In this study of primary carcinoma of the pancreas two groups of cases were investigated.

The first group, consisting of thirty-two cases of primary carcinoma of the pancreas which had been admitted to the University of Minnesota Hospital during the period 1913 to 1931, was critically reviewed in regard to the history of the illness, the clinical course, the operative treatment and course, and the post-mortem findings. These cases will be referred to as the hospital series in this paper.

The second group was selected from the autopsy series of the Department of Pathology of the University of Minnesota for the period 1913 to 1931. A total of ninety-nine cases of primary carcinoma of the pancreas was found. The autopsy material of the Department of Pathology is collected from three general hospitals (including the University Hospital) and several private hospitals in two cities and all coroner’s cases from one city. The autopsy series therefore includes those cases in the first group which came to post-mortem examination at the University Hospital.

Carcinoma is the most frequent of all neoplastic growths found in the pancreas. It was first described by Mondière in 1836 and since that time there has been a rather abundant literature on the subject.

According to the microscopic appearance and gross anatomical structure, Gross differentiates three types of carcinoma: scirrhous, medullary, and gelatinous.

The scirrhous form is of cartilaginous or stony hardness and resembles a sclerotic process in the gland. Microscopically the cell type is usually the cylindrical cell. Medullary carcinoma represents a lessened development of connective tissue as compared with the scirrhous carcinoma, while the gelatinous carcinoma is the result of a regressive process leading to the gelatinous form.

It seems more correct, however, to classify the tumors according to their histologic genesis than according to their gross appearance. On this basis there are three types.

1 Submitted in partial fulfillment of the requirements of the degree of Master of Science in Surgery.
(1) **Tumors Derived from the Epithelium of the Duct System, Cylindrical-cell Carcinoma:** Tumors of this type are usually located in the head or corpus and form somewhat massive growths which are imperfectly separated from the parenchyma. Their structure shows papillary outgrowths and alveoli lined by cylindrical or cuboidal cells. Local extensions have been traced through ducts, lymphatics, nerve trunks, and blood vessels.

The consistency of this type of tumor varies according to the degree of stroma development and regressive changes, so that one may have the picture of either scirrhous, medullary, or gelatinous carcinoma.

(2) **Tumors Derived from the Parenchyma of the Gland:** These are more diffuse, rapidly growing, and firm or soft according to the proportion of fibrous tissue. The cells resemble those of the pancreatic alveoli and are arranged in small or large alveoli separated by fine stroma. In some cases they suggest a simple cirrhosis in an otherwise unaltered pancreas. There may also be a collateral, preexisting hyperplasia of the gland tissue which is difficult to distinguish from invading carcinoma. The islands of Langerhans are usually hypertrophied and may be increased in number. They persist and may be completely surrounded by tumor cells.

(3) **Tumors Arising from the Islands of Langerhans:** These are illustrated by the cases of Wilder, Howland, Thalhimer, Allan, and McClennen and Norris, which showed definite evidence of hyperinsulinism. The first case was reported by Wilder, Allan, Power and Robertson. At autopsy a carcinoma of the pancreas with metastasis to the liver was discovered. Metastatic tumor tissue from the liver was biologically assayed for insulin content and approximately 40 units for each 100 grams of tumor tissue was found. Microscopically the cells of the primary tumor were characteristic of those of the islands, as were also the cells of the metastatic tumor in the liver. In the case reported by Howland, the patient recovered from hypoglycemic attacks after the removal of a tumor from the middle of the pancreas.

Fabozzi believed that all carcinomas of the pancreas have their origin in the islets. In his study of five cases of carcinoma of the pancreas the illustrations were diagrammatic and the descriptions inconclusive.

Horgan believed that carcinoma of the pancreas may develop from ducts, acini, or islets. He attempted to establish the histogenesis of neoplasms arising from islets in a study of pancreatic tissue from autopsies on patients with chronic upper abdominal lesions, postulating that neoplastic changes might be associated with chronic pancreatitis. He found hypertrophy and hyperplasia
in 25 per cent of cases of chronic pancreatitis associated with gastric or duodenal ulcer. Three stages of changes in the islands could be identified: (1) hypertrophic differentiated cells; (2) hyperplastic undifferentiated cells confined to the capsule; (3) hyperplastic undifferentiated cells migrating through the capsule, which he felt undoubtedly represented carcinoma.

