ADENOMATOSIS OF ISLET CELLS, WITH HYPERINSULINISM*

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WE have already reviewed (Whipple and Frantz, 1935) the studies which led to the recognition of islet cell tumors. Beginning with the original observation of Ssobolew, published at the same time as Schulze (1900), that ligation of the pancreatic duct was followed by disappearance of the parenchyma of the gland with the exception of the islets, there came in close succession a series of publications on hypertrophy of the islets in diabetes.

In 1904, Ssobolew described an hypertrophied islet in a diabetic. In 1905, Herxheimer found hypertrophy of the islets in five diabetics, and MacCallum confirmed this in two cases in 1907, and considered it compensatory. Cecil (1909) studied the pancreas in 90 cases of diabetes and found hypertrophy also. Dubreuil and Anderodias (1920) reported striking hypertrophy of the islets in a newborn child of a diabetic mother, and, in the same year, Horgan, in 262 autopsy specimens of chronic diseases of the stomach and biliary tract, looked for neoplastic changes associated with chronic pancreatitis and described three stages of hypertrophy of the islets, which he designated as primary, secondary, and tertiary "adenocytoplasia." In the tertiary stage he showed migration of cells through the connective tissue capsule, and considered this an "early neoplasia." In 1925, Boyd and Robinson described regeneration of islets in an insulin-treated case of diabetes—a child of nine, with an accidental death and postmortem examination. In 1926, Gray and Feemster reported compensatory hypertrophy and hyperplasia of the islets in another newborn infant of a diabetic mother. Womack and Cole (Case 2) (1937), reported a similar infant case, as did Bauer and Royster in the same year. This case was associated with tetany, and their report included a review of the literature. Somewhat contradictory conclusions have been reached by Potter, Seckel, and Stryker (1941). In discussing hyperplasia and hypertrophy of the islets of Langerhans of the fetus and of the newborn infant they say that such may be found "in the presence or in the absence of abnormal sugar metabolism in the mother and in the presence, or in the absence, of abnormal sugar metabolism in the infant itself." Benner, in 1941, reports a case of a newborn of a diabetic mother, dying 24 hours after birth, who showed a tremendous increase in the number and size of islets and morphologic evidence of gonadotropic stimulation.

Another observation is that of John (1931)—an insulin-treated case of diabetes, with complicating hyperthyroidism and cirrhosis of the liver, car-

* Submitted for publication March 16, 1944.

cinoma of the liver and gallbladder, and interstitial pancreatitis. Insulin was discontinued and the patient was readmitted in coma, with a blood sugar of 30 mg. per cent. Autopsy showed both atrophy and hypertrophy of islets, but the other pathologic findings make it impossible to be sure that the hypoglycemia antemortem was due to hyperinsulinism.

In 1924, Nuboer reported finding hypertrophy, islets 300–400 μ in diameter, both with and without diabetes, and suggested that most of the reported adenomas might not be true neoplasms but rather hypertrophy. The cases of adenoma reported up to that time had been those of Nicholls (1902) one case; Reitman (1905) one case; Herxheimer (1906), who found two in a case of diabetes; Morse (1908) two cases; and one case each by Helmholz (1907); Cecil (1911); Heiberg (1911); Alezais and Peyron (1911); Rollett (1912); Lecomte (1913); and Koch (1914). Priesel (1922) reported three cases, and Schneider (1924) two cases. In 1926, Warren reviewed these and added four of his own. He included as the twentieth case the report by Lang (1925), which is the first recorded case of nodular hyperplasia of the islets, called by the author "adenomatosis." The patient, a female, age 39, gave a history of attacks of depression, headache, abdominal pain and vomiting, occurring at intervals. No blood sugar determinations were recorded. At operation, a "tumor mass" involving the tail and most of the body of the pancreas was found, and a palliative gastro-enterostomy was performed. The patient died of bronchopneumonia and the islet adenomatosis was observed at autopsy, together with cholelithiasis, another finding possibly related to the clinical symptoms. The pancreas showed countless yellow nodules varying from 50–5,000 μ in diameter. These were encapsulated. There were no metastases. In none of the cases reported up to 1925, including this first case of adenomatosis, was there any definite clinical suggestion of hypersecretion.

In 1926, Herxheimer produced the first experimental hyperinsulinism by ligation of the pancreatic duct in a chicken. The result was hyperplasia of islets and an increase in the insulin content up to five or six times normal. The chicken died of hypoglycemia. Then came the first clinical case of hyperinsulinism with islet cell tumor (Wilder, Allan, Power, and Robertson, 1927) which, it will be recalled, had multiple nodules of infiltrating growth in the pancreas and metastases in liver, lymph nodes and mesentery, with a high insulin assay in the liver nodules.

In a second publication (Frantz, 1940) we have tabulated the cases with hyperinsulinism and tumor, benign and malignant, found at operation and at autopsy. In the literature since, there are records of additional cases. There are also four cases which we overlooked—three benign tumors which were cited by Cheley, Engel, and Nesselrode in the discussion of a paper by Thomason (1934), and one case of carcinoma with metastases, Jacobsen (1934). The statistics which follow are, therefore, corrected to include these.

In addition to these omissions and the cases which have appeared in the

literature since our 1940 review, we have 16 more cases in our own series explored for supposed hyperinsulinism. Of these one (Case 18) was a carcinoma, proved at autopsy at another hospital. Ballinger (1940) interpreted this as an islet cell carcinoma arising in aberrant pancreatic tissue in the liver. We are inclined to doubt this interpretation. At operation in this hospital, a mass was found in the retroperitoneal area between the upper border of the head of the pancreas and the spigelian lobe of the liver. It was a very large tumor, measuring 10 x 6 x 6 cm. Its upper limits appeared to infiltrate the liver, and the lower limits did not appear to be continuous with the pancreas. This we now feel should be regarded as a carcinoma arising in aberrant pancreatic tissue, behind and above the head of the pancreas where such aberrant structures have been described. In the detailed study by Faust and Mudgett (1940) of 370 cases of aberrant pancreatic tissue, none was found in the liver.

