II** The demonstration of increased amounts of the mRNA for IGF-II in tumour tissue taken from patients with hypoglycaemia-producing tumours established a role for it in the pathogenesis of NICTH (Lowe et al. 1989, Shapiro et al. 1990). It was, however, only after radio-immunoassays for circulating IGF-I, IGF-II, and latterly, the E-domain of the ‘large’ or aberrant form of IGF-II, became available (Perdue et al. 1991) that the key role of IGF-II in the pathogenesis of NICTH has been proved. Indeed the presence, in plasma, of increased concentration of IGF-II, mostly of the ‘big’ but also the normal variety (Daughaday et al. 1988, 1990), coupled with a gross reduction in the amount of IGF-I is so characteristic of NICTH that it is diagnostically useful (Teale & Marks 1990).

It has still to be determined whether the reduced affinity of ‘big’ IGF-II for IGFBPs (Daughaday & Kapadia 1989, Daughaday 1997) or the reduction in circulating amounts of IGFBP-3 and ALS is the main reason that these tumours produce hypoglycaemia. They do so by increasing the availability of ‘free’ IGF-II to bind to IGF receptors - and possibly to insulin receptors - in the tissues.

**Immunooassay** Immunooassays for plasma IGF-I have been used clinically for many years in the assessment of malnutrition, for diagnosing and monitoring the response to treatment in acromegaly and to human growth hormone (hGH) in hypopituitarism (Teale & Marks 1986). Clinical assays for IGF-II are, however, comparatively new and still poorly validated (Baxter 1990). Most antisera fail to distinguish between regular IGF-II and the larger molecular forms possessing the E-domain. This is ordinarily cleaved from proIGF-II during intracellular processing but in NICTH there is a defect which leads to the appearance in the plasma of a disproportionately large amount of the uncleaved peptide. This is analogous to the disproportionate ratio of proinsulin to insulin in the blood of most patients with insulinomas.

**IGF-II:IGF-I ratio** Teale & Marks (1990) were the first to draw attention to the distortion of the IGF-II:IGF-I ratio in patients with NICTH and suggest that it might prove useful in its diagnosis, especially in cases in which IGF-II levels themselves were ‘normal’ or only slightly elevated. Their early conclusions have been confirmed repeatedly and a molar ratio of total plasma IGF-II:IGF-I of more than 10 is virtually pathognomonic of NICTH. Apart from NICTH, abnormally high IGF-II:IGF-I ratios are found only in very rare cases of hypoglycaemia due to sepsis or cachexia, but in them the absolute amounts of IGF-II are generally subnormal as well as those of IGF-I.

Results in 50 consecutive patients with NICTH whose plasma was assayed in Guildford are shown in Table 2. Twenty-eight patients were women and 22 men. Seventy-

| **Table 2** Diagnostic parameters in 50 consecutive cases of NICTH. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Age (years)** | 16 ±15 (30-91)  | **Glucose (mmol/l)** | 2.4 ±2.5 | **Immunoreactive insulin (pmol/l)** | <25 | **C-peptide (pmol/l)** | <75 | **β-hydroxybutyrate (µmol/l)** | 143 ±151 | **Growth hormone (mU/l)** | 4.6 ±6.2 | **Total IGF-I (nmol/l)** | 5 ±2 | **Total IGF-II (nmol/l)** | 102 ±35 | **IGF-II:IGF-I molar ratio** | 21.8 ±10.7 | **'Big' IGF-II (nmol/l)** | 20.1 ±6.0 |
| **Control hypoglycaemic subjects** | **<3.0** | **Variable, depending on cause** | **Variable, depending on cause** | **>300** | **>10** | **18 ±14** | **68 ±12** | **3.8 ±1.5** | **9.8 ±2.0** |

* Including hyperinsulinism: iatrogenic and spontaneous.  ** Excluding hypoglycaemia caused by hyperinsulinism: iatrogenic or spontaneous.
six percent were aged 60 or more, the youngest was 28 years old, the oldest 91. All had blood glucose levels below 2.2 mmol/l at some time in the course of their illness, although only 44 patients were hypoglycaemic at the time blood was collected for hormone assay. Plasma β-hydroxybutyrate levels were below 300 μmol/l in 37 of the 42 patients in whom they were measured whilst hypoglycaemic. In none did they exceed 600 μmol/l.