**Etiology**

About the cause of pancreatic carcinoma as little is known as in other types of carcinoma. Chronic pancreatitis, gallstones, syphilis, alcohol, trauma, and developmental anomalies have been mentioned as etiologic factors. Hulst, Heiberg, Ssobolew, and Ewing noted that many cases of carcinoma of the pancreas occurred in cirrhotic glands. Reasoning from an analogy with the liver, Ewing pointed out that carcinoma of the pancreatic parenchyma may be regarded as beginning in a functional hyperplasia following cirrhosis, and carcinoma of the ducts from chronic irritation and stasis in the canals.

The incidence of carcinoma of the pancreas in autopsy material and hospital admissions is shown in Tables I and II. According to the data presented in Table I, carcinoma of the pancreas repre-
sented 1.3 per cent of all carcinomata (34 carcinomas of the pancreas in a total of 2,626 carcinomas). Körte found the incidence to be 2 per cent of all carcinoma (59 cases in a total of 2,943 carcinoma autopsies). Kaufman states that carcinoma of the pancreas constitutes 1.76 per cent of all malignant tumors.

**Table III: Sex Incidence in Collected Series of Pancreatic Carcinoma**

<table>
<thead>
<tr>
<th>Series</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirallié</td>
<td>106</td>
<td>69</td>
<td>37</td>
</tr>
<tr>
<td>Da Costa</td>
<td>37</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Boldt</td>
<td>56</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>Speed</td>
<td>52</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>Futcher</td>
<td>31</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Ancelet</td>
<td>161</td>
<td>102</td>
<td>59</td>
</tr>
<tr>
<td>Kiefer</td>
<td>33</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Friedenwald and Cullen</td>
<td>37</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Bigsby</td>
<td>28</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Germershausen</td>
<td>25</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>566</strong></td>
<td><strong>363 (64.1%)</strong></td>
<td><strong>203 (35.9%)</strong></td>
</tr>
</tbody>
</table>

**Table IV: Age Distribution of Pancreatic Carcinoma: Collected Series, University Hospital and Autopsy Series**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total of Collected Series*</th>
<th>University Hospital Series</th>
<th>Autopsy Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>31-40</td>
<td>24</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>63</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>82</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>46</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>71-80</td>
<td>23</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>81-90</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>244</strong></td>
<td><strong>32</strong></td>
<td><strong>67</strong></td>
</tr>
</tbody>
</table>

* Futcher, Friedenwald and Cullen, Boldt, Oser, Kiefer, and Hale White.
† The age of one case was not given, reducing the totals to 31 and 98 instead of 32 and 99.

In many of the earlier papers, primary and secondary carcinomas, as well as cases of interstitial pancreatitis, were grouped together, so that comparison of figures is of little value.

Carcinoma of the pancreas occurs more frequently in men than women, the ratio varying from 3:2 to 4:1 according to various authors. Table III indicates the sex distribution.
Carcinoma of the pancreas occurs most frequently in the fifth to seventh decades of life, but may be found at any age. Kühn reports a case of primary carcinoma of the pancreas in a child of two years. Bohn reports a case in a six months old baby, while Rokitansky reports finding a primary carcinoma in the pancreas of a newborn child. In the hospital series reported here the youngest patient was thirty-eight years of age and the oldest seventy-five.

In the autopsy series the extremes of age were twenty-seven and eighty-five years. Table IV shows the age distribution in the hospital and autopsy series in comparison with a collected series.

The most frequent anatomical site of carcinoma of the pancreas is the head of the gland. Table V compares the anatomical distribution of the hospital and autopsy series with that of a series collected from 11 authors.

### Table V: Carcinoma of Pancreas: Anatomical Location of Tumor

<table>
<thead>
<tr>
<th>Series</th>
<th>Head</th>
<th>Body</th>
<th>Tail</th>
<th>Diffuse</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collected series*</td>
<td>300</td>
<td>38</td>
<td>29</td>
<td>184</td>
<td>551</td>
</tr>
<tr>
<td>University Hospital</td>
<td>22</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Autopsy series</td>
<td>60</td>
<td>4</td>
<td>15</td>
<td>18</td>
<td>97</td>
</tr>
<tr>
<td>Total</td>
<td>382</td>
<td>43</td>
<td>45</td>
<td>208</td>
<td>678</td>
</tr>
<tr>
<td>Percentage</td>
<td>56.3</td>
<td>6.3</td>
<td>6.6</td>
<td>30.7</td>
<td>100</td>
</tr>
</tbody>
</table>

* Series collected from Lanceraux, Mirallié, Oser, Boldt, Kiefer, Anelet, Biich, Heiberg, Pearce, Germershausen, and Segrè.

