ANNALS OF SURGERY

VOL. 101 JUNE, 1935 No. 6

ADENOMA OF ISLET CELLS WITH HYPERINSULINISM

A REVIEW

ALLEN O. WHIPPLE, M.D., AND VIRGINIA KNEELAND FRANTZ, M.D.

NEW YORK, N. Y.

FROM THE SURGICAL PATHOLOGY LABORATORY OF THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE SURGICAL DEPARTMENT OF THE PRESBYTERIAN HOSPITAL, NEW YORK

THE literature on the internal secretion of the pancreas has now reached such tremendous proportions that it practically defies review. The subject of this paper, however, cannot be approached with any understanding without a glance backward at the steps which have led us to our present knowledge. Spontaneous hyperinsulinism, of which we now speak almost lightly, is, as a matter of fact, only ten years old, and could not possibly be understood without the painstaking studies of its antithesis, hyposecretion. This phenomenon, veiled for years in the obscurity of the disease diabetes mellitus, has fascinated generations of our predecessors. Only a profound scholar would dare attempt to trace the earliest history of the disease, but there are, in easily available sources, data which, if studied chronologically, make a most dramatic sequence. Correctly they should be listed in order, but for a time at least they were divided into two groups, the findings of those interested primarily in anatomy and histology, and of those interested in physiology and disease. The lines of thought are somewhat arbitrarily separated in the following table, which of necessity shows only the most outstanding features of the study (Table I).

HISTORIC REVIEW

The column under Histology is almost self-explanatory. After Langerhans[86] first described the islands which Laguesse[83] named after their discoverer, little was done until Kühne and Lea,[78] in 1882, described the capillary network in which lie the island cells. Then Lewaschew,[91] in 1886, made a very scholarly study of stimulation by overfeeding or with pilocarpine. Unfortunately, he described cells which he considered intermediate between acinar and islet cells, and he therefore interpreted the islets as functionally exhausted acini. This led to great confusion, and for years retarded any general acceptance of the endocrine nature of these structures.

Beginning in 1893, and studying and publishing with unabated vigor for twenty years or more, Laguesse[82] added greatly to the subject. In

TABLE I

Chronologic Historic Data

HISTOLOGY	PHYSIOLOGY AND DISEASE	TUMORS	HYPERINSULINISM
	1788 Cawley: Calculi. Diabetes		
	1849 Bernard: Hypoglycemia		
1869 Langerhans: Islands			
1882 Kühne and Lea: Capillary net			
	1884 Arnozan: Ligation of duct in animals. No diabetes		
1886 Lewaschew: Islands exhausted acini			
	1890 v. Mering and Minkowski: Ablation produced diabetes		
	1892 v. Mering and Minkowski: Subcutaneous graft prevented diabetes		
	1892 Hédon and Thiroloix: Confirmed graft experiment		
1893 Laguesse: Granules. Endocrine?			
	1894 Hanseman: Saw fibrosis, *etc.*, in human diabetes		
1899 Diamare: Islands independent structures anatomically			
	1900 Ssobolew: Ligation of duct atrophy of acinar cells. Islands remained		
	1900 Schulze: Ligation of duct atrophy of acinar cells. Islands remained		
	1901 Opie: Hyaline degeneration of islands in diabetes		
		1902 Nicholls: Island tumor	
		1904 Ssobolew: Hypertrophy in diabetes	
		1905 Herxheimer: Hypertrophy in diabetes	
		1907 MacCallum: Hypertrophy in diabetes	
		1908 Morse: Two adenomata	
1908 Lane: Alpha and beta granular cells			
		1911 Cecil: Adenoma	
1912 Bensley: Vital staining. Duct origin. "C" cell nongranular	1912 Kirkbride: Lane stain on duct ligated specimens		
	1913 Homans and Allan: Hydropic degeneration of beta cells in overstimulation		
		1920 Dubreuil and Anderodias: Hypertrophied islands in newborn—diabetic mother	
	1922 Banting and Best: Insulin		1922 Banting: Insulin shock
	1923 Copp and Barclay: Restoration of exhausted beta cells after insulin administration		1923 Harris: "Hyperinsulinism"
1924 Bowie: Alpha, beta and gamma granular cells in teleost			
	1925 Boyd and Robinson: Regeneration of islands in insulin treated cases	1925 Lang: Adenomatosis	
		1926 Gray and Feemster: Confirmed Dubreuil	
		1926 Warren: Collected 20 cases	
			1927 Wilder: Island cell carcinoma with hyperinsulinism
			1929 Howland: Island cell adenoma with hyperinsulinism surgically cured (Roscoe Graham)
	1930 O'Leary: Secretion islet cells *in vivo*		
1931 Bloom: Alpha, beta and delta granular cells in man			

1893, he described the histology, including granules in the island cells, and the capillary network, and suggested the possibility of internal secretion on purely anatomic grounds. Diamare,[37] in 1899, confirmed his findings. In 1902, Laguesse[83] also described in detail the histology of the preserved islands in the atrophied pancreas following ligation of the duct.

The next histologic advance was contributed by Lane[84] in his famous description of the staining technic by which he demonstrated two types of granule containing cells, and called them alpha and beta cells. Later Bensley,[13] in 1912, added to the technical procedure a vital staining method for counting the number of the islands, demonstrated the origin of both types of cells from duct epithelium, and not from acinar cells, and described a third nongranular cell "C". The amount of island tissue he found not so inconsiderable as the opponents of the endocrine school claimed, for he estimated that in the adult guinea-pig there were 56,000 islands. All this work is summarized in his Harvey lecture in 1915.

In 1924, Bowie[18] described alpha, beta and gamma granular cells in the teleost, and in 1931 Bloom[16] described alpha, beta and delta granular cells in man.

In the column under Physiology and Disease the first observation antedates the discovery of the islands by nearly a hundred years. In 1788, Cawley[28] described the finding of pancreatic calculi in a case of diabetes, and during the next hundred years it was gradually accepted that the pancreas might be related to diabetes. In 1849, Claude Bernard[14] published his famous monograph in which hyperglycemia and glycosuria are discussed.

Arnozan and Vaillard,[6] in 1884, showed that no diabetes ensued after ligation of the duct. They described the preserved islands but failed to realize their significance.

A long interval elapsed before v. Mering and Minkowski,[103] in 1890, published their famous experiment in which they showed that ablation of the pancreas in dogs, rabbits, and pigeons produced diabetes. Two years later they also completed a very significant and conclusive experiment, a successful subcutaneous graft of pancreas with subsequent extirpation of the remaining gland. The animal developed no glycosuria. Upon removal of the graft an extreme glycosuria developed, leading to death. This work was confirmed in the same year by two independent observers, Hédon[55] and Thiroloix.[151]

Shortly after this, in 1894, Hanseman[52] saw fibrosis and atrophy in the pancreas in 40 cases of diabetes.

At almost the same time (1895) Schäfer,[133] in a popular lecture, pointed to another bit of evidence for the internal secretion theory in that ablation caused death of the animal while a total pancreatic fistula did not. But it remained for two independent workers to make the crucial experiment which relegated this secretion definitely and finally to the islands.

Ssobolew[143] and Schulze,[135] working at practically the same time in 1900, both published experiments on ligation of the ducts. In the animals which survived there was atrophy of the organ as a whole but the islands remained preserved and the animals were not diabetic. In the same paper Ssobolew also records seeing changes in the islands in diabetes, and ends with a paragraph which, had its full import been realized, might have changed the history of medicine considerably. He says, "The future will show how far experiments in this direction will be crowned with success. Even now we may come nearer to the solution of the problem by making exact studies of the islands *in vitro* and *in vivo*. Formerly the entire pancreas was used for this purpose. Now, however, in ligation of the excretory duct we have a means of isolating the islands anatomically and of studying the chemistry of these cells separated from the digestive ferments.

"This anatomic isolation of the islands enables us also to try organotherapy on diabetes in a rational manner. All former attempts to cure diabetes by administering the whole pancreas in various ways have failed. Since it is difficult to secure in any quantity pancreas in which only the island tissue has been preserved, one can substitute pancreas of newborn animals—calves, for instance, in which the islands are well developed in comparison to the digestive apparatus. Moreover, the pancreas of the newborn is little capable of digestive activity and we may expect that its digestive juice will not interfere with the action of the substances secreted by the islands. At all events, we are justified in the hope that in the near future the question will be decided whether or not this method of approach will succeed in relieving the ills of the diabetic patient" (Doctor Laidlaw's translation).

Practically simultaneously, in a paper which seems to have had much wider circulation than Ssobolew's, possibly because his was originally a doctor's thesis published in Russian, Opie[114] recorded hyaline changes in the islands in diabetes. Kirkbride,[74] in 1912, applied Lane's stain to the atrophied portion after duct ligation, and showed granules in island cells. Homans[64] and Allan,[2] in a series of papers (1913–1915) showed changes in experimental diabetes confined to the beta cells of Lane. There followed extensive work on the pathology of diabetes, which cannot be reviewed here, but all of which was confirmatory evidence that disease of the islands led to hyposecretion of some substance necessary to carbohydrate metabolism, without which the patient suffered from hyperglycemia.

A decade followed in which the goal, finally reached by Banting and Best,[7] in 1922, was the aim of a host of eager and tireless investigators. Curiously enough, Banting's inspiration was a short historic review by Baron,[11] written in 1920 as part of an article which dealt chiefly with the relationship of pancreatic calculi to island damage. Recapitulating in their experiments the crucial investigations of the 30 years' work which we have just reviewed, they first obtained insulin, or "isletin," as they called it, from a Ringer solution extract of the pancreas of a dog in which

the duct had been ligated for ten weeks. Next they obtained it from the pancreas of fetal calves in which the proteolytic ferments were absent, and then they succeeded in extracting it from adult ox glands. So this was done! A year later, with insulin at hand, Copp and Barclay[30] repeated Homans' experiment and demonstrated restoration of exhausted beta cells by administration of the extract.

In 1925, a somewhat analogous finding was reported by Boyd and Robinson,[19] who presented evidence of regeneration of the islands in an insulin treated case of diabetes.

In 1930, O'Leary[112] studied islet cells in living animals (mice) and in response to introduction of dextrose saw vacuoles form and migrate to the periphery of the cell next the capillary, where they apparently diffused their contents.

It is almost an anticlimax to review the third column, the pathologists' study of localized hypertrophy or adenoma of island cells. The first is a single tumor reported by Nicholls[109] (1902) without clinical history. Ssobolew,[143] the prophetic scholar, in 1904 described an hypertrophied island in a postmortem on a diabetic. This measured 1.5 Mm. and the rest of the islands were markedly atrophic, but he described some areas of proliferation. In 1905, Herxheimer[59] confirmed this work by describing hypertrophy of the islands of five diabetics together with adenomata in one. MacCallum[95] confirmed the hypertrophy in 1907. In 1908, Morse[105] described two cases of adenoma, and in 1911, Cecil[29] reported another. There were other scattered observations, and probably many not published. As early as 1920, Dubreuil and Anderodias[39] reported hypertrophy of the islands in a newborn child of a diabetic mother, antedating Gray and Feemster's[50] better known article by six years. Lang[85] (1925) published the first case of multiple adenomata—adenomatosis.

Warren,[156] in 1926, reviewed 20 cases, four of his own. This paper stimulated great interest in island cell tumors, although the author did not suggest any possible physiologic significance.

A number of adenomata have been reported since but we must go back a little and examine the fourth column to find the impetus for the work. Here we see that nine months after the discovery of insulin Banting[9] and his associates perforce discovered something else. The dosage was still, naturally, not standardized and the phenomenon of hypoglycemia was dramatically called to their attention. This, they said, was characterized clinically by nervousness, tremulousness, hunger, weakness, sweating, pallor and flushing, anxiety, faintness, vertigo and diplopia, and in the more striking cases by excitement, emotional instability, sensory and motor aphasia, disarthria, delirium, disorientation, confusion, syncope or collapse, and unconsciousness. They did not mention convulsions. The condition was, of course, alleviated by the administration of carbohydrate and avoidance of excess dosage.

A year later, in 1923, Harris[53] suggested that there was a clinical possibility of spontaneous "hyperinsulinism," as he called it, as opposed to

the "hypoinsulinism" of diabetes. He had discussed this possibility with Banting, who, however, knew of no cases. Harris, convinced of the probability of his theory, watched for cases and, in his paper read in June, 1924, reported three with blood sugars below 70 mg. per 100 cc. whose symptoms improved by feeding. Although they did not suggest the term "hyperinsulinism" as such, Parker and Finley[115] antedate Harris by a publication in May, 1924, presenting the results obtained in ten cases of nervous phenomena treated with glucose. These were patients with low blood sugar and severe nervous manifestations, and the authors state that they were impressed with the similarity of these and cases of insulin hypoglycemia.

Four years after this suggestion came the first dramatic case of hyperinsulinism with a tumor of the pancreas. Wilder[163] and his colleagues reported this in 1927, a carcinoma of cells closely resembling island cells which had metastasized to liver, regional nodes and mesentery. The patient suffered from attacks of unconsciousness and had a blood sugar as low as 25 mg. Exploratory operation confirmed the anteoperative diagnosis, and autopsy was performed a month later. Extract of the liver nodule by Best's method for extracting insulin was said to act like insulin when injected into rabbits.

Following this, many cases were investigated for the disease entity hyperinsulinism, and the first surgical cure was effected by Roscoe Graham when he excised an island cell adenoma. This was published by Howland[66] and his co-workers in 1929. A year before this, Finney[43] had explored a case, and, finding no tumor, had resected 22.5 Gm. of the pancreas without alleviation of symptoms.

The clinical picture of the published cases which followed in rapid succession was extremely varied, but in general it may be said that hyperinsulinism is a chronic illness characterized by attacks at irregular intervals. If a careful history is obtained, these can almost always be related to the need of food, and many patients have learned by experience that an attack can be aborted by eating candy or sugar in other forms. In at least two cases frequent high carbohydrate feeding, either voluntary or prescribed, has resulted in extreme obesity. In Doctor Whipple's fourth case the patient had gained 100 pounds, which made the surgical approach difficult.

The symptoms are chiefly vasomotor and nervous. Wilder has grouped them under three main heads: those relating to disturbances of the vegetative nervous system; those of the central nervous system; and the less readily localizable psychic symptoms. The attacks vary all the way from mild feelings of fatigue, restlessness and apprehension, often with hunger, to maniacal seizures, convulsions, delirium and coma. In fact, they present, in varied combination, all the symptoms originally described by Banting in insulin shock. The most frequent diagnoses made before the hypoglycemia is discovered are epilepsy and alcoholism.

During the attacks the blood sugar is low. In cases examined pathologically where the lowest blood sugar is recorded the figures ranged from 4 to 58. It will be recalled that different methods of estimating the blood sugar give slightly different values and that different individuals vary in their tolerance of a low blood sugar. Also in the cases studied the same individual responds differently at different times. In general, children apparently can run a lower sugar without nervous effects than adults. In the intervals between attacks there are no symptoms, except occasionally persisting mental retardation or deterioration, and the blood sugar is often normal.

It is not our province here to detail the clinical findings. They may be found *in extenso* in three excellent reviews in English: Harris,[53] 1932, Wilder,[162] 1933, and Wauchope,[158] 1934, and in a monograph in French by Sigwald,[138] 1932. Also, as every one is aware, there are many causes of hypoglycemia which are not due to lesions of the pancreas, the most important and recognizable being disturbances of the adrenal, pituitary, thyroid and exhaustion of the glycogen reserve such as is found in diseases of the liver, and theoretically in muscular wasting, *i.e.,* the dystrophies. These conditions should be ruled out clinically before exploratory operation is justifiable.