More than 50% of the tumours in which the histology was known were of epithelial origin. Carcinomas of the lung and of the stomach were the most common (Table 1).

**Other hormones** Abnormalities of many other hormones concerned with glucose homeostasis are characteristic of NICTH (Marks 1976). Plasma insulin, proinsulin and C-peptide levels are invariably low during hypoglycaemia and do not respond normally to hyperglycaemia and other insulinotrophic stimuli (Marks & Samols 1966). Plasma GH levels are also low or very low during spontaneous hypoglycaemia and this is thought to be due to a direct suppressant action of IGF-II on GH secretion. Patients with insulinomas may also have low plasma GH levels during spontaneous hypoglycaemia, but in them it is thought to be secondary to hypothalamic adaptation to hypoglycaemia itself. Plasma glucagon levels are invariably low in patients with NICTH and do not respond normally to glucagonotrophic stimuli. This is unlike adrenaline, which responds normally to hypoglycaemia (Eastman et al. 1992), but too few patients have yet been investigated to validate this conclusion.

**Pathophysiology of NICTH**

The initiating factor in NICTH appears to be primary overproduction of predominantly ‘big’, but also of regular IGF-II, by the tumour. Thereon the mechanism is speculative.

Our own view is that primary overproduction of IGF-II by the tumour leads to an increase in the concentration of ‘free’ IGF-II in the plasma and a secondary reduction in GH secretion. One consequence of this is reduced production and secretion by the liver of IGFBP - especially IGFBP-3, which is far and away the most plentiful and ‘GH-dependent’ - as well as of IGF-1 itself. There is also a marked reduction in circulating ALS.

The overall reduction in total IGFBPs - despite a notable and probably ‘compensatory’ increase in IGFBP-2 - permits more of the IGF-II to circulate in the ‘free’ or unbound form and consequently to a greater percentage of it becoming available for binding to IGF receptors - as well as to insulin receptors with which it cross-reacts (Fradkin et al. 1989) - and which are present on liver, muscle and all other peripheral tissues.

That this can be accomplished without a significant increase in total plasma IGF-II was recently demonstrated by Moller et al. (1996) in a case of NICHT in which ‘free’ IGF-II was increased 30-fold and ‘free’ IGF-1 more than 4-fold despite an almost insignificant increase in total plasma IGF-II and an 85% reduction in IGF-1.

Hypoglycaemia results from a combination of decreased release of glucose into the blood by the liver and grossly accelerated glucose utilisation by muscle and other tissues. In NICTH this can reach prodigious proportions, much greater, for example, than is ordinarily encountered in insulinoma in which insulin resistance is a common feature.

The 3- to 5-fold increase in insulin receptor number in a patient with NICTH due to colon cancer described by Stuart et al. (1986) was probably a result of ‘up-regulation’ of insulin receptors in response to suppressed plasma insulin levels that are so characteristic of NICTH. This is, however, unlikely to be the explanation for the increased insulin sensitivity that was held to account for the occurrence of (insulin-induced) hypoglycaemia in an insulin-dependent diabetic patient after he developed a primary hepatoma (Barzilai et al. 1991) since in this patient the sole source of insulin had been from a bottle. Similarly, in a case described by Sturrock et al. (1997), in which the IGF-II:IGF-1 ratio was high as a result of a pancreatic carcinoma, spontaneous hypoglycaemia developed late in the course of her illness necessitating discontinuation of insulin therapy.

Non-insulin-dependent glucose uptake by the tumour itself, reflected in the hyperlactacidaemia often found in these cases, may also make a small contribution to the hypoglycaemia but it is not, as was once thought, a key factor in its pathogenesis.