In five other cases of the 16 in our new series explored for hypoglycemia no tumor was found. One was a case of von Gierke's disease, so demonstrated at postmortem examination. In one case no tissue was removed. Eighteen months after operation this patient continues to hold the slight improvement she showed immediately, which is difficult to explain. She needs her meals, otherwise she has symptoms, but her fasting blood sugar has risen from 44 to 79 mg. per cent. In the remaining three, partial pancreatectomy was performed. In one of these, a girl of seven, half of the pancreas was resected. This showed, if anything, *hypoplasia* of islet tissue. She had no more convulsions after operation, but fasting blood sugar rose only from 42 to 56 mg. per cent. She was then lost to follow-up. The next case in which no tumor was found had a partial pancreatectomy. There was marked hyperplasia of islets but no neoplasia, and the patient was unimproved. He committed suicide three months after operation. The last case without tumor in Doctor Whipple's personal series (with operation, however, performed not at Presbyterian Hospital but at St. Luke's Hospital, New York City) had a partial pancreatectomy, without relief of symptoms. The pancreas showed nothing unusual.

In our series reported in 1940, 16 cases had been explored for hypoglycemia, in only one of which (Case 22) no tumor was found. Subsequent to the time the report was submitted for publication, this patient was reexplored (May, 1940) because of persisting symptoms. At the second procedure a tumor 1.7 cm. in diameter was found situated in the head of the pancreas, and was removed, with relief of symptoms.

Our series, therefore, now comprises 32 cases in all, in 27 of which tumor was found—one irremediable carcinoma and 26 operable cases. Four of these were reported in 1940 as having certain histologic characteristics suggestive of malignant tumor. Four more of the recent cases also show blood vessel invasion, making eight of the 26 under suspicion histologically. One of these, previously reported, was a postoperative death. The other seven are all

symptom-free; the earliest, and, incidentally, the one most characteristic of carcinoma histologically, being now a six-year arrest, and two others having gone more than five and four years, respectively, without return of symptoms.

Before completing the list of published cases to date, with our own added, we wish to present in some detail the histories of our own two cases of *adenomatosis*. Presumably, in both of these cases the same hyperplasia and neoplasia were present in the tissue left behind at partial pancreatectomy, and yet, to date, there has been no return of symptoms in either patient. The second case is very recent (only six months after operation) but as the first now has had no symptoms for 16 months, in spite of carrying heavy work in a war industry, it seems fair to report them both as similar.*

Case 25.—Dr. Allen O. Whipple: S. G., female, age 46, white, English. The patient was referred because of persisting symptoms following two operations. For five years before her admission to St. Luke's Hospital, in New Bedford, Mass., she had had spells of weakness and fainting, worse at the time of the menstrual period. These were somewhat relieved by benzedrin sulfate, and the patient herself noticed that candy would abort or shorten an attack. Administration of orange juice was observed to relieve an episode of semiconsciousness. At this time, the patient was moderately obese, weight 163 pounds. The rest of the physical examination was essentially negative. The fasting blood sugar, 12/24/41, was 23 mg. per cent. There were no other significant laboratory findings.

Operation.—February 24, 1942: Dr. Milton T. MacDonald, St. Luke's Hospital, New Bedford, Mass. Excision of adenoma of pancreas. This measured about 0.5 cm., and was found near the tail of the pancreas at its upper border.

Postoperative Course.—The patient felt somewhat improved for a few weeks and then began to manifest her old symptoms. Blood sugars were found as low as 40 mg. per cent.

Second Operation.—May, 1942: Dr. Milton T. MacDonald, St. Luke's Hospital, New Bedford, Mass. At this procedure a 0.75-cm. tumor was removed from the anterior surface of the pancreas, just below the superior border.

Second Postoperative Course.—The patient again improved for a short time, but blood sugars remained between 40 and 50 mg. per cent.

On admission to the Presbyterian Hospital, New York City, July 7, 1942, her weight was 165 pounds. Fasting blood sugar taken the next morning, with the patient found in shock at 6:30 A.M., was 34 mg. per cent.

Third Operation.—July 10, 1942: Dr. Allen O. Whipple. The abdomen was explored through a right rectus incision. The duodenum was mobilized for satisfactory palpation of the head of the pancreas. No tumor could be felt or seen. A partial pancreatectomy was, therefore, performed, with the removal of tail, body and a portion of the head.

Third Postoperative Course.—The patient made a good recovery, and had no return of symptoms 16 months after operation, in spite of heavy work on a milling machine, 48 hours a week. On her last follow-up examination, in November, 1943, her fasting blood sugar was found to be 90 mg. per cent, and her glucose tolerance test showed

* In connection with these two cases attention is called to the review by David, in 1940, of the results of pancreatectomy in hypoglycemia. We will not repeat these figures. A few other cases with operation *without tumor* may be added: Barnes and Richmond, 1935, Berry, 1935, Boone, 1934, Eagleston and Berkenbilt (Case 2) 1942, Fanta, 1937 (aberrant pancreas), Guerry and McCutcheon, 1936, Harris, 1938, Holman, Wood and Stockton (Case 4) 1943, Magner (Case 2) 1941, Quarrier and Bingham (Case 3) 1942, Reed, 1934, Rynearson and Walters, 1938, Smith, F. G., 1942 (aberrant), Wechsler and Garlock (Case 2) 1944, and Winans, 1933.

