*Brief Notes and Comments*

# Insulinoma Resection Facilitated by the Artificial Endocrine Pancreas

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SUMMARY

**The artificial endocrine pancreas was adapted to assist with the intraoperative localization of an insulin-secreting islet cell adenoma in a 23-year-old patient with a five-month history of hypoglycemic attacks. Glycemia was monitored in continuously withdrawn whole blood, and dextrose was infused to maintain euglycemia by an artificial endocrine pancreas with a closed loop that excluded its usual insulin delivery capability. The dextrose infusion rate was established in accordance with a control algorithm whose parameters were chosen to amplify changes in dextrose delivery rate for small alterations in the measured baseline glucose concentration. The dextrose infusion rate preoperatively was 155 mg. per minute and decreased to 100 mg. per minute with initiation of surgery. An area in the tail of the pancreas suspected of containing the insulinoma was excluded from the circulation by a noncrushing clamp. After 14 minutes the dextrose infusion progressively decreased to 27 mg. per minute reflecting a glycemic rise of 15 mg. per deciliter. These changes were taken to represent a fall in ambient insulin activity. This was subsequently confirmed directly by the demonstration of reduction in immunoreactive insulin and progressive increase in both plasma free fatty acid levels and postoperative glucose intolerance. Exclusion of the insulinoma from the circulation resulted also in a rapid decrease of circulating proinsulin concentration giving an estimated half-life of 25 minutes.** DIABETES **27:774-77, July, 1978.**

The surgical management of insulinoma is complicated either by the inability to locate the tumor intraoperatively in 20 to 25 per cent of cases or by the presence of multiple tumors in 13 per cent of patients.[1,2] Approaches to this problem include blind pancreatic resection, either distal or total, repeated surgery if the initial resection is not successful, and frequent intraoperative glucose monitoring. A rise of blood sugar within 15 to 30 minutes after partial pancreatic resection has been considered to be indicative that all insulinoma tissue, either occult or multiple, has been removed.[3-7] A variation of this approach using the artificial endocrine pancreas modified to monitor glycemia continuously and to vary dextrose infusion rate according to glycemia was used in our patient. A significant decrease in dextrose infusion rate proved to be a sensitive indicator of decreased insulin concentration.

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## CASE REPORT

A 23-year-old legal secretary was investigated for frequent early morning hypoglycemic attacks of five months' duration. The episodes were characterized by night sweats, confusion, bizarre behavior, diplopia, and, on one occasion, a grand mal seizure. Routine laboratory tests were normal. After 6.5 hours of fasting, her plasma glucose fell to 31 mg. per deciliter at which time her immunoreactive insulin (IRI) was 42.5 $\mu$U. per milliliter. Twenty-five per cent of the IRI was proinsulin. Celiac angiograms and abdominal echogram were negative. The diagnosis of insulinoma was made, and the patient was prepared for laparotomy.

## METHODS

Plasma glucose was measured by the glucose oxidase method (Beckman Instruments, Fullerton, Calif.); immunoreactive insulin (IRI) was measured by the back-titration method[8] except that Sephadex was used to separate the free from the bound insulin. Proinsulin in the serum was determined after chromatography of the serum extract on a Bio-gel P-30 column.[9] Free fatty acids were measured by titration, with palmitic acid used as a reference standard.[10]

Glycemia was monitored in continuously withdrawn whole blood, and dextrose was infused to maintain plasma glucose at approximately 70 mg. per deciliter for the three hours before surgery by an artificial endocrine pancreas with a closed loop[11] that excluded its usual insulin delivery capability. The dextrose infusion rate was regulated by a control algorithm (figure 1) with parameters designed to amplify maximally changes in delivery rate for small alterations in the baseline plasma glucose concentration.