The role of depressed counterregulatory hormone secretion presumably by IGF-II in NICTH is difficult to assess. The hyperglycaemic response to exogenous glucagon is often exaggerated unlike the insulinaemic response, which is suppressed. Likewise exogenous GH may alleviate hypoglycaemia in NICHT without affecting plasma IGF-II levels (Teale & Marks 1998).

Unlike the counterregulatory polypeptide hormones, both adrenaline and nor-adrenaline secretory mechanisms are said to remain intact in patients with NICHT (Eastman et al. 1992).

**Associated conditions**

Laurent et al. (1971) drew attention to the high incidence (10%) of thyroid enlargement, with or without thyrotoxicosis, in patients with NICHT and to its association with acromegaly. Skin tags, excessive oiliness of the skin and rhinophyma have also been observed (Trivedi et al. 1995), but whether these features, which are
characteristically associated with over- rather than under-production of GH, are related to, and caused by, over-expression of IGF-II activity is unknown.

**Coincidence of fibromas and insulinomas** The coincident presence of a large mesenchymal tumour capable of producing NICTH in patients harbouring an insulinoma has been reported on several occasions both before and after the advent of immunoassays capable of differentiating between them (Bruno & Ober 1962, Coskey & Tranquada 1964). Since neurofibromatosis has also been described in association with other types of APUDoma the occurrence may be more than coincidental (Fung & Lam 1995).

**Hepatomas**

Hypoglycaemia due to hepatoma was described soon after that due to insulinoma and earlier than that from any other type of non-islet cell tumour. Many of the large series of NICTH due to primary hepatoma have emanated from the far east where hepatomas are common (McFadzean & Yeung 1956, 1969) but it is also disproportionately common in the USA (Wu et al. 1988, Shapiro et al. 1990) as well as in the UK.

McFadzean & Yeung (1969) distinguished two types of hepatoma causing hypoglycaemia: type A tumours, which are far the commonest, are rapidly growing, poorly differentiated tumours that are associated with rapid wasting and muscular weakness; type B tumours, which are slow growing, are histologically well differentiated and occur in patients who appear to be well nourished.

In patients with type B tumours the requirement for glucose to prevent hypoglycaemia can be prodigious, some patients requiring up to 1500 g glucose intravenously per day. Type A patients, on the other hand, require only very modest amounts of glucose to prevent hypoglycaemia, which is usually a terminal event immediately after excision of a pheochromocytoma. Plasma insulin levels were also abnormally high, relative to their prevailing blood glucose levels, in the remaining eight patients (Akiba et al. 1990).

In two patients with fasting hypoglycaemia due to pheochromocytoma studied by Gorden et al. (1981) plasma levels of ‘IGF-like materials’ were described as modestly raised. It seems probable, therefore, that pheochromocytomas, like most other tumours, can produce fasting hypoglycaemia by secreting ‘big’ IGF-II.

**Lymphomas, myeloma and leukaemia**

Hypoglycaemia occurs as an unusual phenomenon in patients with various types of lymphoma (Wanebo et al. 1971). The hypoglycaemia was, at one time, thought to be a consequence of the secretion of abnormal steroids with specific hypoglycaemic properties. This now seems unlikely and, in two recent cases of our own, the chemical pathology was no different from that of other IGF-II-secreting tumours. Nevertheless it seems reasonable, until proved otherwise, to assume that some of the unusual steroids these tumours produce may, in some way, contribute to the production of hypoglycaemia - possibly by interfering with normal glucocorticoid production or action.

**Endocrine-Related Cancer**

**Adrenocortical tumours and pheochromocytomas**

**Steroid-secreting tumours**

Adrenocortical tumours are a rare but well-recognised cause of NICTH (Marks & Rose 1964, Laurent et al. 1971). The hypoglycaemia was, at one time, thought to be a consequence of the secretion of abnormal steroids with specific hypoglycaemic properties. This now seems unlikely and, in two recent cases of our own, the chemical pathology was no different from that of other IGF-II-secreting tumours. Nevertheless it seems reasonable, until proved otherwise, to assume that some of the unusual steroids these tumours produce may, in some way, contribute to the production of hypoglycaemia - possibly by interfering with normal glucocorticoid production or action.