There are also many instances of hypoglycemia in which none of the above conditions is found, and where the symptoms are mild enough so that operation does not seem justifiable. Many of these respond to diet, which can be so arranged that there is no excessive gain in weight. Hypoglycemia also occurs in the terminal stages of diabetes after the withdrawal of insulin. We have found 75 cases in the literature to date which were interpreted as hyperinsulinism or dysinsulinism (Table II).

TABLE II

Chronologic Data on Hyperinsulinism

Date	Author	Number of Cases	Date	Author	Number of Cases	
1924	Harris	3	1931	Gammon	1	
1925	Shih-Hao	1	1931	Moore	1	
1927	Stenström	1	1932	McGovern	1	
1928	Ravid	1	1932	Weil	1	
1928	Laroche	1	1932	Heyn	1	
1928	Pribram	3	1932	Briggs	3	
1929	Zubiran	1	1933	Rosenfeld	1	
1929	Hartmann	1	1933	Levi	1	
1930	Krause	1	1933	Sippe	25	
1930	Winans	3	1933	Love	1	
1930	Nielsen	3	1934	Jacobs	1	
1931	Waters	3	1934	Tedstrom	4	
1931	Valenzuela	3	1934	Rathery	1	
1931	Marsh	8				
		33			42	Total, 75

Also:

1924 Jonas: Hypoglycemia in a diabetic after discontinuance of insulin.
1927 Sjögren: Four diabetics with epileptiform seizures in hypoglycemic phases.
1928 Troisier: Hypoglycemia following traumatic hematoma of pancreas.
1930 Anderson: Tumor of adrenal with fatal hypoglycemia.
1931 Crawford: Primary carcinoma of liver with hypoglycemia.
1931 John: Hypoglycemia in diabetic after discontinuance of insulin.
1932 Stief: Medullary carcinoma of pancreas. No blood sugar recorded. Symptoms suggestive.
1932 Rabinovitch: Hypoglycemia with destruction of adrenal.

The following tables show all the cases which we have been able to find to date where the pancreas has been examined at operation or autopsy. They are listed chronologically, with the author's name, for many of them have been published several times. Table VII shows the cases of island cell tumors without recorded hypoglycemia.

Summarized, these figures are:

TABLE III.	Cases with tumor found at operation 21	(1 a carcinoma with metastases)	
TABLE IV.	Cases with tumor found at autopsy. 10		
	Total cases with tumor... 31		
TABLE V.	Cases explored and no tumor found. 16	Normal pancreas.....	10
		Pancreatitis.....	3
		Hypoplasia (?).....	1
		Hypertrophy.....	1
		Tumor found at autopsy....	1
			16
TABLE VI.	Cases with autopsy, no tumor found 3	All showed hypertrophy	
	Total cases without tumor 18		
TABLE VII.	Cases with tumor without recorded hypoglycemia..... 31		
	Total cases with tumor... 62		

From the surgical standpoint there are several extremely interesting features. There has been only one operative death in the group. This does not mean that the operation is without technical difficulties, but that the operators were men experienced in the surgery of the pancreas and able to obtain adequate exposure without undue trauma. The exposure is of great importance, since the tumors are usually small.

All of the cases with tumors recognized and excised have been relieved of symptoms. Of the cases with no tumor, resection has given complete relief of symptoms in five out of 15. These are the last five cases reported and in these much more of the gland was resected than had been previously attempted. The follow up on these cases is necessarily short.

Pancreatic fistula as a postoperative complication has been reported only four times.

Insulin has been recovered three times from the tumors, or rather an extract of the tumor has acted like insulin on test animals.

In general, it may be said that hypoglycemia may occur without demonstrable lesion in the pancreas, and that tumors can occur without hypoglycemia (30 cases), although this phase was not very thoroughly investigated in the early cases reported. In this connection, through the courtesy of Doctor Pappenheimer of the Department of Pathology, we are able to report that in 4,010 consecutive autopsies five island cell adenomata have been found, roughly one in a thousand cases. In four it was an incidental finding. The fifth case has been published by Wolf.[165]

The tumors are in general small, the most common measurement being 1.5 cm. in greatest diameter. Only two of the surgical cases of benign tumor were large, one 9 by 9 by 11 cm., weighing 500 Gm., and the other a trilobed tumor, the largest lobe measuring 3 by 1.5 by 1 cm. In the cases without recorded symptoms of hypoglycemia the tumors are almost all small with two striking exceptions.

The most common site of the tumors is near or in the tail, where, it will be recalled, the islands are most numerous. They may be multiple, an important fact for the surgeon to bear in mind. The tumors are grossly encapsulated, and the more usual color in the living patient is reddish, in contrast to the yellower surrounding pancreatic tissue. A few of the tumors which showed fibrosis, and sometimes even calcification, were hard, but the consistency is not usually very different from that of the surrounding tissue. This makes it difficult to find the tumors which are deep in the substance of the gland. Most of the surgical cases fortunately have been close to the capsule of the organ.

Microscopically, the tumors are not all encapsulated and in some of them the diagnosis of carcinoma has been suggested on the basis of microscopic invasion, variation in morphology of the cells, and tumor cells in the vessels. Only three of the 62 cases of island cell tumor of the pancreas have shown metastases (Wilder,[163] Hamdi[51] and Judd[72]). Possibly these will appear later in some of the cases of excision where the microscopic appearance of the tumor has suggested malignancy. It is difficult to draw the line on the one hand between the highly differentiated tumors and simple hypertrophy, and on the other between the benign and malignant forms of the less differentiated tumors. Our own series of pathologic findings illustrates this variability, and a longer follow up on all these cases may show whether a diagnosis of carcinoma is justified, though, of course, metastasis may have been prevented in some instances by early removal of the tumor.

All of the tumors show cells which resemble somewhat the cells of normal islands, but there are many deviations. In a few, beta cells have been recognized in large numbers by the specific staining reactions. Many of the tumors were not so studied. The largest single series reported with careful examination is that of O'Leary and Womack[113] (five tumors). It is interesting that these observers, both unusually qualified by previous experience for the study, conclude that "the majority cell type of each (tumor) was closely allied to the beta cells of the normal islets of Langerhans, but pos-

TABLE III

Hypoglycemia with Island Cell Tumor. Cases with Operation

Author	Publication Date	Age	Sex	Duration Symptoms	Type Symptoms	Min. Bld. Sugar	Operation	Site Tumor	Size Tumor	Insulin Recov. Spec.	Pathology	Result	Fistula Postop.	Autopsy
Wilder, R. M. Allan, F. N. Power, M. H. Robertson, H. E.	J. A. M. A., 1927, 89:348–355	40	M.	20 mos.	Mental. Loss consciousness	25	Exploratory	Tail	Whole tail	Yes. From liver metas.	Carcinoma with metas. to liver	Died 1 mo. postop.	o	Carcinoma of pancreas, metas. to liver
Mathias	Med. Klin., 1928, 24:1814	?	?	?	?	Low	Excision of pancreatic cyst	In wall of cyst	?	o	Multiple adenomatous islands in wall of cyst	Mild glycosuria after operation	?	—
Howland, G. Campbell, W. R. Maltby, E. J. Robinson, W. L.	J. A. M. A., 1929, 93:674–679	52	F.	7 yrs.	Coma	40	Excision of adenoma (Roscoe Graham)	Middle	1.5 cm.	o	No capsule microscopically. Parenchymal glands in center	14 wks. clinically cured	*Note:* Erratic response to carbohydrates (dysinsulinism ?)	
Carr, A. D. Parker, R. Grove, E. Fisher, A. O.	J. A. M. A., 1931, 96:1363–1367	19	M.	22 mos.	Confusion. Stupor	44	Excision	Mid portion	1 x 2 cm.	o	Encapsulated beta cell adenoma	Immediate result: good	o	—
Larrimore, J. W. Womack, N. A. Gnagi, W. B. Graham, E. A.	J. A. M. A., 1931, 97:831	44	M.	3 mos.	Convulsions	50	Excision	Junction body and tail	1 x 2 cm.	o	Not encapsulated Adenoma or carcinoma	No attacks 2 yrs.	+	—
Bast, T. H. Schmidt, E. R. Sevringhaus, E. L.	Acta chir. Scandinav., 1932, 71:82	44	M.	Not stated	Coma	27	Excision	Tail	2.5 cm.	o	Not encapsulated	8 wks. improved	—	—
Tomkies, J. S.	Texas State Jour. Med., 1932, 28:523	30	M.	3 yrs.	Unconsciousness	41	Resection part of body and part of tail	Body	Trilobed. Largest lobe: 3 x 1.5 x cm.	o	Encapsulated	14 mos. symptom free	o	—
Derick, C. L. Newton, F. C. Schulz, R. Z. Bowie, M. A. Pokorny, N. A.	New Eng. Jour. Med., 1933, 208:293	56	F.	6 yrs.	Coma	38	Tail resected	Tail	1.6 x 1.2 cm.	+	Encapsulated	Symptom free 20 mos.	o	—
Judd, E. S. Allan, F. N. Rynearson, E. H.	J. A. M. A., 1933, 101:99	45	M.	4 yrs.	Coma	30	Excision	Body	3 cm.	o	Carcinoma of islet cells. Not encapsulated	Symptom free 22 mos.	+ 9 mos.	—
Judd, E. S. Allan, F. N. Rynearson, E. H.	J. A. M. A., 1933, 101:99	32	M.	1 yr.	Mental confusion	40	Excision	(1) Junction body and tail	1.5 cm.	o	Carcinoma	Symptom free 23 mos.	o	—
								(2) Body	2 cm.		Not encapsulated	Mild diabetes		

Graham, E. A. Womack, N. A.	Surg., Gynec. and Obst., 1933, 56:728–742	22	M.	5 yrs.	Petit mal confusion	25	(1) Nodule excised (2) 4 cm. tail excised	Tail	(1) 1 x 0.8 cm. (2) 2 x 1.4 x 1.2 cm.	+	(1) Nodule, adenoma degenerated (2) Nodule, adenoma partially encapsulated	No attacks. Permanent central nervous system damage		—
Graham, E. A. (not published)	1933, quoted by O'Leary and Womack	52	M.	2 yrs.	?	?	Excision	?	9 x 9 x 11 cm. Wgt. 500 Gm.	?	Yellow-gray. Carcinoma (?). Cells in vessels. Encapsulated	Improved	?	—
Aitken and Fischer (not published)	1933, quoted by O'Leary and Womack	44	F.	4 yrs.	?	?	Excision	?	1.5 x 0.8 cm.	?	Yellow-gray. Adenoma. Partially encapsulated	Improved	?	—
Ross, L. I. Tomasch, J. M.	Arch. Surg., 1934, 28:224–231	33	M.	1 mo.	Coma	23	Excision	Middle	1.5 x 2 cm.	0	Adenoma	Symptom free 10 mos.	—	—
Judd, E. S. Faust, L. S. Dixon, R. K.	West. Jour. Surg., 1934, 42:555–557	18	F.	3½ mos.	Coma	45	Biopsy liver Expl.	"Tumor pancreas"	?	0	Multiple metastases in liver. Islet cell carcinoma	Died 4 wks. postop. with hypoglycemia	0	0
Whipple, A. O. Case I. Neurol. Inst. Pres. Hosp. No. 389424	In Press*	33	F.	1 yr.	Unconsciousness	30	Excision	Junction body and tail	1.5 x 1 x 1 cm.	0	Adenoma	Symptom free 15 mos.	0	—
Whipple, A. O. Case II. Neurol. Inst. Pres. Hosp. No. 421465	In Press*	48	F.	9 mos.	Confusion	34	Excision	Junction body and head	1.3 x 1.2 x 1 cm.	0	Adenoma	Symptom free 9 mos.	0	—
Whipple, A. O. Case IV. Neurol. Inst. Pres. Hosp. No. 428308	In Press*	38	M.	12 yrs.	Confusion	30	Excision 2 tumors	(A) Lower border body. (B) Head	(A) 1.5 cm. (B) 1.0 cm.	0 0	Adenoma Adenoma	Symptom free 7 mos.	+ 3 mos.	—
Whipple, A. O. Case III. Neurol. Inst. Pres. Hosp. No. 306695	In Press*	28	M.	3 yrs.	Mania. Delirium	38	(1) Excision (2) Excision	(1) Junction body and head (2) Tail	(1) 1.4 cm. (2) 2 x 1.5 cm.	0	Adenoma	Symptom free 7 mos.	0	—
Whipple, A. O. Case V. Neurol. Inst. Pres. Hosp. No. 434384	Not published	28	F.	6 yrs.	Unconsciousness	30	Resection tail and part of body	Body 2 nodules	(a) 1.2 cm. (b) .3 cm.	0	Adenoma	Symptom free 4 mos.	0	—
Whipple, A. O. Case VI. Neurol. Inst. Pres. Hosp. No. 350794	Not published	45	F.	4 yrs.	Unconsciousness	28	Excision	Junction body and tail	2 x 1.6 x 1.8 cm.	0	Adenoma	Symptom free 2 mos.	0	

* Proc. Inter-State Post-Graduate Med. Assn. of North America.

TABLE IV

Hypoglycemia with Island Cell Tumor. Cases with Autopsy

Author	Publication Date	Age	Sex	Duration Symptoms	Type Symptoms	Min. Bld. Sugar	Site Tumor	Size Tumor	Insulin Recov. Spec.	Pathology	Autopsy
Thalhimer, W. Murphy, F. D.	J. A. M. A., 1928, 91:89–91	57	F.	2½ yrs.	Unconsciousness	33	Junction of tail and body	1 x 1.5 cm.	o	Microscopic invasion of capsule	No metastases
McClenahan, W. U. Norris, G. W.	Am. Jour. Med. Sci., 1929, 177:93–97	41	M.	45 mos.	Loss of memory; unconsciousness	20	Junction middle and distal third	1.5 x .7 x .6 cm.	o	Adenoma not microscopically encapsulated	No metastases
Smith, M. G. Seibel, M. G.	Am. Jour. Path., 1931, 7:723–739	40	M.	7 yrs.	Coma	58	Center of head	1 cm.	o	Mostly encapsulated	No metastases
Terbrüggen, A. (Frank, H.)	Beitr. z. path. Anat. u. z. allg. Path., 1931, 88:37–50	30	F.	1 yr.	Coma	23	Middle and tail	2 x 1.5, 1 and 1.5 cm. and smaller	o	Multiple adenomata	No metastases
Büchner, F. Bielschowsky, F.	Klin. Wchnschr., 1932, 11:1494–1496	57	M.	? Diabetes. Not stated	Coma	31	Distal one-third	1 x 1.1 x .7 cm.	o	Encapsulated	Cirrhosis of pancreas. No metastases
Gibbs, C. B. F.	N. Y. State Jour. Med., 1932, 33:638	34	F.	9 mos.	Coma	17	Tail	1.3 x .7 x 1.0 cm.	o	Encapsulated grossly. No microscopic examination reported	Right adrenal hemorrhagic cyst
Barnard, W. G.	Jour. Path. and Bact., 1932, 35:929–932	40	F.	3 mos.	Coma	20	Head	1.2 cm.	o	Not encapsulated	No metastases
Cairns, R. M. Tanner, S. E.	Brit. Med. Jour., 1933, 1:8	52	F.	1 yr.	Unconsciousness	41	Tail	2 cm.	o	Gray. Adenoma. Encapsulated	No metastases
Wolf, A. Hare, C. C. Riggs, H. W.	Bull. of Neurol. Institute, 1933, 3:232	10	M.	16 mos.	Convulsions	54	Middle. Tail. Head	1 cm. .3 cm. .3 cm.	o	Encapsulated	No metastases
Rienhoff, Wm. F., Jr. Lewis, D.	Bull. Johns Hopkins Hosp., 1934, 54: 386–429	39	M.	18 mos.	Unconsciousness	4	Head	2.2 x 1.2 x .9 cm.	o	Circumscribed	No metastases. See chart

