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Hypoglycæmia of Non-endocrine Origin (Non-islet Cell Tumours)

Hypoglycæmia secondary to 'non-islet cell' neoplasms is well recognized. Though symptoms often develop late in the course of the illness – when they may be attributed to cerebral secondaries – they are frequently the cause of presentation. When this occurs, the anamnesis may be indistinguishable from that of insulinoma and a cause of diagnostic difficulties. Far commoner, and more important, is failure to suspect hypoglycæmia and initiate investigations. Only increased clinical awareness of the diverse symptomatology of hypoglycæmia can overcome this.

This report is based upon a survey of the literature (Table 1) and 9 personal cases of 'non-islet cell' neoplasms (3 of carcinoma and 6 of fibrosarcoma) producing hypoglycæmia, of which some details have already been published in 7 (Samols 1963, Marks *et al.* 1965).

Although more than 200 cases have been described, the mechanism by which they produce hypoglycæmia is still poorly understood. It is unlikely to be the same in all cases, but the evidence suggests that in the majority hypoglycæmia is due to direct or indirect inhibition of hepatic glucose release (Butterfield *et al.* 1960, Samols 1963, Froesch *et al.* 1963) by a humoral factor produced by the tumour which may, or may not, also increase peripheral glucose utilization. Such humoral substances, with rare exceptions, have few of the physical, chemical or biological properties of insulin, so that detection by conventional techniques is difficult or impossible.

Table 1
'Non-islet cell' neoplasms associated with spontaneous hypoglycæmia in man

Type of tumour	*No. of cases recorded in the literature*
Mesenchymal	100+
Other carcinomas:	
Stomach, pancreas, cæcum, lung	15
Hepatic	30
Adrenal	15
Myxomata	3
Leukæmia	1

Mesenchymal Tumours

These are invariably large and their average weight is 2–3 kg (range 0·8 to 21·0 kg). Their histology is varied; most are clearly malignant, but some appear benign. Thirty-six per cent occur in the thorax, 24% retroperitoneally and the remainder (40%) intra-abdominally, including the pelvis (Lipsett *et al.* 1964). Most of the patients are elderly (over 60) but occasionally young adults or adolescents are affected. In almost half, symptoms attributed to hypoglycæmia are the presenting complaint, but in others the tumour was known to have been present for up to twenty years (Crocker & Veith 1965). Further endocrine disorders, e.g. goitre, thyrotoxicosis, gynæcomastia, virilism or acromegaly, occur in at least 10% of cases, suggesting that the association is more than coincidental (Marks & Rose 1965) and is due to the production of one or more hormonally active substances by the neoplastic tissues.

Epithelial Tumours

Only an infinitesimally small proportion of carcinomata arising elsewhere than in the pancreas are associated with hypoglycæmia, but in them it may be their mode of presentation (Marks *et al.* 1965) and major cause of symptoms. Though many types of tumour are involved, e.g. lung, stomach and cæcum, three deserve special attention:

(1) *Primary hepatic carcinoma:* Cases have been reported from all over the world, but most have occurred in the Far East – possibly reflecting the high local incidence of this type of tumour. Death is seldom long delayed once hypoglycæmia has appeared. Polycythæmia is a common associated abnormality and hypercalcæmia may occur (Becker *et al.* 1963).

(2) *Adrenal tumour:* These tumours are usually malignant, but occasionally benign, and invariably large (average weight 1·8 kg). Over-production of adrenal steroids is the rule but, though virilism is often present, Cushing's syndrome is rare and in some cases clinical evidence of adrenocortical over-activity is entirely lacking.