**Catecholamine-secreting tumours**

Both reactive and fasting hypoglycaemia have been described in association with malignant pheochromocytoma (Gorden et al. 1981). The cause is unlikely to be the same in each of these situations.

Severe reactive hypoglycaemia in patients with a pheochromocytoma with remission following its surgical removal has been described on a number of occasions. It has also been reported as occurring for the first time immediately following tumour excision (Hiramatsu et al. 1987, Paineau et al. 1988, Akiba et al. 1990, Chiang et al. 1993). The mechanism in such cases is unknown, but seemingly connected to the presence of excessive catecholamine action either stimulating insulin secretion or through a post-receptor effect.

Episodic, probably stimulative, hyperinsulinism has been demonstrated in at least one patient with reactive hypoglycaemia due to pheochromocytoma and in which fasting hypoglycaemia was not a feature (Hiramatsu et al. 1987).

Very high plasma insulin levels were found in two out of ten patients (12 480 pmol/l and 1144 pmol/l respectively) who developed profound hypoglycaemia immediately after excision of a pheochromocytoma. Plasma insulin levels were also abnormally high, relative to their prevailing blood glucose levels, in the remaining eight patients (Akiba et al. 1990).

In two patients with fasting hypoglycaemia due to pheochromocytoma studied by Gorden et al. (1981) plasma levels of ‘IGF-like materials’ were described as modestly raised. It seems probable, therefore, that pheochromocytomas, like most other tumours, can produce fasting hypoglycaemia by secreting ‘big’ IGF-II.


1971, Marks & Rose 1981, Durig et al. hypoglycaemia and lymphoma or fibrosarcoma (Laurent leukaemia (Makino et al. 1985) just as in patients with hypoglycaemia and lymphoma or fibrosarcoma (Laurent et al. 1971, Marks & Rose 1981, Durig et al. 1996).

**Insulin-receptor antibodies**

Evidence for the existence and pathogenic role of stimulatory insulin-receptor antibodies in hypoglycaemia caused by Hodgkin’s disease has been produced by two groups of authors (Braund et al. 1987, Walters et al. 1987). IGF-II was not measured in either of the cases reported but in one of them IGF-I, measured by bioassay, was said to be just below the reference range. Plasma GH measured during spontaneous hypoglycaemia was 12.5 U/l, which is higher than is customarily found in patients with IGF-II-secreting tumours and consistent with the view that some mechanism other than excessive IGF-II production was involved.

Despite the passage of more than 10 years since these two reports were published, no other cases of lymphoma-induced hypoglycaemia in which antibody receptors were implicated have, to our knowledge, been described.

In this context it is of interest that in the seven or so patients with hypoglycaemia and lymphoma investigated by Gorden et al. (1981) the concentration of plasma ‘IGF-like material’, measured by a radioreceptor binding assay and equating largely with multiplication-stimulating activity (now known to be identical with IGF-II) was either low, or very low compared both with a normal reference population and patients suffering from other types of tumour-producing NICHTH. In a further case of hypoglycaemia due to Hodgkin’s disease investigated by us, plasma insulin, C-peptide and proinsulin levels were all suppressed, and IGF-I, IGF-II and IGF-II:IGF-I ratio were normal. Neither insulin autoantibodies nor insulin-receptor antibodies were measured.

The role of stimulatory, insulin-receptor antibodies in the pathogenesis of NICHTH by neoplasms other than lymphomas has been established by various workers (Rochet et al. 1989, Taylor et al. 1989). It is reasonable to assume, therefore, that they are involved in at least some of the rare cases of hypoglycaemia secondary to lymphoma.

