roles of computed tomography and venous catheterization with selective venous sampling of insulin are yet to be determined.[13] At the present time, venous catheterization does not seem to be a promising or practical procedure.

The operative technique is well standardized and is complemented by the intraoperative monitoring of glucose, which has a success rate of about 94%. The declining incidence of "blind" pancreatectomies and of persistent postoperative hypoglycemia is a direct result of better preoperative and intraoperative diagnostic and monitoring techniques, coupled with increasing surgical experience.

Somewhat less than 10% of the patients have malignancy, and malignant lesions are the most frequent causes of persistent hypoglycemia. In contrast to the ordinary type of pancreatic cancer, malignant insulinomas have a higher resectability rate (four of six patients) and a better prognosis (four of six patients survived 3 years and two of six survived 5 years). The adjunctive therapeutic agent of choice in patients with metastases is streptozotocin. This agent is isolated from cultures of *Streptomyces achromogenes* and selectively destroys the pancreatic β cells by inhibiting the synthesis of deoxyribonucleic acid. About 50% of patients have objective tumor regression.[1]

Persistent hypoglycemia, whether from a benign or malignant insulinoma, usually can be controlled by the use of diazoxide. This drug has no antitumor effect. It accumulates within the β cell, where it inhibits the release of insulin, thus reducing the level of plasma insulin to an asymptomatic concentration. Two of our patients are presently on long-term diazoxide therapy and are doing well. The side effects of this drug are hirsutism, edema and, rarely, hypotension and granulocytopenia. If malignancy exists, streptozotocin and diazoxide may be used in combination.

The possibility of multiple endocrine neoplasia should always be considered when an insulinoma has been diagnosed, because the insulinoma may be one manifestation of the MEN-I syndrome (pituitary tumors, hyperparathyroidism and pancretic adenoma). Four patients (5.5%) in our series had the MEN-I syndrome.

In the Moynihan Lecture on hyperinsulinism by our colleague, Dr. J. T. Priestley, in 1962,[7] he stated, "It has always seemed to me that one of the most significant attributes which a teacher of surgery can possess is the ability to inspire and stimulate the young." In this field of hyperinsulinism, he has seemingly taught us well.

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Discussion

DR. SAMUEL A. WELLS, JR. (Durham, North Carolina): It is always impressive how The Mayo Clinic can accrue such a large number of patients with a seemingly rare disease.

I would like to ask Dr. van Heerden four questions. The authors mentioned in the text that, clinically, they considered a fasting glucose level below 40 mg/dl indicative of an insulinoma. Merimee at the University of Florida and other investigators as well, have reported that in some normal subjects, particularly women, who have fasted for 72 hours, the blood glucose level may drop to levels of 40 g/dl. This has led most of us to equate the fasting plasma glucose level with the concomitant insulin level. I wonder if Dr. van Heerden could tell us, in the Mayo Clinic experience, what ratio of insulin to fasting blood glucose is of diagnostic significance.

From the standpoint of diagnosis, I would also like to ask if he has used any other provocative agents than tolbutamide? Specifically, has calcium been used? This cation is certainly an excellent provocative agent for several of the other neural crest tumors such as medullary thyroid carcinoma and gastrinomas and might well be useful in the diagnosis of insulinomas. Recently, Kaplan, at the University of Chicago, has demonstrated that patients with insulinomas have a very rapid increase in insulin after the intravenous administration of calcium ion.

Last, I wonder if you would say something about malignant insulinomas. This is a somewhat difficult pathologic state to diagnose preoperatively; however, several investigators have demonstrated that patients with these lesions frequently secrete a large amount of high molecular weight insulin. Not only is this helpful in the preoperative diagnosis, but it is also useful in following patients in

the postoperative period, since an increased level of "big" insulin might be the first indicator of recurrent malignant disease.

Last, I would like to ask of his experience with patients having fasting hypoglycemia associated with large mesenchymal tumors. These patients appear to have a cause, other than excessive insulin secretion, for their hypoglycemia. Several of these subjects have undergone pancreatic exploration because their clinical presentation is very similar to that of patients with insulinomas.

DR. WILLIAM H. REMINE (Rochester, Minnesota): Dr. van Heerden has given us an in-depth study. I'll bring you up to date on all of our material. Prior to the time his study started, we reported our experience with 109 cases. At that time we found roughly 10% (10 of 95) in our study were malignant.

Very important developments have taken place in recent years and I refer to arteriography and blood glucose monitoring which aid greatly in tumor detection and location. We previously reported that about one-third of the tumors were palpable and were more firm than normal, a third were about the same consistency as the normal pancreatic tissue, and a third of them were actually softer. Arteriography and blood glucose monitoring have therefore been a great help in localizing these tumors.

Islet cell tumors don't always have to produce insulin. Recently we had a very large one that was sent to us. The patient had been explored for hypercalcemia and no tumor found. During the course of the work-up the internist found a very large, palpable mass in the abdomen, which I operated upon and it was a malignant islet cell tumor causing the hypercalcemia.

I would like to warn you about the potential malingerers among these patients. In the group that we reported several years ago we had eleven malingerers. Most of these patients were in some way or another associated with the medical profession who were able to get surreptitious supplies of insulin and produce insulin-like attacks. Some have gotten all the way to the operating room before we were able to find their supply.

Fortunately, with the insulin antibody studies now available and with the development of this test, one can pick those patients up beforehand and not fall into the trap of operating on someone who has taken surreptitious insulin.

DR. JONATHAN A. VAN HEERDEN (Closing discussion): I learned more from Dr. Wells' discussion about insulinomas than I have for a while.

I think, certainly, the level of blood glucose in the mid-40's can be a most confusing issue. We have been struck by so many of these patients really having blood glucoses in the alarming range, of below 30's. Recently, a patient was in the midteens, for example. But we too have come to rely on the concomitant hyperinsulinemia; although there have been many ratios devised, still, the absolute numbers are better.

As we have said before, we have no experience with the calcium provocative test, as we have had with medullary carcinoma of the thyroid, but we have become quite enthusiastic about either the tolbutamide or the C-peptide suppression tests.

Similarly, we have followed the literature about big insulin, but have no personal experience with this. It would be nice to be able to diagnose a malignant lesion preoperatively. As one recalls with most endocrine tumors, the diagnosis of malignancy is a very difficult one—certainly, for the pathologist—and he has to rely on the surgeon for the demonstration of extrapancreatic sites of tumors.

I think we all have had the rare, occasional patient who has developed ectopic secretion of either insulin or insulin-like substances, producing hypoglycemia. I have personally not had such a patient, but I know Dr. ReMine has had some retroperitoneal sarcomas, for example, which have presented in a very confusing fashion.

I think, as Dr. Cameron alluded to, these are a funny group of patients, and one cannot overemphasize the factitious element. A number of these factitious patients were nurses, physicians, and people who had access to insulin. With the advent of the insulin antibody, we have been able to screen out those patients.