**Metastases and Extensions from Carcinoma of the Pancreas**

Metastases first appear in the regional nodes and liver. Bard and Pic have stated that liver metastases consist of numerous minute nodules without any demonstrable enlargement of the liver, in contrast with the bulky metastasis from gastric carcinoma. Heiberg found liver metastases in nearly all his cases, but during life these had given no palpable findings and therefore were not of diagnostic value. In many of the cases in this series the livers were markedly enlarged, and some of the metastatic nodules measured 4 to 5 cm. in diameter. Oser also states that bulky metastases from carcinoma of the pancreas may occur in the liver.

The next most frequent site of metastasis or extension are the tissues adjacent to the pancreas. The stomach, colon, small intestine, common bile duct, gallbladder, adrenals, and kidneys are frequently invaded. Generalized carcinomatosis of the peritoneal cavity is sometimes seen. Metastasis to the thorax and extension through the diaphragm to the pleura and lungs is not uncommon.
However, generalized metastases are not frequent, for the disease is quite rapidly fatal. The metastases and extensions as found in our autopsy series were as follows:

<table>
<thead>
<tr>
<th>Metastasis</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>69</td>
</tr>
<tr>
<td>Regional nodes</td>
<td>50</td>
</tr>
<tr>
<td>Adrenals</td>
<td>13</td>
</tr>
<tr>
<td>Spleen</td>
<td>11</td>
</tr>
<tr>
<td>Carcinomatosis of peritoneum</td>
<td>11</td>
</tr>
<tr>
<td>Lungs</td>
<td>11</td>
</tr>
<tr>
<td>Gallbladder and ducts</td>
<td>10</td>
</tr>
<tr>
<td>Extension through diaphragm</td>
<td>7</td>
</tr>
<tr>
<td>Pleura</td>
<td>5</td>
</tr>
<tr>
<td>Peribronchial nodes</td>
<td>5</td>
</tr>
<tr>
<td>Kidneys</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total Cases</strong></td>
<td><strong>99</strong></td>
</tr>
</tbody>
</table>

It is of interest that in three instances metastases occurred in the left supraclavicular nodes and in one of these cases the metastatic node was the presenting complaint. Peritoneal and skin transplants appeared in one case following paracentesis. Dyspnea in one patient was due to a metastatic mass surrounding the trachea, esophagus, and pulmonary vein, with invasion of the pulmonary artery.

Obstruction of the ureters was caused by metastatic nodes along the common iliac vessels in one instance. Soyka reported a similar case of complete obstruction of the ureters by metastatic nodes, with anuria and uremia. In another case erosion by the tumor led to spontaneous formation of an entero-anastomosis and enterocolostomy.

The more common results from local extension are: (1) obstruction of the duct of Wirsung with the development of chronic interlobular fibrosis of the pancreas; (2) obstruction of the common bile duct with resultant jaundice and dilatation of the gallbladder (Lachmann reported one case in which the tension in the gallbladder was so great that spontaneous rupture occurred); (3) duodenal or pyloric compression causing partial obstruction and in some cases requiring gastro-enterostomy for relief; (4) pressure on the portal vein or vena cava causing edema and ascites.

**Clinical Features**

The characteristic syndrome of Bard and Pic consisted of progressive jaundice without remissions, distention of the gallbladder, absence of hepatic enlargement, subnormal temperature, and rapid emaciation and cachexia.

*Cachexia:* Cachexia, weight loss, anorexia, and weakness were
the most constant symptoms in the hospital series studied. Speed reported cachexia in 90 per cent of his cases. Kiefer found it to be the first symptom in 22 cases and present in 29 of 33 cases.

Futcher found marked weight loss in 29 of 31 cases. The loss is rapid due to anorexia and impaired absorption of food because of the exclusion of bile and pancreatic juice from the intestine. All of the cases in this series showed some weight loss. The average was 32 pounds, the maximum 75 pounds. The rate of loss was 1 pound per 3.12 days or approximately 10 pounds a month. Mussey in his series found an average weight loss of 26 pounds.

**Jaundice:** Jaundice is perhaps the next most frequent symptom and is usually progressive, becoming extreme in many cases. Occasionally cases of intermittent jaundice may be seen in carcinoma of the pancreas. Three cases in this series showed definite remissions. Hartman, in a study of 400 cases of jaundice, found carcinoma of the pancreas to be the cause in 11.75 per cent of cases. Opie, Mirallié, Friedenwald and Cullen, Futcher, Speed, and Kiefer all found jaundice in from 70 per cent to 80 per cent of their cases. Pruritus accompanied the jaundice in about one-half of these cases.

Jaundice is not always painless, as is frequently stated, but may be accompanied by attacks of colic and pain similar to those seen in cholelithiasis with gallstone colic.