**Myeloma and primary monoclonal gammopathy**

An association between hypoglycaemia and myeloma was first reported 25 years ago and that with monoclonal gammopathy more recently (Russell-Jones et al. 1990, Arnqvist et al. 1993). The cause of the hypoglycaemia is not, however, the same in all cases.

In the case of myeloma reported by Snowden et al. (1994) an increased proportion of the IGF-II present in the plasma was of the ‘big’ variety and the IGF-II:IGF-I ratio was abnormally high. Onset of spontaneous hypoglycaemia was marked by reversal of the patient’s long-standing need for insulin to control her NIDDM which began 15 years earlier. Anti-insulin antibodies were not detected in her serum.

In the cases of monoclonal gammopathy described by Wasada et al. (1989) and by Redmon et al. (1992) hypoglycaemia appears to have been insulin mediated and due to its delayed release from insulin-specific mono-clonal autoantibodies in a manner resembling that seen in insulin autoimmune syndrome (IAS). This was true also for the case of myeloma described by Merlo et al. (1992) whose monoclonal (pro)insulin binding immunoglobulin was produced by the neoplastic cells.

In this form of NICHTH, endogenous insulin - released in response to ingestion of a meal but rendered temporarily ineffective by binding to the autoantibody - is slowly released during the post-absorptive period producing an apparently inappropriate hyperinsulinaemia. But whereas IAS is self-limiting, and part of a more general autoimmune disorder, monoclonal gammopathy appears to be a neoplastic disorder in which the para-protein produced has a specific affinity for insulin or proinsulin.

**Hypoglycaemia and metastatic cancer**

Hypoglycaemia may occur as a terminal or agonal event in patients dying from metastatic disease (Younus et al. 1977, Marks & Rose 1981). It is assumed to have a different cause from hypoglycaemia occurring as a dominant and comparatively ‘early’ feature (Marks et al. 1965, MacDougall et al. 1986) in rare cancer patients (especially those with primary tumours of the lung, stomach, pancreas, caecum and colon) in whom plasma insulin and GH levels are depressed and the IGF-II:IGF-I ratio unusually high.

Hypoglycaemia occurring in patients with overwhelming metastatic disease was formerly attributed to ‘liver failure’ secondary to its destruction by the tumour. An equally plausible explanation, as yet unconfirmed (Fitzpatrick et al. 1995), is that it is mediated by various cytokines including TNF-α, and interleukin-1 and -6 which are known to produce profound hypoglycaemia in animals (Mahony & Tisdale 1990, Clark et al. 1992, Battelino et al. 1996) and probably also in human beings.
They are currently thought to be involved in the production of hypoglycaemia in septicaemia and overwhelming infections with malaria parasites (Krishna et al. 1994, Rockett et al. 1994) possibly by stimulating insulin release (Elasted et al. 1996). The situation is, however, still far from clear.

Diagnosis

The diagnosis of NICTH commences with its recognition as the cause of the patient’s neuroglycopenic symptoms. This rarely poses any problem providing the possibility is considered since fasting hypoglycaemia, once it has developed, is relentless and easily confirmed by measurement of the blood glucose concentration. It proceeds through differential diagnosis (Marks & Teale 1996) to elucidation of the cause upon which rational and specific treatment depends. Only the differential diagnosis of fasting hypoglycaemia will be considered here.

Insulinoma

Diagnosis depends upon establishing inappropriate insulin (or rarely proinsulin) secretion during hypoglycaemia provoked by fasting or rigorous exercise. Paradoxically the measurement of C-peptide in plasma is a more sensitive indicator of inappropriate secretion than the measurement of insulin itself (Hattori et al. 1994) as the concentration of C-peptide may be raised in peripheral blood even when that of insulin is suppressed. This anomaly, which has also been reported in children with PHHI (nesidioblastosis) is probably due to a greater than normal fractional extraction of insulin by the liver. This leaves the C-peptide unaffected and consequently free to appear in peripheral blood at an inappropriately high level.