(3) *Acinar carcinoma of the pancreas:* Though few cases of primary acinar tumour have been recognized as a cause of spontaneous hypoglycæmia, they are of especial interest since, like pancreatic metastases (Yalow & Berson 1965) but in contrast to other hypoglycæmia-producing

Table 2
'Fasting' blood glucose and plasma insulin levels on different occasions in 3 subjects with spontaneous hypoglycæmia due to non-islet cell carcinomas. None was able to tolerate a twelve-hour fast without developing severe symptomatic hypoglycæmia

Patient No.	*Type of tumour*	*Fasting blood glucose (mg/100 ml)*	*Fasting plasma insulin (μU/ml)*
1	Gastric carcinoma	6–30	9, 5, 2
2	Bronchial carcinoma	30–40	7, 5, 2
3	Acinar pancreatic carcinoma	30–40	72, 42, 31, 19, 18, 17

tumours, they may cause inappropriate insulin secretion (Table 2) probably by local involvement of the islets of Langerhans. It is possible that certain 'atypical' insulinomata are really examples of primary acinar pancreatic carcinoma.

Leukæmia
The association of hypoglycæmia with leukæmia is well documented in the rat, but in man only one case has been reported (Marks & Rose 1965), and this may have been factitious due to utilization of glucose in the blood after collection by the abnormal leucocytes despite adequate fluoridization.

Diagnosis
Diagnosis of hypoglycæmia presents few difficulties once the possibility is entertained. Except for a few hours after a meal, when the blood glucose may be abnormally high, hypoglycæmia, once it has appeared, seldom remits and blood analysis after an overnight (twelve-hour) fast – especially when combined with moderate exercise – rarely fails to reveal it. Only in exceptional cases is more prolonged fasting required – or possible.

It cannot be over-emphasized that these conclusions are based on blood *glucose* measurements, as nonspecific techniques for blood *sugar* are of limited value for detecting hypoglycæmia and may be frankly misleading. A glucose-oxidase method should always be used for this purpose.

The tumour, because of its large size, is usually discovered during routine physical and radiological examination, but may escape detection in obese subjects when retroperitoneal or wholly intra-abdominal. Hypoglycæmia may then be wrongly attributed to insulinoma and incorrect treatment given. A further rare, but important, source of difficulty is the association of a non-pancreatic tumour – itself potentially capable of producing hypoglycæmia – with insulinoma, several examples of which have now been observed (Clinico-pathological Conference 1962, Coskey & Tranquada 1964, Yalow & Berson 1965). Under these circumstances diagnosis may be impossible without specialized investigation.

Tests which depend solely upon a change in blood glucose level are of little value in differential diagnosis (Samols 1963) but when combined with insulin assays are extremely valuable (Fig 1).

Investigations
Plasma insulin: Increased ability of plasma from these patients to enhance tissue glucose uptake *in vitro* (ILA) has been reported in a minority of cases, but immunoassays for insulin have invariably yielded normal or low values (Samols 1963, Floyd *et al.* 1963, Boshell *et al.* 1964, Perkoff & Simons 1963, Friend & Hales 1965, Volpe *et al.* 1965, Subauste *et al.* 1965, Yalow & Berson 1965) even when ILA was high. The rare exceptions with high plasma insulin levels either had pancreatic metastases or co-existing insulinomas.
Intravenous tolbutamide tests: The glycæmic response to intravenous tolbutamide in patients with non-islet cell tumours is variable; in many the fall in blood glucose is normal or subnormal, but in about half the pattern is indistinguishable from that of insulinoma. The plasma insulin response, on the other hand, is depressed (or, rarely, normal); the exaggerated insulinæmic response typical of hyperinsulinism (Samols & Marks 1963) does not occur and its presence is indicative of co-existing insulinoma (Coskey & Tranquada 1964).

Glucagon Tests
Although the glucagon test (Marks 1960) bears a superficial resemblance to the oral glucose