Wangensteen states that most patients with occlusion of the common bile duct stand biliary obstruction well for a few months and then suddenly manifest symptoms of severe intoxication, probably due to destruction of the liver tissue *per se*, together with diminution of liver function.

**Pain:** Futcher in his series found pain to be the earliest and most persistent symptom. Speed, Kiefer, Friedenwald and Cullen, and Eusterman reported pain in from 60 per cent to 80 per cent of their cases. In our hospital series all of the patients complained of pain. Gross states that characteristic pain is found relatively early in pancreatic carcinoma.

There are three types of pain which may occur in these cases.

1. A steady, severe, dull mid-epigastric pain radiating to the lower back.
2. A colicky pain in the right hypochondrium radiating to the right scapular region and resembling gallstone colic. Six patients in the hospital series had this type of pain and two of these required morphin during the attacks for relief.
3. A paroxysmal attack of pain beginning near the umbilicus and at times resembling tabetic crises. This type of pain is thought to be due to pressure on the celiac plexus.

Chauffard described a "pancreatico-solaire" syndrome for
carcinoma of the body of the pancreas. He believed that pressure on the solar plexus, which lies just behind the posterior surface of the body, was the cause of this paroxysmal type of pain. Musseay recorded pain in 88 per cent of his cases. He felt that the constancy of the pain might be due to pressure on or involvement of the solar plexus.

One patient in our autopsy series for two months prior to death had attacks of severe epigastric pain requiring morphin for relief. Post-mortem examination of the tissue in the region of the celiac plexus showed infiltration of the sympathetic nerve trunks by tumor tissue, causing extensive compression of these trunks (Fig. 1).

**Fig. 1. Carcinoma Invading a Nerve in the Region of the Celiac Plexus**

**Nausea and Vomiting:** Nausea and vomiting may be due to intestinal or pyloric obstruction, stimulation of the vagus, or exclusion of bile and pancreatic secretion from the intestine. They were common symptoms in the cases of Friedenwald and Cullen (89 per cent) and Kiefer (61 per cent). In our hospital series nausea and vomiting were present in 56 per cent of the cases.

**Constipation and Diarrhea:** Constipation is much more frequently seen in these cases than diarrhea. In the cases with jaundice the stools are acholic. Bulky stools are not frequently seen, as secretory anomalies of the pancreas are not always reflected in the stools since bacteria can duplicate all phases of enzymic digestion. McClure, Vincent and Pratt found that depancreatized dogs could often utilize a considerable percentage of the fat of the food ingested.

**Temperature Variations:** A normal temperature or, during the latter stages of the disease, a subnormal temperature was included
in the characteristic syndrome of Bard and Pic. Heiberg, Gross, and others state that the temperature depression seen in carcinoma of the pancreas is no greater than in other types of carcinoma, and that it is only the result of a disease causing high-grade malarial conditions. Futcher found an intermittent fever in one-third of his series.

Three patients in our hospital series had chills and fever, and one other had an elevated temperature alone. Three cases showed a subnormal temperature, while in the remainder the temperatures were normal.

**Family History:** The family history seems to be of little significance in relation to the disease. Four of the patients in this series had a history of cancer in the immediate family.

**Past History:** Eight of our hospital series of 32 had had typhoid fever. In this age group (fifth to seventh decade) a history of typhoid fever is more common due to its greater incidence before the more general observance of sanitary measures. Eusterman states that typhoid fever, dental sepsis, and syphilis seem to be more important in the etiology of carcinoma of the pancreas than a positive family history of carcinoma.

**Physical Findings:** The most significant and frequent physical findings are emaciation, jaundice, distention of the gallbladder, and enlargement of the liver.

E maciation may be extreme and, as previously indicated, is due to both loss of appetite and interference with digestion and absorption of food because of the exclusion of bile and pancreatic juice from the intestine. In 88 per cent of this series emaciation was marked.

Jaundice is perhaps the most striking finding in these cases. Its frequency is due to the predilection of the tumor for the head of the pancreas, though Kiefer reports one case in which jaundice was due to a metastatic node from the tail of the pancreas, pressing on the hepatic ducts. Germershausen found icterus present in 53 of 107 cases which he had collected. Nearly all authors stress the remissionless course of the jaundice. In two-thirds of the cases in our hospital series jaundice was observed on physical examination.