Inappropriate C-peptidaemia (i.e. >100 pmol/l) and hyperinsulinaemia (i.e. >30 pmol/l) in the presence of fasting hypoglycaemia (blood glucose <2.2mmol/l) is virtually pathognomonic for insulinoma or PHHI except when there is accidental or deliberate overdosing with sulphonylurea or other insulinotrophic drugs. Hyper C-peptidaemia may also, very rarely, appear to occur in those patients with IAS in whom the autoantibodies (to endogenous proinsulin) bind C-peptide as well as insulin (Russell-Jones et al. 1990, Merlo et al. 1992). The high titre of autoantibodies that are invariably present in AIS makes distinction from insulinoma comparatively easy providing the possibility is considered and excluded.

Hyperproinsulinaemia (>20 pmol/l) is not diagnostic of any single condition. Nevertheless the presence in plasma of proinsulin at a concentration >50 pmol/l in a patient with a history suggestive of spontaneous fasting hypoglycaemia is presumptive evidence of an insulinoma, whilst its absence, or presence at concentration <20 pmol/l, renders the diagnosis unlikely though not impossible (Cohen et al. 1986, Hampton et al. 1988, Nauck et al. 1990, Tasaka et al. 1993, Gorden et al. 1995).

The ‘gold standard’ for the diagnosis of hyperinsulinism remains Whipple’s triad (which consists of symptoms due to hypoglycaemia demonstrated during fasting and which are relieved exclusively by intravenous glucose) plus the presence of inappropriately high peripheral plasma IRI (>30 pmol/l), C-peptide (>300 pmol/l) and proinsulin (>20 pmol/l) levels in the presence of fasting (or exercise-induced) hypoglycaemia.

When these conditions are met the diagnosis of insulinoma can be made preoperatively with as much certainty as is realistically possible. If they are not, some other explanation for the patient’s hypoglycaemia should be sought.

Although it is fashionable to do so, calculation of a ‘glucose:insulin ratio’ does not determine the appropriateness of insulinaemia (C-peptidaemia) during hypoglycaemic episodes. The ratio is not only method-dependent but also scientifically spurious and should never be used (Hattori et al. 1994). Instead a reference range for plasma insulin, proinsulin and C-peptide concentrations in the presence of hypoglycaemia (<2.2 mmol/l in children and young adults; <3.0 mmol/l in subjects over 60 years of age) should be established against which those obtained in patients with hypoglycaemia can be assessed (Marks & Teale 1996).

C-peptide suppression tests, in which plasma C-peptide levels act as a surrogate for endogenous insulin production, have enjoyed considerable popularity ever since the discovery of C-peptide and assays for measuring it became available. They are, however, no more than screening tests capable of reducing to a manageable size the number of patients in whom the rigorous exercise test or admission to hospital for prolonged fasting are in order since the incidence of both false positives and false negatives is high. Their main value is for distinguishing recurrence of hyperinsulinism following successful removal of one insulinoma when others were also present but missed at operation from a recurrence of symptoms from psychogenic origin (Sata et al. 1995).

None of the many stimulation tests, e.g. tolbutamide, glucagon, L-leucine, intravenous or oral glucose tolerance tests, that have been advocated over the past half-century adds materially to the diagnosis (Marks & Rose 1981, Marks 1989). Their use should be discontinued except where facilities for C-peptide, insulin and proinsulin measurement are not available.

Localisation

Almost every localisation technique has been advocated as a preoperative aid to surgical removal of insulinomas but none withstands critical survey (Table 3). This includes somatostatin receptor scintigraphy (not

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specifically shown in Table 3) the latest fashionable localising technique and which, though very good for localising gastrinomas (86% positive), is no better than any other for localising insulinomas preoperatively (Pitre et al. 1996, Zimmer et al. 1996).