## RESULTS

The sequence of alterations in plasma glucose concentration and dextrose infusion rate is shown in figure 2 (upper panel). Preoperatively, a mean dextrose infusion rate of 155 mg. per minute was required to stabilize plasma glucose at a mean of 70 mg. per deciliter. With induction of anesthesia and surgical incision and mobilization of viscera the mean dextrose infusion rate decreased to 100 mg. per minute according to the control algorithms, resulting quickly in a new baseline plasma glucose of 80 mg. per deciliter. No tumor was seen, but on palpation of the pancreas a firm area was felt at the junction of the tail and the body. Massaging this area did not change either plasma glucose or the infusion rate. A noncrushing clamp was placed across the pancreas to exclude the tail and distal body from the circulation. The dextrose infusion rate remained at 90 mg. per minute and plasma glucose at 81 mg. per deciliter for 14 minutes. During the next 26 minutes the dextrose infusion rate fell to 27 mg. per minute while the plasma glucose rose to 96 mg. per deciliter. Eight minutes after removal of the clamp the dextrose infusion rate increased from 20 to 49 mg. per minute and glycemia decreased from 99 to 90 mg. per deciliter. These observations were suggestive of a tumor in that region of the pancreas, which was then excised. Eighteen minutes after pancreatic resection the dextrose infusion rate had decreased to 12 mg. per minute and glycemia had increased to 104 mg. per deciliter. After surgery the patient received a continuous infusion of dextrose at 55 mg. per minute and her plasma glucose rose to 221 mg. per deciliter by 4.5 hours. Ketonuria was also noted 14 hours after the operation indicating appropriate mobilization and oxidation of free fatty acids (FFA). Her recovery was uneventful and 10 days postoperatively the plasma glucose was 92 mg. per deciliter and IRI less than 2 $\mu$U. per milliliter after a 19-hour fast.

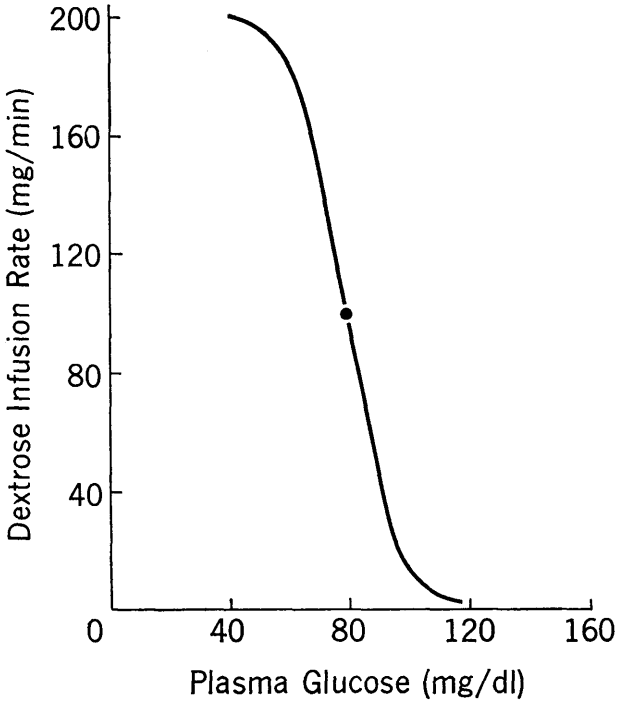


**FIG. 1. Control algorithm relating dextrose infusion rate to prevailing plasma glucose. Parameters are M (maximum infusion rate) 200 mg. per minute, S (slope) 0.06 dl. per minute, B (plasma glucose at half-maximum infusion rate) 80 mg. per deciliter.**

Immunoreactive insulin and FFA concentrations were measured in plasma samples taken at selected times during surgery (figure 2 lower panel). With manipulation of the pancreas, IRI increased from 52 to 70 $\mu$U. per milliliter. During clamping, total IRI decreased progressively; with removal of the clamp IRI increased transiently to 30 $\mu$U. per milliliter and then fell to less than 2 $\mu$U. per milliliter. FFA concentrations increased progressively from 0.33 to 1.5 $\mu$Eq. per milliliter except after clamp removal when there was a transient drop from 0.99 to 0.90 $\mu$Eq. per milliliter.