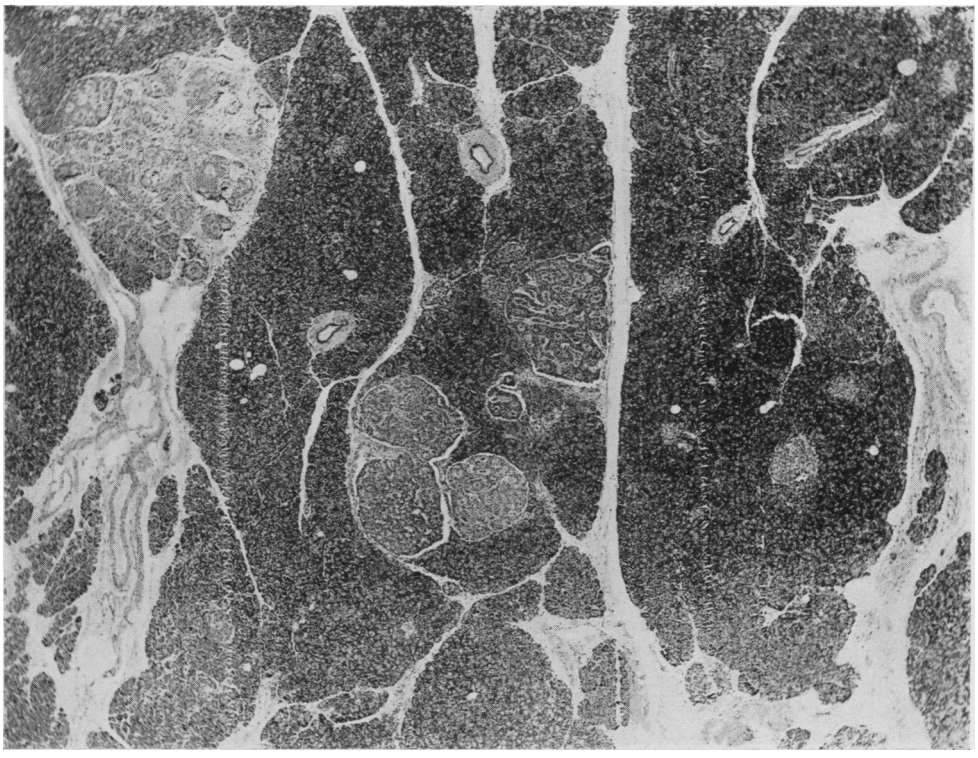

FIG. 1.—Case 1: Photomicrograph showing topography. Normal, hyperplastic and neoplastic islets ranging from 0.14 Mm. in greatest diameter.

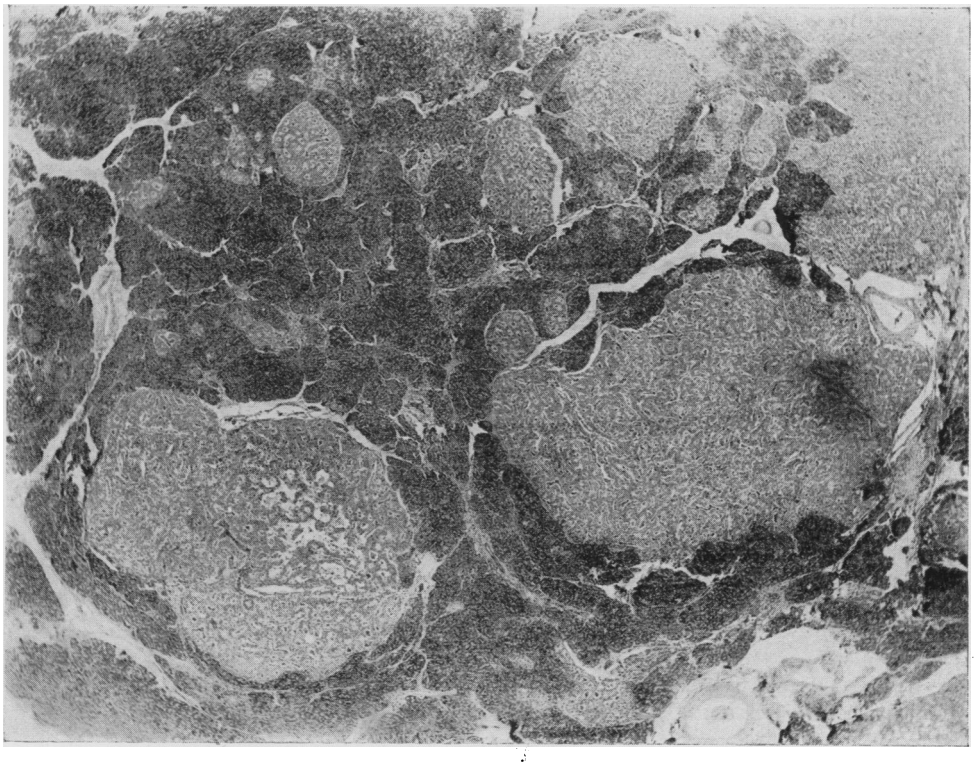

FIG. 1.—Case 2: Comparable field to Case 1. Islet diameters ranging from 0.14–2.4 Mm.

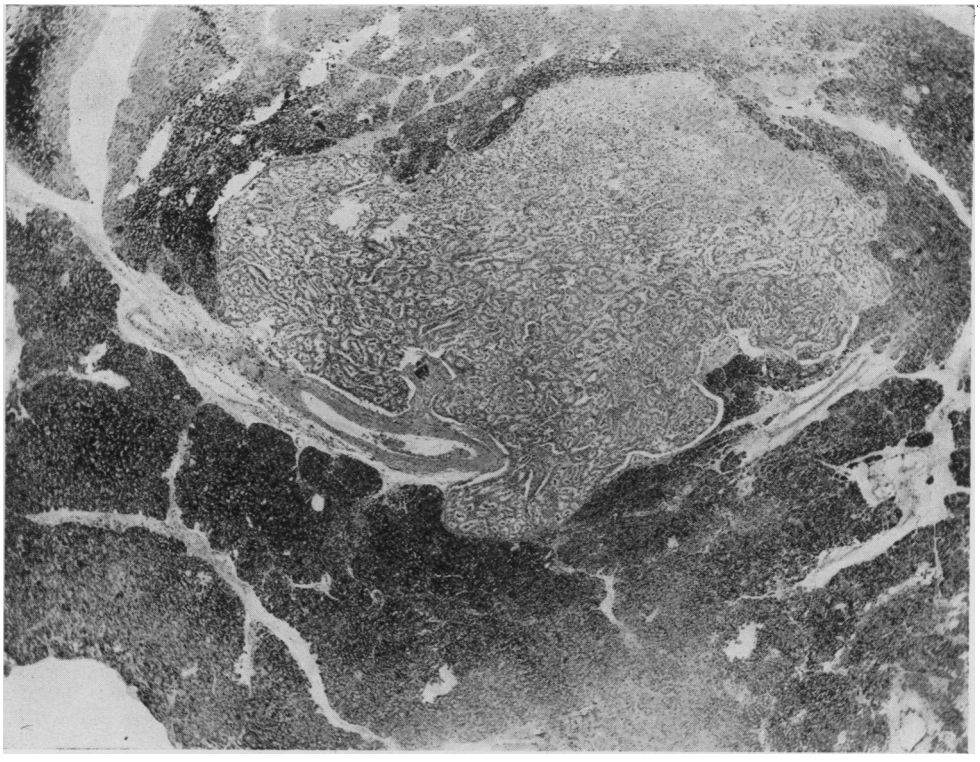

FIG. 2.—Case 2: Comparable field to Case 1. Macroscopic islet 4.0 Mm. in diameter.

