

HYPOGLYCAEMIA IN NEOPLASIA

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THE neoplasm commonly associated with hypoglycaemia is the islet-cell tumour, or insulinoma. Unless malignant, the insulinoma is small. However, severe persistent disabling organic hypoglycaemia may be caused by a group of neoplasms which are not related to the pancreatic islets. These non-islet-cell tumours are nearly always huge, often weighing more than a kilogramme.

A convenient classification of tumours causing hypoglycaemia (Table 1) necessarily requires some histological compromise. Although all published cases are included in this table, variants of the epithelial tumours in the future will not be surprising. The mesenchymal tumours (often labelled as 'fibrosarcomas') predominate in incidence in the non-islet-cell group. More than 60 such cases have been reported in the past decade (mainly in the past five years) in contrast to the five cases between 1940 and 1949. Many of the observations in the present discussion are based on six 'fibrosarcomas' with hypoglycaemia, including five cases which have not been previously reported.

Clinical Features of 'Fibrosarcomas'

Occurring in virtually any age group, these 'fibrosarcomas' may arise anywhere in the abdomen and pelvis (peritoneal or retroperitoneal) or thorax (pleural). Classical symptoms of hypoglycaemia are common. Yet the diagnosis of hypoglycaemia is often missed for a long time. In patients who are known to have a tumour, peculiar behaviour, convulsions or coma may be attributed to cerebral secondaries. Spontaneous recovery from coma does not exclude hypoglycaemia as the cause; in fact, spontaneous recovery is obviously the rule initially, and not the exception, for all tumours causing hypoglycaemia. Sometimes it is difficult to elicit symptoms from patients whose memory and mental ability are impaired. They may not realize that food relieves their condition. Questioning the patient's spouse is usually helpful in establishing the duration and nature of the symptoms.

As these tumours are large, diagnosis should be relatively simple once hypoglycaemia is recognized. The only real differential diagnosis in practice is (i) a co-existing insulinoma in a patient with any other tumour, (ii) a large epithelial tumour in the abdomen and (iii) a malignant insulinoma. Before

TABLE 1

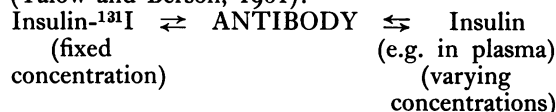
- (a) Islet-cell tumours; benign, malignant.
- (b) Non-islet-cell tumours.
 - (1) Mesenchymal:
 - Fibrosarcoma, mesothelioma, fibroma, etc., peritoneal pseudomyxoma.
 - (2) Epithelial:
 - Liver: carcinoma, cholangioma.
 - (3) Adrenal: carcinoma, adenoma.
 - (4) Caecum: carcinoma.
- (1) Lowbeer (1961): Review. (2) McFadzean and Young (1956): Review. (3) Williams, Kellie, Wade, Williams and Chalmers (1961): Review. (4) Tranquada, Bender and Beigelman (1962).

laparotomy an attempt should be made to exclude (i) and (iii). It is also worth while to define the relationships of the tumour pre-operatively by radiology. Bleeding and collapse during surgery are effectively dealt with if anticipated.

Diagnosis is not an academic exercise, as effective treatment may be curative or at least may provide several symptom-free years. If possible, the tumour is best removed surgically, while radiotherapy is a surprisingly effective alternative (Oleesky, Bailey, Samols and Bilkus, 1961). Treatment of a recurrence may provide further palliation.

Insulin Assay

Radio-immuno assay of insulin is a valuable diagnostic adjunct in hypoglycaemia caused by neoplasms. This immuno assay depends on the competition between labelled and unlabelled insulin for binding sites on antibodies to insulin (Yalow and Berson, 1961):



We usually precipitate the antibody 'bound' insulin with an anti-gamma globulin serum. The amount of bound insulin-¹³¹I is roughly inversely proportional to the concentration of unlabelled insulin (Fig. 1).

