ISLET CELL CARCINOMA OF PANCREAS, WITH METASTASIS

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A NUMBER of islet cell tumors of the pancreas, both benign and malignant, have been recorded in the literature. Nicholls,[45] in 1902, reported the first unequivocal islet tumor, an adenoma discovered as an incidental finding at autopsy. Fabozzi,[18] in 1903, described five cases, four of which showed involvement of other organs. During the next few years additional cases of islet cell adenoma were found.[29, 28, 44, 12] Vecchio,[53] in 1914, described an islet cell tumor found in aberrant pancreatic tissue. Lang[39] was the first to report the finding of multiple adenomata of the pancreas. Reviewing the subject in 1926, Warren[54] could find only 16 reports of islet cell tumors, none of which involved distant or neighboring organs, and he added four cases of his own. In none of the cases which he reported was a clinical summary included. He ventured the opinion that these lesions "probably never give rise to trouble during life and have no clinical significance."

However, following the discovery of insulin by Banting and Best,[2] in 1922, and the recognition of the effects of insulin overdosage,[22, 3] the tumors of the islet cells of the pancreas soon were resurrected from the limbo of mere pathologic curiosities. Interest in these tumors mounted because of the clinical picture which some of them were found to present.

Credit belongs to Harris[26] for suggesting, in 1924, the possibility of hypersecretion of insulin as the causative factor in certain cases of spontaneous hypoglycemia. This hypothesis was confirmed when, in 1927, Wilder, Allan, Power, and Robertson[61] reported their case of the physician who clinically presented a typical picture of severe hypoglycemia and who showed at operation and at autopsy an islet cell tumor of the tail of the pancreas, with metastases to the liver and the regional lymph nodes. Assay of the tumor tissue revealed the presence of a markedly increased insulin content. Warren[55] regarded the demonstration of insulin in the tumor metastases in this case as laying the foundation for the clinical entity of hyperinsulinism and he considered it as the final proof of the etiologic relationship of insulin lack to diabetes mellitus. Since the report of Wilder and his associates, the presence of insulin in increased amounts in the tumor tissue in cases of islet cell neoplasm, with hypoglycemia, has been demonstrated several times.[14, 7, 30]

The incidence of tumors of the islands of Langerhans is a matter of some question. Whipple and Frantz,[59] in 1935, reported only 61 cases, only one of which showed metastases. Three years later Whipple[57] listed 74 cases of islet cell tumor, with hypoglycemia, and, in 1940, Frantz[21]

was able to gather 96 cases. In 1941, Keating and Wilder[37] reported 106 cases. This number has been increased to 134 in Whipple's[58] recent article. More recently a number of additional cases have been recorded.[38, 47, 48, 42, 63] Autopsy estimates as to the frequency of islet cell tumors vary from one per 10,000[40] to five in 4,010 consecutive necropsies.[46] It is of interest to note, in passing, that an islet cell adenoma has been found in a mouse[31] and that malignant neoplasms, with metastases, have been described in dogs on two occasions.[50, 8]

Islet cell adenomata are of interest because of the clinical hypoglycemia which often occurs. Campbell, Graham and Robinson[10] state that in only 20 per cent of the cases of islet cell tumor does hypoglycemia exist. In the series of Whipple and Frantz,[59] however, 31 tumors unassociated with clinical hypoglycemia were found at autopsy as opposed to 30 such tumors accompanied by hypoglycemia; and in Duff's[16] group of 90 case reports there were 64 hypoglycemic cases. The absence of thorough clinical records may well account for at least a portion of the number of cases of islet cell tumor reported with no mention of hypoglycemia.

