Discussion

Dr. Carrington Williams, Jr. (Richmond): This has been an excellent discussion of an interesting endocrinologic disturbance which necessitates prompt surgical treatment to avoid the severe cerebral disturbances that are related to prolonged hypoglycemia.

In this series, as in all others, it is striking that many of these cases are not diagnosed for years. Drs. Scott and Clarke were kind enough to allow me to review their manuscript, and I would like to make a few remarks concerning it.

I was pleased to see that the authors stressed the continuing validity of Whipple's triad, and also that they consider prolonged fasting with serial measurements of serum glucose and insulin as the most reliable diagnostic test. Their case reports emphasize the necessity for very thorough exploration of the pancreas, and in several of their cases adenomas of the head required careful search, and in one case a Whipple procedure.

One of their patients had eight separate adenomas, and I reemphasize this because multiplicity of islet cell adenomas is estimated to occur in only 10 per cent of the occurrences.

Dr. Scott referred to one patient, a nurse, who presumably had been administering insulin to herself for unknown reasons and was precipitating spells of hypoglycemia. It is quite interesting that we had a patient in Richmond several years ago who also was a nurse, suspected of having factitious hypoglycemia. After very diligent observation and search a syringe was found hidden in her vagina. This patient was proven to have had factitious hypoglycemia.

Dr. John R. Brooks (Boston): There was a time, not too distant, when it was impossible to make an accurate preoperative diagnosis of insulinoma, and as a result the surgeon had his hands full when, on opening the abdomen, he found there was no palpable tumor present. Today, with our present technic, we should be able to be 95 per cent accurate in diagnosing an insulinoma preoperatively, even if an arteriogram fails to show the lesion. We feel that if a patient has Whipple's triad; that if the tolbutamide test is positive; that if the serum insulin is elevated; and if there is no extrapancreatic hypoglycemic substance being produced, then the surgeon should be more aggressive. If he fails to palpate a single small tumor in the pancreatic substance, he should start at the tail and approaching the head, remove more and more pancreatic tissue, all the while monitoring the blood glucose. Blood glucose will go up as soon as the tumor comes out, within 15 or 20 minutes, in our experience, and when the tumor has finally been removed, he will see blood glucose rise, and it will continue on, consistently higher and higher. It is our belief that you should do this if your preoperative tests are conclusive, and if you cannot palpate the tumor. In two cases we have ended up doing a 70 to 80 per cent removal of the pancreas in order to find the tumor and to get a rise in serum glucose.

Dr. Frederick H. Bowen (Jacksonville): I think all of us will get into a situation at times where we cannot find the tumor and will resort to an 80 per cent pancreatectomy, or removal of portions of the pancreas, to find the tumor. And after we have done this, I think it is a good idea to go back and take another look at the head of the pancreas, because this maneuver served me very well in the following case.

A 48-year-old woman whom I first saw in 1955 had been having seizures for the preceding 2 years. These seizures occurred usually during the night; and she would void involuntarily with many of these episodes, but she never defecated involuntarily and had never bitten her tongue. She foamed at the mouth with these episodes and fell from the bed to the floor when a seizure occurred.

The family history showed that the patient's father had died of diabetes. There was no other family history of diabetes. The patient had been in a psychiatric hospital on two different occasions in the preceding 2 years, with a diagnosis of schizophrenia.

Physical examination revealed no abnormalities except that the patient slurred her speech when she talked. The laboratory studies revealed that the VDRL was positive. One fasting blood sugar was 34 mg./100 ml.

At operation, through a transverse abdominal incision, the pancreas was exposed through the gastrocolic ligament, and the anterior surface of the pancreas was exposed, and the head of the pancreas was examined and no tumor was found. The duodenum was mobilized and further exploration revealed no tumor. The short gastric and splenic vessels were ligated, and using the spleen as a handle, the tail and body of the pancreas were resected, removing about 80 per cent of the organ. The uncinate process of the pancreas was then mobilized at this point, and a tumor which measured 1 cm. in diameter was found. The pancreatic tissue overlying it was incised, and the tumor was easily removed.