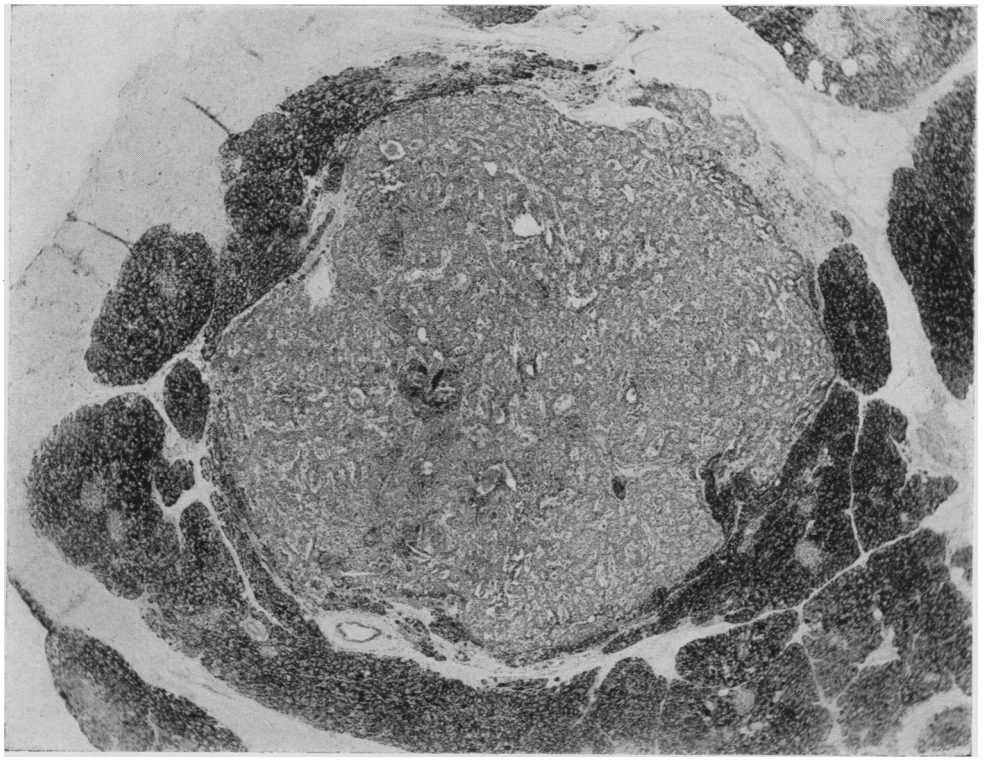

FIG. 2.—Case 1: Photomicrograph showing neoplastic islet 3.7 Mm. in greatest diameter.

figures all on the high side, with a diabetic type of curve. The patient had gained ten pounds and was advised to follow a 1200-caloric diet. She had not reported untoward symptoms since.

Pathologic Examination.—Gross: S. P. No. 82635. The specimen consisted of a segment of pancreas measuring 6.5 x 3 x 0.7 cm., and weighing, fresh, 8 Gm. A number of small purple or violet areas were seen on section, which were slightly raised above the surrounding yellow pancreatic tissue. These were considered as possible multiple adenomata when seen in the fresh state. They were discrete, but showed no striking capsule grossly.

After paraffin section, five discrete adenomata could be seen with the naked eye in hemotoxylin and eosin preparations on the slide. These measured 7, 5, 3, 3, and 2 Mm., respectively.

Microscopically, the sections showed adenomata of the ribbon type, similar to those described by Dr. I. M. Mason, Pathologist, St. Luke's Hosp., New Bedford, Mass., and were composed of islet cells, intimately associated with vascular spaces, some of which showed no endothelial lining. The adenomata were sharply demarcated, but not completely encapsulated. No mitotic figures were seen and no blood vessel invasion was recognized. In addition to these five macroscopic foci, there were many microscopic foci which were similar histologically, and, also, there were an unusually large number of normal and hyperplastic islets. Transitions were seen between these and the adenomata. In some of the small foci it was impossible to decide whether they should be considered hyperplasias or true neoplasms. (See photomicrographs)

Case 30.—Dr. Allen O. Whipple: O. T. V., female, age 46, white, American. The patient came to Vanderbilt Clinic, June 1, 1943, complaining of fainting spells of two years duration. These came on usually in the morning and lasted two to six hours. Return to consciousness was followed by severe headache and muscle pain. There was twitching occasionally during attacks and once she bit her tongue.

Physical examination was essentially negative except for cataract O. D. The condition, thought to be epilepsy, was not relieved by dilantin and phenobarbital. On a clinic visit, September 2, 1943, she volunteered the information that eating sugar helped her, and she was then admitted to the Neurological Institute for study.

At this time, she gave additional history of great irregularity in menstrual periods, a gain in weight of 90 pounds (130–220) since the birth of a child six and one-half years before, with gain most marked during the two years previous to admission, when fondness for sweets became more marked and when they were needed to ward off attacks.

Physical Examination: Height 5 feet 5.5 inches, weight 220 lbs. Except for this obesity there was nothing significant.

Laboratory Data: The serum cholesterol was 252 mg. per cent, and basal metabolic rates —7. The lowest fasting blood sugar was 41 mg. per cent. A roentgenogram of the skull showed no change in the sella turcica. Electro-encephalograms, interpreted by Dr. Paul Hoefer, showed high voltage, slow activity of irregular pattern while the patient was fasting, and a completely normal pattern within one minute after injection of dextrose during hyperventilation. Five examinations were made in all, and it was the impression that there was a striking relation between electro-encephalogram, clinical picture, and food intake.

Blood sugar during an attack was recorded as 37 mg. per cent. The patient was unconscious. She regained consciousness within two minutes after intravenous administration of 50 cc. of 50 per cent glucose. Attacks occurred almost daily in spite of diet, and often required intravenous glucose for relief. Operation was, therefore, advised, and she was transferred to the Presbyterian Hospital.