Undeniable islet cell carcinoma with involvement of neighboring structures or metastases to distant organs is rare. A number of cases of islet cell tumors involving only the pancreas have been thought to be malignant on histologic examination.[30, 19, 52, 43, 13, 35, 4, 53] Frantz[21] lists 21 cases in her total of 91 islet cell neoplasms limited to the pancreas. These tumors have been variously labeled malignant, questionably malignant, adenocarcinoma Grade 1, and of low grade malignancy, because, microscopically, they showed a number of the characteristics associated commonly with malignancy. Lack of capsulation, incomplete encapsulation, blood vessel invasion, and cellular anaplasia with frequent mitotic figures have been described in these tumors. However, the 15 patients in Frantz's group of tumors of questionable or low-grade malignancy who survived surgery have shown no metastases or recurrences in follow-ups of from eight weeks to ten years, only four cases having follow-ups of less than a year. According to Duff,[16] the patient of Howland, Campbell, Maltby, and Robinson,[30] who was operated upon in 1929 for a "malignant" islet cell tumor limited to the pancreas, was reported well 12 years following surgery and 19 years after the onset of his symptoms of hypoglycemia. Frantz[21] expressed doubt as to whether all of the tumors in this "locally malignant" group constitute real malignancies, although she admitted that metastases might occur at later dates. Duff,[16] and Brunschwig[9] concur in the belief that a histologic appearance of malignancy in cases of islet cell tumor is not a valid index of malignancy. This point deserves emphasis. The present authors feel that, as far as can be determined at present, the only true criterion of malignancy in islet cell neoplasms is the presence of involvement of other organs by direct extention or by metastasis, the microscopic characteristics of the tumor tissue notwithstanding. Further reports of longer follow-ups in questionable cases are, of course, to be desired.

A careful search of the literature to date (December, 1942) has revealed only 21 cases of islet cell tumor with involvement of other organs, to which group we should like to report another. These cases, with the available pertinent data, are tabulated in Table I. Willis'[62] unusual case of widespread malignancy may possibly represent an instance of islet cell carcinoma. We are omitting the case reported by Berardinelli[6] because this is, in all probability, a malignancy of the common acinar type. Ballinger's[1] report of a widespread malignancy in which the pancreas was not involved is not included in the tabulation because his surmise that the primary tumor arose from ectopic pancreatic tissue in the liver may not be valid.

It is of interest to note that Fabozzi,[18] in describing his five cases of islet cell tumor, apparently did not realize that he was dealing with an unusual type of neoplasm, for the conclusion which he drew from his observations was that malignant tumors of the pancreas nearly always arise from the cells of the islands of Langerhans.

Case Report.—B. G., white, male, age 68, was admitted, September 10, 1942, to the Graduate Hospital on the Gastro-Intestinal Service of Dr. H. L. Bockus. His chief complaint was upper abdominal pain. He dated the onset of his illness to 21 months ago, at which time he struck himself with a wrench and broke several ribs. After two weeks in bed he had no complaints until 19 months before admission when he experienced a severe, sharp pain in the left lower chest. This was accompanied by dyspnea, fever, and chills, but there was no cough or hemoptysis. A diagnosis of pleurisy was made. It was at this time that he first noted frequent cold sweats accompanied by marked weakness which would come on at about 6 A.M. Though never unconscious, on one occasion he could not speak. His wife would give him milk and bread and he would feel much better. Because of his pleurisy he was treated by bed rest for nine months, during which period he had marked swelling of both legs.

The upper abdominal pain began about nine months prior to admission. It was dull and aching in character, not very well localized, and involved first the right side and then both sides of the upper abdomen, but for the most part was epigastric in location. Though the pain was worse when he was hungry, food or soda gave no noticeable relief, but belching seemed to alleviate the discomfort. The pain was aggravated by deep inspiration. He had lost about 30 pounds in weight during the year prior to hospitalization, and associated with this was loss of strength and energy. He complained of exertional dyspnea, but gave no history of vomiting, jaundice, clay-colored or tarry stools, or a change in bowel habit. Since their onset nine months previously, the episodes of morning weakness, relieved by food, have recurred frequently.