TABLE V

Hypoglycemia. No Tumor Found at Operation

Author	Publication Date	Age	Sex	Duration Symptoms	Type Symptoms	Min. Bld. Sugar	Operation	Pathology	Result	Fistula Postop.
Finney, J. M. T. Finney, J. M. T., Jr.	Trans. Am. Surg. Assn., 1928, 46:268	53	F.	4 yrs.	Spells unconsciousness	30	Resection 22.05 Gm.	Normal pancreas	Attacks continued	o
Allan, F. N. Boeck, W. C. Judd, E. S.	J. A. M. A., 1930, 94:1116	52	M.	2 yrs.	Stupor	40	14 Gm. excised; tail and part of body	Normal	14 mos. no improvement	o
Allan, F. N. Boeck, W. C. Judd, E. S.	J. A. M. A., 1930, 94:1116	47	M.	4 yrs.	Convulsions. Mania	40	8 Gm. excised	Normal	4 yrs. no improvement	+
Harris, S. (Taylor)	J. A. M. A., 1933, 100:321	20	M.	2 yrs.	Narcolepsy	50	½ body and tail excised	Normal	2 yrs.	o
Judd, E. S. Allan, F. N. Rynearson, E. H.	J. A. M. A., 1933, 101:99	50	M.	14 mos.	Coma	40	(1) 8 Gm. tail excised (2) Pancreas clamped	Normal	No permanent improvement	—
Judd, E. S. Allan, F. N. Rynearson, E. H.	J. A. M. A., 1933, 101:99	42	M.	1 yr.	Coma	20	Capsule stripped	Pancreas chronic inflammation½ usual size	Improving but with diet	—
Holman, E. (1928) Railsback, O. C. Judd, E. S. (1932)	Surg., Gynec., and Obst., 1933, 56:591–600	31	M.	2 yrs.	Convulsions Coma	32	(1) Resection 1928 (2) Excision nodule 1932	Interstitial pancreatitis	Unimproved	—
Evans, J. A. McDonough, W.	Jour. Iowa Med. Soc., 1933, 23:454	41	F.	1 yr.	Spells	?	Resection	Normal pancreas	Unimproved	
Winans, H. M.	Am. Jour. Med. Sci., 1933, 185:500	30	F.	15 yrs.	Convulsions	35	Biopsy	Normal. Slight hypoplasia?	No relief	
Ziskind, E. (Bayley)	Arch. Int. Med., 1933, 52:76	19	M.	18 mos.	Coma	40	Resection 7.2 Gm.	Normal pancreas	Unimproved	o
Graham, E. A. Hartmann, A. F.	Surg., Gynec., and Obst., 1934, 59:474	1	M.	9 mos.	Convulsions	6 ("true" sugar)	80–90% resected	Normal pancreas	Symptom free 9 mos.	o
Harris, Seale (Drennan)	Southern Surgeon, 1934, 3:199	32	F.	?	Fainting	60	Excision ½ body and tail	Normal pancreas	Relief of symptoms 4 mos.	o
Harris, Seale (Drennan)	Southern Surgeon, 1934, 3:199	27	M.	4 mos. (8 yrs.)	Convulsions (Petit mal)	65	Excision ½ body and tail	Pancreatitis	Convalescent	o
Simon	Southern Surgeon, 1934, 3:199	26	M.	3½ mos.	Unconsciousness	51	Resection 60 Gm.	Hypertrophy islets	Improved 2 mos. +	o
Thomason, G.	Personal communication, 1934. Western Surg. Assn., Dec. 8, 1934.	?	M.	?	?	?	Subtotal resection. Tail and body	No adenoma	Improved (no. mos. ?)	o
Rienhoff, Wm. F., Jr. Lewis, D.	Bull. Johns Hopkins Hosp., 1934, 54:386–429	39	M.	18 mos.	Unconsciousness	4	Resection tail and half body	Normal pancreas	Died shock first day postop.	—
Boone, J. A.	New England Jour. Med., 1934, 211:49–53	11	F.	10 mos.	Unconsciousness	37	Exploratory. Biopsy	Normal pancreas	See TABLE II To be followed	o

TABLE VI

Hypoglycemia. No Tumor Found at Autopsy

Author	Publication Date	Age	Sex	Duration Symptoms	Type Symptoms	Min. Bld. Sugar	Pathology	Other Autopsy Findings
Massa, M.	Gior. di clin. med., 1929, 10:679	67	M.	2 mos.	Referable to carcinoma	58	Hypertrophy of islands	Adenocarcinoma of pancreas with obstruction of ducts and metastases
Phillips, A. W.	J. A. M. A., 1931, 96:1195	56	M.	11 mos.	Coma (nephritis)	25	Hypertrophy of islands	
Mosenthal and MacBrayer (not published)	1933 Quoted by Wilder	39	M.	3 yrs.	Vertigo	50	Hypertrophy of islands	

TABLE VII

Tumors with No Recorded Hypoglycemia
(Not Interpreted as Simple Hypertrophy)

Date	Author	Age	Sex	Diabetes	Autopsy or Operative Findings	Site of Tumor	Size of Tumor in Mm.	Encapsulation
1902	Nicholls	?	?	?	?	?	3.0 x 2.5 Mm.	+
1905	Reitman	62	M.	+	Chronic interstitial pancreatitis. Cardiovascular disease	?	?	?
1906	Herxheimer	67	F.	+	Diabetes. Chronic cardiac vascular disease	?	2 adenomas. Larger 4 x 2 Mm.	+
1907	Helmholz	65	M.	?	Chronic cardiac vascular disease	?	5 x 5 x 3 Mm.	+
1908	Morse	44	F.	?	Peritonitis	Splenic end	5 Mm.	+
1908	Morse	46	M.	?	Cerebral hemorrhage. Arteriosclerosis. Chronic nephritis	?	3 Mm.	+
1909	Cecil	75	M.	+	Diabetes. Pneumonia	?	1.8 x 1.6 Mm.	?
1910	Weichselbaum	?	?	—	?	?	1.5 Mm.	?
1911	Cecil	63	M.	—	Carcinoma of colon	?	4 x 3.5 Mm.	?
1911	Heiberg	64	F.	+	Diabetic coma	?	6 x 5 Mm.	+
1911	Alezais and Peyron	?	?	?	?	?	"Petit pois"	o
1912	Rollett	25	F.	—	Pulmonary tuberculosis and tuberculous peritonitis	?	11 Mm.	?
1913	Lecomte	42	F.	—	Tuberculosis of cerebellum	Junction of head and body	100 x 70 x 40 Mm.	+
1914	Koch	22	F.	o	Multiple sclerosis. Bronchopneumonia	Middle	14 Mm.	+
1922	Priesel	63	F.	?	Arteriosclerosis. Myocarditis and pneumonia	Lower border	12 x 10 x 9 Mm.	+
1922	Priesel	51	M.	?	Arteriosclerosis. Encephalomalacia. Pneumonia	Head	9 x 10 Mm.	+
1922	Priesel	60	M.	?	Arteriosclerosis	?	35 x 25 Mm.	+
1924	Schneider	84	M.	o	Myocarditis. Bronchopneumonia. Sclerosis of kidneys	Middle	"Pruneau"	+
1924	Schneider	60	F.	o	Tuberculosis	Middle	50 x 45 x 30 Mm.	+
1925	Lang	34	F.	o	Bronchopneumonia—postoperative	Throughout	up to 5 Mm.	+
1926	Warren	53	F.	o	Carcinoma of ovaries	?	1.7 x 1.7 x 1.4 Mm.	+
1926	Warren	63	M.	o	Myocarditis	?	1.3 x 1.1 Mm.	+
1926	Warren	49	F.	o	Pernicious anemia	?	1.2 x 1.2 Mm.	+
1926	Warren	48	F.	o	Chronic nephritis	Junction of head and body	9.0 x 6.5 x 6.0 Mm.	+
1928	Natali	60		o	Carcinoma of stomach with metastases	Tail	14 x 15 Mm.	+
1929	Lloyd	27	F.	o	Hypophyseal tumor. Enlarged parathyroids	5 cm. middle and outer ⅓	Multiple — largest 10 x 7 x 6 Mm.	+
1931	Smith	?	M.	o	Carcinoma of liver	Body	10 Mm.	+
1931	Smith	50	M.	o	Periods of loss of memory. Died following operation for gallstones	?	6 Mm.	+
1932	Smith	48	F.	+	Lobar pneumonia. Thrombosis of iliac veins. Pulmonary embolus	Body	10 Mm.	+
	Hamdi	52	M.	?	Tumor of tail with metastasis in liver. (No clinical history.)	Tail	2 x 2.5 Mm.	?
1933	Cottalorda	32	F.	?	Large pedunculated bilobed tumor attached to tail. Excision	Tail	130 x 80 Mm.	+

sessed definite tumor characteristics," and that "the staining reactions of the specific granules in the majority of tumor cells of each deviated sufficiently from those of the beta cells of normal human islets to lend support to the hypothesis of dysinsulinism."

Our own series consists of eight tumors removed by Doctor Whipple from six patients with symptoms of hypoglycemia (TABLE III). All of the patients were relieved of their symptoms postoperatively. Cases I, II, V and VI had single tumors. Case III had two tumors removed at the same operation; Case IV had one tumor removed which was of the island cell type with some degeneration. Because of persisting symptoms he was operated upon again a month later and a second similar tumor was found and excised. His symptoms were relieved after the second operation.

For comparison with the tumors, Fig. 1 shows a normal human island. An island is a typical endocrine structure of columns of cuboidal and pyramidal cells interwoven with blood capillaries to form an intricate network of three dimensions. The island cells are ranged along the capillaries, and where a capillary has been cut across the island cells appear to form a rosette around it. The majority of the cells in normal islands of average size are beta cells. We have been unable to identify a third granular cell so far in normal guinea-pig or human pancreas. The larger capillaries are lined by endothelium outside of which there is a thin layer of fibrous connective tissue. In many of the smaller blood channels no endothelial lining is seen. Some of them appear to consist of extremely thin tubes of collagen together with a fenestration of reticulin. Around the island there is a delicate capsule of fibrous connective tissue richly provided with blood vessels. In normal human islands the fibrous tissue is scanty. In diabetes it is around the vessels that the hyaline change first described by Opie is seen. In his own words:[114] "The term hyaline degeneration is wholly descriptive and is applied to the ill-defined group of degenerative processes of which the common character is the formation of homogeneous or hyaline material. In the island of Langerhans hyaline occurs as conspicuous masses in contact with capillaries, the endothelium of which is well preserved. The islet cells are partly or completely destroyed and replaced."

Our first tumor (Fig. 2) measured 1.5 by 1 by 1 cm. and was removed from the junction of the body and the tail where it lay just beneath the capsule of the pancreas. A small rim of pancreatic tissue was removed with it. The tumor in the fresh state was pinkish-red, more vascular than the surrounding gland. Microscopically, it is completely encapsulated. There is no evidence of compression of the surrounding pancreatic tissue, nor is any striking hyperplasia of island tissue seen in the pancreas. Only a rare mitotic figure is seen in the tumor cells and no tumor cells are found in vessels. In architecture this tumor very closely resembles a normal island. There is the same grouping of cuboidal and pyramidal cells in columns along the capillaries or in rosettes around a capillary. The endothelial lining of the vessels is sometimes distinct, sometimes not. Where

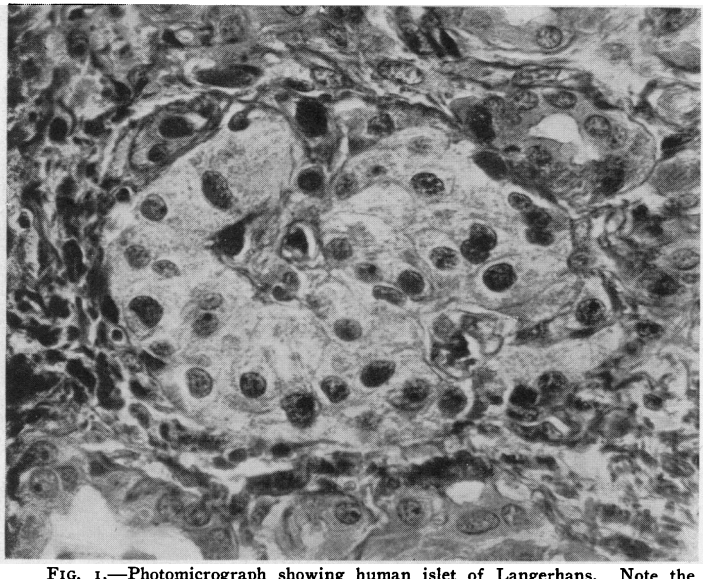

FIG. 1.—Photomicrograph showing human islet of Langerhans. Note the granular cells and their relation to the capillaries. The surrounding pancreas is not entirely normal but shows some fibrosis.

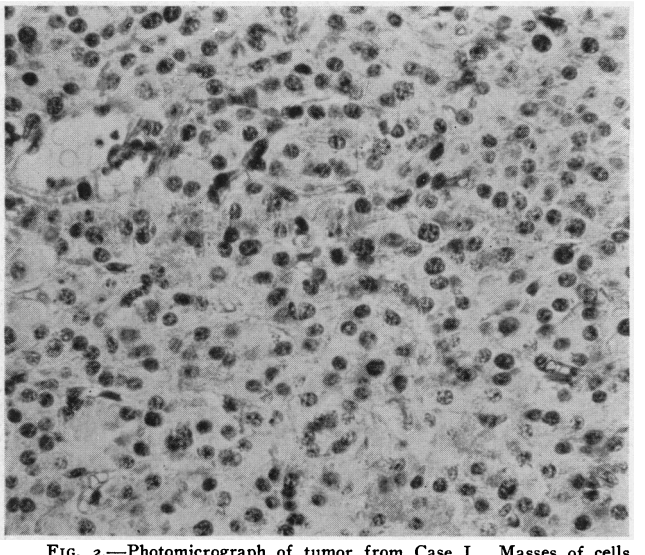

FIG. 2.—Photomicrograph of tumor from Case I. Masses of cells are seen in intimate relationship with capillaries. This closely resembles a normal islet.

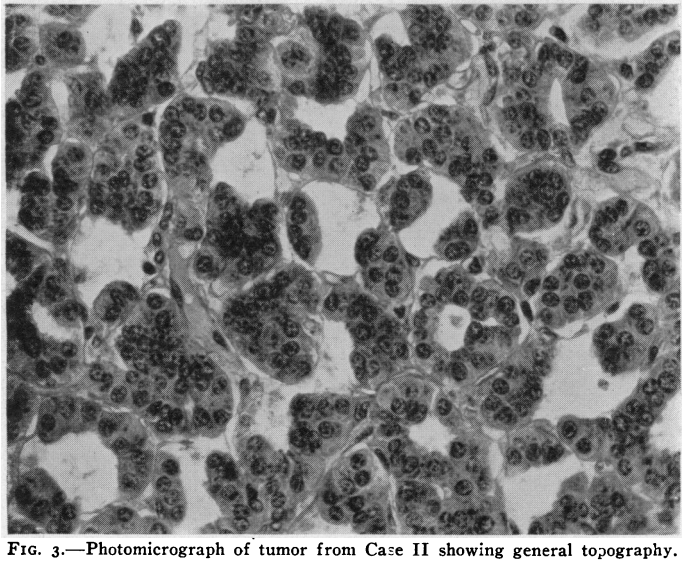

FIG. 3.—Photomicrograph of tumor from Case II showing general topography.