Operation.—October 19, 1942: Dr. Fordyce B. St. John and Dr. Allen O. Whipple. The abdomen was explored through a long, curved transverse incision. The pancreas was small. There was a hard nodule palpable in the tail which was thought to be

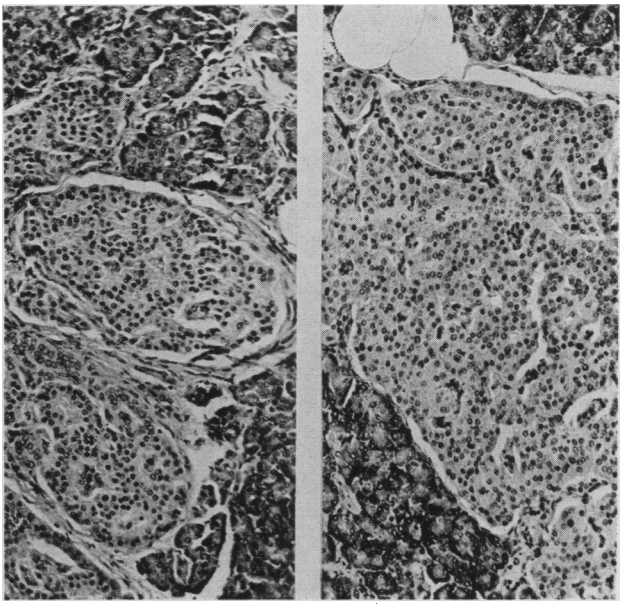

FIG. 3.—Case 1: Higher power photomicrographs showing detail of neoplastic islets.

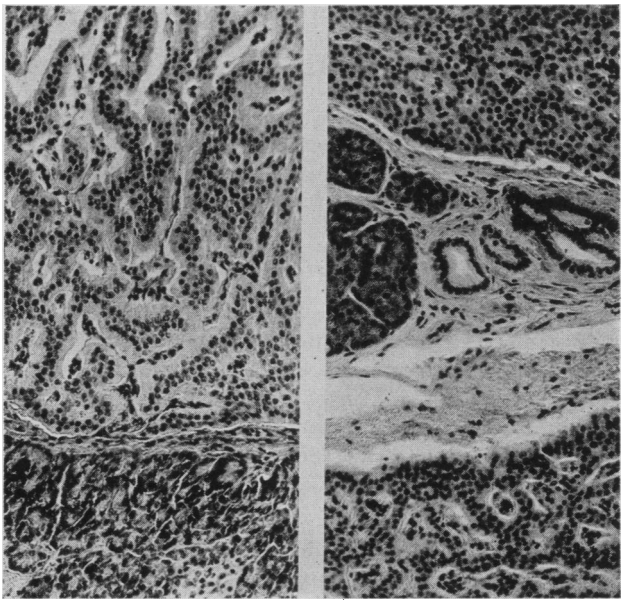

FIG. 4.—Case 2: Comparable fields to Figure 3.

tumor, but satisfactory palpation was difficult because of the patient's obesity. The tail and part of the body were resected. Stubborn bleeding was encountered deep in the left upper quadrant which was controlled by the application of two long, curved clamps, left *in situ*, together with a cigarette drain.

Postoperative Course: The clamps were removed on the seventh postoperative day. The sinus was closed at the end of the fifth week. The patient was discharged on the 47th postoperative day, and the wound was healed in eight weeks.

Subsequent Course: She came for follow-up examination three months after operation, at which time her blood sugar, not fasting, was 103 mg. per cent. Previous fasting blood sugars in the hospital had been as low as 68 mg. per cent on the 46th postoperative day. The patient, however, was on a reducing diet which she continued after leaving the hospital. Six months after operation, April 18, 1944, she again reported at the Follow-up Clinic, free of symptoms of hypoglycemia.

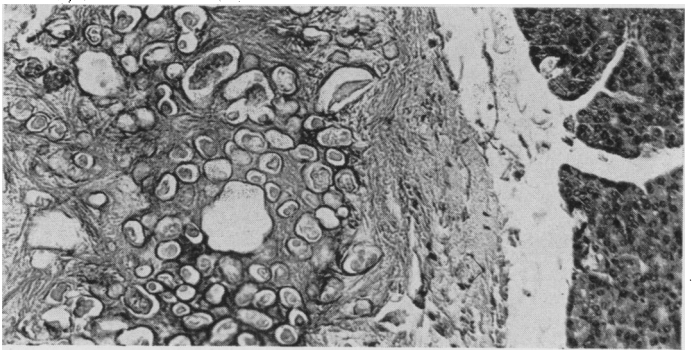

FIG. 5.—Case 2: Typical calcified nodule.

Pathologic Examination.—Gross: S. P. No. 87322. The specimen consisted of a segment of pancreas measuring 5 x 4 x 3 cm., and weighing, fresh, 13 Gm. Attached to the splenic end there was some fat in which there were numerous calcified nodules, 1–2 Mm. in diameter. On section of the pancreas two circumscribed, nonencapsulated, soft, red areas, each about 5 Mm. in diameter, were found. Scattered throughout the rest of the pancreas there were tiny, translucent red areas similar to the two larger ones, and the lesion, after frozen-section at the time of operation, was interpreted as adenomatosis.

Microscopically, on examination of paraffin preparations, this impression was confirmed. Hypertrophy and hyperplasia of islets was seen, and ribbon-like arrangements of islet cells with finger-like extrusions into the adjacent pancreatic tissues. These were typical adenomata. Multiple microscopic areas of calcification were found, interpreted, after considerable study, as calcification of multiple adenomata. The gross calcified masses adjacent to the tail showed tiny remnants of pancreatic tissue also, and were interpreted as larger calcified tumors. (See photomicrographs)

This brings us to the statistical summary of the cases *with tumor,* as we have been able to find them to date (Table I).

