Islet Cell Carcinoma of the Pancreas *

JAMES R. HANSEN, M.D.
Burlingame, California

ACCORDING to Whipple in his Banting Memorial lecture at Toronto, Canada in May 1951, the first pathologic description of an islet cell tumor of the pancreas was made by Nicolls in 1902. It was as late as 1922 that Warren had described only 20 cases of similar type tumors, but no physiological significance had been attached to any of them at this time.

It was Wilder who first reported an example of carcinoma of islet cell origin with fatal hypoglycemia in 1927. The first successful removal of an adenoma of islet cell tissue was carried out in Toronto, Canada in 1929 by Roscoe Graham, and since that time, there have been more than 400 islet cell tumors reported in the combined world literature. These tumors, as reported, were usually small, seldom exceeding 1.5 cm. in diameter, and frequently were overlooked unless serial sections were taken of the entire pancreas.

Genesis of Islet Cell Tumors

The study of Bensley and others on the embryology and regeneration of the pancreas has firmly established the view, now universally accepted, that the epithelial cells of the islands of Langerhans are derived by differentiation from the epithelium of pancreatic ductuals. In the embryo the pancreas develops from hollow epithelial buds which grow out from the duodenum as branching pancreatic ducts. At intervals, differentiation gives rise to acinar cells or islet cells. This ability to differentiate is carried throughout life.

On the basis of this knowledge, it has been suggested that islet cell tumors represent a response of pancreatic duct epithelium to a stimulus which calls into action its islet forming potentiality and, to a lesser extent, its ability to build ducts while its power to form pancreatic acini remains virtually in abeyance.

Moreover, it has been noted that the presence of mitotic figures in islet cells contain specific granules, indicating the ability of these cells to carry on independent proliferation once they have differentiated from the duct epithelium.

Although these observations have been made exclusively an islet cell adenomata, it seems justifiable to apply the obvious conclusions to the genesis of malignant islet cell tumors as well.

Pathology of Islet Cell Tumors

According to Whipple,[5] in general, it may be said that four pathologic changes have been described in the islands of Langerhans with severe hypoglycemia: 1) diffuse hyperplasia; 2) benign adenomas; 3) malignant adenomas? (questionably); and 4) carcinomas with metastases.

A certain number of all of the pathological entities are nonfunctional in that they are not accompanied by an over production of insulin. In general, the incidence of severe hypoglycemia increases with the carcinomatous features of the tumor. It is also apparent that the recurrence of hyperinsulinism and hypoglycemia is more likely to take place in the diffuse adenomatosis and the questionably malignant type of ade-

* Submitted for publication August 11, 1961.

nomas than in the encapsulated single adenomas.

Here again, according to Whipple [5] and as previously mentioned by Duff,[1] the majority of these tumors were not large and averaged 1.5 cm. in size. Howard [3] presented 398 cases several years ago: 1) 78.6 per cent benign adenomas—313 cases; 2) 12.1 per cent suspiciously malignant—48 cases; and 3) 9.3 per cent carcinomas—37 cases.

In questionably malignant or carcinomata of low grade malignancy, or slow growing carcinomata, all instances in which autopsy was obtained from such tumors, metastases from such tumors was lacking. In all cases where surgical excision was carried out, there was no evidence of recurrence. Duff,[1] therefore, placed these lesions in the benign grouping even though they were malignant histologically.

Undeniable malignant islet cell tumors are rare, but peculiar tumors of the pancreas have occasionally been reported, which might well have been unrecognized islet cell carcinomata; for example, the diffuse carcinoma of the pancreas, *rare type* described by Willis.

In view of the small number of cases available for analysis, it can only be stated that the sex and age incidence of islet cell carcinoma of the pancreas does not appear to differ materially from that of other types of pancreatic carcinoma.

According to Suracki, Marshall and Horn [4] encapsulation of pancreatic islet cell tumors are a rarity. In their series it appeared complete in only one benign and one malignant tumor. The *trapping* or engulfing of normal pancreatic tissue by tumor is a feature of benign tumors almost as frequently as it is of carcinoma.

In their series there was a slightly greater tendency to nuclear pleomorphism and nucleolar prominence among the benign tumors, but, here again, the difference was not great enough to serve as a basis for distinction of benign and malignant lesions.