The patient recovered from the operation with no difficulty, and had sugar in her urine for a few days, which gradually cleared. She was asymptomatic when she was last seen, 2 years after operation. Five years after operation I filled out an insurance form certifying that she could take out life insurance, but I have not seen her.

In conclusion, I would like to emphasize that you ought to take one more look at the head of the pancreas after you have resected the tail.

Dr. William C. McGarity (Atlanta): I wish to emphasize the value of preoperative angiography in localizing the tumor.

(Slide) This is a patient who had the typical symptoms of insulinoma and had preoperative

selective arteriograms with insertion of the catheter in the celiac axle.

(Slide) The next slide shows a late venous phase with a cherry-like tumor stain in the area of the head of the pancreas. Actually, you can see the vein draining the tumor.

(Slide) I think this bears out the importance of preoperative localization, because even knowing the tumor was in this area, the lesion was not easy to palpate at the operative procedure. The tumor was found deeply buried in the head of the pancreas, and required a Whipple resection.

(Slide) This shows a cut section of the adenoma in the head of the pancreas.

(Slide) Next is a close-up, showing the relationship of the large adenoma in the head of the pancreas to the common duct, with a probe in the common duct.

(Slide) This is a close-up of the cut section of the adenoma.

(Slide) This is another case with selective arteriogram with a catheter in the celiac axis, showing a tumor stain at the junction of the body and tail of the pancreas.

(Slide) This is still a later venous phase, showing the tumor stain in the same area.

(Slide) Resection was required because we were unable to enucleate the lesion.

(Slide) This shows two adenomas, and emphasizes one of the disadvantages of arteriograms. The second adenoma is seen in the tail and measures less than 0.5 cm. One must always look for another adenoma, even though you see only one on the arteriogram, because they will not, as a general rule, show if they are less than a half centimeter in size. There are others that will not give a tumor stain if they are not as vascular as most of the adenomas.

(Slide) This is a third case—the last case—showing a tumor stain in the head of the pancreas.

(Slide) We were able to enucleate this tumor, similar to one that Dr. Scott showed.

(Slide) The next shows the cut section of the tumor.

We found that arteriography will show the tumor in about 50 to 70 per cent of the cases, and we feel it is a very helpful procedure.

DR. D. O. FERRIS (Rochester): I certainly enjoyed the masterful presentation that Dr. Scott gave of a very interesting subject, and I want to emphasize what he emphasized in the diagnosis of these cases: the prolonged fast. By "prolonged fast" I mean up to 72 hours.

Four years ago at the Western Surgical Association meeting I presented our experience with 154 tumors causing hyperinsulinism. Eleven per cent were malignant. The tumors were multiple in 5 per cent of the cases.

When I returned home, I decided that if we had multiple tumors in 5 per cent of cases, I would like a little more information during surgical exploration of these cases, and we added selective arteriography and the monitoring of blood glucose during operation.

You have seen some excellent slides from the immediately previous discussor on selective arteriography.

(Slide) In the last 4 years I have had nine patients. We did selective arteriography in all except the first, and, as you see, the fourth from the bottom is a case of multiple tumors. The third from the bottom is carcinoma, one of nine cases; again, carcinoma occurred in 11 per cent of the occurrences.

I want to compliment Bill Scott, in that my figure for multiple tumors is seven, but he beat me by one.

Monitoring the blood sugar during operation, we used the glucose oxidase method in the early cases, and then, more recently, the oxygen sensor method, which uses 0.2 cc. of blood and gives us a report within 10 seconds. As you can see in the column—hyperglycemia rebounds in minutes.