Physical Examination.—This revealed a rather florid-faced, elderly white male who showed evidence of marked weight loss. He was in no acute distress and the sensorium was clear. The scalp, eyes, ears, and nose were essentially negative. There was partial edentia, and the tongue was rather red and showed very slight atrophy of the markings at the margins. The lungs were moderately emphysematous. The heart size was within normal limits, and the rate, rhythm, and sounds were normal. B. P. 142/80. Examination of the abdomen revealed a large, hard, irregularly rounded, dome-shaped mass in the epigastrium. The mass was tender and moved very slightly with deep respiration. The liver edge was palpable three centimeters below the right costal border, and the area of splenic dullness was enlarged. Rectal examination disclosed a moderately enlarged prostate, which was thought to be benign. Bilateral hydrocele was noted, and there was slight pitting edema of the right ankle. Neurologic examination was negative.

TABLE I

A TABULATION OF CASES OF ISLET CELL CARCINOMA, WITH INVOLVEMENT OF OTHER ORGANS

Case No.	Author	Year	Age	Sex	Survival After Onset of Symptoms	Hypoglycemia	Site in Pancreas	Size of Tumor	Involvement of Other Organs
1.	Fabozzi[18]	1903	65	?	No clinical data	No clinical data	Head	Orange-sized	Gallbladder
2.	Fabozzi[18]	1903	30	M.	No clinical data	No clinical data	Head	Not mentioned	Liver, and hilum of spleen
3.	Fabozzi[18]	1903	56	M.	No clinical data	No clinical data	Tail	"Head of fetus"	Stomach, liver, and retroperitoneal nodes
4.	Fabozzi[18]	1903	?	?	No clinical data	No clinical data	Head	Not mentioned	Gallbladder
5.	Zanetti[65]	1927	56	M,	No clinical data	No clinical data	Entire pancreas	Not mentioned	Stomach, liver, peritoneum, and regional nodes
6.	Wilder, *et al.*[61]	1927	40	M.	21 months	Present	Tail	Not mentioned	Liver, perigastric and peripancreatic nodes
7.	Lloyd[40]	1929	?	?	No clinical data	No clinical data	Not mentioned	Not mentioned	Stomach
8.	Hamdi[25]	1932	52	M.	No clinical data	No clinical data	Tail	2 x 2.5 cm.	Liver
9.	Judd, Faust, and Dixon[36]	1934	18	F.	4 months	Present	Not mentioned	Not mentioned	Liver (no autopsy)‡
10.	Jacobsen[33]	1934	36	M.	1 to 2 years	Present	Head	Grapefruit-sized	Liver
11.	Bickel, Mozer, and Junet[7]	1935	56	M.	10 mos. (approx.)	Present	Body and tail	7 x 2.5 x 5 cm.	Skin, pleura, peritoneum, adrenals, heart, lungs, liver, pleura, and gallbladder
12.	Evangilisti[17]	1935	65	M	No clinical data	No clinical data	Body and tail	Not mentioned	Omentum, and liver
13.	Cragg, Power, and Lindem[14]	1937	41	F.	7 months	Present	Entire pancreas	Not mentioned	Liver, pancreatic, mesenteric and aortic nodes
14.	Joachim and Banowitch[32]	1938	31	F.	3 months	Present	Distal half	"Tangerine-orange"	Regional nodes (no autopsy)‡
15.	Seckel[49]*	1939	36–38	M.	1 year	Present	Proximal half	4 x 2 x 2 cm.	Liver, one adrenal, spine, lungs, pleura, peripancreatic, periaortic and mediastinal nodes
16.	Duff[15]	1939	32	M.	3 months	Absent	Entire pancreas	Not mentioned	Regional nodes, liver, peritoneum, pericardium, thyroid, adrenals, kidney, and vertebrae
17.	Duff[15]	1939	60	M.	7 months	Absent	Entire pancreas	Not mentioned	Liver, kidney, lung, myocardium, skin, abdominal and mediastinal nodes
18.	Duff[15]	1939	45	M.	5½ months	Absent	Entire pancreas	Not mentioned	Abdominal, mediastinal, cervical and axillary nodes, liver, stomach, gallbladder, adrenal, peritoneum, pituitary, ureter, kidney, bladder, lungs, and brain
19.	Flinn, *et al.*[20]	1941	45	F.	6 mos. (approx.)	Present	Head	Not mentioned	Liver, and retroperitoneal nodes
20.	Gray[24]†	1942	48	F.	4½ years	Present	Tail	1.8 x 1.8 x 1.3 cm.	Liver
21.	Quarrier and Bingham[47]	1942	73	M.	3½ weeks	Present	Tail	3 cm. in diameter	Liver, and regional nodes
22.	Hanno and Banks	1943	68	M.	19 months	Present	Tail	8 x 8 x 6.5 cm.	Liver

*This case has been reported also by Brunschwig[9], Gomori[23], and Cannon.[11]

†This case has been reported also by Joslin *et al.*[34]

‡Operative findings.