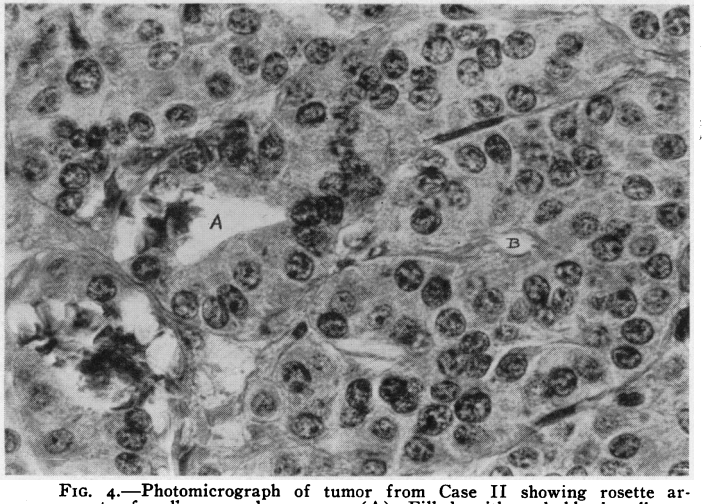

FIG. 4.—Photomicrograph of tumor from Case II showing rosette arrangement of cells around spaces. (A) Filled with red blood cells or (B) lined by a delicate layer of collagen.

it is not recognized, thin walled tubes of collagen are seen together with a fine network of reticulin. In one area near the capsule there is a disseminated fibrosis limited to the capillaries. Around many of these there is a thick wall of fibrous connective tissue. The fibrosis often takes the form of a solid block of collagen situated on one side of the capillary. The distribution of the fibrous connective tissue, both collagen and reticulin, is shown best by Masson's trichrome, Van Gieson and Laidlaw's silver connective tissue stain.

Our second tumor (Figs. 3 and 4) measured 1.3 by 1.2 by 1 cm. It was removed from the junction of the body and head. Grossly it was encapsulated and had attached to it a small rim of pancreatic tissue. It was dark bluish-red and uniform. Microscopically, this tumor is also encapsulated, but the capsule was exceedingly delicate. Only a rare mitotic figure is seen, there is no invasion and no tumor cells are found in vessels. There is more distinct rosette formation than in the first. Sometimes the rosettes are distinctly formed about endothelial lined capillaries, sometimes about small tubes of collagen and sometimes there are lumina lined directly by tumor cells. These appear as ductlike structures. Whether they are to be interpreted as adult ducts from the original pancreatic tissue, or new formed tumor ducts, is difficult to say. The low columnar cells lining them have their polarity well preserved and show between their distal extremities the "Schlussleisten" characteristic of the adult form. But they occur in the center of the tumor and may well represent new growth. The point is rather an academic one, since the origin of island cells from duct epithelium has been demonstrated. We have regarded this tumor as a somewhat more embryonal form than Case I. It shows, however, a considerable degree of fibrosis and some degeneration closely related to the "hyaline" type already discussed.

Our third and fourth tumors (Figs. 5 and 6) removed from Case IV at the same operation show what we have interpreted as a still more embryonal, less differentiated type. These tumors measured 1.5 cm. and 1 cm. in greatest diameter respectively. Tumor A was removed from the body and tumor B from the head of the pancreas. They were both encapsulated grossly. Both were grayish-red. Microscopically, the tumors are not completely encapsulated, but the tumor cells show in sharp contrast to the acinar cells because of the characteristic mitochondria which are very striking in the latter. This tumor likewise shows only a rare mitotic figure, no evidence of invasion and no tumor cells in blood vessels. The cells are cylindrical or polyhedral cells arranged in cords giving the appearance of winding ribbons. Sometimes the ribbon appears to be wound around a capillary so as to form a rosette. Occasionally ducts are seen as in Case II. Tumor A differs from tumor B in this case by showing a much greater degree of degeneration and fibrosis. The same pale blue staining material (Masson stain), which does not show reticulin fibers in the special stains, and which is paler than the collagen fibers, is found in

masses about the capillaries, sometimes with distinct shadows of cell outlines, and sometimes as blue masses in otherwise well preserved cells. In all of our cases this material does not appear strictly hyaline, in that it is not homogeneous, but somewhat granular. It does not react for mucin with the mucicarmine stain nor is it amyloid.

FIG. 5.—Gross photograph of two tumors removed from Case IV showing size against a centimeter scale.

Our fifth and sixth tumors (Figs. 7 and 8) removed from Case III one month apart came from the junction of the body and head and from deep in the substance of the tail. The first measured 1.4 cm. in greatest diameter, the second 2 by 1.5 cm. Both appeared partially encapsulated and

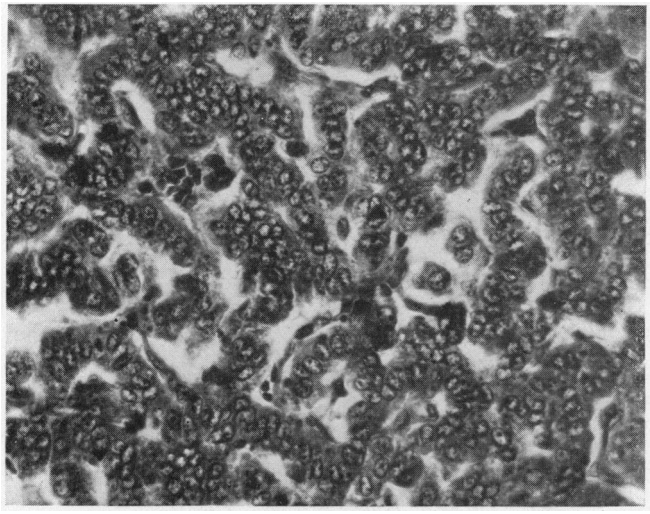

FIG. 6.—Photomicrograph of a section from the smaller of the two tumors from Case IV, showing ribbon-like arrangement of cells.

reddish. Microscopically, these tumors are not sharply demarcated from the surrounding pancreatic tissue. Acinar cells, distinguishable by their mitochondrial striations and their zymogen granules, are found among the tumor cells in the periphery of the tumor. Whether this indicates in-

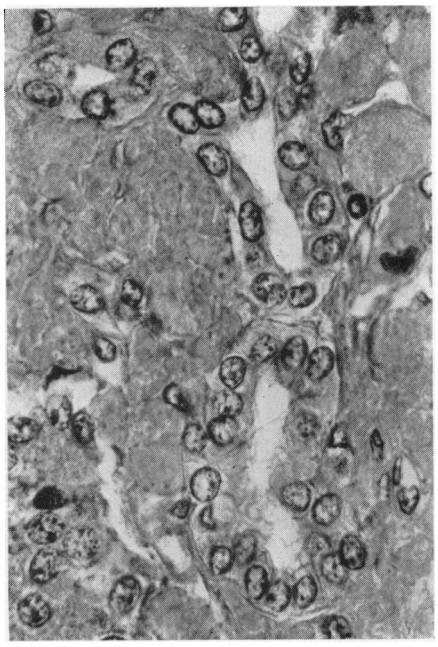

FIG. 7.—Photomicrograph of tumor I from Case III showing duct formation.

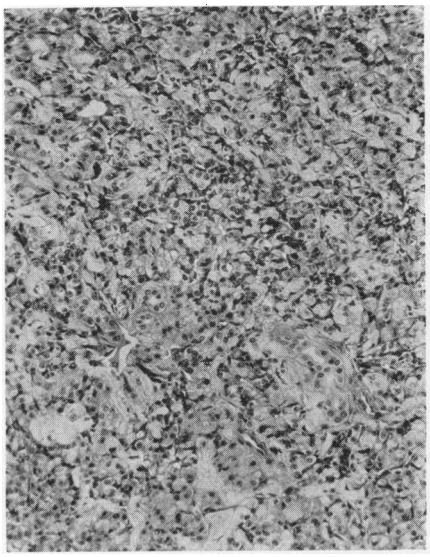

FIG. 9.—Photomicrograph of tumor from Case V showing ducts.

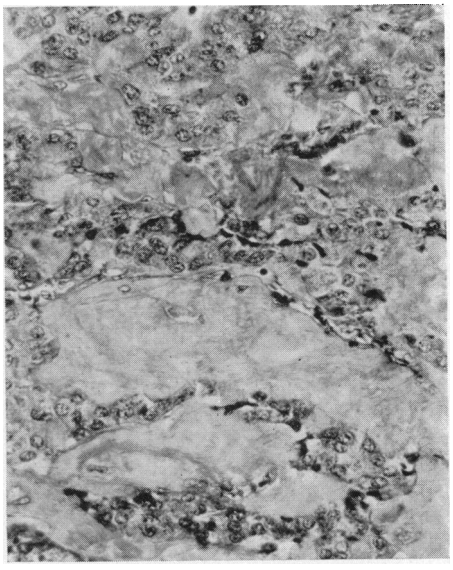

FIG. 8.—Photomicrograph of tumor II from Case III showing degeneration.

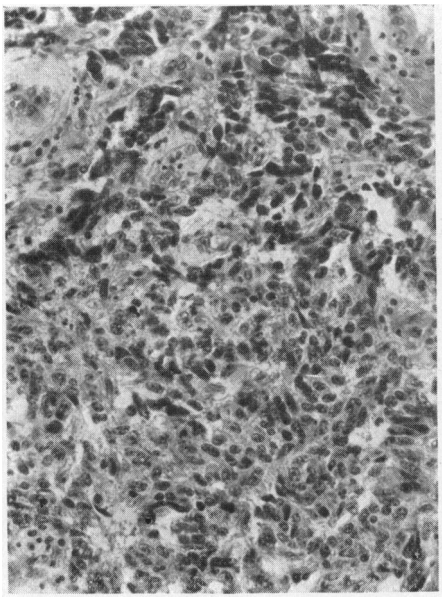

FIG. 10.—Photomicrograph of tumor from Case VI.

vasiveness on the part of the tumor cells is difficult to say. Only a rare mitosis is observed and no cells are found in blood vessels. The striking feature of both these tumors is the degeneration. Broad bands of pale blue staining material (Masson stain) are found everywhere in the section so that the predominant arrangement of the tumor cells is hard to distinguish. Some ribbon arrangement is seen, some rosette formation around capillaries, and some tubules or ducts.

Our seventh tumor (Fig. 9) from Case V came from the body of the pancreas and consisted of a circumscribed mass 1.2 cm. in greatest diameter. A third of this was calcified. Adjacent to this portion there was a second smaller completely encapsulated mass 4 by 3 by 3 Mm. Both of these tumors closely resemble the tumors from Case IV in the extensive degeneration and fibrosis. The tumor cells are arranged in strands with occasional rosette formation around a capillary. More ducts are present in this tumor than in any other of our series. No mitotic figures are observed.

Our eighth tumor (Fig. 10) from Case VI was the largest of our series, measuring 2 x 1.6 by 1.8 cm., and came from the junction of the body and tail. It was nodular, and apparently completely encapsulated. On section portions of the mass were firm and white, while other areas were softer and yellower. Microscopically, this tumor shows extensive areas of degeneration and fibrosis, and only an incomplete capsule. The relationship of cells to the capillaries is not as striking as in the previous cases, and there are many more ducts in the tumor than in any of the others. No mitoses are seen. Dr. Margaret Murray will report on the cultivation *in vitro* of the tumor cells of these last two cases.

With the specific stains for alpha and beta granules neither the tumor cells nor the island cells of the surrounding pancreas uniformly show the granules definitely colored. In the two tumors from Case III, a few cells are scattered through the section with granules staining like beta cells. In the tumor from the last case with the acid fuchsin-methyl green method of Bensley the majority of the tumor cells show granules similar to those in the majority of cells in the normal islands of the adjacent pancreas. Further work on these specific stains is in progress, and we are not, therefore, in a position to make any positive statement about the granular properties of the tumor cells at this time. (See note p. 1327.)

We have classified these eight tumors as adenomata, for the present at least, and only in the fifth, sixth, and eighth have we seen any evidence of what might be considered an infiltrating tendency. Marked variation in the size and shape of cells, mitotic figures in any appreciable number and blood vessel invasion are nowhere present. In each case the tumor appears to have been completely excised. In all of the tumors the morphology is that of an endocrine gland. That they were functionally active is obvious from the fact that the patients no longer suffer from hypoglycemia after their removal. It is unfortunate that we are unable to report any successful attempt to extract insulin from the tumors.

Case Reports

Case I.—F. K. (Presbyterian Unit No. 389424. Neurological Institute No. 1), a 33-year-old Polish woman, married, complaining of spells of unconsciousness for one year.

Family and Past History.—Entirely irrelevant.

Present Illness.—In January, 1933, without prodromata of any sort she was suddenly seized with a "spell." She remembers nothing concerning this and when the "spell" was over she felt as well as ever. A few days later she developed headache which recurred from time to time with no known cause. The "spells" continued, and August 8, 1933, she was admitted to the Neurological Institute in coma. Her husband said that her "spells" were associated with dizziness and vomiting. There was a definite histronic spasm prior to this attack, and in others a peculiar type of giggling and grimacing. No visual disturbance or motor disability other than that of speech.

Under the impression that the patient had some sort of encephalitis she was treated with forced spinal drainage with intravenous solution of glucose. The blood sugar two days after admission with this treatment showed 145 mg. per 100 cc. Her next sugar determination was not until September 12, at which time a value of 65 mg. was found. She was then intensively studied. Her first sugar tolerance test was performed November 9, at which time her fasting blood sugar was 30.3 mg. per 100 cc.

The patient continued to have periodic seizures. Blood sugar determination at these times invariably showed a low level. She was also tested out by calculated diets, by insulin, and by adrenalin, with no significant change in the sugar level. She was then transferred January 6, 1934, to the Surgical Service at the Presbyterian Hospital. Further blood studies were done before operation.

Physical Examination.—Well-developed, well-nourished, slightly obese. Temperature, 98°; respirations, 20; pulse, 84; blood pressure, 120/80. General physical examination, essentially negative. Reflexes, normal.

Operation.—January 11, 1934, under spinal anesthesia. A transverse incision was made through both recti. A tumor about 1 cm. in diameter was removed from the junction of the body and tail of the pancreas.

Postoperative Course.—The wound healed by primary union. No pancreatic fistula. The sutures were removed on the seventh day. The patient was allowed up on the fourteenth day, and discharged from the hospital on the twentieth day. She had no seizures following operation.

Follow Up.—Fifteen months postoperative. Patient symptom free. No complaints. No hernia. Working at full capacity. Scar firm.

Case II.—S. B. (Presbyterian Unit No. 421465. Neurological Institute No. 2), a Jewish housewife, 48 years of age, was admitted to the Neurological Institute April 4, 1934.

Family and Past History, negative.

Present Illness.—Since August, 1933, about nine months ago, patient has become unusually irritable and shows episodes of agitation without adequate cause. The attacks usually last about 20 minutes and are preceded by colored scotomata in the form of rings. Mental confusion is also present and the patient does not remember the episodes clearly. They are followed by somnolence. The attacks usually come around 11:30 A. M., no breakfast being eaten as a rule, because of a late supper at night. The family states that an attack can be prevented occasionally by giving food. The attacks have continued and become longer as well as more frequent, so that for the past six to seven months they have occurred almost daily. Occasionally they are accompanied by purposeless, thrashing movements of the extremities, body and head, as well as negativism, muttering, facial flushing, and profuse diaphoresis.