In discussing carcinoma of islet cells attention must be drawn to a general article by Duff and Murray (1942), and an excellent review by Hanno and Banks (1943). We have emphasized before the difficulty of being sure of the histogenesis of tumors in which no hypoglycemia is noted. In the

TABLE I

HYPOGLYCEMIA—ISLET CELL TUMORS IN WHICH METASTASES WERE FOUND—FIFTEEN CASES

	Author	Date	Sex	Age	Min. Bld. Sugar Mg. %	Operation	Single or Multiple	Result	Autopsy
1	Wilder, Allan, Power, and Robertson	1927	M	40	25	Cholecystectomy. Biopsy of liver	Single	Died one month	Metastases in liver
2	Judd, Faust, and Dixon	1934	F	18	45	Biopsy of metastasis in liver	Single	Died four weeks	Metastases in liver
3	Jacobsen	1934	M	36	25	Biopsy. Tumor size of a grapefruit	Single	Died four months Hemorrhage from duodenum	Extension to duodenum. Metastases in liver
4	Bickel, Mozer, and Junet	1935	M	56	Originally diabetic. Bld. sugar dropped 325—8	None	Single	Autopsy	Metastases in liver, peritoneum, and epicardium. Interstitial pancreatitis
5	Cragg, Power, and Lindem	1937	F	41	30	Biopsy of metastasis in liver	Multiple (diffuse through pancreas)	Died five months	Metastases in liver and lymph nodes. Cysts of ovary
6	Joachim and Banowitch	1938	F	31	30	Resection of spleen and portion of tumor in tail of pancreas and a lymph node showing metastasis. Liver apparently negative	Multiple	Postoperative death	Not done
7	Seckel*	1939	M	36	16	Exploratory	Single	Died ten weeks postoper.	Metastases in liver, one adrenal, spine, lungs, pleura, retroperitoneal and mediastinal nodes
8	Flinn, Beatty, Ginsberg, and Hemsath	1941	F	45	29	None	Single	Autopsy	Metastases in regional nodes and liver. Adrenals enlarged
9	Ballinger (Whipple—Case 18)	1941	M	53	30	Biopsy. Tumor of aberrant pancreas	Single	Died four months postoper. Montefiore Hospital	Extension to liver. Metastases in retroperitoneal nodes, mesentery, lung, adrenals, heart, vena cava, spleen, and subcutaneous tissue of clavicular region
10	Quarrier and Bingham (Case 1)	1942	M	73	21	None	Single	Autopsy	Metastases in liver and regional lymph nodes
11	Gray†	1942	F	48	27	Excision. Tumor in tail	Single	Died six weeks	Metastases in liver. Marked basophilism of pituitary
12	Hanno and Banks	1943	M	68	21	Biopsy of liver metastasis	Single	Died two days	Metastases in liver
13	Holman, Wood, and Stockton (Case 3)	1943	M	45	27	Biopsy of tumor in tail of pancreas and of metastasis in liver	Single	Died 27 days	Metastases in liver. Focal cortical hyperplasia of adrenals
14	Browning	1943	M	36	12	Biopsy of metastasis in liver	Single	Died two months	Metastases in liver and regional nodes
15	Brunschwig, Allen, Owens, and Thornton	1944	M	32	14	1. Sept., '39. Excis. 2 tumors 2. Jan., '40. Excis. large tumor of body and tail 3. Aug., '42. Excis. of most of head. (Liver metastases present) 4. Dec., '43. Pancreaticoduodenectomy. Excis. of liver metastases	Multiple	Died two hours after last operation	Metastases in liver

*Reported also by Brunschwig, Gomori, and Cannon (cited by Gray).
†Reported also by Joslin.

22 cases listed by Hanno and Banks one case is included erroneously (Lloyd). This leaves 21 cases which may be interpreted as malignant. In seven there were no clinical data to establish the diagnosis of hyperinsulinism. (Fabozzi (1903), four cases quoted, considered by many doubtful as to islet cell origin; Zanetti (1927), one case; Hamdi (1932), one case; Evangelisti (1935), one case). In three cases reported by Duff and Murray (1942) hypoglycemia was known to be absent, and the remaining 11 cases, *i.e.*, 11 of 21, were cases of hyperinsulinism, roughly one-half the cases. Our own table lists only 15 cases of carcinoma. These were all cases with hypoglycemia, with metastases, and they include all of the cases of Hanno and Banks in which hypoglycemia was known to be present.*

We have had two cases *without* hypoglycemia, which we have interpreted as islet cell carcinomas.† One was a man, age 69, with extensive liver metastases, found at operation. The pancreas at autopsy proved to be the primary site of tumor, almost six years after the operation, which demonstrated metastatic disease, a longer history than any of the cases *with* hypoglycemia and metastatic disease. The other case is a woman, age 53, who underwent resection of the body and head of the pancreas together with pylorus and duodenum. She has shown no evidence of recurrence to date, four years after operation, and no hypoglycemia.

The cases of hyperinsulinism with islet cell tumor considered benign, removed at operation, we listed in 1940 in Table II. Forty-six cases were listed, one incorrectly, Mathias (see footnote). Of the 45 cases correctly listed five had more than one tumor; Graham and Womack (1933), two tumors; Whipple and Frantz, Case 3 (1935), two tumors; Whipple and Frantz, Case 4 (1935), two tumors; Kalbfleisch, Case 3—Heupke and Obert (1937), five tumors; Frantz, Case 9—Whipple (1940), two tumors. To Table II must be added 31 cases as follows:

The cases of hyperinsulinism with islet cell tumor considered benign found at autopsy we listed in 1940 in Table III. Twenty-four cases were listed, of which three had more than one tumor. (Terbrüggen, Case 1—Frank (1931), multiple; Wolf, Hare, and Riggs (1933), three tumors; Frank, Case 2, (1931), two tumors). To Table III must be added six cases as follows:

The cases of hyperinsulinism with islet cell tumor suspected of being malignant, removed at operation, we listed in 1940 in Table IV. Nineteen cases were listed, of which three had more than one tumor (Judd, Allan, Frank and Rynearson (1933), two tumors; Ziskind and Bayley (1937), two

* There is a sixteenth case of hyperinsulinism, with metastatic islet cell carcinoma, reported by Slye and Wells (1935) but the patient was a dog.

† The difficulties of interpretation are well illustrated by a case with multiple metastases reported by Willis (1936), in which the author is uncertain of the origin; and also by the case of Mathias (1928), which has been repeatedly misquoted, and is wrongly listed in our own report in 1935, where it should appear in Table VII instead of Table III, and again in 1940 where it should not appear in Table II as there was no recorded hypoglycemia.