In patients with insulinomas the fasting insulin is typically higher than the normal range for normoglycaemia controls, which is 19μU per ml. S.D. ± 7.5. A high level may, however, be missed, depending on sampling time, as spontaneous fluctuations in plasma insulin may occur (Samols and Marks, 1963). Such spontaneous fluctuations (Fig. 2) are useful diagnostically, as they are not

A paper read to the Harveian Society of London on April 17, 1963.

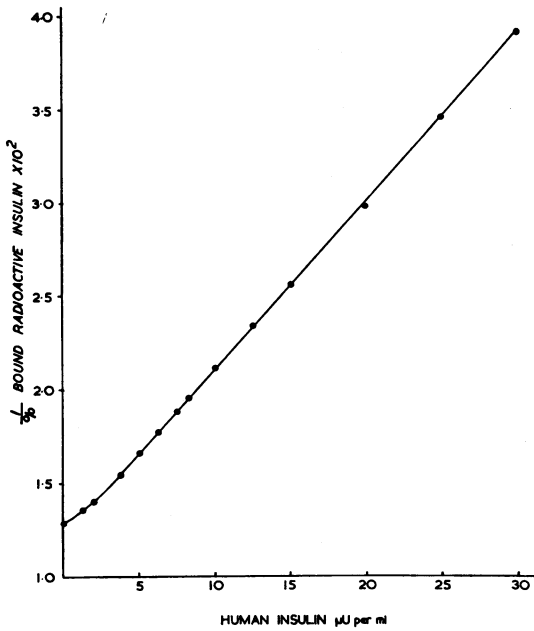


FIG. 1.—Standard curve for human insulin. The amount of bound insulin given by a particular plasma will indicate the endogenous insulin concentration.

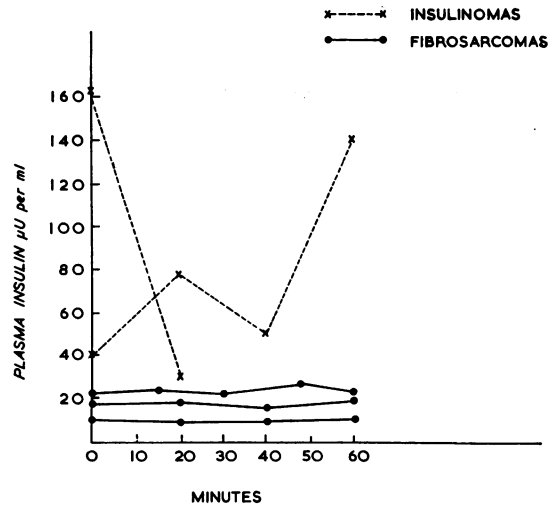


FIG. 2.—Spontaneous fluctuations in plasma insulin during constant hypoglycaemia. Changes in plasma insulin are insignificant in mesenchymal tumours and normal subjects.