The greatest delay we had was with carcinoma, the only male patient in the group, 25 minutes. The peak blood glucose in mg./100 ml. that followed the removal of the functioning tumor was 357; and as you see, all of them were markedly elevated.

One of the other interesting things we did was to monitor the blood insulin levels also. Our radioimmunoprecipitation assay takes 4 days; but we had this delayed information which to me was very, very valuable.

The next to the last column shows how long it was before the fasting blood glucose level returned to the normal range. The longest delay, as you can see in the column, was 7 days. Apparently the islet cells were so atrophic or so suppressed by the function of the insulin-producing tumor that it took them that long to recover.

Then the insulin assay bore out exactly our findings on the blood glucose. It confirmed our blood glucose rebound in every single case.

I would also like to say that in the eight patients in whom we did selective arteriography, if we included the retrospective view of the patient with seven tumors, then we disposed the tumors accurately in 75 per cent. This is a tremendous help to the surgeon.

DR. RICHARD FIELD (Centerville): Thank you, Dr. Scott, for another great presentation on insulinomas, which we too have been interested in down in Mississippi. I would like to have Dr. Jim Hardy with me, because he has been a real activator down our way in his interest in this type of tumor, and he did two operative procedures on the patient I would like to present very briefly.

With Dr. Scott's permission, we would like to make two observations regarding the malignant insulinoma, and both have been shown in this case.

(Slide) This is a 59-year-old man, and this picture was taken 2 weeks ago. In 1963 we

initially operated on this man, and removed a 340 Gm. malignant insulinoma. This man's longevity, I am sure, is dependent upon a conversation we had with Dr. Warren the night before operation, in which he admonished us to remove the tumor if at all possible. We did so. He did well for 4 years. In 1967 his symptoms reoccurred. Dr. Hardy at that time operated upon him and removed another large tumor.

He did well until 1970, when his symptoms recurred. We operated upon him again. This time, however, we were whipped. There were massive liver metastases, and we were unable to remove any tumor.

Therein lies the first point with an islet cell carcinoma. These are usually low grade, slow growers. As Dr. Warren reminds us, they can be removed, and these patients can live a long time, even in palliation.

Following the operation in November, 1970, we first tried Diazoxide, unsuccessfully, on this man. Then in August of this year, at which time he was having a hypoglycemic episode every 3 hours, he set his alarm clock to eat to stay alive. We tried an interesting new antibiotic, streptozotocin. Since that time we have given him transarterial infusion, through the celiac axis, of Streptozotocin. His blood sugar level has been normal. He has had no hypoglycemic attacks, and we have been very impressed over this short interval with the palliation of this antibiotic, Streptozotocin.

We enjoyed Dr. Scott's paper very much. I would like to ask him and his group of their interest in Streptozotocin, and would it be possible that we might even, with this drug, treat those benign cases of insulinoma which we cannot find at operation.

DR. KENNETH W. WARREN (Boston): Dr. Scott has shown my slides, so I do not have to repeat them.

Dr. Richard Field called me the night before he did his remarkable operation. I urged him on, described how complicated this would be, in the expectation that he would send the patient up to Boston. But he decided to do it himself, and he did it well.

I think most of the features have been covered here. I would like to emphasize one thing. If you operate upon a large number of these patients, you will find the tumor in about 80 to 85 per cent of cases. With arteriography we are going to find more.

Three per cent of these tumors are aberrant, and one should always look for the usual areas where an aberrant tumor may be before one does a distal pancreatectomy.

I would like to emphasize also that some of these patients have large retroperitoneal fibromas, and that they produce the same symptoms. These tumors, despite their size, can be removed.

We have one patient with massive liver metastases, treated by continuous, long-term hepatic arterial infusion with 5-FU, who lived comfortably for 3 or 4 years with massive metastasis.

Dr. Scott has covered this subject comprehensively. Above all, he has emphasized that the simpler tests, and especially the starvation test, is far superior to any exotic test that has yet been devised.