From all of the available information it would appear that the islet cell carcinoma of the pancreas is a rapidly growing tumor which spreads quickly from the pancreas into neighboring structures and metastasizes widely via lymphatic and blood channels. The tendency of the tumor to spread rapidly beyond the limits of the pancreas might be regarded as a property inherent in this particular tumor were it not known that the same tendency is shared in a marked degree by pancreatic carcinomata of other histological types when they are located in the tail or the body of the pancreas. According to Frantz [2] in an article concerned with benign, malignant, and questionably malignant tumors of the pancreas, these cases of islet cell carcinoma were occasionally designated as the "suspiciously malignant tumors."

By definition, no metastases are present, and the localized tumor shows either absence or invasion of the capsule, blood vessel invasion, or cellular anaplasia with numerous mitoses. Thus, although it histologically appears malignant, subsequent metastases have not yet been shown, and the patients have remained well after resection of the tumor. Malignant tumors unquestionably occur; however the microscopic picture is not unlike the aforementioned group, so that here again, be definition, metastases must be demonstrated to prove the diagnosis of malignancy.

According to Duff [1] and Murray, tumors of any of the mentioned groups may secrete insulin in sufficient amounts to produce a hypoglycemia, or they may produce no recognizable endocrine manifestations (nonfunctioning tumor). It has been suggested that the alpha cells do not secrete insulin and, therefore, are the cells of the so-called nonfunctioning tumors, whereas the beta cells make up the functioning insulin secreting tumors. This differentiation has not been established with certainty.

In the large series of cases presented in all of the literature reviewed, the life his-

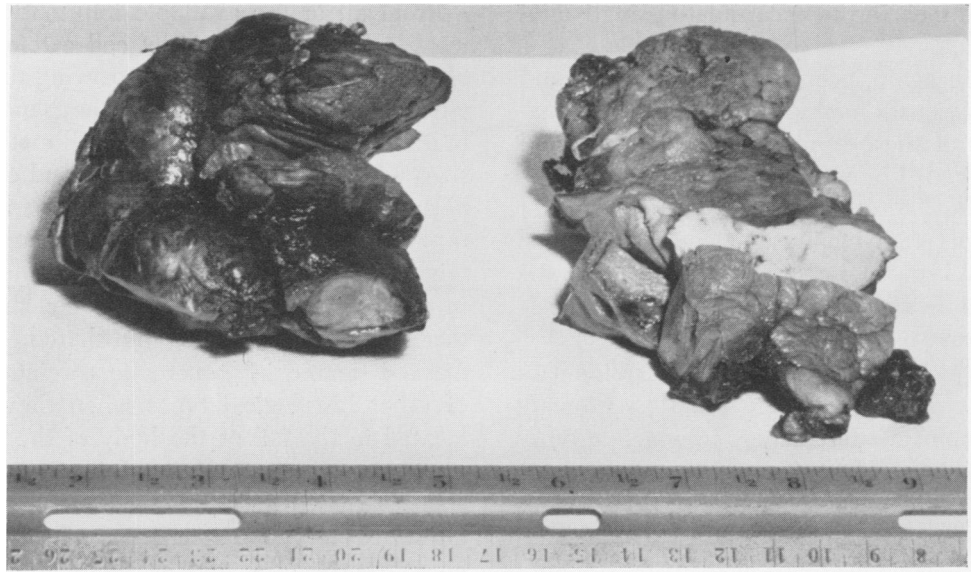

FIG. 1. The bulky tumorous mass with its numerous umbilications and large and small areas of nodularity is demonstrated. Cross-sectional cut across the body of this tumorous mass revealed a glistening, whitish gray surface which was rather uniform throughout the entire tumorous mass. Total tumor weight—590 Gm. Measured 16 × 9 × 4.5 cm. Spleen weighed 226 Gm.

tory of these tumors was not consistent or clear cut. The nonfunctioning tumors were usually incidental findings except when malignant. There is nothing to suggest that nonfunctioning, localized tumors are a premalignant lesion or develops into a functioning tumor.

According to Howard,[3] the treatment of carcinoma of the islets has been, in general, unsuccessful. In his report only one of the 37 cases reported is alive. The patient was living four years after the cholecystogastrostomy, the tumor being considered unresectable. At the time of his report, only three or four surgeons had attempted resection, and they had been unsuccessful. It should be stated that excision of suspiciously malignant tumors may at times represent the treatment of the early carcinoma. In such a case, the over-all result would be much more encouraging.