It is quite clear that no preoperative localising technique - including endoscopic ultrasonography, undoubtedly the most sensitive currently available - is sufficiently reliable to make a diagnosis of insulinoma if the biochemical findings are negative nor to justify delay in operating if they fail to localise a tumour proved biochemically to be present (Daggett et al. 1981, Owens et al. 1995, Marks & Teale 1996).

In contrast to preoperative localisation, intraoperative ultrasonography has proved to be extremely useful by enabling even experienced surgeons to localise tumours that their unaided fingers have missed.

**NICTH**

The diagnosis of NICTH is suggested by the association of severe fasting hypoglycaemia with low plasma NEFA and β-hydroxybutyrate levels and undetectable plasma insulin, C-peptide and proinsulin levels, and low GH levels. It is established by the presence of an abnormally high IGF-II:IGF-I molar ratio (>10:1; normal ratio circa 3:1).

An increased concentration of the E-domain of IGF-II is also typically found but is not, in our experience, as predictive as the IGF-II:IGF-I ratio in arriving at a diagnosis (Table 2). Measurements of IGF-II alone should not be relied upon for diagnosis and may be misleading.

Despite earlier optimism, measurements of IGFBPs have not proved clinically useful as yet but have helped to throw light on the mechanism by which tumours produce NICTH. We expect, however, that measurements of 'free' IGF-II and IGF-I will be so when they become more readily available and have been properly evaluated (Chung & Henry 1996, Moller et al. 1996).

Localisation of the IGF-II-secreting tumour producing NICTH rarely gives rise to difficulty once the diagnosis has been established. Occasionally, however, when the tumour is unusually small or obscured by the pelvis, for example, it may come to light only after very thorough investigation using modern imaging techniques. Since

**Table 3** Accuracy of localisation of insulinomas for various imaging techniques: literature survey.

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<tr>
<th>Authors</th>
<th>Angiography</th>
<th>CAT</th>
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<td>38</td>
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<td>79</td>
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*Multicentre trial in endocrine pancreatic tumours: cases include, but not exclusively, insulinomas. CAT = computerised axial tomography; MRI = magnetic resonance imaging.
some of these tumours contain somatostatin receptors which can be visualised using $^{111}$In-octreotide imaging (Perros et al. 1996) the possibility of using this technique to localise a hidden tumour or see whether it has metastasised should be borne in mind in case of difficulty.

**Treatment**

**Insulinoma**

Treatment of tumour-induced hypoglycaemia, as in all types of hypoglycaemia, can be divided into two phases: palliation of an acute episode with intravenous glucose or intramuscular glucagon and definitive, specific treatment directed at its ultimate cause. Intramuscular glucagon will invariably relieve fasting hypoglycaemia in patients with insulinoma, but, because of its propensity to stimulate endogenous insulin secretion, may cause profound rebound hypoglycaemia unless food is given as soon as the swallowing reflex is re-established.

Benign insulin-secreting tumours are best treated surgically unless there are overwhelming clinical reasons for not doing so. Removal of an adenoma is extremely effective although some long-term follow-up series, but not all, suggest that there may be an increased incidence of neuropsychiatric aberration, peptic ulcer disease and NIDDM in those who survived the operation (Dunn 1971, Galbut & Markowitz 1980). Operative mortality is now down to less than 2% in the hands of experienced pancreatic surgeons and virtually confined to those over 70 years of age. In them palliative therapy with diazoxide/chlorothiazide may be worth using since it is often remarkably effective and produces few if any unpleasant side-effects.

Malignant insulin-secreting tumours are often very slow growing and providing hypoglycaemia can be avoided many years of good life may follow initiation of antihypoglycaemic therapy and/or ablation of the primary tumour and as many of the metastases as possible (Marks & Rose 1981, Krentz et al. 1996).