Physical Examination.—Patient is a rather obese, white woman, very irritable and uncoöperative. Temperature, 99.4°; pulse, 75; blood pressure, 160/100. The general examination is essentially negative otherwise.

Laboratory Findings.—Urine negative. Hemoglobin, 87 per cent; red blood cells, 4,800,000; white blood cells, 9,000; polymorphonuclears, 80 per cent. Wassermann, negative. Blood urea, 10.9. Blood sugar, 43 mg. per 100 cc. Skull roentgen ray negative. Gastro-intestinal series, negative.

Course.—It was found that the patient could be relieved quickly of an attack by the administration of glucose intravenously, or by mouth if the symptoms were mild. It was found that the fasting blood sugar varied between 34 and 60 mg. (as determined on 12 consecutive hourly specimens). The blood sugar also seemed to be raised by adrenalin, whole adrenal by mouth, and eschatin hypodermically.

A sugar tolerance test gave the following results:

Fasting	41 mg. per 100 cc.
½ hr.	117 mg. per 100 cc.
1 hr.	86 mg. per 100 cc.
2 hrs.	93 mg. per 100 cc.
3 hrs.	63 mg. per 100 cc.

The patient was put on a high carbohydrate diet (270-42-26) with frequent feedings and remained relatively symptom free. She was transferred to Presbyterian Hospital June 14, 1934, and an exploratory celiotomy was done four days later.

Operation.—June 18, 1934. Spinal anesthesia. A transverse incision was made, exposing the pancreas through the gastrocolic omentum. A tumor about 1 cm. in diameter was removed from the upper border of the pancreas at the junction of the body and the head.

Postoperative Course.—The patient did well and suffered no more attacks. The lowest fasting blood sugar was 115 mg. per 100 cc. She was discharged on the eighteenth day.

Follow Up.—Nine months postoperative. Patient symptom free, no complaints. Scar firm, no hernia. Working at full capacity.

CASE III.—E. S. (Presbyterian Unit No. 306695. Neurological Institute No. 3), a white Irish male, 28 years old, was admitted to the Presbyterian Hospital July 13, 1934, complaining of episodes of excitement and maniacal attacks for three years.

Family History.—Essentially negative.

Past History.—Appendicectomy five years ago, followed by phlebitis of left leg. Suprapubic cystostomy for removal of bladder calculus was done three weeks before admission.

Present Illness.—Three years before admission patient began to have attacks somewhat as follows: "Feeling of light-headedness and drawing in arms and legs," with excitement which at times became a real manic episode—tearing his clothes and throwing things around. These last from 30 minutes up to two or three hours. Patient remembers most of the events but is unable to control himself at the time. Mental confusion is marked. They are always worse when fasting, especially early in the morning. The attacks have become more frequent and worse in character, so that now he requires orange juice practically every two hours to ward off attacks.

Patient was admitted to Neurological Institute twice in July, 1931, three years ago. At that time blood studies showed a persistently low sugar, varying from 42 to 75 mg. per 100 cc. He was relatively free from attacks on a high-carbohydrate diet and calories up to 5,000 daily. Since then the patient has been followed in the clinic, and has been given thyroid and pituitary substance with no evident improvement. He has gained about 100 lbs. during this time and now weighs 250 lbs. It is becoming increasingly difficult to ward off the attacks.

Physical Examination.—The patient is a very obese, white male, moderately irritable but fairly coöperative. Temperature, 99.8°; pulse, 60; respirations, 22; blood pressure, 122/80. The only other positive physical findings are moderate hyperactivity of the deep reflexes; palpable liver; right lower quadrant and lower midline abdominal scar.

Laboratory Findings.—Urine, negative. Hemoglobin, 92 per cent; red blood cells, 4,650,000; white blood cells, 5,700; polymorphonuclears, 72 per cent. Wassermann, negative. Roentgen ray of skull: Slight broadening of sella turcica but otherwise normal. Blood amylase, 9.

A sugar tolerance test September 8, 1931, gave the following results:

Fasting	71 mg. per 100 cc.
½ hr.	200 mg. per 100 cc.
1 hr.	150 mg. per 100 cc.
1½ hrs.	187 mg. per 100 cc.
2 hrs.	187 mg. per 100 cc.

The blood sugar showed also a slight rise after injection of 6 cc. of adrenalin (from 76 mg. to 103 mg. in one hour).

Preoperative Course.—During the preoperative stay in this hospital the fasting blood sugars were low, usually about 45 mg. per 100 cc., and at one time 38 mg.

First Operation.—August 13, 1934. Spinal anesthesia. Transverse incision was made, exposing the pancreas through the gastrocolic omentum. A firm, vascular node about 1 cm. in diameter was removed from the inferior border of the pancreas at the junction of the body and head. No other tumors could be felt.

Postoperative Course.—On the morning after operation the blood sugar had fallen to 54 mg. per 100 cc. and later in the day was 47 mg. The patient had no symptoms of hypoglycemia, however, for several days. It was necessary to administer glucose frequently to keep the blood sugar up, but less was needed than before operation. It was felt that a second adenoma had been overlooked, and one month after operation a second exploration was done.

Second Operation.—September 12, 1934. Spinal anesthesia. A tumor in the tail of the pancreas was removed, with six cm. of the tail of the gland. A rubber tube drain was left in. Following this the fasting blood sugar remained normal, the values ranging from 82 to 120 mg. per 100 cc., though one value on the fifth postoperative day was 66 mg. There were no symptoms of hypoglycemia following the second operation.

Postoperative Course.—A pancreatic fistula developed after the last procedure and drained freely, but closed six weeks after operation. The patient has been entirely free from his former hypoglycemic attacks, and his personality changes for the better have been marked.

Follow Up.—Five months postoperative. No recurrence of symptoms. Working regularly 12 hours daily. Scar firm. Fistula closed.

CASE IV.—(Presbyterian Unit No. 428308. Neurological Institute No. 4), W. P., a white male jeweler 38 years of age, was admitted to the Presbyterian Hospital August 24, 1934.

Family History.—Negative.

Past History.—Patient has been well except for influenza in 1918. Operation for inguinal hernia was done in 1914.

Present Illness.—In October, 1922, 12 years before admission, patient began to have peculiar attacks of mental confusion and disorientation. The first one occurred while on a long walk, and was accompanied by contraction of the back muscles, so that he walked bent backwards, finally falling to the ground from exhaustion. Since that time the attacks have increased in severity and in number. At first they occurred a few weeks or months apart, but have come on almost every day for the last one to two years, either in mild or severe form. They have assumed varied forms and were considered as epileptic equivalents or petit mal, by the many physicians who saw him. He has become very irritable and fatigues easily, being somewhat drowsy most of the time, and has lost interest in social activities, which formerly he enjoyed. Recently he has had frequent attacks while going home on the train, at times going beyond his station in his confusion and inability to think clearly. Diplopia has been noted several times.

The patient has been admitted to the Neurological Institute four times; in 1926, 1931, 1933, and August 21, 1934. During this time the diagnosis was not made until the last admission. A fasting blood sugar was taken May 27, 1931, and was 83 mg. per 100 cc. (patient had no symptoms when the blood was taken, though he had an attack later in the day). At the last admission, three days ago, the persistent hypoglycemia and relief by glucose were noted and the patient transferred to the Presbyterian Hospital after being studied.

Physical Examination.—The patient is a rather short, well-developed, white male, alert and somewhat anxious. Temperature, 98.6°; pulse, 72; blood pressure, 125/68. The only positive findings physically are slight inequality of the pupils; lack of eye coördination in convergence; and slight tremor of the hands.

Laboratory Findings.—Hemoglobin, 103 per cent; red blood cells, 5,000,000; white blood cells, 6,600; polymorphonuclears, 76 per cent. Blood calcium, 11.0. Blood phosphorus, 2.9. Urine negative. During the previous admissions in the Neurological Institute the patient had been worked up completely as a brain tumor suspect, including spinal puncture and encephalogram. All these studies were negative. A roentgen ray of the skull showed suggestive early Paget's disease. This has not changed over a period of years. The other bones show no changes. Blood sugars on numerous occasions while fasting and during slight attacks have varied from 30 mg. to 60 mg. per 100 cc.

A sugar tolerance test gave the following results:

Fasting	57.5	mg. per 100 cc.
½ hr.	102	mg. per 100 cc.
1 hr.	78	mg. per 100 cc.
2 hrs.	65	mg. per 100 cc.
3 hrs.	68	mg. per 100 cc.

Operation.—August 7, 1934. Spinal anesthesia. Transverse incision. Pancreas explored through gastrocolic omentum. Two tumors were removed—one about 1 cm. in diameter at the lower border of the body, and the other about .6 cm. in the head of the pancreas.

Course.—Recovery was uneventful. The fasting blood sugar varied between 85 and 100 mg., though on the second postoperative day it went down as low as 57 mg. The patient's personality has changed completely, and he explained his feeling "as if a veil had been lifted." He was discharged on the fifteenth day.

Follow Up.—January 23, 1935. Five months postoperative. Patient feels 100 per cent well. Scar linear and well healed. Working at full capacity.

CASE V.—H. K. (Presbyterian Unit No. 434384. Neurological Institute No. 5), a white female, 28 years old. First admitted to the Presbyterian Hospital November 30, 1934, complaining of attacks of drowsiness and unconsciousness of six years' duration.

Family History.—One brother died of brain tumor and an aunt has diabetes.

Past History.—Essentially negative.

Present Illness.—Began about six years before admission, and is characterized by a feeling of drowsiness with at times unconsciousness in the early morning. The attacks are preceded by a feeling of mental abnormality, such as irritability and irrelevant remarks. They are relieved by food such as orange juice, and are usually followed by severe headache and perspiration. At times there is diplopia with a feeling of numbness of the extremities. Amnesia is also noted at times, and occasionally incontinence of urine. The attacks were at first about one month apart, but have gradually become more frequent, so that during the past two or three months they have occurred almost daily.

Patient was admitted to Neurological Institute November 12, 1934. A "work-up" was done there and revealed hypoglycemia. The system review is otherwise negative.

Physical Examination.—Between attacks the patient is perfectly normal. Tempera-

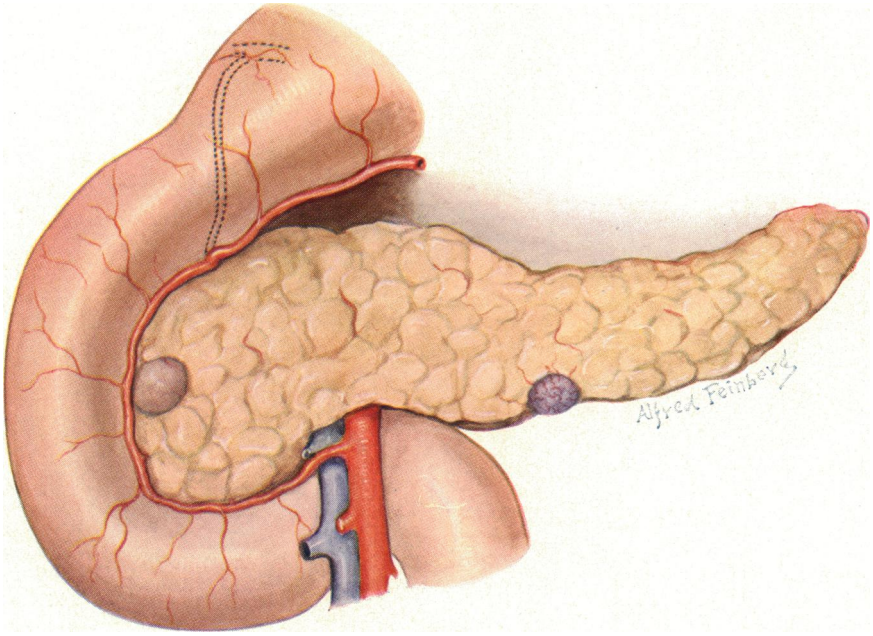

FIG. 13.—The difference in appearance between an adenoma and an enlarged lymph node. Note the richer capillary network over the adenoma at the junction of the body and tail of the pancreas.

ture, 99; pulse, 80; blood pressure, 130/90. The general examination is essentially negative.

Laboratory Data.—Urine, negative. Red blood cells, 4,000,000; hemoglobin, 70 per cent; white blood cells, 9,400; polymorphonuclears, 70 per cent. Wassermann, negative. Roentgen rays of skull and chest, negative. Fasting blood sugar varied between 32 and 65 mg. per 100 cc.

A sugar tolerance test gave the following results:

Fasting	64	mg. per 100 cc.
1 hr.	108	mg. per 100 cc.
1½ hrs.	148	mg. per 100 cc.
2½ hrs.	133	mg. per 100 cc.
Blood amylase	10.9	

Preoperative Course.—Patient was prepared for operation on a high-carbohydrate diet, and transferred to Presbyterian Hospital November 30.

Operation.—Excision of adenoma of pancreas with resection of the tail and part of the body. Spinal anesthesia. Transverse incision just above the umbilicus, with division of both recti muscles. The pancreas was approached through the gastrocolic omentum, and on inspection no tumor could be noted. However, mobilization of the inferior border of the pancreas allowed sufficient palpation so that a tumor could be felt near the junction of the tail and body of the pancreas. Resection of the tail of the pancreas so as to include the tumor was then carried out. A drain was placed in the denudated area and the gastrocolic omentum closed with interrupted silk sutures. The abdomen was also closed in layers with interrupted silk.

Postoperative Course.—Drain removed on the third day, and sutures on the eighth day. Patient's course was entirely uncomplicated. No fistula developed. The blood sugar rose to 220 mg. on the first day, dropped to 110 on the second, and thereafter remained at around 100.

Follow Up.—Four months postoperative. No recurrence of symptoms. No complaints. Scar firm. Working at full capacity.

CASE VI.—F. MacD. (Presbyterian Unit No. 350794. Neurological Institute No. 6).

Chief Complaint.—Fainting spells one and a half years' duration.

Family and Personal History.—Negative.

Past History.—General health, good. Acute infectious diseases, negative except for frequent colds to age of 38. Allergic phenomena, negative. Operations or injuries, T and A as a child. Broke coccyx falling down. Head negative. Respiratory negative. Cardiac, occasional slight edema of ankles. Gastrointestinal, negative. Genitourinary, nocturia once always. Menses, leukorrhea. Neuromuscular negative, calm disposition up to present illness. At present cries easily, worries over condition.

Present Illness.—First admission, August 15, 1932. One and a half years ago she began to have uncontrollable dizzy spells. These progressed in severity in a short time to loss of consciousness. There were no prodromata and she remembered nothing of the attack on recovery. They lasted several hours, and were not accompanied by vomiting or craving for food. The attacks occurred at intervals of about one month, usually before or during a regular period. A white vaginal discharge began at this time which was irritating and required the wearing of a pad. Edema of the ankles was more marked after the onset of these attacks. In August, 1932, about one hour after the onset of one of these attacks, she was taken to Neurological Institute where she remained in a semicomatose state for about one week, during which time she developed a left hemiplegia. She had a rapid pulse and fever, her blood sugar was found to be 25 to 38 mg. per 100 cc., and as she did not respond to moderate amounts of intravenous sugar she was referred to the Presbyterian Hospital.

First Admission.—August 15, 1932, to September 6, 1932. Temperature, 99.4°; pulse,

88; respiration, 20; blood pressure, 110/75. Physical examination was essentially negative except for anxious expression, deviation of the tongue to the right, slight weakness on the left, hyperreflexia, left greater than right, positive Babinski, slight edema of ankles, profuse cervical discharge (uterus normal).