Case Report

A 44-year-old woman was first seen in February 1960, with a visible lump in the epigastrium just to the left of the midline, which had been noted approximately one month prior to her examination. At that time she had no complaints in regard to the lesion, as such, except that she had noted some gurgling sensation at intervals during the preceding two or three weeks, and that it had been increasing in size. There had been no pain associated with this mass, but she had noted a definite change in its configuration, and the fact that it had moved more to the left side of the abdomen. Her recent past history was probably significant in that approximately a year and a half prior to being seen, she had had intermittent diarrhea, at which time, a barium enema had been performed, and this was reported as being within normal limits. For this reason she was treated for functional bowel distress, but despite this, her symptoms persisted.

On examination the significant findings were limited to the abdomen where there was a visible mass in the left hypochondrium which was firm, easily palpable, and the superficial portion of this tumor appeared to measure 10 cm. in diameter. The leading edge of the left lobe of the liver was palpable as separate from this lesion. Above this mass there appeared to be a gurgling sensation on depression of this area that was felt to represent bowel adherent to the tumor.

Surgical Findings. The patient was explored through a long supra-umbilical transverse incision,

and a large bulky, rounded, lobulated anaplastic appearing lesion involving the entire body and tail of the pancreas, extending up to the splenic pedicle, was found. This mass displaced the stomach anteriorly and was quite firm and fixed in all areas. The color, grossly, was bluish-pink with whitish areas scattered on its external surface and measuring about 1.0 × 4.0 cm. in size, many of these were umbilicated. The tumor mass was approached through the gastrocolic ligament, and because of the nature of the lesion, it was thought that biopsy should be taken prior to any attempt at resection. The frozen section revealed this to be an anaplastic carcinoma, the exact type of which was undetermined. Further exploration revealed the abdominal cavity to be free of metastases, and the liver was similiarly free of apparent metastatic disease. The tumor mass itself appeared to be movable and, for this reason, it was believed that an attempt at resection should be performed.

The mass appeared to weigh approximately 600 Gm. It extended laterally to the splenic pedicle. Medially it came across the superior mesenteric vessels approximately 3.0 to 4.0 cm. and was intimately wrapped around these vessels, but there was no direct invasion of the wall of either the vein or the artery. Superiorly the mass touched the undersurface of the diaphragm, and inferiorly the mass was intimately adherent with the transverse mesocolon. The transverse colon was attached superiorly to the leading edge of this bulky tumorous mass. In division of the head and body of the pancreas, a tongue of tumorous tissue was found to extend into the major pancreatic duct, and this was simply shelled out of the duct rather than making any attempt at total pancreatectomy.

It should be mentioned at this point that the collateral venous circulation around this tumor was excessive, and in many areas, the collateral veins

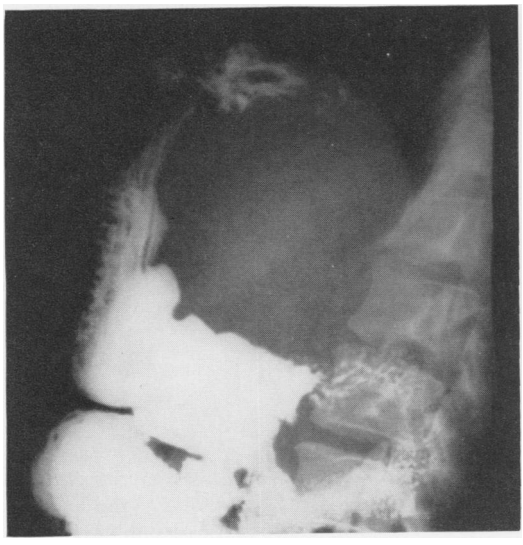

FIG. 2. Right anterior oblique view of the stomach shows anterior displacement of the body and extrinsic compression deformity of the lesser curvature. The duodenal loop is normal. Appearance is consistent with a mass in the region of the body of the pancreas.

