

CARCINOMA OF THE PANCREAS*

I. A CLINICAL AND PATHOLOGIC STUDY OF 609 NECROPSIED CASES

II. THE RELATION OF CARCINOMA OF THE PANCREAS TO DIABETES MELLITUS

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This study includes all of the cases of carcinoma of the pancreas in the necropsy records of the Department of Pathology at the University of Minnesota from January 1, 1911, through December 31, 1954. The records comprise 46,847 males and 26,340 females (Table I).

During the period 1911 to 1954, protocols and gross specimens of practically all necropsies performed in the Twin City area (Minneapolis and St. Paul) were filed in the Department of Pathology. Contributors included all the private hospitals and the large municipal hospitals of Minneapolis and St. Paul, the University Hospitals, the Coroner's service of Hennepin County, and, in recent years, the Veterans Administration Hospital at Minneapolis. During the last decade the number of necropsies was much greater than in earlier years. During the 4-year period 1949 to 1952, the number of necropsies was equal to about one third of the deaths in males and about one fourth of the deaths in females in the Twin City area. This is a large, widely distributed sample, and at least in recent years it is probably fairly representative of the diseases in this locality. Certainly such a large necropsy sample gives a more accurate estimate of the incidence of carcinoma of the pancreas than that based upon death certificates, since the clinical diagnosis of this neoplasm is often uncertain.

Only primary carcinomas of the pancreas are tabulated. Carcinomas arising in the papilla of Vater or the extrapancreatic portions of the bile ducts are excluded. Also omitted are a few cases in which the pathologist was unable to exclude a primary source outside the pancreas. The carcinoma was an accidental necropsy finding in two cases; in all others it was the major cause of death.

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Frequency

Carcinoma of the pancreas was found in 0.91 per cent of all the males, and in 1.23 per cent of those over 40 years of age (Table I). It was somewhat less frequent in females, occurring in 0.70 per cent of the entire group and in 1.10 per cent of those over 40 years of age (Table I).

Age Incidence. In males, 97 per cent of carcinomas of the pancreas occurred in subjects over 40 years of age. The youngest male was 27 years old. The tumor increased in frequency with advancing age, reaching a maximum in the eighth decade (Table I). In females, 98 per cent of the tumors occurred in subjects over 40 years of age, but there was no increase in frequency with advancing age as in males. The youngest female was 27 years old (Table I). Several

TABLE I
Incidence of Carcinoma of the Pancreas in Necropsies

Decades	Males			Females		
	Total necropsies	Carcinoma of pancreas		Total necropsies	Carcinoma of pancreas	
		No.	%		No.	%
0- 10 yrs.	6,815	0	0.00	4,793	0	0.00
10- 20 yrs.	1,173	0	0.00	962	0	0.00
20- 30 yrs.	2,125	1	0.05	1,843	1	0.05
30- 40 yrs.	3,367	14	0.42	2,211	2	0.09
40- 50 yrs.	5,616	40	0.71	2,950	12	0.41
50- 60 yrs.	8,590	82	0.95	3,748	48	1.28
60- 70 yrs.	9,441	140	1.48	4,246	52	1.22
70- 80 yrs.	6,969	120	1.72	3,786	52	1.37
80-100 yrs.	2,751	27	0.98	1,801	18	1.00
Total	46,847	424	0.91	26,340	185	0.70
40-100 yrs.	33,367	409	1.23	16,531	182	1.10

reports mention a case in the third decade. Corner¹ described a primary carcinoma of the pancreas in an infant 7 months old, and stated that he found reports of five cases in children. Grant and Perceval² reported a carcinoma of the pancreas in a girl 16 years of age. The disease is evidently rare before the age of 30 years.

Sex Incidence. In our necropsy records there were 424 males and 185 females, but there were about twice as many adult males as adult females in the necropsy population. When computed on a percentage basis, the preponderance in males was only about 15 per cent.

In necropsy statistics from other sources there are usually over twice as many males as females, but the authors do not give the proportion of males to females in the necropsy population from which their statistics are derived. In clinical reports, males usually predominate in a ratio of about 2 to 1; but the diagnosis is commonly based on necropsy findings and is subject to the same error.

The Increase in Carcinoma of the Pancreas. Since over 85 per cent of all cancer deaths and over 97 per cent of all deaths from carcinoma of the pancreas occur after the age of 40 years, a more accurate estimate is obtained by tabulating the subjects over 40 years of age as in Table II. The incidence of carcinoma of the pancreas in males over 40 years old at death increased from 0.98 per cent in the 35-year period, 1911 to 1944, to 1.57 per cent in the 10-year period, 1945 to 1954. This represents an increase of 60 per cent. During these corresponding periods, deaths from all malignant neoplasms in males

TABLE II
Incidence of Fatal Neoplasms and Carcinoma of Pancreas for Two Periods

Males over 40 years of age					
Period	Total necropsies	Fatal neoplasms		Carcinoma of pancreas	
		No. of cases	Percentage of total necropsies	Percentage of total necropsies	Percentage of fatal neoplasms
1911-1944	19,526	3,827	19.60	0.98	5.00
1945-1954	13,841	3,651	26.38	1.57	6.00
1911-1954	33,367	7,478	22.41	1.23	5.49
Females over 40 years of age					
1911-1944	9,139	2,211	24.20	1.03	4.25
1945-1954	7,392	2,013	27.23	1.19	4.37
1911-1954	16,531	4,224	25.55	1.10	4.31

over 40 years old advanced from 19.60 per cent to 26.38 per cent, an increase of about 35 per cent (Table II). This relatively greater increase of carcinoma of the pancreas is indicated by the fact that it comprised about 5 per cent of the fatal neoplasms in the period 1911 to 1944 and 6 per cent during the period 1945 to 1954 (Table II). The increased frequency of fatal neoplasms in males in recent years is due to the decreased number of deaths from infectious diseases and the increased number of very old men in the community. Carcinoma of the pancreas has its maximum incidence in males in the eighth decade, and two thirds of its victims are over 60 years of age.

It is not surprising, therefore, that it now comprises a larger percentage of fatal neoplasms than it did formerly.

In females over 40 years of age fatal neoplasms have increased only 12.5 per cent in the two periods mentioned (Table II), about one third of the increase noted in males. This phenomenon is probably due to the fact that cancer is more common in women than in men under 50 years of age, and less frequent in women than in men thereafter. The increasing age of the population, therefore, has less effect on the incidence of cancer in females. Carcinoma of the pancreas has increased about the same as other fatal neoplasms, and it comprises about the same percentage of fatal neoplasms in the two periods (Table II).