Separation of the serum IRI into proinsulin and insulin by gel filtration allowed for the monitoring of the disappearance of proinsulin and insulin independently. Data presented in table 1 demonstrate that proinsulin disappeared more slowly than insulin.

The resected portion of pancreas contained a single, well encapsulated 1-cm. tumor, and, on histologic examination, cells resembling normal islet cells were seen.

## DISCUSSION

The diagnosis of insulinoma was based on symptomatic fasting hypoglycemia accompanied by inappropriately elevated insulin concentrations and by a high percentage of proinsulin in serum.

Glucose monitoring during surgery for insulinoma has been used for the past 26 years as an indicator of functional tumor removal. Several investigators[1-6] have demonstrated that a rise in glycemia within five to 30 minutes of resection correlates with total removal of pathologic islet cell tissue whether obvious, occult, or multiple. Others,[7] however, have noted that similar increases in glycemia during surgery can occur in patients documented later to have retained tumor or multiple adenomatosis.

In our patient, with biochemically documented hyperinsulinism but no preoperative localization of tumor, the artificial endocrine pancreas proved to be a valuable tool. It had the advantage of allowing computer-controlled dextrose infusion according to an algorithm designed to accentuate changes in glucose requirements while operating within a safe glycemic range. As illustrated in figure 2, clamping the portion of pancreas under suspicion produced, after a 14-minute delay, a rise in glycemia at a mean rate of 0.6 mg. per deciliter per minute accompanied by a de-

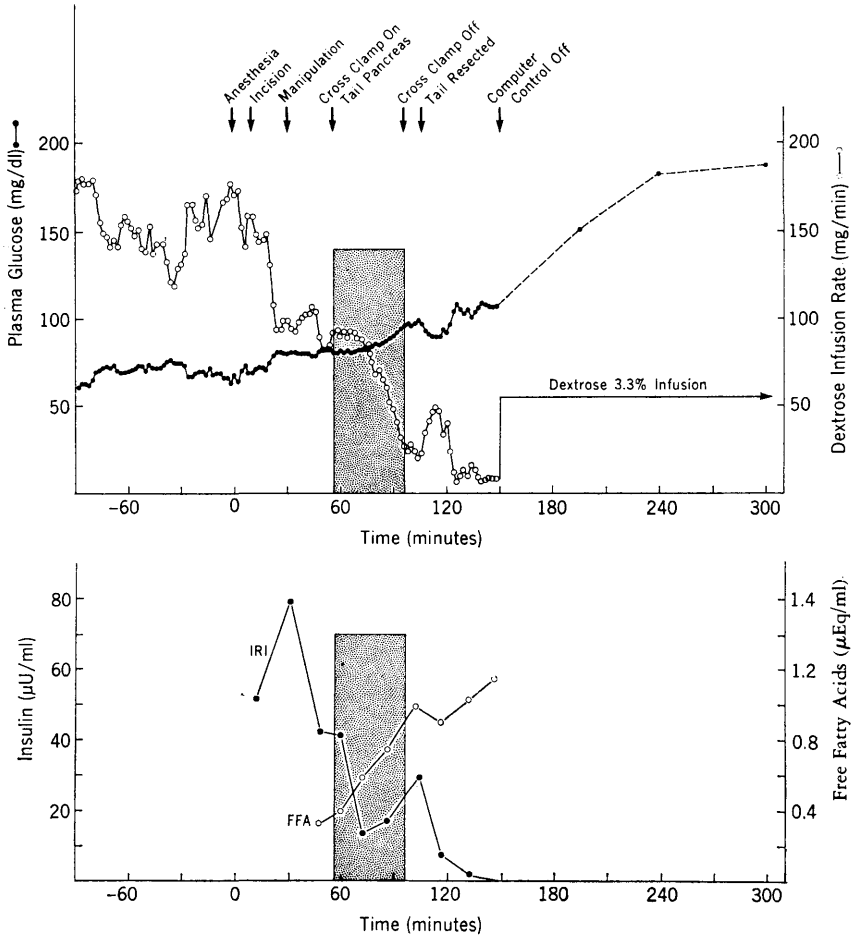


**FIGURE 2**

**Upper panel: Continuous glucose monitoring and dextrose infusion controlled by computer in the artificial endocrine pancreas. Closed circles indicate plasma glucose and open circles dextrose infusion rate. In the lower panel, intraoperative immunoreactive insulin concentrations (IRI) are closed circles and free fatty acid concentrations (FFA) open circles.**