Note: All but two cases were autopsied.

Laboratory Data.—Erythrocytes, 5.1 millions; hematocrit, 39; hemoglobin 13 grams (78%); leukocytes 6700. with 72% neutrophiles, 7% monocytes, 1% basophiles, and 20% lymphocytes; urinalysis was negative except for traces of albumin and occasional leukocytes; flocculation and complement fixation tests for syphilis were negative; serum bilirubin was less than 0.2 mg. per cent; prothrombin time by Quick's method 13 seconds (100%); serum phosphatase 5.2 and 4.4 Bodansky units; blood urea nitrogen 17 mg. per cent; cholesterol 216 mg. per cent; fasting blood sugar 54 mg. per cent. serum albumin 3.85 grams per cent; serum globulin 2.79 grams per cent. There was seven per cent dye retention 30 minutes after the intravenous injection of two milligrams of bromsulfalein per kilogram of body weight. The stools were repeatedly negative for occult blood and positive for bile. Gastric analysis revealed 48 units of free acid and 74 units of total acid at the end of one hour. Roentgenologic study of the colon was negative and a barium progress meal disclosed only some displacement of the stomach to the left.

The patient was placed on a smooth meat-free diet and given a maintenance dose of one and one-half grains of digitalis daily. At 1:30 A.M. the third morning after admission, he began to moan and perspire profusely, complaining also of weakness. He was unconscious by the time he was seen by a physician. A blood sugar was taken and 25 cc. of 50 per cent glucose was administered intravenously, whereupon the patient "awoke" quickly, sat up in bed, and drank some orange juice. The blood showed 44 mg. per cent of sugar.

At 5:00 A.M. the following morning a similar episode occurred. Six minims of adrenalin subcutaneously was without effect, but 15 cc. of 50 per cent glucose revived him. The next morning the blood sugar at the time of another attack was 21 mg. per cent. That same day, at 11:00 A.M., he had another period of unconsciousness which was quickly controlled by intravenous glucose.

Because of the repeated attacks of hypoglycemia, he was placed on a high fat, high protein diet with a small midnight feeding. No further episodes of hypoglycemia occurred while he was on this regimen.

After an eight-hour fast a glucose tolerance test was performed, using 100 grams of glucose dissolved in water. The values obtained are shown below. At the beginning of the test the patient complained of weakness and was perspiring. Again at the end of five hours he began to perspire profusely and complained of weakness. The test was not carried out for the full six-hour period because between the fifth and sixth hours the patient became unconscious and had mild generalized convulsions, which promptly responded to intravenous glucose.

Fasting— 34 mg. per cent of sugar
½ hour — 73 mg. per cent of sugar
1 hour —104 mg. per cent of sugar
2 hours—151 mg. per cent of sugar
3 hours—133 mg. per cent of sugar
4 hours— 69 mg. per cent of sugar
5 hours— 32 mg. per cent of sugar
5 to 6 hours— 26 mg. per cent of sugar

Operation.—September 23, 1942: A celiotomy was performed by Dr. Walter Estell Lee. The liver was found to be enlarged and studded with circumscribed whitish-gray masses which varied in size from that of a pea to that of a walnut. A large mass posterior to the peritoneum, and just inferior and adherent to the spleen, was palpated. The exact origin of the mass could not be definitely determined. A biopsy of one of the liver nodules was taken, and the abdomen closed.