Kehr has stated that jaundice may lead to slowing of the pulse, somnolence, comatose states, and above all to the hemorrhagic diathesis, causing bleeding into the gastro-intestinal canal, the skin, the serous cavities, joints, and mucous membrane of the mouth. In 4 cases in the hospital series studied there was evidence of rather extensive hemorrhage into the gastro-intestinal tract. In one of the cases death was sudden and accompanied by severe pain. Post-mortem examination revealed large hemorrhagic casts
of the small bowel. In another case there was slow postoperative bleeding into the gastro-intestinal tract, controlled only after repeated transfusions of large amounts of whole blood. Frequently this latent bleeding is slow and insidious, causing no change in blood pressure, but close observation usually reveals an increasing pallor beneath the jaundice and hemoglobin estimations verify the diagnosis.

In a comprehensive review Wangensteen pointed out that the retention of bile in the organism is probably not responsible *per se* for the hemorrhagic diathesis of obstructive jaundice, but that the destruction of liver tissue and the diminution of liver function consequent upon the biliary obstruction would appear to be the chief etiologic factors. He also stressed the value of early relief of biliary obstruction in the avoidance of hemorrhage, and the use of intravenous injections of calcium chloride and the transfusion of unmodified blood.

The liver was found to be enlarged in 81 per cent of this series. In 5 cases the increase in size was due to metastasis alone, since no jaundice was present; in 11 cases bile stasis was the causative factor, no metastasis being demonstrable. It is a well known fact that stasis in the biliary tract may lead to hepatic enlargement. Bard and Pic deny that liver enlargement is ever due to metastasis from carcinoma of the pancreas. Kiefer noted that the liver was palpable in 26 of 33 cases.

Courvoisier's law is well demonstrated by this group of cases. Dilatation of the gallbladder was a cardinal point in Bard and Pic's syndrome. This dilatation is important in differentiating between biliary obstruction due to stone and that due to new growth. Ecklin, in a study of 172 cases of common duct stone, found the gallbladder dilated in only 28, while in 139 cases of obstruction due to other causes the gallbladder was distended in 121 and in 61 cases of carcinoma of the pancreas the gallbladder was dilated in 58. In Kehr's material the gallbladder was palpable as a distended tumor in more than one-half the cases of carcinoma of the pancreas, while in obstruction of the common duct by stone the gallbladder was contracted in 80 per cent of the cases. Heiberg believes that an enlarged gallbladder is of diagnostic significance on the operating table, but is not frequently of clinical significance in examination of the patient. Futcher found dilatation of the gallbladder in two-thirds of his cases. In one the gallbladder ruptured spontaneously, as in the case reported by Lachmann.

In our series the gallbladder was palpable in 14 of 20 cases presenting jaundice. At operation 13 of 15 gallbladders were found to be distended and 12 of these had been palpable prior to operation.
A tumor mass other than the liver and gallbladder was found on physical examination in 7 cases. Oser, Futcher, Kiefer, and Friedenwald and Cullen found a palpable tumor in from 20 to 40 per cent of their cases. The mass is usually in the epigastrium, although it may be found in either the right or left upper quadrant of the abdomen. The tumor is usually fixed and if overlying the aorta may transmit pulsations to the abdominal wall. If the aorta is compressed, a systolic bruit may be heard over the tumor.

Tenderness over the abdomen is commonly present but is not usually marked nor of diagnostic significance. Tenderness was noted in two-thirds of our cases, usually in the epigastric region or over the liver or gallbladder. Friedenwald and Cullen found tenderness in 70 per cent of their cases.

Ascites and edema are due to pressure on the portal vein or vena cava, secondary liver involvement, biliary cirrhosis, and carcinomatosis of the peritoneal cavity. Occasionally chylous ascites may be seen secondary to pressure on the receptaculum chyli, as pointed out by Andrews. Naturally ascites represents a late stage of the disease.

Edema was found on physical examination in 11 cases and ascites in 7 cases of this series. In 24 autopsies in the hospital series ascites was present in 13, the amount of fluid varying from a few hundred cubic centimeters up to 3,000 cubic centimeters. In our second series of 99 autopsies ascites was found in 48. Occasionally intestinal obstruction ensues, due to pressure on the gastro-intestinal tract from extension of the primary tumor. Superficial veins over the abdomen may be dilated in cases of obstruction of the vena cava.

While peripheral lymph nodes are rarely enlarged, a left supraclavicular node was the first complaint in one of our hospital cases. As previously mentioned, in two instances in the autopsy series there were supraclavicular and cervical metastases on the left side.

It has been frequently stated that bradycardia may be an effect of jaundice. In 8 of our cases with jaundice the pulse rate was consistently below 70 per minute.

X-ray Findings: Roentgenographic study of the gastro-intestinal tract, when correlated with the clinical findings, may be of definite diagnostic value. The typical picture of widening of the duodenal curve is not always present, but other encroachments on the duodenal lumen may be suggestive. As a method of excluding from the diagnosis carcinomas of the gastro-intestinal tract and renal tumors it is very useful.