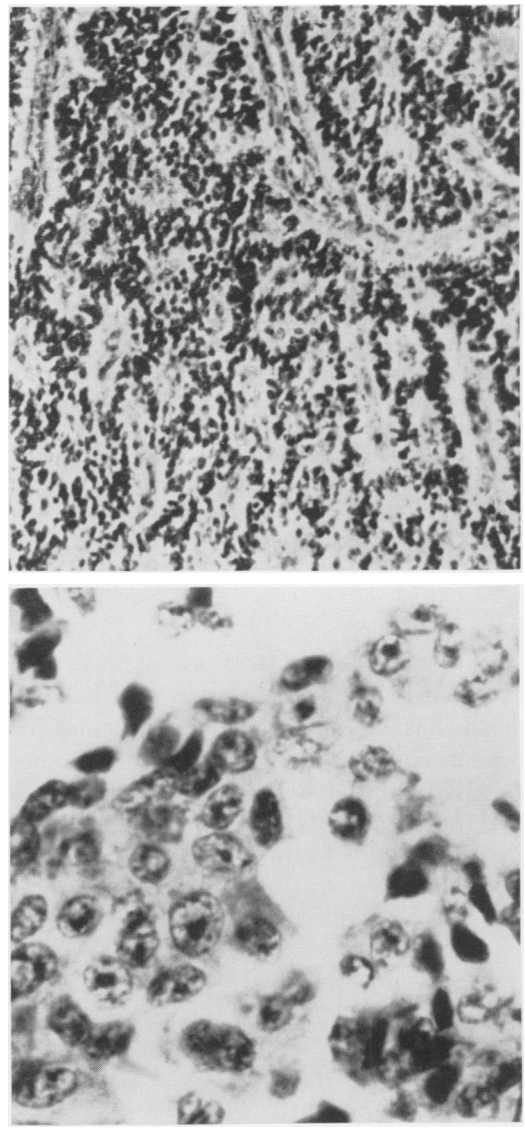

FIG. 3. (Upper) The neoplasm resembles normal islets with groups and cords of fairly uniform cells supported by a delicate stroma of fibrous connective tissue (from × 130).

FIG. 4. (Lower) Under higher power the cells show a moderate degree of nuclear pleomorphism with irregular clumping of the chromatin (from × 530).

measured 1.0 to 1.5 cm. in diameter. Excessive bleeding was a continuous problem, and the dissection was difficult in almost all regions. It became apparent that unless the major arterial supply to the area were divided, resection of this mass would be impossible. The region of the celiac artery was then entered. After a moderately difficult dissection, the splenic artery was identified and found free of tumor for a distance of approximately 4.0 mm. At this point the artery was divided, thus controlling the excessive bleeding to a great degree. The tumorous mass was then dissected from its attachments to the superior mesentery vessels, and when this had been accomplished, the remaining removal of the mass was not difficult. The adrenal was not involved on this side, and no further resection was carried out.

Progress—Postoperative and Survival. This patient had a rather uneventful postoperative course, and there were no complications following this operation other than a slightly prolonged ileus which was followed by some intermittent diarrhea for several days. She is now one and a half years postoperative and when last seen, demonstrated no evidence of recurrent malignancy, and her general health has been excellent. She has gained weight since her surgery and is feeling perfectly well at the present time. A recent chest x-ray film shows no evidence of metastatic disease, and she is being followed at six-month intervals.

Summary

A review of the literature in regard to carcinoma of the pancreas of islet cell origin has been carried out. Particular attention has been directed toward nonfunctioning type islet cell carcinoma. The literature on this subject is limited and only a few cases have been reported recently. To my knowledge, this is the largest nonfunctioning islet cell carcinoma which has been removed and reported in the literature to this date.

The most important feature of this neoplasm which deserves re-emphasis is the fact that apparently with certain numbers of these tumors, they are locally malignant, but if adequately resected, the hope for a good survival rate is excellent. The basic problem would appear to be at the time of operation in differentiation between a carcinoma of pancreatic acinar origin and one from islet cell tissue. This obviously can be difficult and even with frozen section an answer cannot be obtained at the time of operation. For this reason resection of all tumorous masses in this region, if at all possible, should be encouraged. The prognosis would, of course, be entirely different if ultimately it were determined that this were a tumor of pancreatic origin.

Bibliography

1. Duff, G. L.: Pathology of Islet Cell Tumors of Pancreas. Am. J. Med. Sci., **203**:437, 1942.
2. Frantz, V. K.: Tumors of Islet Cells with Hyperinsulin—Benign, Malignant, and Questionable. Ann. Surg., **112**:161, 1940.
3. Howard, M. R.: Hyperinsulin and Islet Cell Tumors of Pancreas. Internat. Abstr. Surg., **90**: No. 5, May, 1950.
4. Suracki, Marshall and Horn: Tumors of Pancreatic Islets. Cancer, **13**:347, 1960.
5. Whipple, A .O.: Tumors of Pancreas. Canad. Med. J., **66**:1952.