DR. JOHN DONALD (Mobile): I wish to call attention to the complication of pancreatic pseudocyst.

Dr. Scott mentioned in his paper one patient in his series of 13 who developed this complication and died 6 months later. We experienced the complication of pancreatic pseudocyst a few months ago. The pseudocyst developed despite what we considered very careful technic in removal of the insulinoma. Fortunately, this patient's pseudocyst was handled very easily by a cystogastrostomy, and he made a complete recovery.

I believe that this complication occurs more frequently than is realized. There are not very many surgeons who have had a large enough experience with this procedure to justify reporting their results, and therefore I do not believe we have accurate figures on the actual incidence of this complication following surgery for insulinoma.

I therefore would like to ask Dr. Scott whether or not he thinks that good drainage is essential after distal pancreatectomy or excision of the insulinoma. We feel that it is, and should include sump drainage. But even then I have a feeling that this is not always adequate. I would like to ask him if he feels that good drainage alone is adequate in preventing this complication, or should we consider some other procedure, such as pancreatojejunostomy?

DR. JOHN HOWARD (Chester): In addition to reiterating the validity of the two advances made —namely, the measurement of serum insul levels and the use of selective arteriography in the localization of the tumor—I would like to say that pancreatography at operation may help to localize these tumors.

In the normal pancreas, if one injects the pancreatic duct and overdistends it slightly, one gets a diffuse blush of the pancreas. A negative shadow may be demonstrated by a space-taking nonasinar tumor. This may prove of help in localizing it at the operating table.

Finally, I would like to say that I have seen one patient with a metastatic lesion to the liver from an islet cell carcinoma, proved at operation and proved at autopsy, who survived without definitive therapy for a period of 10 years between the demonstration of the hepatic metastasis and death.

DR. MICHAEL CLARKE (Closing): Dr. Donald, yes, we definitely drain all these instances. In

every instance in our series the pancreatic resection was drained. In 14 of the 15 resections a Penrose drain was used, and in one a sump drain was used. We had one fistula which cleared in approximately a month's time.

To Dr. Field's question, I cannot comment knowledgeably about Streptozotocin. We have not used it.

Dr. Marion S. DeWeese, from the University of Missouri, had hoped to comment on this paper, but he left this morning, so I am going to show his patient.

(Slide) He had the difficult experience of having the preoperative diagnosis of an insulinoma primarily by Whipple's triad. He did the distal pancreatectomy, as we have suggested, found no adenoma in serial sections. He then went ahead with serial sections of the head up to a 95 per cent pancreatectomy. The adenoma was still not found. He had the courage of his convictions, and did the total pancreatectomy, and a small adenoma was found in the specimen.

(Slide) That shows the adenoma.

(Slide) The next slide is the patient postoperative. He is doing well. He takes insulin and oral pancreatic enzymes.

I want to reiterate the need for concomitantly obtained serum insulin and sugar. They are most diagnostic during the prolonged fast. The only type of hypoglycemia we cannot rule out with this type of evaluation is the factitious hypoglycemia due to self-administered insulin. This was beautifully brought out by Dr. Williams' case.

I certainly want to reiterate that wedge resection has no place in the pancreatic surgery for these adenomas.

Postoperatively, our experience was similar to the other discussants'. The blood sugar rises very rapidly, and is a very good indicator of whether one has removed all the adenomatous tissue.

We do have one experience of a sarcoma which secreted "an insulin-like substance." This patient was evaluated with serum insulins, similar to the way in which we would evaluate any other patient with Whipple's triad, and the insulins were not at all elevated.

Arteriography in our experience has not been as helpful as it has been in others'. For instance, we had one 43 mm. tumor which was not revealed on arteriography. It was located in the tail of the pancreas.

In conclusion, I would say that these are very fascinating occurrences and, if evaluated properly, as we have suggested, and carefully operated upon, as Dr. Scott has outlined, the results are very gratifying.