Pathologic Examination.—Dr. Eugene A. Case. "The specimen received is a small biopsy of a tumor nodule in the liver. Very little liver tissue is present, its place being taken by an epithelial tumor whose cells have a well-stained, rounded

nucleus with scattered granules of chromatin and a considerable clear cytoplasm. Some of the cells are elongated and some rounded or polyhedral, and they are arranged in nests or processes suggesting glandular origin. Mitosis occurs but is not frequent. The fibrous stroma is rather loose in texture and fairly abundant. From the clinical history it is highly probable that this tumor arose from cells of the islands of Langerhans, though we were unable to demonstrate the granules found in these cells. *Pathologic Diagnosis:* Metastatic carcinoma of islet cell origin."

The patient's postoperative course was rapidly downhill. Glucose intravenously either every four hours as a 50 per cent solution or continuously as a 10 per cent infusion was necessary to prevent severe hypoglycemia. He developed dyspnea and tachycardia and went into shock several times during the second postoperative day, being revived each time by intravenous glucose. That evening he went into shock once more and expired a few moments later. Postmortem examination was performed by one of us (H. A. H.) 16 hours after death.

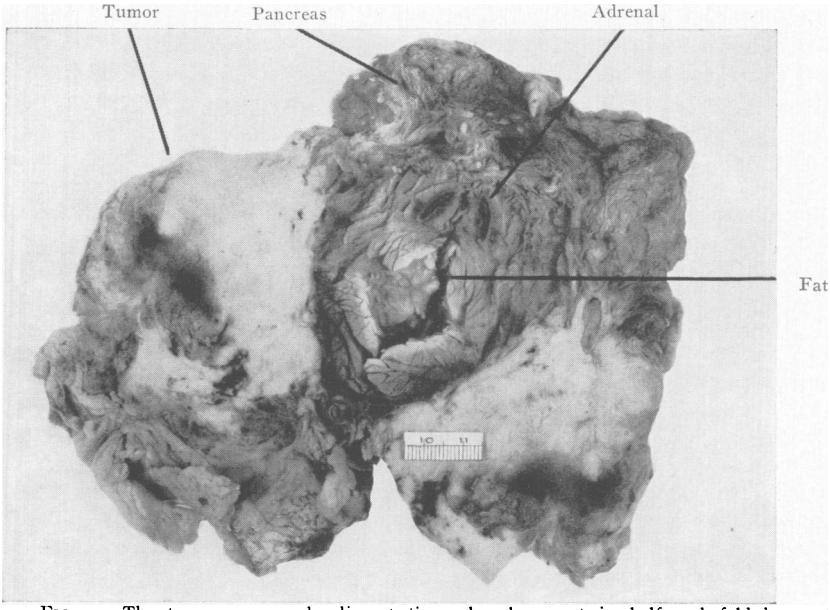

FIG. 1.—The tumor mass and adjacent tissue has been cut in half and folded back. The distal half of the pancreas can be seen to be continuous with the tumor mass proper, and the hemisected left adrenal is visible in the fatty tissue between the halves of the tumor.

Necropsy Findings.—Gross: Recent midline abdominal surgical wound; bilateral avascular pleural adhesions; healed calcified tuberculosis of the left lung; pulmonary congestion; coronary sclerosis; atherosclerosis of the aorta; retention cysts of the kidneys; possible benign nephrosclerosis; benign prostatic hyperplasia; bilateral hydroceles; bilateral cysts of the hydatids of Morgagni; carcinoma of the tail of the pancreas; and widespread metastatic carcinoma of the liver.

When the abdomen was opened the stomach was found to be deviated to the left, and in the left upper quadrant was a large firm mass the size of a small grapefruit. The spleen was firmly adherent to the upper and anterior surfaces of the mass and the splenic flexure of the colon was adherent to it anteriorly and inferiorly. The omentum was adherent to the tumor mass anteriorly, and posteriorly the left adrenal was attached to the mass by a thickness of soft fatty tissue. The left kidney was freely movable with respect to the tumor and adherent structures and was not involved by the neoplasm. Posteriorly, the pancreas was found to be directly continuous with

the tumor mass; there was no line of cleavage between the mass proper and the distal portion of the pancreas. The head and the body of the pancreas were grossly normal; the tumor involved the tail.