Macroscopic Types of Carcinoma of the Pancreas

On the basis of the gross structure, four types of carcinoma may be recognized: carcinoma of the head, of the body, of the tail, and a diffuse form. The separation of the several types is somewhat arbitrary. In this discussion, carcinoma of the head includes all cases with massive involvement of the head with or without extension into the rest of the gland. It also includes all small tumors restricted to the head. Carcinoma of the body refers to cases in which the head is free of gross tumor and the growth occupies the body alone or the body and the tail. Carcinoma of the tail includes all cases in which the only gross tumor is in the tail. The diffuse type refers to those with multiple nodules throughout the gland without complete replacement of any segment. It is obvious that there may be gross invasion or compression of the common bile duct in carcinoma of the head and in diffuse carcinoma; but in carcinoma of the body or tail, obstruction of the duct can be accomplished only by extension or metastases. One would anticipate, therefore, that jaundice would be absent or delayed in carcinomas of the body or tail, and that small tumor masses in the head would not necessarily cause jaundice. On the basis of the above definitions, the 609 carcinomas were grouped as follows: Carcinoma of the head, 360 cases, 59.1 per cent; of the body, 111 cases, 18.2 per cent; of the tail, 45 cases, 7.4 per cent; and the diffuse type, 93 cases, 15.3 per cent. The reports of various observers are in agreement that about two thirds of the cancers involve the head. Minor discrepancies are due to differences in the number classified as diffuse.

The four gross anatomical types of carcinoma of the pancreas will now be analyzed with respect to their clinical features. The over-all

ratio of males to females is about 7 to 3, and this ratio obtains roughly for the four groups. There is no evident sex predisposition to any type.

Duration of Symptoms

The duration of symptoms is by no means an accurate measure of the length of time a neoplasm has been present. Symptoms commonly do not develop until the tumor obstructs the common bile duct or extends beyond the pancreas by infiltration or metastases. The occasional finding of an asymptomatic carcinoma at necropsy indicates that there is an asymptomatic early stage, but we do not know its duration. It appears highly probable that many cancers are present a long time before the appearance of pain or jaundice. This consideration should be kept in mind in determining the relation between pancreatic carcinoma and diabetes mellitus.

Our 547 cases in which the duration of symptoms was known are shown in Table III. Broadbent and Kerman,³ as well as Silver and Lubliner,⁴ found a much longer duration of symptoms in carcinomas of the body and tail than in carcinomas of the head, but Duff⁵ found about the same average duration in the two groups. Our data (Table

TABLE III
*Duration of Clinical Symptoms for the Four Anatomical Types
of Carcinoma of the Pancreas (547 Cases)*

Duration of symptoms	Head	Body	Tail	Diffuse
With known duration, 547	331	95	38	83
o to 3 months	77	18	10	21
3 to 6 months	86	26	10	21
6 to 12 months	108	35	15	24
1 to 2 years	42	10	1	13
2 to 5 years	18	6	2	4
Unknown duration	29	16	7	10

III) show no significant differences in the duration of symptoms in the four groups. The duration varied from 1 month to 5 years. About one half of the patients died within 6 months after the appearance of the first symptom; and 17.5 per cent survived over 1 year. In those who survived over 2 years there may be inaccuracies in determining the time of onset, since some cases were complicated by the presence of gallstones.

Initial Symptoms

We are concerned here only with the initial or presenting symptoms and not with the late manifestations of the neoplasm. The frequency with which the various symptoms and signs appeared at the onset

of the illness is shown in Table IV, with respect to the four gross anatomical types. More than one symptom was usually present initially.

TABLE IV
Initial Symptoms in Carcinoma of the Pancreas with Respect to the Four Anatomical Types

	Anatomical type				Total	
	Head	Body	Tail	Diffuse	No.	Per cent
No. of cases analyzed	333	107	43	90	573	100.0
Abdominal pain or distress	183	61	22	55	321	56.0
Jaundice	142	2	0	13	157	27.4
Nausea and vomiting	49	9	3	11	72	12.6
Anorexia	47	13	8	7	75	13.1
Weakness	42	9	5	3	59	10.3
Loss of weight	19	10	6	11	46	8.0
Constipation	13	4	2	6	25	4.4
Diarrhea	23	8	1	3	35	6.1
Backache	12	10	2	1	25	4.4
Belching	7	1	1	2	11	1.9
Fever	4	0	1	1	6	1.0
Enlarged abdomen	6	10	3	6	25	4.4
Pulmonary metastases	4	2	1	2	9	1.6
Metastases to bone	0	3	0	3	6	1.0
Metastases to brain or spinal cord	0	1	3	2	6	1.0
Metastases to peripheral lymph nodes	4	1	0	1	6	1.0
Thrombophlebitis	3	1	2	3	9	1.6

TABLE V
The Incidence of Jaundice in the Four Anatomical Types of Carcinoma of the Pancreas

Site	No. of cases analyzed	Jaundice present at onset		Jaundice appeared later		Painless jaundice		No jaundice	
		No.	%	No.	%	No.	%	No.	%
Head	339	142	41.9	137	40.4	78	23.0	60	17.7
Body	109	2		19		0		88	80.7
Tail	45	0		7		0		38	84.4
Diffuse	92	13		38		2		41	44.7
Total	585	157	26.8	201	34.4	80	13.7	227	38.8

Abdominal Pain or Discomfort. This is the most frequent initial symptom in all four types of pancreatic carcinoma. It varies in intensity from a feeling of abdominal discomfort to a severe boring pain. It is most often located in the epigastric region but may be

felt in either hypochondriac region or in the lower abdomen. It is often described as deeply placed. In our 573 cases with adequate history, abdominal pain was an initial symptom in 56 per cent, and its frequency was about the same in the four anatomical types. In the later stages of the disease this symptom is present in a much higher percentage of the patients. A number of observers reported abdominal pain as an initial symptom in 50 per cent or more of their patients (Duff,⁵ Country and Foulk,⁶ Brown *et al.*,⁷ Smith and Albright,⁸ Berk,⁹ Sanders and McBurney¹⁰).

Jaundice. The occurrence of jaundice is shown in detail in Table V. It was present initially in 41.9 per cent of carcinomas of the head, and developed later in an additional 40.4 per cent. In one sixth of the carcinomas of the head, jaundice never developed. In 78 cases (23 per cent) there was a painless jaundice at the onset of the disease. In 109 cases of carcinoma of the body of the pancreas, jaundice was present initially in two and developed later in 19. In 80.7 per cent there was no jaundice at any time. No case of carcinoma of the tail showed an initial jaundice and in 84.4 per cent jaundice never appeared. In the diffuse type, 13 of 92 cases showed an initial jaundice and 38 developed jaundice later. In the entire group of 585 cases, jaundice was an initial symptom in 26.8 per cent and appeared later in 34.4 per cent. There was no jaundice at any time in 38.8 per cent. Painless jaundice was an initial symptom in 23 per cent of carcinomas of the head and in 13.7 per cent of the entire group. In collected statistics Berk⁹ found painless jaundice to be an initial symptom in 17.4 per cent of pancreatic carcinomas. An onset of jaundice with pain is just as frequent as painless jaundice.

In carcinomas of the head, jaundice is clearly due to invasion or compression of the common bile duct. Those cases without jaundice had smaller tumors that did not destroy the entire head of the gland. In a few cases of carcinoma of the body or tail, jaundice appeared late in the disease without gross involvement of the head. Kaplan and Angrist¹¹ have shown that this jaundice is also obstructive in origin, being due to small metastases about the bile duct. It does not seem to be due to destruction of the liver, since there are a number of cases in this series with massive metastases in the liver without jaundice.