TABLE II (1940)—Continued

(Ref. Annals of Surgery, 112, No. 2., 167-168, August, 1940)

HYPOGLYCEMIA—ISLET CELL TUMORS REMOVED AT OPERATION. CONSIDERED TO BE BENIGN. TOTAL CASES—SEVENTY-SIX. MULTIPLE TUMORS—ELEVEN

	Author	Date	Single or Multiple
46	Cheley	1934	Single
47	Engel	1934	Single
48	Nesselrode	1934	Single
49	Duncan, Hayward and Fleck (Case 1)	1939	Single
50	Windfild (Case 1)	1940	Single
51	Windfild (Case 2)	1940	2 tumors
52	Windfild (Case 3)	1940	Single
53	Greenlee, Lloyd, Bruecken, and McEllroy	1940	Single (Hyperthyroidism*)
54	Burtness, Koehler, and Saint	1941	Single
55	Magner (Case 1)	1941	Single
56	Meyer, Antman, and Perlman	1941	Single
57	Rudd and Walton	1941	Single (aberrant†)
58	Brown	1942	Single
59	Stein	1942	Single
60	Romano and Coon	1942	Single
61	Erb, Dillon, and Ferguson	1942	Single
62	Thomas	1943	Single (aberrant†)
63	Ceballos and Rosenblatt	1943	Single
64	Spangler	1943	Multiple
65	Holman, Wood, and Stockton (Case 1)	1943	2 tumors (1 aberrant†) Hypertrophy of islets
66	Rayner, Rogerson, and Jones	1943	Multiple
67	Wechsler and Garlock (Case 1)	1944	Single
68	Cole	1944	Single
69	Priestley, Comfort, and Radcliffe	1944	Single (Total pancreatectomy‡)
70	Whipple (Case 11). Not published	1944	Single (reoperation)
71	Whipple (Case 16) Not published	1944	Single
72	Whipple (Case 25) Not published	1944	Adenomatosis
73	Whipple (Case 26) Not published	1944	Single
74	Whipple (Case 27) Not published	1944	Single
75	St. John and Whipple (Case 30) Not published	1944	Adenomatosis
76	Whipple (Case 31) Not published	1944	Single

*The association of thyroid pathology with hypoglycemia has been discussed by John (1931), Aitken (1936), Womack and Cole (1937), and Greenlee, Lloyd, and Bruecken (1940).

†Islet cell tumors of aberrant pancreas have been reported by Vecchi (1914), Stewart and Hartfall (1928), White and Gildea (1937), Rudd and Walton (1941), Ballinger (Whipple—Case 18) (1941), Thomas (1943), and Holman, Wood, and Stockton (1943).

Excision of aberrant pancreatic tissue, not tumor, has been reported by Smith, Frederick G. (1942), and Fanta (1937), both with relief of symptoms. Possible sites of aberrant pancreatic tissue are shown by Faust and Mudgett (1940) in a review of 370 reported cases, and Thorsness (1940).

‡The only other total pancreatectomy recorded is that of Rockey (1943), which was done for carcinoma, *not* islet cell. Survival in this case was only 15 days. In the case of Priestley, Comfort, and Radcliffe (1944), survival has been 16 months, and the resultant diabetes is mild.

TABLE III—Continued

(Ref. ANNALS OF SURGERY, *112*, No. 2., 169, August, 1940)
HYPOGLYCEMIA—ISLET CELL TUMORS FOUND AT AUTOPSY.
CONSIDERED TO BE BENIGN. TOTAL CASES—THIRTY.
MULTIPLE TUMORS—THREE

	Author	Date	Single or Multiple
25	Duncan, Hayward, and Fleck (Case 2)	1939	Single
26	Heyn and Sommer	1940	Single
27	Kerwin	1942	Multiple
28	Quarrier and Bingham (Case 3)	1942	Single
29	Stevenson and Rannie	1942	Single
30	Holman, Wood, and Stockton (Case 2)	1943	Single (aberrant)

TABLE IV—Continued

(Ref. ANNALS OF SURGERY, *112*, No. 2., 170, August, 1940)
HYPOGLYCEMIA—ISLET CELL TUMORS REMOVED AT OPERATION.
SUSPECTED OF BEING MALIGNANT. TOTAL CASES—TWENTY-SIX.
MULTIPLE TUMORS—FOUR

	Author	Date	Single or Multiple
20	Forbes, Davidson, and Duncan	1939	Single
21	Quarrier and Bingham (Case 1)	1942	Single
22	Quarrier and Bingham (Case 4)	1942	Multiple
23	Whipple (Case 20) Not published	1944	Single
24	Whipple (Case 22) Not published	1944	Single
25	Whipple (Case 23) Not published	1944	Single
26	Whipple (Case 29) Not published	1944	Single

TABLE V—Continued

(Ref. ANNALS OF SURGERY, *112*, No. 2., 171, August, 1940)
HYPOGLYCEMIA—ISLET CELL TUMORS FOUND AT AUTOPSY.
SUSPECTED OF BEING MALIGNANT. TOTAL CASES—TWO (NO NEW CASES).
MULTIPLE TUMORS—NONE

tumors; J. Smith (1939), multiple). To Table IV must be added seven cases as follows:

Two cases of hypoglycemia with islet cell tumors suspected of being malignant, found at autopsy listed in 1940 in Table V. Both were single. We have found no new cases of this sort reported at autopsy since then.

It will be noted that of tumors considered benign 14.2 per cent were multiple; of suspicious tumors, 14.3 per cent; and of tumors of proven malignancy, 20 per cent. We must emphasize again that in the group of suspicious tumors *the suspicion, of the pathologist not the surgeon, has yet to be confirmed in a single case by follow-up data.*

To the cases of multiple tumor and of true adenomatosis there must be added for completeness those cases with hypoglycemia in which, in the pathologist's opinion, although there was no true neoplasia, there was hypertrophy and hyperplasia. There are 11 such cases, and Table VI, therefore, is an analysis of the whole group.

Summarized, all of the foregoing figures give us totals seen in Table VII.

TABLE VII

SUMMARY OF STATISTICS

	Single	Multiple	Total	Per Cent Multiple
Tumors removed at operation and considered benign	65	11	76	
Tumors found at autopsy and considered benign	26	4	30	
Total benign tumors	91	15	106	14.2
Tumors removed at operation and suspected malignant	22	4	26	
Tumors found at autopsy and suspected malignant	2	0	2	
Total suspicious tumors	24	4	28	14.3
Total cases of tumor *without proven malignancy*	115	19	134	14.2
Carcinoma with metastases, *proven malignancy*	12	3	15	20.0
TOTAL CASES OF TRUE NEOPLASM	127	22	149	14.8
HYPERTROPHY AND HYPERPLASIA WITHOUT NEOPLASM			11	

SUMMARY

The review of published cases and those in our own series, presented in 1940, is here extended to include the rest of the cases in the literature, as we have been able to find them, and the new cases in our own series.