The tumor mass was roughly rounded, but presented a number of nodular projections. On the whole, it was firm and whitish, but several soft areas were noted which, on section, were found to contain a sticky, purplish material. The cut surface of the tumor revealed areas of focal hemorrhage and presented a fasciculated appearance. The mass (Fig. 1) measured 8 x 8 x 6.5 cm., and the combined weight of the pancreas and tumor was 370 grams.

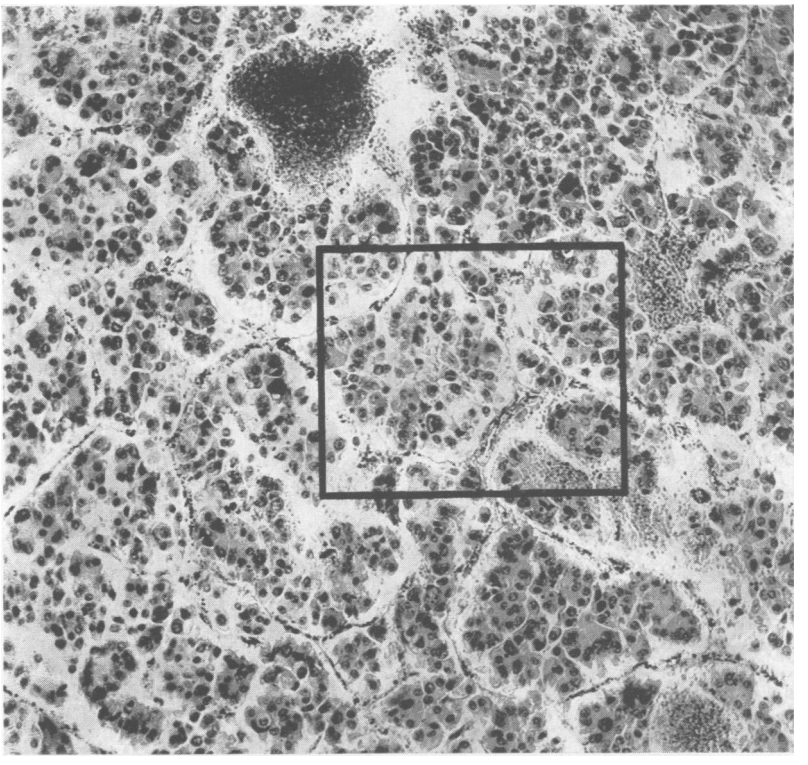

FIG. 2.—A photomicrograph of the tumor tissue in one of the metastatic nodules in the liver. The tendency toward an acinar arrangement is pronounced, although a sheet-like formation of the cells can be seen at the left. The resemblance of the tumor cells to the cells of the islands of Langerhans is striking. Areas of focal hemorrhage are present. (× 150—Hematoxylin and eosin stain)

The liver was enlarged and weighed 2500 grams. The parenchyma was brownish in color and firm in consistency. The liver was riddled throughout with whitish, circumscribed nodules of varying size, from that of a pea to that of a lime. The largest of these masses was located in the right lobe and measured seven centimeters in diameter. On the section, the larger of the nodules were found to contain a sticky, bluish-red material, which was considered as evidence of degeneration.

Both adrenals were entirely negative on section. The bowel was normal except for the area of the splenic flexure which was adherent to the tumor mass; only the serosa was involved, and the bowel wall was intact. No lymphadenopathy was found.

Microscopic.—The tumor tissue was found to be made up of sheets and nests of small polyhedral cells with pale basophilic cytoplasm. The cells varied somewhat in size and shape, and in some areas columnar cells were common. The nuclei were large and oval or round. The majority were vesicular, but many were pycnotic and hyper-

chromic. The nucleoli were prominent. Large multinucleated cells were occasionally seen. Mitotic figures were very few. In some areas the cells tended toward an acinar arrangement which was sometimes marked; in other places they were arranged in sheets or thin strands. The resemblance of the tumor cells to the cells of the islands of Langerhans was striking. The supporting stroma consisted of ill-defined and palely-staining collagenous material which was found in thin strands or, less frequently, in wide trabeculae. Many small blood vessels were seen, and focal hemorrhage and degeneration were noted.