Other Initial Symptoms. Anorexia, nausea and vomiting were frequent early symptoms. Weakness and loss of weight often occurred several months before any other symptoms were noted. Constipation was noted as an initial symptom in 25 cases (4.4 per cent). This low incidence is probably due to incomplete clinical records since Thomp-

son and Rodgers¹² found constipation at the onset in 36 per cent, Brown *et al.*⁷ in 45 per cent, and Berk⁹ in 38.7 per cent.

Diarrhea was an outstanding initial symptom in 35 patients (6.1 per cent). Thompson and Rodgers¹² found an initial diarrhea in 15 per cent; Dashiell and Palmer,¹³ in 20 per cent; and Berk,⁹ in 10.8 per cent. The stool was usually described as watery and foul-smelling, but occasionally it was bulky and fatty and considered as typical of steatorrhea. Fatty stools are presumably due to destruction of the acinar tissue of the pancreas. Cantor and Haking¹⁴ reported a patient with intractable watery diarrhea who presented the roentgen pattern in the intestines of non-tropical sprue.

Fever was an initial symptom in only 6 cases (1 per cent). The patient first consulted a physician because of enlargement of the abdomen in 25 instances (4.4 per cent). The enlargement was due to ascites, a large liver, or to the pancreatic carcinoma.

There were 27 patients in whom the initial symptoms were due to distant metastases (4.6 per cent). In nine patients the presenting symptoms were cough, dyspnea, and hemoptysis resulting from extensive pulmonary metastases. In six subjects severe bone pain called attention to metastases which were then demonstrated by roentgen examination. The primary sites of the neoplasm were not known at that time. In five subjects the first sign was enlargement of cervical lymph nodes; and in one patient enlarged inguinal nodes, which proved to be metastatic carcinoma on biopsy. In six cases the disease began with signs of a tumor of the brain or spinal cord, which later proved to be metastatic from the pancreas.

Venous Thrombosis

In recent years a number of papers have been published which emphasize the frequency of venous thrombosis in association with pancreatic carcinoma. It is stated that venous thrombosis occurs more frequently with pancreatic than with other carcinomas, and some writers believe that venous thrombosis suggests carcinoma of the body or tail of the pancreas.

Phlebothrombosis. It is necessary to distinguish terminal phlebothrombosis from thrombophlebitis. Phlebothrombosis of the veins of the lower extremities is a common terminal complication of many diseases, notably cardiac failure and cancer. Such thrombi may be found in the legs in over 50 per cent of middle-aged or elderly subjects. They are attributed to circulatory failure and are not specific for any disease. They may cause edema of the lower extremities.

Bilateral edema of the lower extremities was noted in about 30 per cent of our cases, and unilateral edema in 5 per cent. Since the veins were not often dissected out, it is not known how many of these cases were due to venous thrombosis. Edema of the legs may also be caused by ascites as well as by neoplastic invasion of the vena cava or iliac veins. None of the investigations dealing with terminal phlebotrombosis indicate that it is peculiar to carcinoma of the pancreas.

Thrombophlebitis. In rare instances of unsuspected malignant neoplasm, thrombophlebitis may be the first symptom which attracts the patient's attention. It is generally agreed that in older persons with multiple thrombophlebitis one should consider the possibility of a malignant neoplasm. Woolling and Schick¹⁵ found an initial thrombophlebitis in 15 cases of unsuspected malignant disease.

Does thrombophlebitis suggest carcinoma of the pancreas? Sproul¹⁶ found multiple venous thrombi in 2 of 81 cancers of the lung and in 2 of 147 cancers of the stomach, but in 8 of 47 cancers of the pancreas. Woolling and Schick¹⁵ found the cancer in the pancreas in 3 of 15 cases. Wright¹⁷ stated that the cancer is frequently in the pancreas but may arise in various other organs. Leach¹⁸ found that venous thrombosis was not a prominent feature in his 39 cases of pancreatic carcinoma. Our records show an initial thrombophlebitis in only 9 of 609 pancreatic carcinomas (Table IV). The available data indicate that thrombophlebitis is seldom a conspicuous feature of pancreatic carcinoma.

Does thrombophlebitis associated with pancreatic carcinoma indicate that the neoplasm is situated in the body or tail? The widely quoted paper by Sproul¹⁶ is based upon the finding of thrombophlebitis in 5 of 16 cases of carcinoma of the body and tail and in only 3 of 31 cases of carcinoma of the head. Kenney¹⁹ reported two cases, one carcinoma of the body and one carcinoma of the tail, associated with thrombophlebitis. Gore²⁰ believes that the correlation of carcinoma of the body or tail with thrombophlebitis is significant. In two cases of thrombophlebitis, Oelbaum and Strich²¹ found one carcinoma in the tail and the other in an undetermined site. Wright¹⁷ stated that in his experience the site of the tumor in the pancreas was unimportant. The above data are inadequate for statistical study. The nine cases of initial thrombophlebitis listed in Table IV do not suggest that the site of the tumor in the pancreas is important. Still less significant are the reports that arterial thrombosis (Buttross and Salatch²²) and terminal endocarditis (Smith and Yates²³) are related to pancreatic carcinoma.

Ascites

Ascites is an occasional presenting symptom in carcinoma of the pancreas, and at necropsy it was found in 54 per cent of the subjects. Moderate ascites, less than 1,000 cc. of fluid, was found in 23 per cent; and severe ascites, 1,000 to 5,000 cc., was observed in 31 per cent. When the cases are arranged according to the anatomical types it is found that there are no significant differences in the incidence or severity of ascites in the different groups. Among the important causes of ascites are thrombosis or compression of the portal vein, massive metastases in the liver, and peritoneal metastases; but frequently no adequate explanation was found. Ascites was occasionally noted when there were no gross metastases.

Metastases

The incidence and distribution of gross metastases found at necropsy are shown in Table VI. It should be emphasized that these are only the grossly visible metastases. The absence of gross metastases does not mean that the patient could have been cured by pancreatectomy, since it is practically impossible to exclude the presence of microscopic metastases at necropsy. We know that these tumors usually recur after removal of all visible tumor tissue. It must also be emphasized that the necropsy discloses only the end-stage of the disease and does not tell us when the metastases occurred. However, in the carcinomas that do not produce jaundice it is highly probable that the initial symptoms are usually due to extension of the cancer beyond the pancreas.

The distribution of the metastases of carcinomas of the body and tail and the diffuse type were so similar that the three forms have been combined in Table VI for comparison with carcinoma of the head. It is noted that gross metastases were absent in 25 per cent of carcinomas of the head but in only 5 per cent of the other three types. This has been noted by others (Russum and Carp²⁴). It may mean that carcinomas of the body and tail metastasize earlier, but it probably indicates that they are present a longer time before fatal complications develop.

The more common sites of metastases in order of frequency are the liver, the regional nodes about the pancreas, the peritoneum, and the lungs. In necropsy reports, metastases are found in the liver in about two thirds of the cases. In most of the organs, metastases are less frequent from carcinoma of the head than from carcinoma of the body or tail (Table VI).