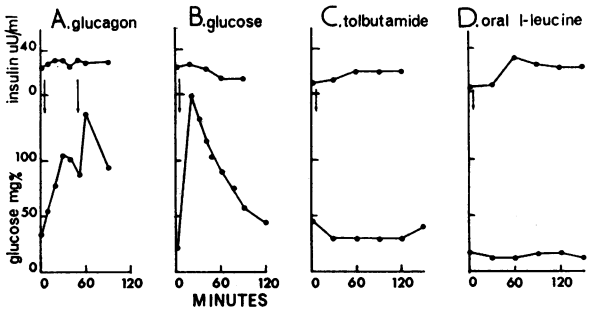

Fig 1 *Effect of conventional stimuli to insulin secretion on blood glucose and plasma insulin levels on four different occasions, after an overnight fast in a patient with a 'hypoglycæmia-producing' fibrosarcoma.* A, *two injections of glucagon (1 mg) given intravenously sixty minutes apart produced a normal rise in blood glucose but no increase in plasma insulin.* B, *25 g glucose intravenously had no effect upon plasma insulin.* C, *sodium tolbutamide (1 g intravenously) produced a normal fall in blood glucose but no change in plasma insulin.* D, *l-leucine (150 mg/kg bodyweight, by mouth) produced a small significant rise in plasma insulin but no change in the blood glucose*

tolerance test, recent evidence that glucagon stimulates insulin secretion directly (Samols *et al.* 1965) has shown that it is fundamentally different, accounting for its greater clinical usefulness in the recognition and differential diagnosis of spontaneous hypoglycæmia.

Following intramuscular or intravenous injection of glucagon to patients with insulinomas, there is a normal rise in *arterial* blood glucose concentration during the first thirty minutes, with a rapid fall to hypoglycæmic levels within one and a half to three hours. This is due to excessive and often prolonged insulin release in response to the glucagon stimulus, and is further reflected in the smallness of the rise in *venous* blood glucose concentration in many of these cases (unpublished observations). In contrast, in non-islet cell neoplasms causing hypoglycæmia glucagon does not cause excessive insulin release (Fig 1) and the rise in both arterial and venous blood glucose concentration is normal or, since islet unresponsiveness is common, supra-normal and prolonged (Volpe *et al.* 1965).

L-leucine Test

It is doubtful, in patients with non-islet cell neoplasms, whether l-leucine (150 mg/kg) ever accelerates development of hypoglycæmia (Fig 1). In rare cases in the literature (Oleesky *et al.* 1962) in which it was claimed to do so, control studies using inert material were not carried out. Plasma insulin remains unchanged, or rises normally, following ingestion of l-leucine in patients with non-islet cell tumours, but rises excessively in patients with leucine-sensitive insulinomas.

Glucose Tolerance Test

Neither oral nor intravenous glucose tolerance tests, with or without plasma insulin assays, have any place in the recognition and differential diagnosis of hypoglycæmia in these patients. They may reveal increased or normal, but most often decreased, glucose tolerance, and the insulin response is usually subnormal (Fig 1) or, after high carbohydrate feeding, occasionally normal.

Prognosis and Treatment

Treatment, when possible, is that of the primary lesion. Complete excision of the tumour is sometimes feasible with abolition of hypoglycæmia, and disappearance of associated endocrine disorders. However, whatever their pathological appearance or site of origin, most non-islet cell tumours causing hypoglycæmia are malignant; even those considered histologically benign tend to recur, sometimes many years later after apparently total excision. With recurrence of the tumour, hypoglycæmia usually reappears.

In cases where surgery is impracticable, palliative treatment by radiotherapy or with anti-mitotic drugs may alleviate hypoglycæmia, which is often the most distressing and debilitating aspect of the illness and, unfortunately, usually refractory to conventional treatments.

Diazoxide offers further hope. Although of proven value in the treatment of hypoglycæmia due to malignant insulinoma and idiopathic hypoglycæmia of childhood (unpublished observations), it must still be considered experimental and used cautiously with rigorous biochemical control. No published data of its use in non-islet cell neoplasms are yet available, but we are aware of one case in which diazoxide did cause a rise in blood glucose.

Summary

Malignant and, rarely, benign non-islet cell neoplasms are a cause of spontaneous fasting hypoglycæmia in man. Insulin is not implicated in the production of hypoglycæmia which is probably, in the majority of cases, due predominantly to inhibition of hepatic glucose release by a tumour-produced humoral factor. The anamnesis may be indistinguishable from that of insulinoma, and differential diagnosis may only be possible by means of plasma insulin immunoassays while fasting and during provocative tests.

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Gynæcomastia Dr J Ginsburg