Speed had two positive x-ray diagnoses in a series of 23 cases, while Kiefer in 13 cases had no positive diagnosis and concluded that x-ray examination was chiefly of negative value.
Gastro-intestinal examination by x-ray was carried out in 24 of the 32 cases in our hospital series. In 3 cases the picture was definitely that which would be presented by a tumor of the head of the pancreas. In 3 others the findings were suggestive of a tumor in that region, while in the remaining 18 the examination was of no aid in establishing diagnosis of carcinoma of the pancreas. It is of interest that all of our positive diagnoses were made in the last four years, which indicates that more positive roentgenographic aid is possible if this condition is continually borne in mind.

Urine Examination: In cases of complete biliary obstruction the bilirubin content of the urine is usually increased, while urobilin and urobilinogen are absent. In 10 cases of our hospital series a test was made for urobilin; it was absent in 9.

Glycosuria is an infrequent finding in carcinoma of the pancreas and when present is usually intermittent in type. It was observed in 3 cases of this series and in 2 of these there was a definite previous history of diabetes. Pearce, Eusterman and others believed that glycosuria occurred in less than 10 per cent of cases and usually was intermittent in character.

Certain cases of such complete destruction of the pancreas by carcinoma as reported by Hansemann and by Litten are analogous to the extirpation experiments of von Mering and Minkowski. Absence of glycosuria is explained by these authors by assuming that tumor cells arising from the parenchyma inherit the function of internal secretion peculiar to the islands of Langerhans. This would presuppose that all primary carcinomata arise from the islands of Langerhans. In view of the fact that experimental diabetes does not result if one-fourth to one-fifth of the gland is spared, it is probable that persistence of insular tissue accounts for the absence of diabetes.

Warren reports a case of a woman aged sixty-nine years who had suffered from diabetes in a relatively mild form for ten years. A few months before death there was a marked increase of insulin requirement, 50 to 100 units a day being necessary. At autopsy a large carcinoma of the pancreas was found, which had destroyed the bulk of the gland. In 300 autopsied cases of diabetes, Warren found some form of malignant disease present in 12; 2 of these were carcinoma of the pancreas.

Much work has been done on the quantitative estimation of amylase in the urine in pancreatic disease since Wohlgemuth devised a quantitative test in 1908. Geyelin and others have shown that the diastatic value of the urine of normal individuals varies within very narrow limits and for a given individual is constant provided a twenty-four hour specimen of urine is used.
In cases of pancreatic disease the diastatic value is often definitely increased. This test, although not pathognomonic of pancreatic disease, has been shown by others to be of definite corroborative value. In our series no estimations of diastatic activity of the urine were made.

**Gastric Contents:** The acidity of the gastric contents may be normal, but hypacidity and anacidity are not uncommon. In 5 of 10 cases Heiberg found complete or nearly complete lack of free hydrochloric acid. Speed found hypacidity in 5 of 26 cases, while Friedenwald and Cullen found an anacidity or hypacidity in 14 of 18 cases. In our series a study of the gastric contents was carried out in 16 cases following a test meal, and in 8 there was an absence of free hydrochloric acid.

**Duodenal Contents:** McClure, Jones and Reynolds studied the enzymic concentrations of duodenal contents and believe that they are an index of the secretory function of the pancreas and that abnormalities are found only in the presence of some lesion involving the pancreas primarily or secondarily. Crohn states that total absence of bile or pancreatic juice in the duodenal contents is found only in malignant obstructions of the common bile duct or pancreatic duct. Duodenal findings seem to point clearly to the fact that stones do not completely block the ducts, while neoplasms usually do. In two cases in this series in which such a study was carried out, bile was absent and the enzymic concentrations were markedly diminished.

In cases in which there is difficulty in differentiating whether an obstruction at the ampulla is due to stone or neoplasm, examination of the duodenal contents should prove of definite value.

**Examination of Blood:** There is usually a secondary anemia in carcinoma of the pancreas. According to this study it is not severe, the average of hemoglobin readings being 79.4 per cent. A moderate polymorphonuclear leukocytosis was found in about one-half of our cases, 16 having leukocyte counts above 8,000 per c.mm. and 16 having counts below 8,000 per c.mm.

An estimation of the icterus index of the blood serum (as compared to a standard potassium dichromate solution according to the method of Farahough and Medes) was made in 12 cases. In 10 of these the icterus index was above 90 units, the average being 136.2 units, with a maximum of 288 units. In 3 cases in which a cholecystenterostomy was performed the icterus index was reduced postoperatively, from 96 units to 20 units, from 118 to 32 units, and from 112 to 16 units.