The pancreas itself was histologically normal. The islet cells were smaller than the cells composing the tumor.

The metastatic nodules in the liver presented the same microscopic characteristics as did the parent tumor tissue (Figs. 2 and 3). The supportive stroma was more abundant in the hepatic lesions.

The microscopic examination of the other organs was essentially negative.

Attempts to demonstrate specific granules in the cells of the tumor tissue were inconclusive. Assay of the tumor tissue for insulin content was not performed.

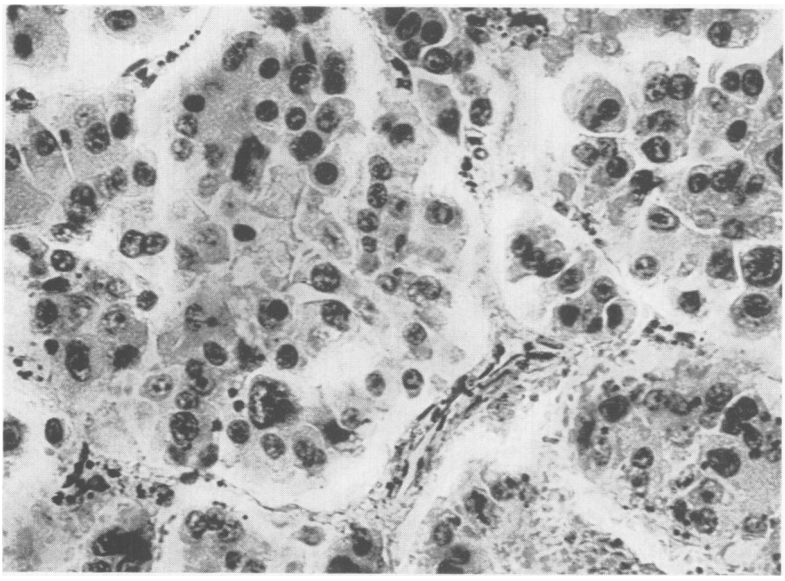

FIG. 3.—A higher-powered view of the blocked-in portion of the field shown in Figure 2. The vesicular and hyperchromic types of nuclei can be seen, and the nucleoli are prominent. (x 620—Hematoxylin and eosin stain)

DISCUSSION

An analysis of the various features presented in the series of cases of islet cell carcinoma tabulated in Table I is of both pathologic and clinical interest.

Pathologically, the size of the pancreatic masses varied considerably. The smallest tumor measured 1.8 x 1.8 x 1.3 cm.; the largest, with recorded dimensions, measured 8 x 8 x 6.5 cm., although lesions the size of a fetal head and the size of a small grapefruit have been reported.

So far as the site of the tumor in the pancreas is concerned, five of them occurred in the head, six in the tail, two in the head and body, and two in the tail and body. The entire pancreas was involved in five instances. In

no case has the body of the pancreas alone been the site of an islet cell carcinoma. Maximov and Bloom[41] state that the islands of Langerhans are somewhat more numerous in the tail of the pancreas, and Duff[16] has pointed out that islet cell adenomata are found most frequently in the tail. In the series of islet cell malignancies, however, the head and the tail have been the site of the tumor in almost an equal number of instances.

Grossly, the lesions were, as a rule, fairly well circumscribed, although in some cases surrounding adhesions and infiltration of neighboring organs have been described. The tumors were whitish or yellowish in color, and generally firm in consistency. Areas of focal hemorrhage and necrosis have been mentioned. Nodularity of the tumor mass was the rule. The metastatic lesions have presented much the same appearance grossly as did the primary pancreatic tumors.