Two of our own cases are analysed in detail as they are the first in which a diagnosis of hyperinsulinism with adenomatosis has been made.

CONCLUSIONS

Multicentric origin of benign and malignant tumors of islet cells is suggested by the pathologic findings in the cases reviewed.

In the multicentric cases with hyperinsulinism there seems to be a good possibility that hyperplasia and neoplasia in the remaining pancreas may result in return of hypoglycemic symptoms.

In the multicentric cases the possibility of malignant disease must be considered.

Such cases should be followed for long periods in order to establish a basis for prognosis in others.

TABLE VI

HYPOGLYCEMIA—HYPERTROPHY, HYPERPLASIA, MULTIPLE TUMORS, AND ADENOMATOSIS

	Author	Date	Sex	Age	Min. Bld. Sugar Mg. %	Operation or Autopsy	Pathology	Result
1	Massa	1929	M	67	58	Autopsy	Hypertrophy of islets. Adenocarcinoma of pancreas with obstruction of ducts and metastases	Autopsy
2	Terbruggen	1931	F	30	23	Autopsy	Five tumors encapsulated, and many tiny ones. Islets normal. Adenomatosis?	Autopsy
3	Phillips	1931	M	56	25	Autopsy	Hypertrophy of islets	Autopsy
4	Graham and Womack	1933	M	22	25	1. Excis. of tumor. 2. 4 cm. of tail excised	1. Adenoma 1 x 0.8 cm. 2. Adenoma 2 cm.	1. No improvement 2. Symptoms relieved. Mental deterioration
5	Mosenthal and MacBrayer... (Quoted by Wilder)	1933	M	39	50	Autopsy	Hypertrophy of islets	Autopsy
6	Wolf, Hare, and Riggs	1933	M	10	54	Autopsy	Three tumors, middle, tail, and head. 1, 0.3, 0.3 cm.	Autopsy
7	Judd, Allan, Frank and Rynearson (Case 7)	1933	M	32	40	Two tumors, 1.5 cm. and 2 cm., respectively	Carcinoma?	Symptom-free 23 months
8	Simon	1934	M	26	51	Resection 60 Gm.	Hypertrophy of islets	Improved 2 months
9	Frank (Case 2)	1935	F	14	11	Autopsy	Two tumors, head and tail	Autopsy
10	Dannenberg, Bell and Gouley.	1935	M	3	71	Autopsy	Hypertrophy and hyperplasia of islets. Fibrosis of pancreas	Autopsy
11	Whipple and Frantz (Case 3)	1935	M	28	38	1. Excis. tumor junction body and tail 2. Excis. tumor tail	1. Adenoma 2. Adenoma	Symptom-free. Died duodenal hemorrhage 18 months
12	Whipple and Frantz (Case 4)	1935	M	38	30	Excis. tumors—1 cm. in body, 0.6 cm. in head	Adenomas	Symptom-free 105 months
13	McCaughan and Broun (Case 1)	1937	M	20	54	Resection of tail 8 Gm.	Number of islets increased	Some improvement
14	McCaughan and Broun (Case 2)	1937	M	17	36	Resection — body and tail (22.5 Gm.)	Hypertrophy of islets	No improvement
15	McCaughan and Broun (Case 6)	1937	F	24	70	Resection 35 Gm.	Hypertrophy of islets	No improvement

16	Kalbfleisch..... (Neupke and Obert—Case 3)	1937	M	23	20	Excis. tumor of body	Adenoma	Died two days postoper. Four of five tumors found at autopsy. Adenoma of hypophysis and of parathyroid. Hyperplasia of thymus
17	Ziskind, Bayley, and Mauer...	1937	F	19	40	Explor. No tumor. Reoper. P.P. two tumors in body	Carcinoma?	Died 32 hours postoper. Third tumor in remaining body. No metastases
18	Brinck and Sponholz.....	1938	F	49	59	Autopsy	Hyperplasia of islets. Pancreaticolithiasis	Autopsy
19	Smith, Joseph.....	1939	F	35	31	Resection (22 Gm.)	Multiple nodules. Incomplete capsules. Carcinoma?	Symptom-free five months
20	Frantz..... (Whipple—Case 9)	1940	F	45	26	1. Subtotal pancreatectomy; tumor 0.4 mm. in tail 2. Excision tumor in head	1. Adenoma 2. Adenoma	Not improved
21	Winfild..... (Case 2)	1940	M	22	37	Resection	Two tumors 2 cm. apart. Each 0.5 cm. in diameter	Slight hypoglycemic attacks — six months
22	Magner..... (Case 2)	1941	F	20	55	Resection of body and tail	Diffuse hypertrophy and hyperplasia	Symptom-free two years
23	Kerwin.....	1942	F	42	43	None. Autopsy	Two tumors	Autopsy
24	Quarrier and Bingham.....	1942	F	20	23	Excision tumors of pancreas and adrenal	Three islet cell tumors. Carcinoma? Adrenal carcinoma	Died postoper.
25	Spangler.....	1943	M	26	32	Excision of tumors	Three adenomas. (Bilateral urinary calculi)	Symptom-free three weeks
26	Holman, Wood, and Stockton (Case 1)	1943	F	Adult	37	1. Partial pancreatectomy 2. Excision of aberrant tumor	1. Adenoma and hypertrophy of islets 2. Adenoma	Symptom-free one year
27	Rayner, Rogerson, and Jones.	1943	F	46	21	1. Resection (36 Gm.) 2. Excision of tumors in head	1. No tumor 2. Three small, round tumors grouped together	1. Symptoms continued 2. Relief of symptoms
28	Whipple..... (Case 21). Not published	1944	M	50	36	Resection (38 Gm.)	Hyperplasia	Unimproved. Suicide two months postoper.
29	Whipple..... (Case 25). Not published	1944	F	46	23	1. Excision of tumor (MacDonald) 2. Excision of tumor (MacDonald) 3. Resection (8 Gm.) (Whipple)	1. Adenoma 0.5 cm. 2. Adenoma 0.75 cm. 3. Adenomatosis	Symptom-free 16 months
30	St. John-Whipple..... (Case 30). Not published	1944	F	32	41	Resection (13 Gm.)	Adenomatosis	Symptom-free six months

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