crease in dextrose infusion rate of 2.6 mg./min./min. The decreasing dextrose requirements are consistent with the falling IRI (figure 2). During clamping, IRI dropped to 4 μU. per milliliter and with excision of the tumor it dropped further. Interestingly, with removal of the clamp there was a transient rise in IRI suggesting washout of hormone with reperfusion. During surgery this was associated with a transient increase in dextrose requirement and a decrease in glycemia.

Anesthesia and surgery may produce changes in glycemia[7] secondary to release of hormones with counter-regulatory effects to insulin. This was evident early in surgery in this case, with a 30 per cent decrease in dextrose requirements even before pancreatic manipulation.

Close monitoring of this patient during surgery allowed for the demonstration of a number of hormone:metabolite relationships. It was evident preoperatively that to maintain normoglycemia (figure 2) a dextrose infusion rate of 155 mg. per minute was required. This corresponded closely to the predicted total hepatic glucose production rate in fasted individuals,[12,13] suggesting that under basal conditions our patient's endogenous glucose production was minimal. This is consistent with a hyperinsulinized state and suggests that her hypoglycemia was more a function of inadequate endogenous glucose production than accelerated peripheral utilization. Further evidence of effective hyperinsulinemia was reflected by low fasting FFA levels. An abrupt and rapid reversal of the hyperinsulinism became apparent upon clamping and resection of the insulinoma. Within 12 minutes the concentration of circulating insulin fell by 66 per cent, and this was reflected by an abrupt decrease in dextrose infusion rate as endogenous glucose production increased. Another manifestation of apparent insulin deficiency was a progressive rise in FFAs.

Total serum IRI fell rapidly after both initial clamping and subsequent removal of the insulinoma. Column fractionation of circulating IRI into insulin and proinsulin revealed changing relationships pre-

TABLE 1

Disappearance of plasma insulin and proinsulin after cross-clamping the pancreas

| Sample no. | Time after anesthetic induction (min.) | Serum insulin (ng./ml.) | Serum proinsulin (ng./ml.) | Proinsulin/insulin ratio |
|---|---|---|---|---|
| 1 | 12 | 2.2 | 0.64 | 0.29 |
| 2 | 31 | 3.6 | 0.63 | 0.18 |
| 3 | 47 | 2.7 | 0.66 | 0.24 |
| 4 | 72 (29) | 0.03 | 0.36 | 12.0 |
| 5 | 87 (44) | 0.08 | 0.25 | 3.1 |

Insulin and proinsulin were determined by immunoassay after chromatographic separation of the serum extract. The time in brackets for samples 4 and 5 indicates the time after cross-clamping of the tail portion of the pancreas containing the tumor.

dictable from known differences in metabolic degradation rates. In table 1 it can be seen that proinsulin disappeared more slowly than insulin, in agreement with the reported differences in disappearance rates of exogenous porcine proinsulin in experimental animals.[14] Based on the proinsulin concentrations in the two serum samples obtained during the period when the tumor was excluded from the circulation (samples 4 and 5 in table 1), the half-line of circulating human proinsulin was estimated to be about 25 minutes.

In summary, the artificial endocrine pancreas has facilitated the surgical management of this patient with an insulinoma. It produced a stable glycemic baseline before surgery, prevented hypoglycemia, and indirectly amplified the fall in plasma IRI as detected by changes in glucose metabolism consequent to removal of a functioning islet cell adenoma. This approach merits further use in other cases in order to establish its reproducibility. Of particular interest would be those cases with multiple adenomas, microadenomatosis, and islet cell carcinoma.

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