Elman, Arneson and Graham are of the opinion that the determination of blood amylase is of undoubted clinical value both in excluding suspected disease of the pancreas and in adding con-
clusive confirmatory evidence when the clinical picture is indefinite or vague. They use a method of determining blood amylase dependent on the rate of diminution of the viscosity of a starch solution, and find that the normal values vary within narrow limits. Low amylase values they consider indicative of more or less complete atrophy of the acinar cells, and high values as due to obstruction of the ducts leading to increased absorption in the blood. No estimations of blood amylase values were made in our series.

Blood sugar values were elevated in five of our cases, but two of these definitely had diabetes mellitus. In none of the other three was glycosuria present.

Blood urea nitrogen findings were consistently within normal limits except for a terminal elevation in two cases.

According to Linton, bleeding and coagulation time determinations do not seem to be reliable criteria in predicting a tendency to latent hemorrhage in obstructive jaundice. He considers the sedimentation rate a more accurate index and believes that patients with obstructive jaundice who have a rapid rate in the absence of fever are apt to bleed.

The clotting time was prolonged in 6 of 19 cases in our series.

Stool Examination: Stool examinations are of value in determining the presence of blood, bile, increased fat content, and undigested meat fibers. Melena, if present, may be due either to erosion of a vessel in the gastro-intestinal tract by carcinomatous extension or to a hemorrhagic diathesis often an accompaniment of jaundice.

Blood in the stool as determined by chemical tests was present in 6 of 16 cases in which such examination was made. In 4 of the 6 cases there was a co-existing jaundice.

Microscopic fat was present in 9 cases and undigested food particles in 5 cases. Tests for bile showed an absence in 10 cases of 11 so studied. Following cholecystenterostomy in 3 of these the stools became normal.

Duration of Illness after Onset of Symptoms: Mayo-Robson found that the average duration of the disease was six to eight months, while in Heiberg's cases the course was but half as long. In Friedenwald and Cullen's series the average course was 8 months.

Of the 32 hospital cases in this series the average duration from the onset of the first symptom was 6.3 months, in the operated cases 6.7 months, and in the unoperated cases 6.1 months. The maximum in the operated series was 17.5 months and in the unoperated series 12 months.
Diagnosis

A correct clinical diagnosis was made preoperatively and, in the unoperated cases, prior to death in 21 cases. Since the majority of the tumors are located in the head of the pancreas, a correct diagnosis should be made in a high percentage of cases. Lesions in the body or tail of the pancreas are extremely difficult and often impossible to diagnose correctly. In cases showing no jaundice a correct clinical diagnosis could be made in only 30 per cent in Eusterman's series.

In differential diagnosis the following conditions must be considered: obstruction of the common bile duct due to stone, chronic pancreatitis associated with jaundice, carcinoma of the gallbladder, carcinomas of the common bile duct, ampulla of Vater, and duodenal mucosa, carcinomatous metastasis to the liver, biliary cirrhosis, and acute catarrhal jaundice. If there is occlusion of both the biliary tract and the pancreatic duct by malignant tumors other than those arising in the pancreas, an accurate diagnosis cannot be made. Moynihan states that there are some cases of obstructive jaundice in which it is impossible to achieve a correct diagnosis by any other method than exploratory incision of the abdomen.

Treatment

Most of the therapy both medical and surgical is directed toward palliation.

High-voltage x-ray therapy was used in 4 cases of this series and in only 3 was a full course completed. Two of the 4 patients died before the effect of the x-ray dosage was complete, while the other 2 survived two months and five months respectively. Inasmuch as a cholecystenterostomy had been performed in each of these cases, it is difficult to evaluate any change in their condition.

In one of our cases gold implants of radium emanation were placed in and about a small tumor in the head of the pancreas at the time that a cholecystogastrostomy was performed. Unfortunately the patient bled spontaneously into the gastro-intestinal tract and died on the third postoperative day.

Surgical Treatment: In 1903 v. Mikulicz stated that operative interference for diseases of the pancreas was an incomplete chapter for three reasons: (1) the topographical location, rendering approach to the pancreas very difficult; (2) the difficulty of diagnosis; (3) the dangers of operation. Usually these patients are in poor general condition; hemorrhage in the pancreas is difficult to control, and there is danger of leakage of pancreatic secretion postoperatively.

Coffey points out that as far as surgical work is concerned the
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pancreas has the fundamental defect that it is devoid of peritoneum. The fat-splitting ferment of pancreatic juice evidently will not penetrate the peritoneum to any serious extent.