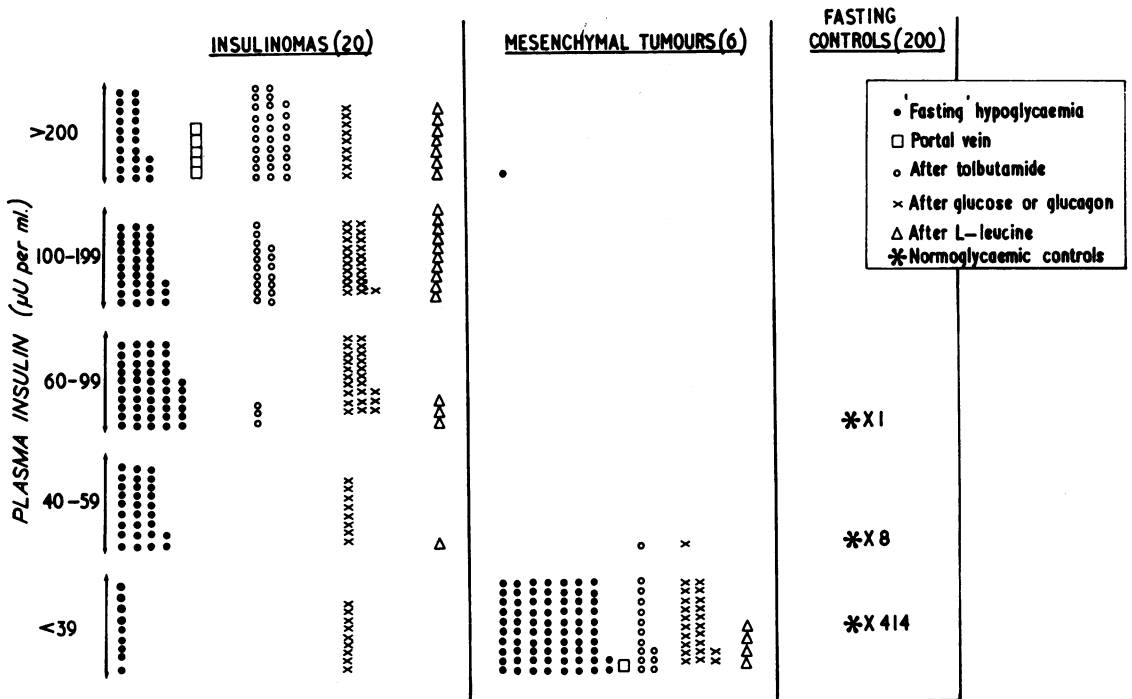


FIG. 3.—Comparison of insulinomas and fibrosarcomas during fasting hypoglycaemia and after various tests. The mean normal insulin level is $19 \mu\text{U/ml}$. $\text{SD} \pm 7.5$.

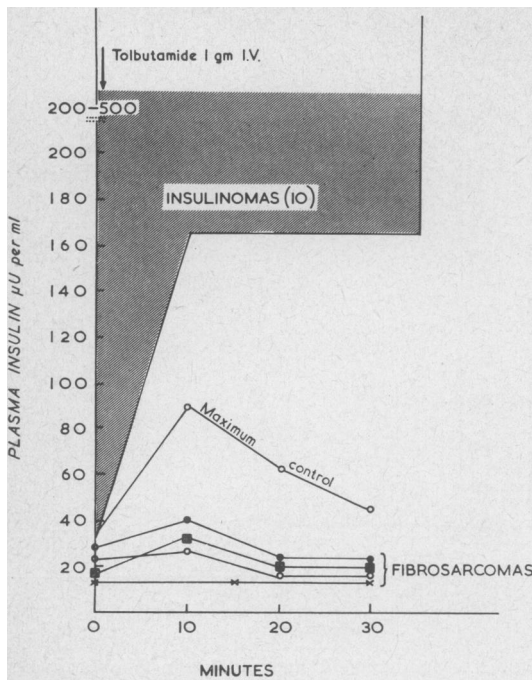


FIG. 4.—Plasma insulin response to intravenous tolbutamide. Mean normal values (not in graph): 45 μ U/ml. at 10 minutes, 35 μ U/ml. at 20 minutes, 22 μ U/ml. at 30 minutes.

found in control subjects or in patients with mesenchymal tumours. In the latter, fasting insulin is not raised (Fig. 3). The solitary exception, a 'black sheep', represents the only serum taken from one patient (Oleesky and others, 1961). This case is exasperating, unless one postulates that the occasional non-islet cell tumour does stimulate the pancreatic islets. Multiple plasma samples failed to show a high insulin in all the other fibrosarcomas, but always revealed at least one abnormal level in all 20 insulinomas.

We have found that the most useful single differential diagnostic test is plasma insulin assay at 10-minute intervals for 20 to 30 minutes after the injection of 1g. of Na tolbutamide i.v. There is a striking contrast between the exaggerated plasma insulin response in insulinomas (Fig. 4) and control subjects. In mesenchymal tumours the equivalent plasma insulin response is either normal or depressed.