Palliative drug therapy with a combination of diazoxide and a diuretic thiazide is often effective in relieving the hypoglycaemia if this persists after surgery. Long-acting and synthetic somatostatin preparations have been used with varying success in palliation. They may either improve hypoglycaemia, by inhibiting insulin secretion by the tumour, or worsen it by inhibiting secretion of the counterregulatory hormones - glucagon and somatostatin without affecting insulin production itself (Alberts & Falkson 1988, Stenhower et al. 1989, Gama et al. 1995, Meeking et al. 1997). Since improvement is commoner than the reverse a therapeutic trial is probably worthwhile.

Tumoricidal therapy with streptozotocin and other antineoplastic agents of which 5-fluorouracil and adriamycin are the most valuable is sometimes beneficial. Favovable results have also been achieved with hepatic artery thromboembolisation, which may produce remissions lasting a year or more, and cryogenic destruction of metastases. These manoeuvres can be repeated if and when relapse occurs (Krentz et al. 1996).

**NICTH**

Patients with NICTH may undergo complete remission following surgical removal of a benign or locally invasive tumour. Even partial removal often reduces or abolishes hypoglycaemia although it usually recurs if and when the tumour re-establishes itself.

Complete removal of the tumour abolishes any tendency to fasting hypoglycaemia. It also produces a rise in IGF-I and restores the blood glucose and plasma insulin responses to food to normal. Immunoreactive IGF-II levels fall - even if they were not abnormally high (in absolute terms) preoperatively - and the IGF-II/IGF-I ratio returns to normal (i.e. <10). The plasma GH and glucagon responses to hypoglycaemia and other appropriate stimuli are restored and the plasma IGFBP-3 concentration rises to a level which, in molar terms, exceeds the combined concentration of IGF-I and IGF-II (Perros et al. 1996, Teale & Marks 1998).

Contrary to expectations, diazoxide-chlorothiazide treatment often alleviates NICTH - though less predictably than with insulinomas. Both hGH and prednisolone have been used sometimes with great and seemingly specific effect (Mitchell et al. 1965, Khaleeli et al. 1991, Teale et al. 1992, Hunter et al. 1994, Agus et al. 1995, Katz et al. 1996, Perros et al. 1996). In the case of hGH the effect was thought to be mediated by increasing the production of IGFBP-3 but this now seems unlikely (Teale & Marks 1998). In the past the failure to observe a sustained beneficial effect of exogenous hGH after an early favourable response was reported and may have been due to the relatively low doses used or to the development of GH-specific antibodies (Samaan et al. 1990).

Large doses of prednisolone may bring about a remarkable improvement in both glucose homeostasis and other biochemical markers of NICTH (Baxter et al. 1995, Perros et al. 1996). In particular there is a rise in plasma ALS and IGFBP-3 levels (Teale & Marks 1998) and a fall in ‘big IGF-II’ (Baxter et al. 1995). The insulininaemic response to oral glucose is restored and there may be restoration of the endogenous GH response to appropriate stimuli including hypoglycaemia.

Treatment with other anti-inflammatory and immuno-suppressive agents is worthy of trial in cases where insulin antibodies are implicated. It may produce prolonged
remissions (Taylor et al. 1989) as may specific antitumour chemotherapy.

References


Baltic V, Levanat S, Petek M, Bratic-Mikes V, Pavelic K & Vuk-Pavlovic S 1985 Elevated levels of substances immunologically cross-reactive with insulin in blood of patients with malignant and nonmalignant pulmonary tissue proliferation. *Oncoology* 42 174-178.


Endocrine-Related Cancer (1998) 5 111-129
Marks and Teale: Tumours producing hypoglycaemia


Kane LA, Grant CS, Nippoldt TB & Service FJ 1993 Insulinoma in a patient with NIDDM. *Diabetes Care* 16 1298-1300.


Marks V 1989 Diagnosis and differential diagnosis of hypoglycaemia. Mayo Clinic Proceedings 64 1558-1561.


Marks and Teale: Tumours producing hypoglycaemia


Teale JD & Marks V 1998 Glucocorticoid therapy suppresses abnormal secretion of big IGF-II by non-islet cell tumours
inducing hypoglycaemia (NICTH). Clinical Endocrinology (In Press).