Laboratory Findings.—Hemoglobin, 90 per cent; red blood cells, 4,200,000; white blood cells, 11,800; polymorphonuclears, 75 per cent; lymphocytes, 16; mononuclears, 6. Smear, normal.

Glucose tolerance test: 100 Gm. glucose:

Fasting	58 mg.
½ hour	104 mg.
1 hour	130 mg.
2 hours	119 mg.

Cervical smear, no GC found. Urine, normal, Stools, normal. BMR, 13 per cent on two examinations.

Course.—To establish definitely that hypoglycemia was the cause of her attacks she was put on a starvation diet and blood sugars were taken at intervals. The blood sugar dropped to 46 mg. at midnight, at which time she suddenly became comatose. She was given 50 per cent glucose by vein and roused immediately. Thereafter she was put on a high carbohydrate diet (400 Gm.), with much improvement in her general state and some clearing of the hemiplegia. Her blood sugar taken at frequent intervals ranged from 69 to 104 mg. Doctor Whipple was called into consultation and advised operation, but the patient was reluctant to undergo an operative procedure and was discharged on a high carbohydrate diet to be followed in the clinic.

She visited the clinic up to November, 1932, and was improving steadily at that time. She had had no attacks, was following her diet and taking food at night. There was still some residue of the hemiplegia. Her blood sugar was taken at each visit and was 80 ± mg. Operation was urged and her fear of this caused her to stop her visits to the clinic, and put herself under the care of a local doctor.

She returned to the clinic February 8, 1935, with the history of being in good health during the interval, but she had gained 50 pounds and in the last year, in spite of her high carbohydrate diet, she had five or six attacks. Six days before coming in she went without lunch and had had an attack lasting four hours, during which she had had convulsive movements and incontinence of urine. Operation was again urged, and patient was admitted February 14, 1935, for operation for possible adenoma of the pancreas.

Physical Examination on Second Admission.—Temperature, 99.2°; pulse, 88; respiration, 20; blood pressure, 115/75. Obese, healthy, young-looking woman. Mentally alert. Skin, clear. Head, negative. Eyes, negative. Throat, negative. No thyroid enlargement or tracheal deviation. Spine, negative. Lungs, clear. Heart not enlarged, sounds good, no murmurs. Abdomen, negative. Extremities: No tremor, clubbing or edema. Left KJ slightly more active than right. All reflexes hyperactive. No Babinski. Face, symmetrical. Tongue deviates slightly to right.

Operation.—Excision of adenoma of pancreas. February 19, 1935. Spinal pantocaine anesthesia. A characteristic adenoma measuring about 1½ cm. in diameter, having a vascular network, fairly well encapsulated and not difficult to enucleate, was found at the junction of the tail and body of the pancreas. It lay just beneath the splenic artery, which was not damaged in the course of the removal of the adenoma. The rest of the pancreas felt normal and on carefully palpating the head, body and tail for further adenomata nothing resembling an islet neoplasm was felt after the removal of the one described above.

Final Note.—Wound healed by primary union. Silk technic. Patient has been relieved of all her preoperative symptoms, and shows normal blood sugar readings. Home on seventeenth day. Two months: No recurrence of attacks. Blood sugar 102 mg. per 100 cc.

SURGICAL THERAPY

From the study of the reports of the several surgeons who have operated on these cases—some 29 case reports are now available in the literature—and from our own experience in six cases, we offer the following suggestions:

After the diagnosis of chronic hypoglycemia is established and hepatic and pituitary causes have been ruled out, the patient should have a course of medical therapy of three to four weeks to determine the response of the individual to conservative measures. If it is found that the blood sugar values are continuing to remain low, and that the seizures are controlled only on a high-carbohydrate intake, an exploratory celiotomy is indicated.

(1) Spinal pantocaine anesthesia has given us the best operative and postoperative results. Complete relaxation is essential.

(2) A wide transverse incision (Fig. 11), including both recti, provides by far the best approach. We believe a left split rectus fails in the majority of cases to give adequate exposure.

(3) A wide division of the gastrocolic omentum (Fig. 12) exposes the entire pancreas to inspection and palpation—head, body and tail.

(4) The typical gross appearance of the adenoma (Fig. 13) is characterized by a purplish-pink nodule 1 to 2 cm. in diameter, usually standing out distinctly from the whiter pancreatic tissue, and covered with fine vessels which bleed easily, but are readily ligated. The adenoma is usually encapsulated, and is shelled out without difficulty after the small vessels have been ligated with the finest of silk ligatures.

(5) If one adenoma is discovered, search should be made for others. If no adenoma or adenomata are seen on the anterior surface, the pancreas should be mobilized by incising its inferior peritoneal attachment and gently elevated, inspected and palpated on its posterior aspect. Hemorrhage is most apt to occur around the head.

(6) Adenomata are most frequently found in the tail and body, and should be looked for in these areas first.

(7) If no adenoma or adenomata can be seen or felt, the next most effective measure is the removal of at least two-thirds of the pancreas—that is, the tail and body—leaving the portion of the head in the curvature of the duodenum. Doctor Thomason in a personal communication says that in his operation he followed the suggestion of Dr. Emil Holman, of San Francisco, who stated that if he had another case to do he would ligate the splenic artery, because of the difficulty in dealing with the bleeding of its branches going into the pancreas. Doctor Thomason did this, which of course necessitated a splenectomy as well, but the ligation of the splenic artery rendered the operation practically bloodless, and the mechanical features were greatly simplified. He removed the tail and body, excising the pancreas with a Percy cautery, searing the end very thoroughly. A Penrose drain was used, but there was no discharge and the patient made an absolutely uninterrupted recovery with primary wound healing.

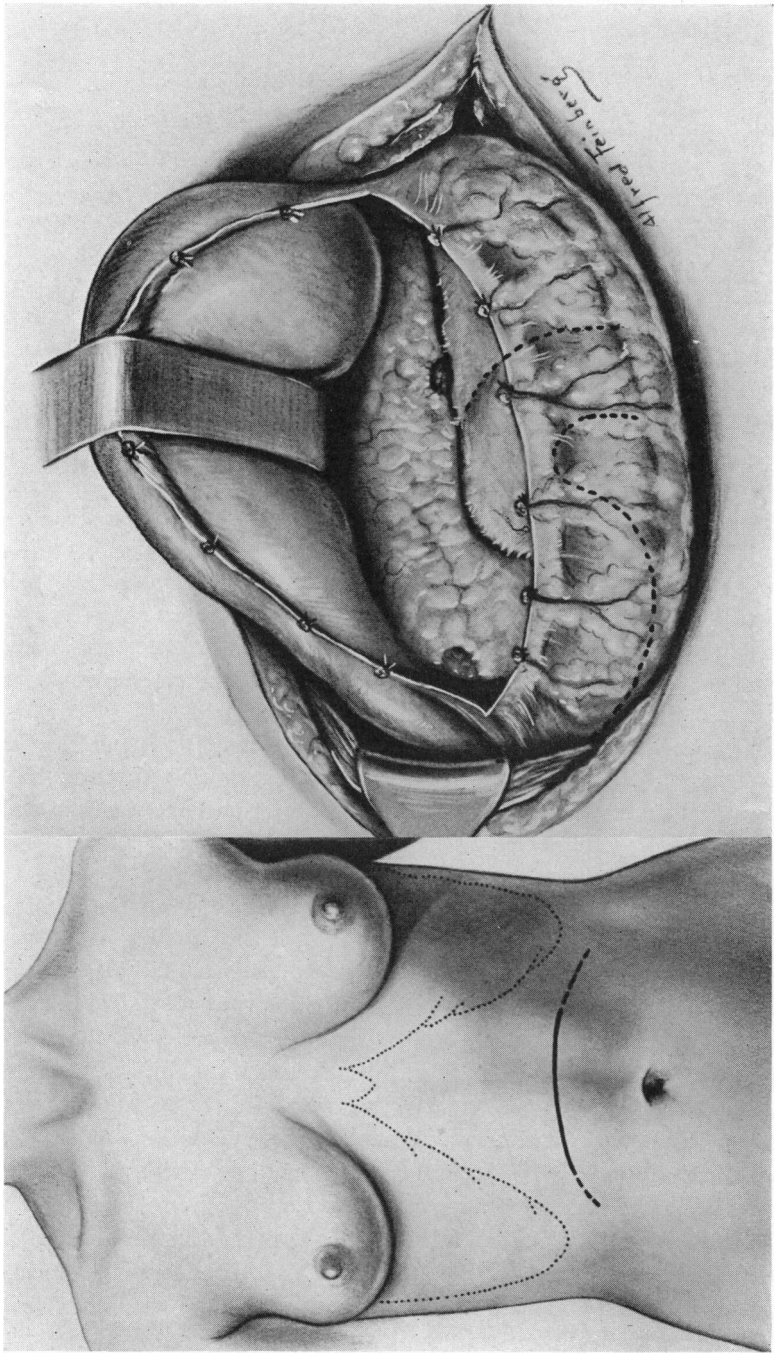

FIG. 11.—The site and type of transverse incision used in exploring a tumor of the pancreas.

FIG. 12.—Exposure of the lesser sac, with head, body and tail visualized by incising through gastrocolic omentum.

(8) A drain should be placed down to the bed of the pancreas, if the organ is resected, to provide for oozing or a leakage of pancreatic juice. As a rule, the site of an enucleated adenoma does not have to be drained.

(9) Silk technic, using the finest grade of silk for ligatures of small vessels and a slightly heavier grade for the larger vessels and the rectus sheaths, has given us perfect wound repair.

The test of any therapy is the final result. In the reported cases, including the six of our own, there have been no fatalities. All of the patients from whom adenomata have been removed have been cured their hypoglycemia. In the cases treated medically there has been no proof that the hypoglycemia was due to adenoma of the islet cells. Because of the deep-seated lesions and the important structures involved, the operation should not be attempted by surgons who are not experienced in the anatomy and surgery of the pancreas.

CONCLUSIONS

We have reviewed the study of the pancreas from the viewpoint of its endocrine function, have tabulated the cases of hypoglycemia and of island cell tumor, so far as we have been able to find them reported, have presented our study of eight tumors, and have outlined the surgical therapy of these lesions.

NOTE.—We are indebted to Dr. George F. Laidlaw for countless microscopic preparations with special stains; to Miss Schramm of the Janeway Library for her assistance in obtaining the bibliographic references, and to Dr. Arthur P. Stout for his advice in interpreting the histology.

Since this article has been in press Doctor Laidlaw reports further progress in granule stains as follows: "The tumor cells are filled with fine granules resembling the granulation of normal island cells. As in normal islands, most of the tumor cells resemble the so-called beta cells, with here and there a single cell or a small group of cells resembling an alpha cell." A more detailed study of the histology will appear later.

BIBLIOGRAPHY

[1] Alezais, and Peyron: Adénome langerhansien provenant du pancréas. Compt. rend. de la Soc. de biol., vol. 70, p. 400, 1911.

[2] Allan, F. N.: Glycosuria and Diabetes. Cambridge, Mass., 1913; Studies Concerning Diabetes. J.A.M.A., vol. 63, p. 939, 1914; Hyperinsulinism. Report of Two Cases. Arch. Int. Med., vol. 44, pp. 65–70, 1929; Histological Changes in the Islands of Langerhans in Diabetic Animals. Proc. N. Y. Path. Soc., vol. 14, p. 147, 1914; Carcinoma of Islands of Pancreas with Hyperinsulinism; Case. Proc. Staff Meeting, Mayo Clinic, vol. 2, p. 88, 1927.

[3] Allan, F. N., Boeck, W. C., and Judd, E. S.: Surgical Treatment of Hyperinsulinism. J.A.M.A., vol. 94, p. 1116, 1930.

[4] Alpern, D. E., and Besuglow, W. P.: Beobachtungen über die Hyperfunktion des Inselapparates Bauchspeicheldrüse. Klin. Wchnschr., vol. 7, pp. 586–589, 1928.

[5] Anderson, H. B.: A Tumor of the Adrenal with Fatal Hypoglycemia. Am. Jour. Med. Sci., vol. 180, p. 71, 1930.

[6] Arnozan, X., and Vaillard, L.: Contribution à l'étude du pancréas du lapin; lésions provoquées par la ligature du canal de Wirsung. Arch. de Physiol. Norm. et Path., vol. 3, p. 287, Paris, 1884.

[7] Banting, F. G., and Best, C. H.: Internal Secretion of Pancreas. Jour. Lab. and Clin. Med., vol. 7, pp. 251–266, 1922.

[8] Banting, F. G., Best, C. H., Collip, J. B., Campbell, W. R., and Fletcher, A. A.: Pancreatic Extracts in the Treatment of Diabetes Mellitus. Canad. Med. Assn. Jour., vol. 12, p. 141, 1922.

[9] Banting, F. G., Campbell, W. R., and Fletcher, A. A.: Clinical Experience with Insulin in Diabetes. Brit. Med. Jour., vol. 1, pp. 8–12, 1923.

[10] Barnard, W. G.: A Functioning Tumor of the Islands of Langerhans. Jour. Path. and Bact., vol. 35, pp. 929–932, 1932.

[11] Baron, M.: The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis. Surg., Gynec., and Obst., vol. 31, p. 437, 1920.

[12] Bast, T. H., Schmidt, E. R., and Sevringhaus, E. L.: Pancreatic Tumor with Hypoglycemic Status Epilepticus. Acta chir. Scandinav., vol. 71, p. 82, 1932.

[13] Bensley, R. R.: Studies on the Pancreas of the Guinea Pig. Am. Jour. Anat., vol. 12, p. 297, 1912; Structure and Relationships of the Islets of Langerhans. Harvey Lecture, J. B. Lippincott and Co., 1914–1915.

[14] Bernard, C.: Leçons sur la physiologie et la pathologie du système nerveux, vol. 2, p. 442, 1858.

[15] Bielschowsky, F.: Zur Klinik und Pathologie der Spontan-Hypoglykämie. Klin. Wchnschr., vol. 2, pp. 1492–1494, 1932.

[16] Bloom, W.: A New Type of Granular Cell in the Islets of Langerhans of Man. Anat. Rec., vol. 49, p. 363, 1931.

[17] Boone, J. A.: A Case of Hyperinsulinism without Demonstrable Pancreatic Changes, in an Eleven-year-old Child. New England Jour. Med., vol. 211, pp. 49–53, 1934.

[18] Bowie, D. J.: Cytological Studies of the Islets of Langerhans in a Teleost, Neomaenis Griseus. Anat. Rec., vol. 29, p. 57, 1924.

[19] Boyd, G. L., and Robinson, W. L.: Evidence of Regeneration of Pancreas in Insulin Treated Case of Diabetes. Am. Jour. Path., vol. 1, p. 135, 1925.

[20] Briggs, J. F.: Spontaneous Hypoglycemia. Minnesota Med., vol. 17, p. 526, 1934.

[21] Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands. XVII. The Nervous Control of Insulin Secretion. Am. Jour. Physiol., vol. 74, pp. 291–308, 1925.

[22] Bru, P.: Cancer langerhansien généralisé chez un chien. Rev. méd. chir., des maladies du foie, du pancréas et de la rate, vol. 2, pp. 40–44, 1927.

[23] Büchner, F.: Inselzellenadenom des Pankreas mit Hypoglykämie bei Diabetes. Klin. Wchnschr., vol. 2, pp. 1494–1496, 1932.

[24] R. C. B.: A Case for Sherlock Holmes. Guy's Hosp. Gaz., vol. 45, p. 127, 1931.

