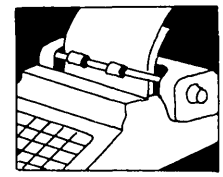
Editorial



Update on Insulinomas or The Case of the Missing (Pro)Insulinoma

The diagnosis of hypoglycemia with insulin hypersecretion is one of the most intriguing challenges facing physicians. The entities to exclude constitute a host of rare organic maladies and less rare psychologic maladies, among them "lay-press–induced hypoglycemia." The possibility of an insulinoma formed a major plot element in a recent novel in which murder was suspected and the detective was "a top Washington endocrinologist" who had done diabetes research and "thanked (his) lucky stars (he) didn't have to write another grant application (1)." In some instances, the diagnosis can be established on clinical grounds without resort to the laboratory. A case in point is a recent patient with abrupt onset of profound and recurrent hypoglycemia. One of his pharmacy bottles—labeled acetazolamide—was found, after initiating the workup, to contain acetohexamide and the pharmacy was able to confirm its error. Frequently, however, physicians are quite dependent on the laboratory and provocative testing for establishing the diagnosis in these patients.

The gold standard for the biochemical diagnosis of insulinoma remains the 72-h fast (2,3). The presence of detectable circulating insulin in the face of symptomatic hypoglycemia has been regarded as the end point, yet in research-quality insulin assays that permit the detection of ≤1 μU/ml, that criterion is not appropriate. Service et al. (3) have recommended a threshold of 6 μU/ml (36 pM) for inappropriate hyperinsulinism in the face of hypoglycemia. If the patient becomes hypoglycemic within the first few hours, the fast is relatively straightforward to perform and interpret. However there is easily a role for an accurate test that is simple and inexpensive compared to: *1*) the discomfort for the patient and logistical problems of close supervision and frequent sampling by health-care personnel in a prolonged fast not resolved within the first few hours; or *2*) a variety of provocative tests (e.g., tolbutamide injection, calcium infusion, C-peptide suppression either by insulin infusion to hypoglycemia or by hyperinsulinemic-euglycemic clamp) that are labor intensive, sometimes risky, and usually require a research environment. Current economic pressures on the use of days of hospitalization and the diagnostic uncertainties alluded to above further support the potential benefits of such a test. A screening test may prove capable of making a biochemical diagnosis of inappropriate β-cell hypersecretion, possibly distinguishing degrees of tissue differentiation (carcinoma, adenoma, "hyperplasia") or at least establishing a level of certainty for excluding the diagnosis and reducing the number of patients who will require extensive evaluation.

Pre- or intraoperative localization, including intraoperative ultrasound, may permit enucleation of a discrete tumor. If the biochemical diagnosis is made but no discrete tumor is anatomically identifiable, up to 90% pancreatic resection is the recommended procedure in one major surgical text (4) but is considered controversial in another (5). The appropriateness of extensive resection when tumor cannot be identified, even in the operating room, deserves reevaluation in 1988, given the possibility of resulting diabetes, the possible need for postoperative medical therapy in any case, and new

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therapeutic options. The total operative mortality of up to 8–10% for islet tumor surgery (5) and the report that up to 24% of patients will not have hypoglycemia relieved by a single operation (6) should give the referring physician pause. In cases when a diagnosis has not been made even in the operating room, it may remain unclear even after the tissue is on the pathologist's table.

Using histomorphometric techniques, Goudswaard et al. (7) compared *1*) pancreases from normal fetuses, neonates, children up to age 3 yr, adults age 44–71 yr and children with hyperinsulinism; and 2) the nontumor tissue from eight adults with benign insulin-producing adenomas. They concluded "it seems that any morphological pattern, including a normal pattern, may be identified as nesidioblastosis [or islet cell hyperplasia], as long as the clinical condition fulfills the criteria for organic hyperinsulinism" (7). The meaning and clinical utility of the pathologic diagnosis of islet cell hyperplasia, in the absence of standards by which to compare the response of the normal human β-cell mass not only to age but to obesity and perhaps other factors, are uncertain. There have not been adequate studies of the response of islet cell hyperplasia to single and combined medical therapies including not only diazoxide but also new therapeutic options such as a long-acting somatostatin analog (8,9) and the calcium channel blockers verapamil and diltiazem, which have been reported anecdotally to control hypoglycemia in some patients (10–12). If it becomes possible to treat these patients medically, it will become important to determine that inappropriate insulin hypersecretion is due to an entity other than a discrete tumor.

Since the discovery of proinsulin, studies from a number of laboratories using various earlier assay techniques have demonstrated abnormalities in serum proinsulin in patients with insulinomas (reviewed in refs. 13 and 14). Major technical improvements in proinsulin measurement have occurred in the last few years as a result of the availability of biosynthetic human proinsulin (15–23). The newer assays probably will provide an improvement over the previous assays in the diagnosis of β-cell hypersecretion, partly by virtue of better-defined specificity and partly by making proinsulin measurements easier and more available. Still, there are several subtleties to the interpretation of any proinsulin assay for this use. C-peptide is present in the circulation at ~100 times and insulin at ~20 times the concentration of proinsulin. For proinsulin measurements to be helpful in difficult cases, the contribution of either C-peptide or insulin to the total proinsulin immunoreactivity should be <1%. Therefore C-peptide cross-reactivity in the proinsulin assay should be <0.01% (on a molar basis) and insulin cross-reactivity <0.05%. Also, the extent and pattern of cross-reactivity of the intermediates in the process of conversion of proinsulin to insulin need to be taken into account. They may contribute to variations in the normal range between laboratories and in the correlation between measured hormone concentration and the degree of hypoglycemia observed.

We had the opportunity to measure samples from 20 patients with proven tumors in a specific proinsulin radioimmunoassay. The fasting serum proinsulin concentration from patients with β-cell tumors were higher than those from normal and obese control subjects by >3SD (17), a degree of discrimination not achieved by measuring fasting insulin alone. Heding and Kruse (24) reported in abstract form in 1984 that 204 of 206 patients with islet tumors had abnormal plasma proinsulin concentrations, a remarkable sensitivity of 99%. In a small series, mean circulating percent proinsulin (by gel filtration) differed between histologically defined subsets which in turn predicted the response to hormonal/pharmacologic intervention (25). But because of the rarity of these tumors, none of these laboratories has had the opportunity to establish *1*) both sensitivity and specificity of proinsulin measurements for the diagnosis of hypoglycemia with insulin hypersecretion in the context of adequate clinical and pathologic data, *2*) the relationship of proinsulin results to the islet pathology, or *3*) the usefulness of postsurgical proinsulin measurements in predicting recurrent hypoglycemia in a large series of patients. These questions remain to be answered in the coming years and we look forward to seeing how, in the long run, the use of proinsulin measurements will contribute to unravelling the mysteries of hypoglycemia.

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