In the insulinomas there is also an excessive rise in insulin after ingestion of L-leucine (Samols and Marks, 1963). A similar response is seen in children with 'leucine-sensitivity', probably because their islet cells are hyperactive and hyperplastic. L-leucine induces only a small rise in plasma insulin in normal subjects. Yet the normal regulatory mechanism for insulin secretion, the

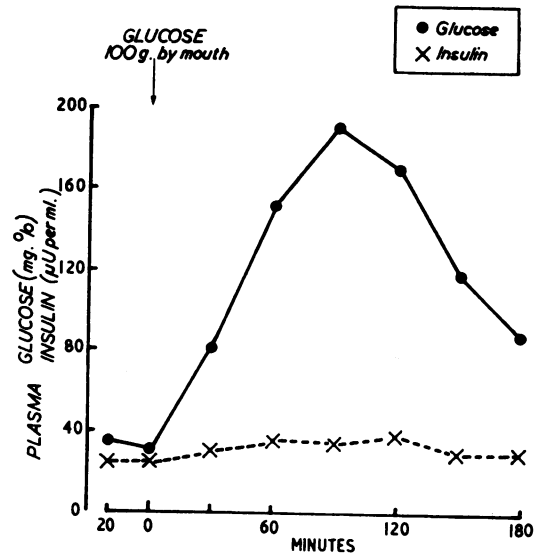


FIG. 5.—Effect of oral glucose on plasma glucose and insulin in a patient with a fibrosarcoma and hypoglycaemia.

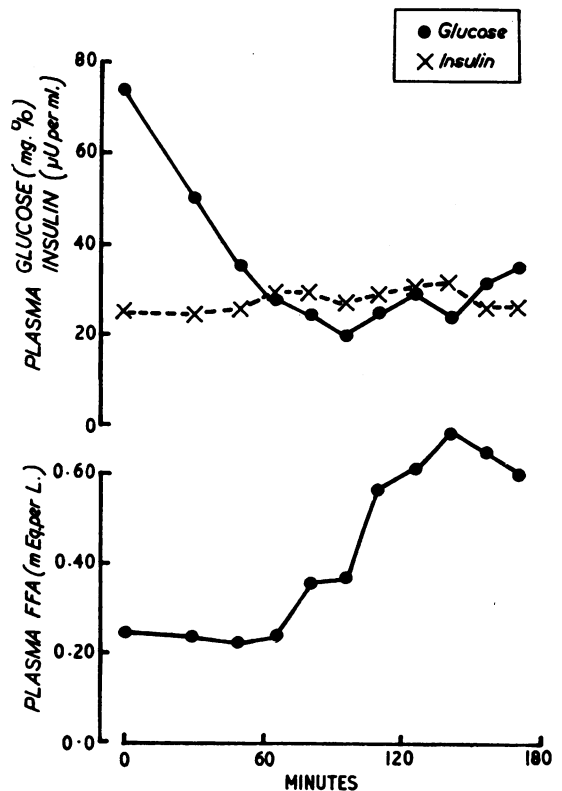


FIG. 6.—Plasma glucose, insulin and F.F.A. in a fibrosarcoma. Test started 2½ hours after a meal. Any substance given during the first 40 to 50 minutes of the test would have provoked a 'hypoglycaemic response'. In fact, nothing was given.