Microscopically, the appearance has been essentially identical in all cases. The tumor tissue was composed of small polyhedral or columnar cells arranged in places in sheets, clusters, or strands, and characteristically showing a decided tendency toward acinar formation. The resemblance of the tumor cells to the cells of the island of Langerhans has been remarked upon repeatedly. Some degree of variability in the size of the cells has been present. The cytoplasm of the tumor cells has taken either a pale basic or a pale acid stain, more commonly the former. A tendency toward infiltration of the adjacent pancreatic parenchyma and cellular anaplasia of various degrees have been described. The nuclei of the cells have been vesicular or hyperchromatic. Multinucleated cells have been described in two instances (Cases 11 and 22). Mitotic figures have, as a rule, been infrequently found. In four instances staining for specific granules has been successfully accomplished (Cases 14, 15, 10 and 20). The supporting stroma has varied from delicate strands to wide bands of connective tissue. The metastatic lesions have shown, histologically, essentially the same characteristics as the parent tumor.

Metastases were widespread and generalized in five cases. The liver was involved metastatically in 18 cases, and the regional nodes in 11.

In three of the cases reported insulin assay of the tumor tissue has been successful (Cases 6, 11 and 13). With respect to the benign islet cell adenomata, successful insulin assay has been reported in at least eight instances.[47, 38, 21]

From the clinical point of view a number of interesting facts are to be gained from a survey of the cases of islet cell carcinoma reported:

Of 19 cases in which the sex of the patient could be ascertained, 14 occurred in males and five in females.

The age of the youngest case reported was 18; that of the oldest 73. The average age of the patients was 47.8 years. Six cases occurred in persons 39 or under; ten in the age-group of 40 to 60; and four in patients 61 or over.

Figures of the duration of survival after the onset of symptoms were

available in 14 of the 22 cases. The shortest period of survival was three and one-half weeks; the longest recorded was four and one-half years. Five patients lived a year or more after their symptoms began; and six died in six months or less. The average duration of life once symptoms were noted was 11.9 months.

In all of the 11 cases, where adequate clinical data was available, hypoglycemia of marked degree was present and the progressive increase in the severity and the frequency of the hypoglycemic episodes constituted the principal clinical feature. In the three cases mentioned briefly by Duff,[15] the absence of hypoglycemia was remarked upon. In the hypoglycemic cases blood sugar levels in the low twenties have not been uncommon; in one case a blood level of 16 mg. per cent was noted. According to Womack[64] "cancer of the islet cell type presents the most profound states of hypoglycemia that are encountered clinically." The clinical and pathologic aspects of hypoglycemia have been thoroughly reviewed by several authors.[60, 64, 56]

Jaundice has been noted in only two instances (Cases 1 and 2). These cases were among the group of 12 tumors which involved the head, five of which were limited to the head alone. Berk,[5] in his review of pancreatic carcinoma of the common acinar type, found jaundice in 81.3 per cent of the malignancies involving the head of the pancreas.

In two of the 11 cases, where adequate clinical data was obtained, there was a history of diabetes mellitus prior to the onset of the symptoms of hyperinsulinism (Cases 10 and 11). One of the five cases reported by Harris[26] in his original article had had glycosuria, and Herxheimer,[29] Heiberg,[27] and Smith and Seibel,[51] have reported islet cell adenomata in diabetics. It is of interest to note, in passing, that Berk,[5] in his review of the acinar variety of pancreatic malignancy, found that 6.9 per cent of the patients in this group had antecedent diabetes, whereas the incidence of diabetes mellitus in the cancer group, at large, he placed at one to two per cent.

SUMMARY

1. The literature on the subject of carcinoma of the islet cells of the pancreas has been reviewed.

2. It has been pointed out that, at present, the only valid criterion of malignancy in cases of islet cell tumor is the presence of metastases or invasion of neighboring organs, the histologic characteristics of the tumor notwithstanding.

3. Twenty-one cases of islet cell carcinoma with involvement of other structures have been culled from the literature and an additional case added. An analysis of these cases has been presented.

We are indebted to Drs. Eugene A. Case, Henry L. Bockus, and Walter Estell Lee for permission to publish the case presented and for their kind assistance in the preparation of this paper.

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