TABLE VI

Distribution and Frequency of Metastases in the Four Anatomical Types of Carcinoma of the Pancreas

	Metastases						
	Head		Body	Tail	Diffuse	Total no.	
	No. of cases	%	No. of cases	No. of cases	No. of cases	Body, tail diffuse	%
Total number	360		111	45	93	249	
No gross metastases	93	25.8	6	2	5	13	5.2
Liver	212	58.9	75	32	62	169	67.9
Regional lymph nodes	137	38.0	51	14	41	106	42.6
Peritoneum	67	18.6	45	18	37	100	40.2
Lungs	59	16.4	31	10	26	67	26.9
Adrenal glands	27	7.5	15	5	11	31	12.4
Duodenum	24	6.7	4	0	4	8	3.2
Kidneys	12	3.3	8	3	8	19	7.6
Stomach	9	2.5	16	3	7	26	10.4
Gallbladder	8	2.2	1	6	2	9	3.6
Spleen	7	1.9	4	1	6	11	4.4
Bones	6	1.7	4	0	6	10	4.0
Pleura	6	1.7	6	3	8	17	6.8
Brain and meninges	6	1.7	2	2	4	8	3.2
Skin	5	1.4	2	0	1	3	1.2
Heart and pericardium	4	1.1	2	2	4	8	3.2
Ovaries	4	1.1	2	2	0	4	1.6
Mediastinal lymph nodes	4	1.1	2	0	2	4	1.6
Peripheral lymph nodes	2	0.5	1	1	2	4	1.6
Thyroid gland	2	0.5	1	0	1	2	0.8
Uterus	2	0.5	2	0	0	2	0.8
Urinary bladder	2	0.5	0	0	0	0	0.0
Testes	1	0.3	0	0	0	0	0.0
Spinal cord	1	0.3	1	1	1	3	1.2

TABLE VII

The Incidence of Cholelithiasis in Subjects with Carcinoma of the Pancreas

	Carcinoma of head		Body		Tail		Diffuse		All types	
	Total no.	Percentage with cholelithiasis	Total no.	Percentage with cholelithiasis	Total no.	Percentage with cholelithiasis	Total no.	Percentage with cholelithiasis	Total no.	Percentage with cholelithiasis
Males	205	13.2	68	11.8	29	17.2	58	17.2	360	13.9
Females	96	39.6	29	41.4	7	42.9	21	23.8	153	37.9
Total	301	21.6	97	20.6	36	22.2	79	19.0	513	21.0

Cholelithiasis

The incidence of gallstones in the several anatomical types of pancreatic carcinoma is shown in Table VII. Gallstones were found at necropsy in about 15 per cent of males and 25 per cent of females of the older age groups. The incidence in females shown in Table VII is higher than is usually reported. When the data for males and females are combined, it becomes apparent that the incidence of gallstones is unrelated to the anatomical type of cancer. Obstruction of the common bile duct does not increase the frequency of cholelithiasis. We may conclude that carcinoma of the pancreas is unrelated to cholelithiasis.

SUMMARY OF PART I

This study comprises 609 cases of carcinoma of the pancreas necropsied at the University of Minnesota during a period of 45 years, 1911 to 1954. The percentage of deaths in males over 40 years of age due to this neoplasm increased from 0.98 per cent in the period 1911 to 1944 to 1.57 per cent in the period 1945 to 1954. In females during the corresponding periods the increase was from 1.03 to 1.19 per cent.

Carcinoma of the pancreas in males comprised 5 per cent of the fatal neoplasms during the period 1911 to 1944, and 6 per cent during the period 1945 to 1954. This increase appears to be due to the great increase in the number of old men, since carcinoma of the pancreas in males reaches a maximum in the eighth decade.

The percentage of deaths in males over 40 years of age due to malignant neoplasms was 35 per cent greater in the period 1945 to 1954; in females the increase was only 12.5 per cent. Since cancer affects a much higher proportion of younger women than younger men, the increased span of life has less effect on total cancer incidence in the female.

Of the 609 cases, cancer of the head of the pancreas comprised 59.1 per cent; of the body, 18.2 per cent; of the tail, 7.4 per cent; and the diffuse type, 15.3 per cent. About one half of the patients died within 6 months after the appearance of the first symptom and 17.5 per cent survived over 1 year. There were no significant differences in the duration of symptoms in the four groups.

Abdominal pain or distress was the most frequent initial symptom in each group. Jaundice was an initial symptom in 41.9 per cent of carcinomas of the head, and developed later in an additional 40.4 per cent. In carcinomas of the body and tail, jaundice was an initial symptom in only 2 of 154 cases, but it developed late in the course

of the disease in 26 other cases. Thrombophlebitis was an initial symptom in 9 cases. The number of cases is small but there is no indication that this complication is more frequent in carcinomas of the body and tail.

Apart from the development of jaundice, there are no consistent clinical differences in the four anatomical forms of carcinoma. Distant metastases were found at necropsy in 75 per cent of carcinomas of the head and in 95 per cent of the other three types.

II. THE RELATION OF CARCINOMA OF THE PANCREAS TO DIABETES MELLITUS

It is well known that carcinoma of the pancreas is frequently associated with glycosuria and hyperglycemia, especially in advanced stages of the disease. This is the more significant since other malignant neoplasms that produce a similar emaciation often cause hypoglycemia but never hyperglycemia. Starvation of a diabetic patient reduces sugar of the blood and urine.

Glycosuria. From collected statistics, Berk⁹ found glycosuria in 9.4 per cent of cases of pancreatic carcinoma. By combining the data reported in references 6, 7, 12, 13, and 23, we find glycosuria in 77 (19 per cent) of 405 cases. In our 443 cases of carcinoma of the pancreas in which the urine was examined, glycosuria was found in 64 (14.4 per cent).

Hyperglycemia. Berk,⁹ in collected statistics, found hyperglycemia in 19.4 per cent. The combined data from references 3, 6, 12, 23, and 25 give 69 instances of hyperglycemia among 338 cases of pancreatic carcinoma—an incidence of 20.4 per cent. Data on glucose tolerance are not reviewed since this test is not dependable in emaciated subjects.

Diabetes Mellitus. The combined data from references 6, 7, 23, 26, 27, and 28 furnish 30 cases which the authors regarded as diabetes among 390 cases of pancreatic carcinoma—an incidence of 7.7 per cent. The diabetes may precede the symptoms of carcinoma, or it may appear concurrently with the signs of cancer. Sometimes it develops after the carcinoma has been diagnosed. Several of the authors seem uncertain of the diagnosis of diabetes when the signs of its presence coincide with or follow the evidences of carcinoma; but they are more confident when the diabetes precedes the carcinoma. No one would question a diagnosis of true diabetes when it was recognized several years before the signs of carcinoma developed; but it is clear that a majority of observers have found it difficult to draw a sharp line between true diabetes and the glycosuria associated with pancreatic carcinoma.