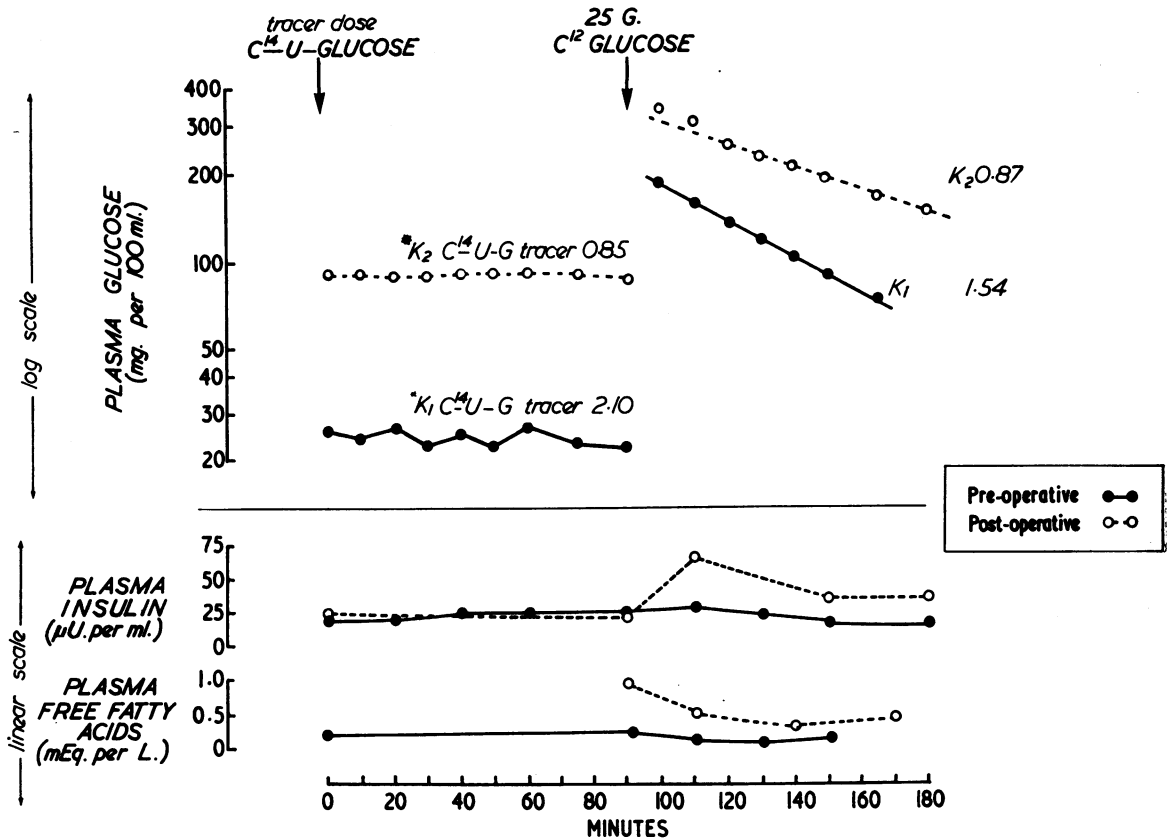


FIG. 7.—Glucose assimilation coefficient (K), plasma insulin and F.F.A. values before and after the successful removal of a large intrathoracic fibrosarcoma.

blood glucose level, may not control the tumorous islet-cell. The plasma insulin response to an increase in blood glucose varies in different patients with insulinomas. Administration of glucose or glucagon may be followed by (i) a normal rise, (ii) no change, (iii) an excessive rise, or (iv) fluctuations (presumably spontaneous) in the levels of plasma insulin. After glucose, oral (Fig. 5) or i.v. patients with mesenchymal tumours characteristically show a subnormal rise in plasma insulin.

There are several fallacies about tests which depend on changes in blood glucose. The glucose response to intravenous tolbutamide is a useful screening test for insulinomas, which characteristically show prolonged hypoglycæmia (less than 66% of the fasting value) for 180 minutes after tolbutamide (Fajans, Schneider, Schteingart and Conn, 1961). In patients with invariable fasting hypoglycæmia, as often occurs in mesenchymal tumours, this test has little value. Such patients will show a hypoglycæmic reaction to any substance, including water, because of the inevitability of hypoglycæmia (Fig. 6). Similarly, a prolonged

glucose tolerance curve will always show hypoglycæmia after four to five hours in this group. Insulinomas and mesenchymal tumours may produce any shape of glucose tolerance curve, but the late, prolonged hyperglycæmia or 'diabetic' pattern (Fig. 6) is usual in mesenchymal tumours and not uncommon in insulinomas. Demonstration of Whipple's triad is a sophisticated way of saying that a patient has persistent hypoglycæmia.