[25] Cairns, R. M., and Tanner, S. E.: Adenoma of Islets of Langerhans Associated with Hypoglycemia. Brit. Med. Jour., vol. 1, pp. 8–11, 1933.

[26] Cammidge, P. J.: Chronic Hypoglycemia. Practitioner, vol. 119, p. 102, 1927.

[27] Carr, A. D., Parker, R., Grove, E., Fisher, A. O., and Larrimore, J. W.: Hyperinsulinism from Beta Cell Adenoma of the Pancreas. J.A.M.A., vol. 96, pp. 1363–1367, 1931.

[28] *Cawley, T.: London Med. Jour., vol. 9, p. 286, 1788.

[29] Cecil, R. L.: A Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus. Jour. Exper. Med., vol. 11, p. 266, 1909; Concerning Adenomata Originating from the Islands of Langerhans. Jour. Exper. Med., vol. 13, p. 595, 1911.

[30] Copp, E. F. F., and Barclay, A. J.: The Restoration of Hydropically Degenerated Cells of the Pancreatic Islands in Dogs under Insulin Treatment. Jour. Metab. Res., vol. 4, p. 445, 1923.

[31] Cottalorda, J., and Escarras: Epithelioma langerhansien, Extirpation guérison. Lyon Chir., vol. 30, pp. 248–253, 1933.

[32] Crawford, W. H.: Hypoglycemia with Coma in a Case of Primary Carcinoma of the Liver. Am. Jour. Med. Sci., vol. 181, p. 496, 1931.

[33] Cushing, H.: Lister Memorial Lecture, July, 1930. Lancet, vol. 2, p. 119, 1930.

[34] Derick, C. L., Newton, F. C., Schulz, R. Z., Bowie, M. A., and Pokorny, N. A.: Spontaneous Hyperinsulinism. New England Jour. Med., vol. 208, pp. 293–298, 1933.

[35] de Takats, G.: Correlations of Internal and External Pancreatic Secretion. Arch. Surg., vol. 19, p. 771, 1929; *Ibid.*, p. 775.

[36] de Witt, L. M.: Morphology and Physiology of Areas of Langerhans in Some Vertebrates. Jour. Exper. Med., vol. 8, pp. 193–239, 1906.

[37] Diamare, V.: Studii comparativi sulle isole di Langerhans del pancreas. Jour. Internat. d'Anat., vol. 16, pp. 155–205, 1899; Internat. Monatsschr. f. Anat. u. Physiol., vol. 22, pp. 129–187, 1905.

[38] *Dieckhoff: Beitrag. s. path. Anat. des Pankreas. Festschr. zum 70 Geburtstag Th. Thierfelders. Langkammer, Leipzig, 10 Dez. 1894.

[39] Dubreuil, G., and Anderodias: Ilôts de Langerhans chez un nouveau né, issu de mère glycosurique. Compt. rend. Soc. de biol., vol. 83, p. 1490, 1920.

[40] Elias, H., and Waller, K.: Zur Wiederherstellung der Funktion des Inselapparates nach partieller Pankreas-extirpation. Ztschr. f. d. ges. exp. Med., vol. 74, pp. 81–95, 1930.

[41] Evans, J. A., and McDonough, W.: Hyperinsulinism; Case Reports and Discussion. Jour. Iowa Med. Soc., vol. 23, pp. 454–460, 1933.

[42] Fabozzi, S.: Ueber die Histogenese des primären Krebses des Pankreas. Beitr. z. path. Anat. u. z. allg. Path., vol. 34, pp. 199–214, 1903.

[43] Finney, J. M. J., and Finney, J. M. J., Jr.: Resection of the Pancreas. Tr. Am. Surg. Assn., vol. 46, p. 268, 1928; ANNALS OF SURGERY, vol. 88, pp. 584–592, 1928.

[44] Fletcher, A. A., and Campbell, W. R.: The Blood Sugar Following Insulin Administration and the Symptom Complex—Hypoglycemia. Jour. Metabol. Res., vol. 2, p. 637, 1922.

[45] Frank, H.: Letale Hypoglykämie bei Pankreasadenom. Arch. f. klin. Med., vol. 171, pp. 175–184, 1931.

[46] Gammon, G. D., and Tenery, W. C.: Hypoglycemia; the Clinical Syndrome, Etiology and Treatment; Report of Case Due to Hyperinsulinism. Arch. Int. Med., vol. 47, p. 829, 1931.

[47] Gibbs, C. B. F.: Insulin in Hypoglycemia. New York State Med. Jour., vol. 33, p. 638, 1932.

[48] Graham, E. A., and Hartmann, A. F.: Subtotal Resection of the Pancreas for Hypoglycemia. Surg., Gynec., and Obst., vol. 59, p. 474, 1934.

[49] Graham, E. A., and Womack, N. A.: The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and Other Conditions. Surg., Gynec., and Obst., vol. 56, pp. 728–742, 1933.

[50] Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother. Arch. Path., vol. 1, p. 348, 1926.

[51] Hamdi, H.: Ein insulargenetisches Pancreascarcinom (Insulom). Ztschr. f. Krebsforsch., vol. 37, pp. 411–413, 1932.

[52] Hanseman, D.: Die Beziehungen des Pankreas zum Diabetes. Ztschr. f. klin. Med., vol. 26, pp. 191–224, 1894.

[53] Harris, S.: Hyperinsulinism and Dysinsulinism. J.A.M.A., vol. 83, p. 729, 1924; Hyperinsulinism and Dysinsulinism (Insulogenic Hypoglycemia), with Chronological Review of Cases Reported in U. S. and Canada. Endocrinology, vol. 16, pp. 29–42, 1932; Internat. Clin., vol. 1, pp. 9–29, 1932; Hyperinsulinism, a Definite Disease Entity. J.A.M.A., vol. 101, pp. 1958–1965, 1933; Epilepsy and Narcolepsy Associated with Hyperinsulinism. J.A.M.A., vol. 100, p. 321, 1933; The Diagnosis of Surgical Hyperinsulinism. Southern Surgeon, vol. 3, p. 199, 1934; Nomenclature of the Disorders of Insulin Secretion; Diabetes Mellitus, Hyperinsulinism and Dysinsulinism. Ann. Int. Med., vol. 7, pp. 1084–1100, 1934.

[54] Hartmann, F. L.: Hypoglycemia. Med. Clin. N. Amer., vol. 12, pp. 1035–1046, 1929.
[55] Hédon, M. E.: Contribution a l'étude des fonctions du pancréas. Greffe sous-cutanée du pancréas; ses résultats au point de vue de la théorie du diabète pancréatique. Compt. rend. Soc. de biol., vol. 9, pp. 678–680, s.iv, 1892.
[56] Heiberg, K. A.: Ein Fall von Adenom in den Langerhansschen Inseln der Bauchspeicheldrüse bei einem Diabetiker. Zentralbl. f. allg. Path. u. Path. Anat., vol. 22, p. 532, 1911.
[57] Heinz, T. E., and Palmer, W. L.: A Study of the Effect of Insulin on Gastric Motility. Proc. Soc. Exp. Biol. and Med., vol. 27, pp. 1047–1049, 1930.
[58] Helmholz, H.: An Adenoma of Island of Langerhans. Bull. Johns Hopkins Hosp., vol. 18, p. 185, 1907.
[59] Herxheimer, G.: Weitere Untersuchungen am Pankreas von Diabetikern. Verhandl. d. deutsch. Path. Gessell., vol. 9, p. 263, 1905–1906; Pankreas-Zellinseln und Insulin nach Unterbindung der Ausführungsgänge der Bauchspeicheldrüse. Klin. Wchnschr., vol. 5, pp. 2299–2302, 1926; Ueber Pankreascirrhose (bei Diabetes). Arch. f. path. Anat. u. Phys., vol. 183, p. 228, 1906.
[60] Heyn, L. G.: Hyperinsulinism. J.A.M.A., vol. 98, pp. 1441–1443, 1932.
[61] Hinteregger, F.: Ueber das Verhalten der Spezifischen Zellgranulationen in den Langerhansschen Inselzellen bei Störungen des Kohlehydratstoffwechsels. Beitr. z. path. Anat. u.z.allg. Path., vol. 87, p. 555, 1931.
[62] Holman, E.: Partial Pancreatectomy for Hyperinsulinism. S. Clin. North America, vol. 13, pp. 71–76, 1933.
[63] Holman, E., and Railsback, O. C.: Partial Pancreatectomy in Chronic Spontaneous Hypoglycemia. Surg., Gynec., and Obst., vol. 56, pp. 591–600, 1933.
[64] Homans, J.: The Relation of Islets of Langerhans to the Pancreatic Acini under Various Conditions of Secretory Activity. Proc. Roy. Soc. London, Ser. B., vol. 86, p. 73, 1913; A Study of Experimental Diabetes in the Canine and Its Relation to Human Diabetes. Jour. Med. Res., vol. 33, p. 1, 1915.
[65] Horgan, E. J.: The Histogenesis of Carcinoma in the Islets of the Pancreas. Jour. Lab. and Clin. Med., vol. 5, pp. 429–442, 1920.
[66] Howland, G., Campbell, W. R., Maltby, E. J., and Robinson, W. L.: Dysinsulinism: Convulsions and Coma Due to Islet Cell Tumor of the Pancreas with Operation and Cure. J.A.M.A., vol. 93, pp. 674–679, 1929; Tr. Am. Neurol. Assoc., vol. 55, pp. 551–561, 1929.
[67] Jacobs, S.: Hyperinsulinism. New Orleans Med. and Surg. Jour., vol. 86, pp. 724–726, 1934.
[68] John, H. J.: Hyperinsulinism. Report of a Case. J.A.M.A., vol. 97, pp. 1708–1709, 1931; Med. Clin. North Amer., vol. 17, pp. 979–985, 1934.
[69] Jonas, L.: Hypoglycemia. Med. Clin. North Amer., vol. 8, pp. 949–956, 1924.
[70] Judd, E. S., and Allan, F. N.: Résection du pancréas pour hyperinsulinisme. Arch. franco-belges de Chir., vol. 33, pp. 281–291, 1932.
[71] Judd, E. S., Allan, F. N., Frank, N., Rynearson, E. H.: Hyperinsulinism. J.A.M.A., vol. 101, p. 99, 1933.
[72] Judd, E. S., Faust, L. S., and Dixon, R. K.: Carcinoma of the Islands of Langerhans with Metastases to the Liver Producing Hyperinsulinism. Report of Case. Western Jour. Surg., vol. 42, pp. 555–557, 1934.
[73] Kamimura, N.: Ueber die Bedeutung der Langerhansschen Inseln für den Kohlehydratstoffwechsel. Mitt. med. Fak. d. Univ. zu Tokyo, vol. 17, p. 95, 1917.
[74] Kirkbride, M. B.: The Islands of Langerhans after Ligation of the Pancreatic Ducts. Jour. Exper. Med., vol. 15, p. 101, 1912.
[75] Koch, K.: Ein Adenom aus Inselzellen im Pankreas eines Nicht-diabetikers. Arch. f. path. Anat. u. Phys., vol. 216, p. 25, 1914.

[76] Kraus, E. J.: Die pathologisch-anatomischen Veranderungen des Pankreas beim Diabetes mellitus. Handbuch der speziellen pathologischen Anatomie und Pathologie. Henke und Lubarsch. Pp. 622–747, Julius Springer, Berlin, 1929.

[77] Krause, F.: Hyperinsulinismus mit Hypoglykämischen Symptomkomplex. Klin. Wchnschr., vol. 9, pp. 2346–2349, 1930.

[78] Kühne, W., and Lea, A. S. L.: Beobachtungen ueber die Absonderung des Pankreas. Untersuchungen a. d. physiol. Institute d. Univ. Heidelberg, vol. 2, p. 488, 1882.

[79] Kylin, E.: Erfahrungen mit der Funktionsprobe des Inselapparates nach Depisch-Hasenöhrl. Deutsch. Arch. f. klin. Med., vol. 160, pp. 348–360, 1928.

[80] LaBarre, J.: Sur l'existence d'un insulinémie physiologique. Compt. rend. Soc. de biol., vol. 96, pp. 196–198, 1927.

[81] LaBarre, J., and Destreé, P.: L'influence des variations glycémiques sur la motilité gastrique. Compt. rend. Soc. de biol., vol. 103, pp. 532–534, 1930.

[82] Laguesse, E.: Sur la formation des ilôts de Langerhans dans le pancréas. Compt. rend. Soc. de biol., vol. 45, pp. 819–820, 1893; Structure et Developpement du Pancréas. J. de l'Anat. et de la Physiol., vol. 30, pp. 591–731, 1894; Récherches sur l'histogenie du pancreas chez le mouton. J. de l'Anat. de la Physiol., vol. 32, pp. 171 and 209, 1896; Sur la structure du pancréas chez quelques ophidiens et particulierement sur les ilôts endocrines. Arch. d'Anat. Micr., vol. 4, pp. 157–218, Paris, 1901; Preuve Expérimentale du Balancement dans les Ilôts Endocrines du Pancréas. J. de Physiol. et de path. gén., vol. 13, pp. 5–8, 1911.

[83] Laguesse, E., and de la Roche, A. G.: Les Ilôts de Langerhans dans le Pancréas du Cobaye après ligature. Compt. rend. Soc. de biol., vol. 54, pp. 854–857, 1902.

[84] Lane, M. A.: On the So-called Transitional Cells of Lewaschew in the Islets of Langerhans. Proc. Assn. Am. Anatomists, Am. Jour. Anat., Baltimore, vol. 5, pp. 16–17, 1906; The Cytological Characters of the Areas of Langerhans. Am. Jour. Anat., vol. 7, pp. 409–422, 1908.

[85] Lang, F. J.: Ueber einige Geschwulstbildungen des Pankreas. Arch. f. path. Anat. u. Physiol., vol. 257, p. 235, 1925.

[86] *Langerhans, P.: Beitrage zur mikroskopischen Anat. der Bauchspeicheldrüse. Inaug. Diss. Lange, Berlin, 1869.

[87] Laroche, Guy Lelourdy, and Bussière, J. A.: Un cas d'hypoglycémie spontanée avec accidents nerveux graves. Bull. et mém. Soc. méd. d. hôp. de Paris, vol. 52, p. 375, 1928.

[88] Lecomte, R. M.: Adenomata of the Islands of Langerhans. Jour. Med. Res., vol. 29, p. 251, 1913.

[89] Lemaire, A.: Tumeurs pancréatiques et sécrétion insulinique. Progrès méd., vol. 44, pp. 1205–1211, 1929.

[90] Levi, C.: Hyperfunktion des Inselsystems. München. med. Wchnschr., vol. 80, p. 733, 1933.

[91] Lewaschew, S. W.: Ueber eine eigentümliche Veränderung der Pankreaszellen warmblütiger Thiere bei starkes Absonderungsthätigkeit der Drüse. Arch. für. mikr. Anat. u. Entwichlungsgesch., vol. 26, p. 453, Bonn, 1886.

[92] Lloyd, P. C.: A Case of Hypophyseal Tumor with Associated Tumor-like Enlargement of Parathyroids and Islands of Langerhans. Bull. Johns Hopkins Hosp., vol. 45, p. 1, 1929.

[93] Love, J.: Dysinsulinism. A Discussion and Case Report. J.A.M.A., vol. 100, p. 814, 1933.

[94] MacBrayer, R.: Personal communication to the author—Russell M. Wilder, Internat. Clin., vol. 2, 1933.