If we define diabetes mellitus as a clinical syndrome due to insufficiency of insulin, we may recognize at least three independent forms of the disease; viz., diabetes due to removal or destruction of the pancreas, steroid diabetes, and true idiopathic diabetes. Our immediate problem is to determine whether there is an increased incidence of true diabetes in subjects with pancreatic carcinoma or, conversely, whether subjects with true diabetes show an increased incidence of carcinoma of the pancreas. These two methods of approach to the problem meet with the same difficulty, viz., the distinction between true diabetes and the glycosuria associated with pancreatic carcinoma.

*The Incidence of Diabetes in Subjects with
Carcinoma of the Pancreas*

It was noted above that the combined reports of several observers give 30 cases of diabetes among 390 cases of pancreatic carcinoma—an incidence of 7.7 per cent. The several authors do not explain how they distinguished true diabetes from the glycosuria associated with carcinoma of the pancreas, and some do not insist that all of their cases were idiopathic diabetes.

In Table VIII the incidence of diabetes in the total necropsy

TABLE VIII
*Incidence of Diabetes in the Total Necropsies Compared with Its Incidence in Subjects
with Carcinoma of the Pancreas*

Males						
Age	No. of necropsies	Diabetic cases		Carcinoma of pancreas		
		No.	%	Total No.	Diabetic cases	
					No.	%
0-20 yrs.	7,998	18	0.23	0	0	0.0
20-40 yrs.	5,492	81	1.47	13	0	0.0
Over 40 yrs.	33,367	859	2.57	412	22	5.3
Females						
0-20 yrs.	5,755	17	0.30	0	0	0.0
20-40 yrs.	4,054	86	2.12	3	0	0.0
Over 40 yrs.	16,531	905	5.47	185	16	8.6

population is compared with its incidence in subjects with carcinoma of the pancreas. It will be noted that in males over 40 years of age diabetes is twice as frequent in those with carcinoma of the pancreas as in the general necropsy population. In females the incidence of diabetes is 50 per cent greater.

The cases classified as diabetes are listed in Table IX. With the exception of the last case in Table IX, which was classified as diabetes because of the hyaline islets, they were all good clinical examples of diabetes of mild to marked severity. The patients were treated as having diabetes and usually responded to insulin. But how many of them have true idiopathic diabetes? We know that pancreatic carcinoma may cause glycosuria. When the glycosuria is mild and asymptomatic it is labeled "glycosuria"; when severe enough to require treatment it is called diabetes. If the tumor causes mild glycosuria, why may it not produce a severe glycosuria? If we exclude from the group of true diabetes the eight males and five females (Table IX) in whom the symptoms of carcinoma antedated or coincided with the discovery of the diabetes, the incidence of diabetes in males with carcinoma of the pancreas is reduced to 3.4 per cent, and in females to 5.9 per cent; and the differences are no longer significant.

If it be admitted that carcinoma of the pancreas may produce the clinical syndrome of diabetes mellitus, it then appears possible that it may cause glycosuria before other signs of its presence appear. Therefore, some of the cases in which the diabetes antedates the carcinoma by several months may not be true diabetes. It is evident that we cannot distinguish true diabetes from the glycosuria induced by pancreatic carcinoma when the diabetes is of short duration.

In what respects do the 38 cases listed in Table IX differ from diabetic patients who did not have pancreatic carcinoma? Marble²⁹ was impressed by the short duration of the diabetes; the average duration of the diabetes in his 31 cases associated with carcinoma of the pancreas was only 3.4 years. The average duration of the diabetes in our 38 cases (Table IX) was likewise only 3.4 years; and the duration was less than 1 year in ten cases. This might mean that the carcinoma shortened the lives of the diabetic patients, but it could indicate that it caused the diabetes.

How does a pancreatic carcinoma cause glycosuria? It is generally assumed that this phenomenon is due to extensive destruction of pancreatic tissue, as in acute hemorrhagic pancreatitis. The pancreatic tissue may be replaced by the neoplasm or destroyed by an associated suppurative inflammation. But this interpretation is not supported by anatomical study of the pancreas. In 85 per cent of our cases, glycosuria did not develop although the destruction of the gland was just as great in this group as in those with glycosuria. The bulk of the islet tissue is contained in the body and tail of the pancreas, and one would expect a higher incidence of glycosuria when these seg-

TABLE IX
Carcinoma of the Pancreas Associated with Diabetes

Necropsy no.	Age	Sex	Duration of diabetes	Severity of diabetes*	Duration of carcinoma	Site of carcinoma	Hyaline islets*	Renal arterio-sclerosis*	Comment
52-1312	67	M	16 yrs.	3	2 mos.	Head	-	-	Retinitis
53-2325	64	M	14 yrs.	2	18 mos.	Head	-	0	
48-997	69	F	12 yrs.	{ 1 3	15 mos.	Head	-	-	
47-2476	74	M	9 yrs.	{ 1 2	3 mos.	Head	-	0	Coronary sclerosis
54-1208	80	M	9 yrs.	{ 1 3	10 mos.	Head	-	0	Coronary thrombosis
25-480	45	M	7 yrs.	2	1 mo.	Head	0	-	Gangrene of toes
51-2034	73	M	7 yrs.	1	4 mos.	Head	-	0	Insulin terminally
50-1712	72	M	6 yrs.	2	8 mos.	Head	1	1	
47-801	53	F	5 yrs.	2	5 yrs.	Body	0	1	Steatorrhea for 5 yrs.
53-1574	73	M	5 yrs.	2	6 mos.	Tail	0	1	
50-291	75	F	4.5 yrs.	{ 1 2	2 mos.	Diffuse	-	3	Gangrene, intercapillary glomerulosclerosis
42-122	75	F	4 yrs.	1	5 mos.	Tail	0	1	
46-2193	49	M	4 yrs.	1	19 mos.	Head	0	1	
30-1795	44	M	3 yrs.	1	9 mos.	Head	-	0	
34-337	69	F	3 yrs.	2	2 mos.	Body	-	1	
38-2467	60	M	2 yrs.	2	9 mos.	Tail	0	0	

47-2532	68	M	2 yrs.	2	2 mos.	Diffuse	0	0
52-548	54	F	21 mos.	2	6 mos.	Head	0	1
18-93	42	M	15 mos.	3	15 mos.	Tail	0	-
40-1279	74	F	15 mos.	2	2 mos.	Head	-	-
48-2392	75	F	15 mos.	3	7 mos.	Diffuse	-	1
49-2452	75	M	15 mos.	1	15 mos.	Head	-	-
34-660	56	M	1 yr.	2	1 yr.	Head	0	0
31-1465	42	F	1 yr.	3	5 mos.	Tail	1	0
51-1313	69	M	1 yr.	1	10 mos.	Body	0	0
54-991	57	F	1 yr.	3	1 yr.	Tail	0	0
54-2601	60	M	1 yr.	3	6 wks.	Diffuse	0	0
						Diffuse	1	0
44-351	67	F	Indefinite	1	Indefinite	Body	0	0
44-766	59	F	9 mos.	2	3 mos.	Tail	-	0
53-2270	52	M	8 mos.	2	18 mos.	Head	-	0
48-766	60	M	7 mos.	3	7 mos.	Head	0	0
38-834	43	M	6 mos.	1	6 mos.	Head	-	-
38-528	60	F	6 mos.	3	6 mos.	Head	0	0
34-955	71	F	6 mos.	3	6 mos.	Head	-	-
52-2001	61	M	6 mos.	2	8 mos.	Body	0	0
44-1551	56	F	5 mos.	1	5 mos.	Tail	0	-
30-1136	61	M	4 mos.	3	4 mos.	Head	1	2
48-1662	74	F	7 wks.	1	Indefinite	Head	1	0

* The numerals refer to the intensity of the process; 1 indicates mild, 2 moderate, and 3 severe. An initial mild diabetes (1) may terminate in a severe type (3). - indicates no observation.