Mechanism of Hypoglycæmia in Mesenchymal Tumours

It is reasonable to assume that the tumour is in some way responsible for hypoglycæmia because removal of the tumour results in normoglycæmia. The mechanism is tantalizingly baffling because it looks simple. Basically, hypoglycæmia is caused by either:

- (i) Increased rate of disappearance of glucose from the blood;
 - (ii) decreased hepatic output of glucose; or
 - (iii) both (i) and (ii) occurring simultaneously.
- Insulin may act by (i), (ii) or (iii). A hypothetical insulin-like substance, often called 'in-

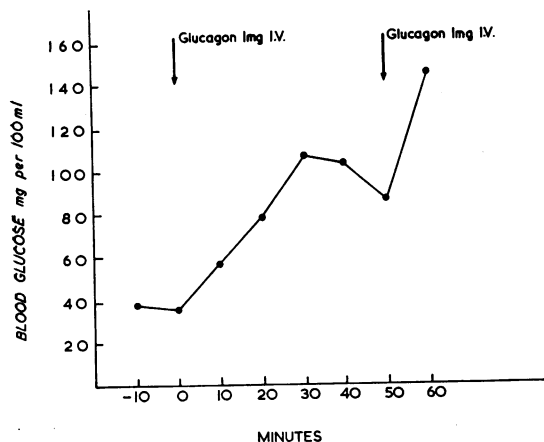


FIG. 8.—Effect of glucagon in a fibrosarcoma. Note the excellent rise in blood glucose from the initial hypoglycaemic level.

sulinoid', could presumably do the same. The third possibility, suggested by the large size of these neoplasms, is a 'hungry' tumour, consuming glucose excessively.

The rate of disappearance of glucose from the blood stream is considered an index of tissue glucose assimilation when measured by intravenous glucose tolerance tests. Tracer amounts of radioactive (^{14}C) glucose will not affect the blood glucose level, which rises after a 25-g. load of unlabelled (^{12}C) glucose. The higher the glucose assimilation coefficient (K) the faster is the rate of disappearance. Fig. 7 shows that hypoglycaemia is primarily caused by excessive glucose utilization, as the pre-operative K values during constant hypoglycaemia and after a load of glucose are higher than the post-operative K figures for both ^{14}C and ^{12}C glucose. This should not occur if a decreased hepatic glucose output was solely responsible for the hypoglycaemia.

F.F.A. levels are remarkably low pre-operatively during hypoglycaemia. In another case a very low F.F.A. level persisted for some time during hypoglycaemia, but did eventually rise (Fig. 6). The interest of this finding is that insulin is the only human hormone known to cause the combination of hypoglycaemia + low F.F.A.

Finally, it can be shown that there is also some suppression of hepatic glucose output because of the 'hypoglycaemia unresponsiveness' after intravenous glucose pre-operatively (Fig. 7). The effect of injecting glucagon confirms such suppression, as the extra stimulus is able to release hepatic glucose during hypoglycaemia. Hepatic glycogen stores were adequate, as hyperglycaemia could be induced by the glucagon (Fig. 8).

The tentative conclusions drawn are:

- The tumour may produce a substance which increases sensitivity to insulin. This could account for all the findings, including the immediate post-operative behaviour of glucose and F.F.A. (Fig. 7). This transient 'diabetic' state could be due to the unopposed action of hormonal or other insulin antagonists which take a while to disappear.
- Insulinoid is still a possibility.
- If the tumour is 'hungry' for glucose, it must, in addition, be producing substances suppressing both lipolysis (to cause the low F.F.A. level) and hepatic glucose output. The alternatives ((a), (b)) are perhaps more acceptable in theory, since the metabolic gymnastics require only one hypothetical event.

The role of insulin may soon be tested directly, by injection of anti-insulin antiserum. The antiserum would neutralize circulating insulin temporarily. Although hypoglycaemic substances (insulinoid) have been demonstrated in these tumours, such insulinoid appears to be present in neoplasms not associated with hypoglycaemia and in normal tissues. It is tempting to imagine that large non-islet-cell epithelial tumours share a similar hypoglycaemic mechanism with the mesenchymal tumours.

In conclusion, tumours causing hypoglycaemia may be diagnosed with greater certainty today with the help of insulin assay. Insulinomas cause hypoglycaemia by hypersecretion of insulin, but non-islet-cell tumours probably cause hypoglycaemia by increasing sensitivity to endogenous insulin or by producing an insulin-like substance.

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