[95] MacCallum, W. G.: Hypertrophy of the Islands of Langerhans in Diabetes Mellitus. Am. Jour. Med. Sci., vol. 133, p. 432, 1907; The Internal Secretion of the Pancreas. J.A.M.A., vol. 56, p. 655, 1911.

[96] McClenahan, W. U., and Norris, G. W.: Adenoma of the Islands of Langerhans with Associated Hypoglycemia. Am. Jour. Med. Sci., vol. 177, pp. 93–97, 1929.

[97] McGovern, B. E.: Epileptoid Attacks and Hyperinsulinism. Endocrinology, vol. 30, pp. 339–343, 1932.

[98] Marsh, H. E.: Hyperinsulinism, with Report of Cases. Wisconsin Med. Jour., vol. 30, pp. 339–343, 1931.

[99] Martin, W. B.: Neutral Stains as Applied to the Granules of the Pancreatic Islet Cells. Anat. Rec., vol. 9, p. 475, 1915; Experimental Studies in Diabetes. Series III. 2. Granule Stains of the Islands of Langerhans of the Diabetic and Non-diabetic Pancreas. Jour. Metab. Res., vol. 1, p. 43, 1922.

[100] Massa, M.: Stati ipoglicemici ed iperinsulinismo. Gior. di clin. med., vol. 10, pp. 679–721, 1929.

[101] Mathias: Adenomartige Inselwucherungen in der Wandung einer Pankreas-cyste. Med. Klin., vol. 24, p. 1814, 1928.

[102] Mattioli, M.: Sull'iperinsulinismo e sua azione sugli organi a secrezione interna. Morgagni, vol. 75, pp. 611–616, 1933.

[103] von Mering, J., and Minkowski, O.: Diabetes mellitus nach Pankreasextirpation. Arch. f. exper. Path. u. Pharmacol., vol. 26, p. 371, 1890.

[104] Moore, H., O'Farrell, W. R., Malley, L. K., and Moriarty, M. A.: Acute Spontaneous Hypoglycemia. Brit. Med. Jour., vol. 2, p. 837, 1931.

[105] Morse, M. E.: Two Adenomata of the Islands of Langerhans. J.A.M.A., vol. 51, p. 1075, 1908.

[106] Mouzon, J.: La Pancréatectomie Partielle dans le Traitement des États d'Hyperinsulinisme. Presse méd., vol. 38, pp. 1157–1161, 1930.

[107] Minkowski, O.: Weitere Mittheilungen ueber den Diabetes Mellitus nach Extirpation des Pankreas. Berl. klin. Wchnschr., vol. 29, p. 90, 1892.

[108] Natali, C.: Sugli adenomi insulari del pancreas. Tumori, vol. 14, p. 244, 1928.

[109] Nicholls, A. G.: Simple Adenoma of the Pancreas Arising from an Island of Langerhans. Jour. Med. Res., vol. 8, p. 385, 1902.

[110] Nielsen, J. M., and Eggleston, E. L.: Functional Dysinsulinism with Epileptiform Seizures; Treatment. J.A.M.A., vol. 94, pp. 860–863, 1930; Functional Dysinsulinism with Epileptiform Seizures; Treatment. Bull. Battle Creek Sanitarium & Hosp. Clin., vol. 26, pp. 88–94, 1931.

[111] Nuboer, J. F.: Hypertrophie der Langerhansschen Inseln. Zentralbl. f. allg. Path., vol. 34, p. 595, 1924.

[112] O'Leary, J.: An Experimental Study of the Islet Cells of the Pancreas in Vivo. Anat. Rec., vol. 45, p. 27, 1930.

[113] O'Leary, J. L., and Womack, N.: Adenoma of Islands of Langerhans. Histology. Arch. Path., vol. 17, pp. 291–310, 1934.

[114] Opie, E. L.: The Histology of the Islands of Langerhans. Bull. Johns Hopkins Hosp., vol. 11, p. 205, Baltimore, 1900; The Relation of Diabetes Mellitus to Lesions of the Pancreas. Hyaline Degeneration of the Islands of Langerhans. Jour. Exper. Med., vol. 5, p. 527, 1901; On the Relation of Chronic Interstitial Pancreatitis to the Islands of Langerhans and to Diabetes Mellitus. Jour. Exper. Med., vol. 5, p. 397, 1901; Cytology of the Pancreas. Special Cytology, Cowdry, vol. 1, p. 375; Disease of the Pancreas, Lippincott, Philadelphia, 1903.

[115] Parker, J. T., and Finley, C. S.: Some Results Obtained by the Treatment of Nervous Phenomena with Glucose. Proc. Soc. Exper. Biol. & Med., vol. 21, p. 517, 1923–1924.

[116] Phillips, A. W.: Hypoglycemia with Hypertrophy of Islands of Langerhans. J.A.M.A., vol. 96, p. 1195, 1931.

[117] Pribram, E.: Chronic Glycopenia. J.A.M.A., vol. 90, pp. 2001–2002, 1928.

[118] Priesel, A.: Beiträge zur Pathologie der Bauchspeicheldrüse. Frankfurt. Ztschr. f. Path., vol. 26, p. 453, 1922.

[119] Quigley, J. P., Johnson, V., and Solomon, E. I.: Action of Insulin on the Motility of the Gastrointestinal Tract. I. Action on the Stomach of Normal Fasting Man. Am. Jour. Physiol., vol. 90, pp. 89–98, 1929.

[120] Rabinovitch, J., and Barden, F. W.: Hypoglycemia Associated with a Tumor of the Islands of Langerhans and with Adrenal Insufficiency Respectively. Am. Jour. Med. Sci., vol. 184, p. 494, 1932.

[121] Rathery, F., Froment, P., Derot, M., and Jammet, M. L.: Hyperinsulinisme spontané post diabetique. Bull. Acad. de Med., vol. 111, pp. 38–42, Paris, 1934.

[122] Ravid, J. M.: Transient Insulin Hypoglycemic Hemiplegias. Am. Jour. Med. Sci., vol. 175, p. 756, 1928.

[123] Reitman, K.: Beiträge sur Pathologie der menschlichen Bauchspeicheldrüse. Ztschr. f. Heilk., vol. 26, p. 1, 1905.

[124] Rennie, J.: On the Occurrence of a "Principal Islet" in the Pancreas of Teleostei. Jour. Anat. and Physiol., vol. 37, p. 375, 1902–1903; The Epithelial Islets of the Pancreas in Teleostei. Qt. Jour. Micros. Sci., vol. 48, p. 379, 1905.

[125] Rienhoff, Wm. F., Jr., and Lewis, D.: Surgical Affections of the Pancreas Met with in the Johns Hopkins Hospital from 1889 to 1932, Including a Report of a Case of an Adenoma of the Islands of Langerhans, and a Case of Pancreatolithiasis. Bull. Johns Hopkins Hosp., vol. 54, pp. 386–429, 1934.

[126] Roffo et Correa: Présence dans les tumeurs malignes d'une subtance analogue à l'insuline. Prensa med. Argent. 20 dec., p. 668, 1926.

[127] Rollett, H.: Ueber ein reines Adenoma des Pankreas. Frankfurt. Ztschr. f. Path., vol. 10, p. 268, 1912.

[128] Rosenfeld, G.: Ein eigenartiger Fall von Hyperinsulinismus. Monatschr. f. Kinderh., vol. 57, pp. 269–275, 1933.

[129] Ross, L. I., and Tomasch, J. M.: Hyperinsulinemia Secondary to an Adenoma of the Pancreas. Arch. Surg., vol. 28, pp. 224–231, 1934.

[130] Rowntree, L. G.: Hyper-Parathyroidism; Hyper-Insulinism; Addison's Disease. Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North Amer. (1930), vol. 6, pp. 482–488, 1931.

[131] Rynearson, E. H., and Moersch, F. P.: Neurologic Manifestations of Hyperinsulinism and Other Hypoglycemic States. J.A.M.A., vol. 103, pp. 1196–1199, 1934.

[132] Sauerbeck, E.: Die Langerhansschen Inseln des Pancreas und ihre Beziehung zum Diabetes mellitus. Ergbn. der allg. Path. u. Path. Anat., Abth 2, pp. 538–679, 1902; Neue experimente zur Frage nach der Bedeutung der Langerhansschen Inseln. Verhandl. deutsch. path. Gessellsch., vol. 8, p. 217, 1904.

[133] Schäfer, E. A.: Internal Secretions. Lancet, vol. 2, p. 321, 1895.

[134] Schneider, H.: Contribution a l'étude de l'adenome langerhansien (Insulome). Rev. med. de la Suisse Rom., vol. 44, p. 222, 1924.

[135] Schulze, W.: Die Bedeutung der Langerhansschen Inseln in Pankreas. Arch. f. Miks. Anat. u. Entwick., vol. 56, pp. 491–504, 1900.

[136] Sendrail, M., and Planques, J.: Les états hypoglycémiques. Gaz. d. hôp., vol. 100, pp. 1105 and 1137, 1927.

[137] Shih-Hao, Liu, and Hsiao-Chien, Chang: Hypoglycemia. Report of a Case Unassociated with Insulin Administration. Arch. Int. Med., vol. 36, pp. 146–148, 1925.

[138] Sigwald, J.: L'hypoglycémie. Paris, Gaston Doin et Cie, p. 320, 1932.

[139] Simon, H. E.: Surgery in the Treatment of Hyperinsulinism. Southern Surgeon, vol. 3, p. 211, 1934.

[140] Sippe, C., and Bostock, J.: Hypoglycemia. Med. Jour. Australia, vol. 20, pp. 207–218, 1933.

[141] Sjögren, T., and Tillgren, J.: On Peculiar States of Confusion in Insulinism. Acta med. Scandinav., vol. 65, pp. 684–698, 1927.

[142] Smith, M. G., and Seibel, M. G.: Tumors of the Islands of Langerhans and Hypoglycemia. Am. Jour. Path., vol. 7, pp. 723–739, 1931.

[143] Ssobolew, L. W.: Ueber die Structur der Bauchspeicheldrüse unter gewissen pathologischen Bedingungen. Zentralbl. f. allg. Path. u. path. Anat., vol. 11, p. 202, 1900; Zur normalen und pathologischen Morphologie der inneren Secretion der Bauchspeicheldrüse. Virchow's Arch. f. path. Anat., vol. 168, pp. 91–128, 1902; Ueber die Struma die Langerhansschen Inseln der Bauchspeicheldrüse. Virchow's Arch. f. path. Anat., vol. 177, p. 123 (supp.), 1904.

[144] Stenström, T.: Einige Beobachtungen von "spontaner" hypoglykämischer Reaktion beim Menschen. Acta med. Scandinav., vol. 25, pp. 170–186, 1927.

[145] Stief, S.: Spontaneous Hyperinsulinism. Riv. di pat. nerv., vol. 39, pp. 139–144, 1932; also Orvosi hetil., vol. 76, pp. 355–356, 1932.

[146] Tarsitano, A.: Iperinsulinismo. Morgagni, vol. 73, pp. 1035–1043, 1931.

[147] Tedstrom, M. K.: Hypoglycemia and Hyperinsulinism. Ann. Int. Med., vol. 7, pp. 1013–1025, 1934.

[148] Terbrüggen, A.: Anatomische Befunde bei spontaner Hypoglykämie infolge multipler Pankreasinseladenome. Beitr. z. path. Anat. u. z. allg. Path., vol. 88, pp. 37–50, 1931; Ueber Diabetes Mellitus, Inselregeneration und Inseladenome. München. med. Wchnschr., vol. 80, p. 1705, 1933.

[149] Terbrüggen, A., and Heinlein, H.: Hypoglykämie nach experimentelle Röntgenbestrahlung des Pankreas. Klin. Wchnschr., vol. 11, pp. 1139–1142, 1932.

[150] Thalhimer, W., and Murphy, F. D.: Carcinoma of the Islands of the Pancreas; Hyperinsulinism and Hypoglycemia. J.A.M.A., vol. 91, pp. 89–91, 1928.

[151] Thiroloix: Données experimentales pouvant servir à éclairir la pathogénie du diabète sucré. Gaz. d. hôp., vol. 11, p. 142, 1894.

[152] Tomkies, J. S.: Adenoma of Islet Cells of Pancreas with Hyperinsulinism, Hypoglycemia, Operation and Recovery. Texas State Jour. Med., vol. 28, p. 523, 1932.

[153] Troisier, J., and Casaubon, R. A.: L'hypoglycémie et la saccarocorie dans la pancréatite traumatique avec pseudo-kyste formation. Soc. med. d. hôp. Paris, vol. 52, p. 357, 1928.

[154] Valenzuela, Oyama: Hipercrinia insular. Med. ibera, vol. 2, pp. 555–559, 1931.

[155] Wagner, R., and Parnas, J. K.: Ueber eine eigennartige Störung des Kohlenhydratstoffwechsels und ihr Beziehungen zum Diabetes mellitus. Ztschr. f. d. ges. exper. Med., vol. 25, pp. 361–384, 1921.

[156] Warren, S.: Adenomas of Islands of Langerhans. Am. Jour. Path., vol. 2, pp. 335–340, 1926.

[157] Waters, W. C., Jr.: Spontaneous Hypoglycemia; the Rôle of Diet in Etiology and Treatment. Southern Med. Jour., vol. 24, pp. 249–252, 1931.

[158] Wauchope, G. M.: Critical Review. Hypoglycemia. Qt. Jour. Med., vol. 2, pp. 117, 1933.

[159] Weichselbaum, A., and Stangl, E.: Ueber der Veränderungen des Pankreas bei Diabetes Mellitus. Wien. klin. Wchnschr., vol. 15, p. 969, 1902.

[160] Weil, C.: Functional Hyperinsulinism; Epileptiform Convulsions Accompanying Spontaneous Hypoglycemia. Internat. Clin., vol. 4, pp. 33–50, 1932.

[161] Whipple, A. O.: The Therapy of Chronic Hypoglycemia. Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North Amer., October, 1934. (Still in press.)

[162] Wilder, R. M.: Tumor der Langerhansschen Inseln mit Hyperinsulinismus. Verhandl. d. deutsch. Gesellsch f. inn. Med., Kong. 40, pp. 223–228, 1928; Hyperinsulinism (Colver Lecture). Internat. Clin., vol. 2, pp. 1–18, 1933.

[163] Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia. J.A.M.A., vol. 89, pp. 348–355, 1927.

[164] Winans, H. M.: Hypoglycemic Convulsions with Hypoplasia of Pancreas. Am. Jour. Med. Sci., vol. 185, p. 500, 1933; Chronic Hypoglycemia. Southern Med. Jour., vol. 23, pp. 402–406, 1930.

[165] Wolf, A., Hare, C. C., and Riggs, H. W.: Neurological Manifestations in Two Patients with Spontaneous Hypoglycemia; with Necropsy Report of a Case of Pancreatic Island Adenomata. Bull. Neurol. Inst., vol. 3, p. 232, 1933.

[166] Womack, N. A.: Adenoma of Islands of Langerhans. Southern Med. Jour., vol. 27, pp. 135–139, 1934.

[167] Womack, N. A., Gnagi, W. B., and Graham, E. A.: Adenoma of the Islands of Langerhans with Hypoglycemia. J.A.M.A., vol. 97, p. 831, 1931.

[168] Zeckwer. I.: Hypoglycemia in Diabetes Associated with Obstruction of Pancreatic Duct. Arch. Int. Med., vol. 54, p. 330, 1934.

[169] Ziskind, E.: Hyperinsulinism; Report of Case of Spontaneous Hypoglycemia with Studies in Dextrose Tolerance. Arch. Int. Med., vol. 52, pp. 76–85, 1933.

* These references were not available.