Gangrene of toe

ments are involved; but this is not true. In the 64 cases (Tables IX and X) of glycosuria and diabetes the tumor involved the head in 37, the body or body and tail in 11, the tail in 6, and the entire pancreas in 10.

Carcinomas that involve the head only produce atrophy of most of the acinar tissue of the pancreas; but the islets persist in the atrophic areas and the beta cells are filled with insulin granules (Fig. 1). Islets persist unless they are actually replaced by the neoplasm, and it is not unusual to find persistent islets filled with insulin and completely surrounded by cancer cells (Fig. 2). Stobbe³⁰ called attention to this feature. In almost every case in which intact pancreatic tissue was available, well granulated islets were found. Usually, however, the islets are embedded in atrophic pancreas or neoplastic tissue and it is possible that the insulin they form does not gain access to the circulation. The mechanism responsible for the glycosuria is not understood.

Hyaline Islets

In 208 cases of carcinoma of the pancreas without glycosuria in which intact pancreatic tissue was available for study, hyaline islets were found in eight. There was no clinical evidence of diabetes in these eight cases and the structure of the renal arterioles did not support a diagnosis of diabetes. Hyaline islets were found in only five of 22 cases listed as diabetic in Table IX. There was no intact pancreatic tissue available in 16 cases. One expects to find hyaline islets in 40 per cent of elderly diabetic patients, but the group is too small to interpret.

Renal arteriolosclerosis was found in only 10 of 28 cases (Table IX) in which tissue was available. This lesion is found in over two thirds of patients with genuine diabetes in this age group (Bell³¹). In only two cases was it greater than grade 1 in degree. There was only one case of intercapillary glomerulosclerosis, whereas in patients with genuine diabetes of this age group it is found in about 20 per cent of males and 30 per cent of females. The gangrene found in three cases and the coronary sclerosis in two others suggest true diabetes. The clinical and laboratory data therefore suggest that at least one third of the cases listed in Table IX are not idiopathic diabetes but a glycosuria induced in some way by carcinoma of the pancreas.

The 26 cases regarded as simple glycosuria are listed in Table X in the order of the known duration of the glycosuria. With respect to the duration of the glycosuria they merge gradually with those listed as diabetes and no sharp separation can be made. The glycosuria

TABLE X
Carcinoma of the Pancreas Associated with Glycosuria

Necropsy no.	Age	Sex	Urine sugar*	Blood sugar (mg. per 100 ml.)	Duration of glycosuria	Duration of carcinoma	Site of carcinoma	Hyaline islets*	Renal arterio-sclerosis*
48-661	54	F	3	—	5 mos.	7 mos.	Head	0	0
41-511	52	M	2	186	4-5 mos.	5-5 mos.	Head	0	0
54-3145	62	M	3	High	3 mos.	Indefinite	Diffuse	-	0
44-2038	62	F	1	246	3 mos.	8 mos.	Body	-	0
51-1768	66	M	2	110	2 mos.	2 mos.	Tail	0	1
48-501	71	F	1	288	5 wks.	5 mos.	Diffuse	-	0
53-3656	78	M	2	—	1 mo.	5 wks.	Diffuse	-	-
59-1026	55	M	1	—	1 mo.	4 mos.	Head	-	1
53-972	80	F	4	—	1 mo.	5 mos.	Head	-	0
51-2580	74	M	1	—	3 wks.	6 wks.	Head	0	0
59-733	78	M	2	—	3 wks.	2 mos.	Head	-	0
36-28	74	M	3	—	2 wks.	9 mos.	Head	0	-
47-930	47	M	2	—	2 wks.	3 mos.	Head	0	0
53-2729	68	M	1	—	2 wks.	6 wks.	Body	-	-
59-1767	78	M	4	375	9 days	14 mos.	Tail	0	1
42-1043	80	M	1	—	8 days	3 mos.	Head	-	0
43-1542	61	F	4	—	5 days	6 wks.	Head	-	-
53-1190	72	F	4	368	5 days	1 mo.	Body	-	1
53-3438	79	M	2	129	3 days	1 mo.	Body	-	-
54-1671	58	M	1	—	2 days	6 mos.	Tail	0	0
52-230	73	M	2	—	2 days	1 mo.	Diffuse	0	0
49-778	40	F	-	404	1 day	9 mos.	Head	0	-
44-2151	62	M	4	400	1 day	3 mos.	Body	-	-
41-2349	71	F	1-	232	1 day	10 mos.	Tail	-	-
45-1749	79	F	4	—	? days	10 mos.	Head	-	-
54-2842	52	M	2	70	? days	9 mos.	Body	-	-
							Tail	0	0

* The numerals refer to the intensity of the process, 1 being minimal and 4 severe; - indicates no observation.

was usually of short duration but was sometimes severe. It was generally first noted late in the disease. Hyperglycemia and glycosuria were the only evidence of diabetes. There was no supporting anatomical evidence of diabetes.

These data indicate that the apparent increased incidence of diabetes in subjects with carcinoma of the pancreas does not represent an increase of true idiopathic diabetes.

The Incidence of Cancer in Diabetic Patients

There are several statements in the literature to the effect that cancer occurs more frequently in diabetic than in non-diabetic patients. Ellinger and Landsman³² reported 39 cancers among 1,280 diabetic patients, an incidence of 3.04 per cent. They stated that only four of the patients were still living but did not give the ages at death. By the use of vital statistics in New York, they concluded that there definitely is a higher incidence of cancer in diabetic subjects. Jacobson³³ stated that diabetic patients have at least one third more cancer deaths than those without diabetes. Marble²⁹ observed 256 cancers among 10,000 diabetic patients of all ages—an incidence of 2.56 per cent, but two thirds of the patients were still alive. He thought that his data indicated that cancer is more common among patients with diabetes, but was not sure of this conclusion.

The data from our necropsies are shown in Tables XI and XII. It appears that the total incidence of cancer in males over 40 years of age is about twice as large in non-diabetic as in diabetic cases, and in females there is an even greater preponderance in the non-diabetic cases. This is to be expected since every disease which shortens life shows a decreased incidence of malignant disease. The total incidence of cancer is likewise greatly reduced in tuberculosis, heart disease, and cirrhosis of the liver.

Does cancer of the pancreas constitute a larger proportion of the cancers in diabetic than in non-diabetic cases? Ellinger and Landsman³² found one carcinoma of the pancreas among 39 cancers in patients with diabetes; but Marble²⁹ found that 33 of 256 cancers in diabetic patients (13 per cent) originated in the pancreas.

The data derived from our necropsies are shown in Tables XI and XII. In Table XI it appears that all forms of cancer are greatly decreased in diabetic subjects except carcinoma of the pancreas and carcinoma of the large intestine. There is only a moderate decrease in the incidence of carcinoma of the large intestine. Carcinoma of the pancreas is more than twice as frequent in diabetic subjects. When we compare the percentage of total cancer arising in the several

TABLE XI
A Comparison of the Total Incidence of Cancer and of the Major Forms of Cancer in Non-Diabetic and Diabetic Males Over 40 Years of Age

No. of necropsies	Non-diabetic males over 40 years of age				Diabetic males over 40 years of age			
	32,508		A 850		B 851		B 852	
	No. of cases	Percentage of necropsies	Percentage of cancers	No. of cases	Percentage of necropsies	Percentage of cancers	No. of cases	Percentage of necropsies
Stomach	1,193	3.67	15.48	9	1.05	8.49	9	1.06
Colon and rectum	977	3.01	12.68	18	2.10	17.00	18	2.12
Lung	813	2.50	10.55	8	0.93	7.55	8	0.94
Prostate	711	2.19	9.23	12	1.40	11.32	12	1.41
Pancreas	390	1.20	5.06	22	2.56	20.75	14	1.64
All other cancers	3,619	11.13	46.98	37	4.31	34.90	37	4.35
Total cancer	7,703	23.70		106	12.34		98	11.52

Group A includes all cases listed as diabetic in Table IX. Group B omits 8 cases in which the symptoms of carcinoma antedated or were concurrent with the discovery of the diabetes.

TABLE XII
A Comparison of the Total Incidence of Cancer and of the Major Forms of Cancer in Non-Diabetic and Diabetic Females Over 40 Years of Age

No. of necropsies	Non-diabetic females over 40 years of age				Diabetic females over 40 years of age			
	15,656		A 905		B 900		B 901	
	No. of cases	Percentage of necropsies	Percentage of cancers	No. of cases	Percentage of necropsies	Percentage of cancers	No. of cases	Percentage of necropsies
Stomach	404	2.59	9.8	8	0.88	8.8	8	0.89
Colon and rectum	568	3.64	13.8	14	1.55	15.4	14	1.56
Breast	630	4.03	15.2	10	1.10	11.0	10	1.11
Uterus	438	2.80	10.6	6	0.66	6.6	6	0.67
Pancreas	167	1.07	4.0	16	1.77	17.6	11	1.22
All other cancers	1,930	12.35	46.7	37	4.09	40.7	37	4.11
Total cancer	4,137	26.48		91	10.05		86	9.56

Group A includes all cases listed as diabetic in Table IX. Group B omits 5 cases in which the symptoms of carcinoma antedated or were concurrent with the discovery of the diabetes.

organs in non-diabetic and diabetic patients it appears that there is a slight increase in cancer of the prostate and colon, but a striking increase in the proportion arising from the pancreas in the diabetic patient.

This observation suggests that some of the diabetic subjects with carcinoma of the pancreas did not have true idiopathic diabetes but a form of diabetes produced by pancreatic carcinoma. Accordingly, group B was constructed excluding the eight cases in males in which the symptoms of carcinoma antedated or were concurrent with the discovery of the diabetes (group B, Table XI). This decreases the ratio of pancreatic to total carcinoma but the proportion is still three times as great as in non-diabetic patients, viz., 14 per cent. It was noted above that Marble²⁹ found that 13 per cent of the cancers in diabetic patients arose in the pancreas.

A similar situation obtains in females, Table XII. After exclusion of five doubtful cases, cancer of the pancreas comprises three times the proportion of total cancer in diabetic as in non-diabetic cases.

It is to be noted that carcinoma of the large intestine is the most frequent form of cancer in diabetic patients.

The prominence of cancer of the pancreas in diabetic patients is difficult to explain. Three explanations may be considered. (a) Cancer of the pancreas may produce diabetes before it manifests any other signs of its presence. (b) Diabetic patients are more prone to malignant disease of the pancreas. (c) The difference brought out above is not real but is a statistical error due to a relatively small sample. It is to be noted that carcinoma of the colon exhibits a relative increase in diabetic cases. Much more data must be collected before any firm conclusions can be established.

SUMMARY OF PART II

There is a high incidence of glycosuria and hyperglycemia in association with carcinoma of the pancreas. No sharp distinction can be made in carcinoma of the pancreas between simple glycosuria and diabetes.

If we exclude those cases of diabetes in which the symptoms of cancer antedated or were concurrent with the recognition of diabetes, then the incidence of diabetes in subjects with carcinoma of the pancreas is not significantly greater than its incidence in the general necropsy population of corresponding age.

Diabetic patients with carcinoma of the pancreas differ from other patients with diabetes in the shorter duration of the diabetes as well

as in the decreased frequency of hyaline islets in the pancreas and vascular renal changes.

Carcinoma of the pancreas produces glycosuria probably more by interference with the escape of insulin from the pancreas than by actual destruction of islets.

The total incidence of cancer in diabetic patients is less than one half its incidence in non-diabetic patients.

According to the data presently available, which are admittedly inadequate, carcinoma of the pancreas comprises three times the proportion of total cancer in diabetic patients that it does in non-diabetic patients.

REFERENCES

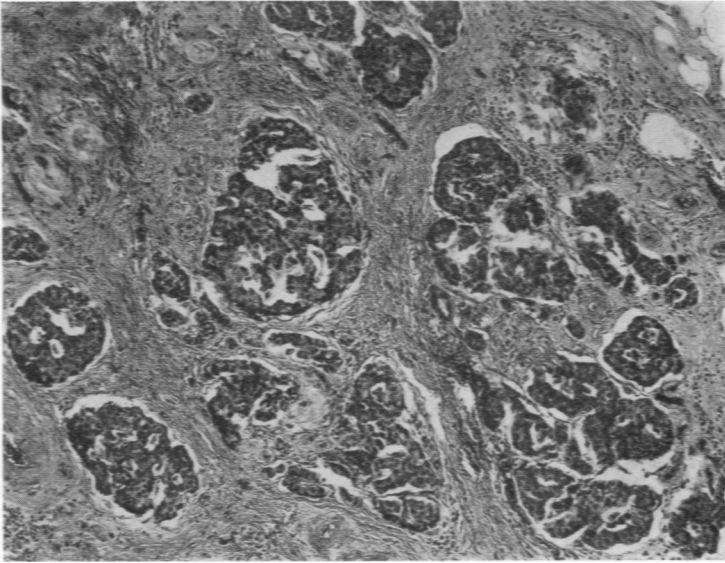
1. Corner, B. D. Primary carcinoma of the pancreas in an infant aged 7 months. *Arch. Dis. Childhood*, 1943, 18, 106-108.
2. Grant, G. H., and Perceval, P. E. Carcinoma of the pancreas in a girl of 16, presenting as carcinomatosis of lungs. *Brit. M. J.*, 1954, 1, 857.
3. Broadbent, T. R., and Kerman, H. D. One hundred cases of carcinoma of the pancreas: a clinical and roentgenologic analysis. *Gastroenterology*, 1951, 17, 163-177.
4. Silver, G. B., and Lubliner, R. K. Carcinoma of the pancreas. A clinico-pathologic survey. *Surg., Gynec. & Obst.*, 1948, 86, 703-716.
5. Duff, G. L. The clinical and pathological features of carcinoma of the body and tail of the pancreas. *Bull. Johns Hopkins Hosp.*, 1939, 65, 69-98.
6. Country, J. C., and Foulk, R. A clinical review of thirty cases of carcinoma of the pancreas. *U. S. Armed Forces M. J.*, 1953, 4, 831-838.
7. Brown, R. K.; Moseley, V.; Pratt, T. D., and Pratt, J. H. The early diagnosis of cancer of the pancreas based on the clinical and pathological study of one hundred autopsied cases. *Am. J. M. Sc.*, 1952, 223, 349-363.
8. Smith, B. K., and Albright, E. C. Carcinoma of the body and tail of the pancreas: report of 37 cases studied at the State of Wisconsin General Hospital from 1925-1950. *Ann. Int. Med.*, 1952, 36, 90-97.
9. Berk, J. E. The diagnosis of carcinoma of the pancreas. *Arch. Int. Med.*, 1941, 68, 525-559.
10. Sanders, L. C., and McBurney, R. Carcinoma of the pancreas. *Am. J. Gastroenterol.*, 1956, 25, 59-65.
11. Kaplan, N., and Angrist, A. The mechanism of jaundice in cancer of the pancreas. *Surg., Gynec. & Obst.*, 1943, 77, 199-204.
12. Thompson, C. M., and Rodgers, L. R. Analysis of the autopsy records of 157 cases of carcinoma of the pancreas with particular reference to incidence of thromboembolism. *Am. J. M. Sc.*, 1952, 223, 469-478.
13. Dashiell, G. F., and Palmer, W. L. Carcinoma of the pancreas: diagnostic criteria. *Arch. Int. Med.*, 1948, 81, 173-183.
14. Cantor, M. O., and Haking, L. Carcinoma of the pancreas with roentgen pattern of nontropical sprue. *J. Internat. Coll. Surgeons*, 1951, 16, 631-636.
15. Woolling, K. R., and Schick, R. M. Thrombophlebitis: a possible clue to cryptic malignant lesions. *Proc. Staff Meet., Mayo Clin.*, 1956, 31, 227-233.

16. Sproul, E. E. Carcinoma and venous thrombosis: the frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thrombosis. *Am. J. Cancer*, 1938, 34, 566-585.
17. Wright, I. S. The pathogenesis and treatment of thrombosis. *Circulation*, 1952, 5, 161-188.
18. Leach, W. B. Carcinoma of the pancreas. A clinical and pathologic analysis of thirty-nine autopsied cases. *Am. J. Path.*, 1950, 26, 333-347.
19. Kenney, W. E. The association of carcinoma in the body and tail of the pancreas with multiple venous thrombi. *Surgery*, 1943, 14, 600-609.
20. Gore, I. Thrombosis and pancreatic carcinoma. *Am. J. Path.*, 1953, 29, 1093-1103.
21. Oelbaum, M. H., and Strich, S. J. Thrombophlebitis migrans and carcinoma of body and tail of pancreas. *Brit. M. J.*, 1953, 2, 907-909.
22. Buttross, D., Jr., and Salatich, J. Venous and arterial thromboses in association with carcinoma of the pancreas. *Ann. Int. Med.*, 1955, 43, 213-216.
23. Smith, J. P., and Yates, P. O. The thrombotic syndrome associated with carcinoma. *J. Path. & Bact.*, 1955, 70, 111-117.
24. Russum, B. C., and Carp, O. Carcinoma of the body and tail of the pancreas. A clinical and pathological entity. *Am. J. Surg.*, 1942, 56, 414-422.
25. Grauer, F. W. Pancreatic carcinoma; a review of 34 autopsies. *Arch. Int. Med.*, 1939, 63, 884-898.
26. Arkin, A., and Weisberg, S. W. Carcinoma of the pancreas, a clinical and pathologic study of seventy-five cases. *Gastroenterology*, 1949, 13, 118-126.
27. Levy, H., and Lichtman, S. S. Clinical characteristics of primary carcinoma of the body and tail of the pancreas. *Arch. Int. Med.*, 1940, 65, 607-626.
28. Sloan, L. E., and Wharton, G. K. Cancer of the pancreas. *Am. J. Gastroenterol.*, 1954, 21, 441-458.
29. Marble, A. Diabetes and cancer. *New England J. Med.*, 1934, 211, 339-349.
30. Stobbe, H. Langerhanssche Inseln in Pankreaskarzinom. *Ztschr. ges. inn. Med.*, 1954, 9, 917-918.
31. Bell, E. T. Renal vascular disease in diabetes mellitus. *Diabetes*, 1953, 2, 376-389.
32. Ellinger, F., and Landsman, H. Frequency and course of cancer in diabetics. *New York State J. Med.*, 1944, 44, 259-265.
33. Jacobson, P. H. A statistical study of cancer among diabetics. *Milbank Mem. Fund Quart.*, 1948, 26, 90-118.

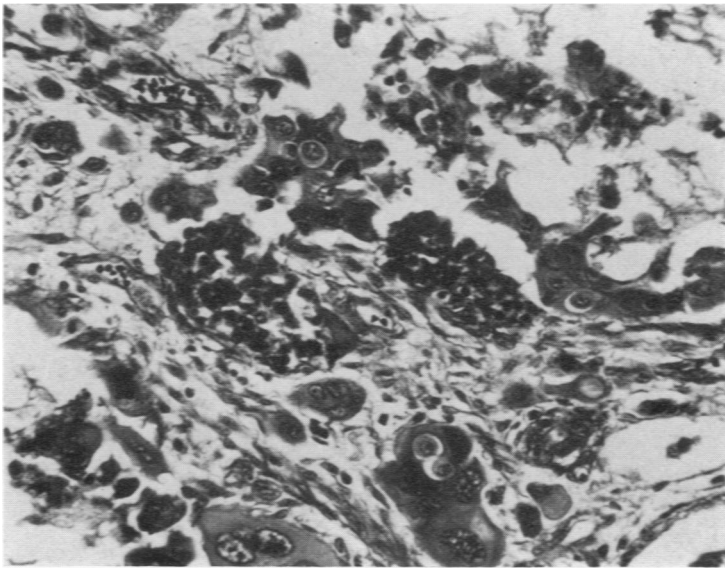
LEGENDS FOR FIGURES

FIG. 1. Area of pancreas showing atrophy of all acinar tissue, but persistence of islets. Hematoxylin and eosin stain. $\times 150$. The Gomori stain showed the beta cells filled with insulin granules.

FIG. 2. Area of pancreas showing two persistent islets in a mass of carcinomatous tissue. The beta cells are filled with insulin granules. Gomori's stain. $\times 150$.



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