Sauvé and Desjardins, working independently, developed a technic for partial and total pancreatectomy. The operation consists of (1) anastomosis of the gallbladder or common duct to the stomach or duodenum; (2) gastro-enterostomy; (3) resection of the head of the pancreas and duodenum; (4) implantation of the remainder of the pancreas into the jejunum. (Sauvé brought the pancreatic stump to the skin forming a pancreatic fistula.) Coffey successfully developed a similar operation experimentally in dogs. Kausch, using an operation similar to that of Sauvé and Desjardins, did only a cholecystenterostomy as a first stage. After the patient had recovered, the operation was completed at a second sitting. Redwitz pointed out that the immediate mortality in radical operations for carcinoma of the pancreas was 50 per cent and that no patient survived more than six months. Guleke found only 3 cases in the literature in which such a duodenopancreatectomy had been performed, and only Kausch's patient had survived over a long period, nine months. In Kausch's case the operation had been performed for a carcinoma at the papilla of Vater.

Crohn states that in a person over middle age who becomes deeply jaundiced, whether painlessly or not, and shows evidence of complete blockage of the ducts, exploration should be done at once; a cholecystenterostomy at this time will be of greater assistance to the patient and a dangerous delay is avoided. At exploration some difficulty may be experienced in differentiating carcinoma of the pancreas and a chronic fibrosis. Cullen and Friedenwald reported 3 such cases, all clearing up after cholecystostomy. Judd and Parker reported a similar case which became symptomless after cholecystenterostomy.

In many cases of severe jaundice marked relief is obtained following operations anastomosing the biliary tract to the upper gastro-intestinal tract. Judd and Parker found that the life expectancy of those surviving the operation was 7.7 months and that 63.63 per cent were completely and permanently relieved of jaundice.

Kehr had 71 patients with carcinoma of the pancreas in whom a palliative operation was carried out. Ten of these were alive two years after the operation. Guleke cites one patient who survived a palliative cholecystenterostomy more than two and one-half years. Murphy in 1897 stated that the operative mortality of cholecystenterostomy was exceedingly high in cases of obstruction due to malignancy. Ten of twelve patients with malignant
obstruction of the lower biliary tract so treated died while only 3 patients in 67 in whom the obstruction was non-malignant died.

Speed points out that in all operations on the biliary tract the pancreas should be carefully palpated, since in several cases a cholecystectomy has been performed without examination of the pancreas, thus removing the best means of palliative treatment for a biliary obstruction which later proved to be due to carcinoma of the pancreas.

In the series here reported three types of operation were carried out: (1) simple exploration, in which, due to the extensive pathologic findings, no palliative procedure could be done; (2) cholecystostomy; (3) cholecystogastrostomy or cholecystoduodenostomy. The results of these procedures are shown in Table VI and compared with a similar series by Kiefer.

<table>
<thead>
<tr>
<th>Table VI: Results of Treatment in Carcinoma of the Pancreas</th>
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<tbody>
<tr>
<td><strong>Number of Cases</strong></td>
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<tr>
<td><strong>Simple Exploration</strong></td>
</tr>
<tr>
<td>Kiefer ................. 8</td>
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<tr>
<td>Present series .......... 6</td>
</tr>
<tr>
<td><strong>Cholecystostomy</strong></td>
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<tr>
<td>Kiefer ................. 4</td>
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<tr>
<td>Present series .......... 3</td>
</tr>
<tr>
<td><strong>Cholecystenterostomy</strong></td>
</tr>
<tr>
<td>Kiefer ................. 9</td>
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<tr>
<td>Present series .......... 8</td>
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That cholangitis frequently follows anastomosis between the gallbladder and the gastro-intestinal tract is a well established fact in experimental surgery. Beaver states that, regardless of the time after operation, inflammatory changes developed in the liver and gallbladder, varying from round-cell infiltration with replacement by fibrous connective tissue to acute purulent inflammation with extensive destruction, necrosis, and abscess formation. He feels that absence of clinical evidence of such infections does not preclude the possibility that pathological changes in the biliary tract and liver are occurring in patients who have been subjected to cholecystogastrostomy. Gateswood and Lawton conclude that, because of the potential danger of ascending biliary infection, such anastomoses should not be done for other than the most definite indications.

Judd and Parker found a partial or complete contraction of the stoma in 9 cases in a series of 137 cases in which anastomoses of
the biliary and gastro-intestinal tracts were carried out. Reconstruction of the stoma was carried out in each instance. Wangensteen is of the opinion that narrowing or partial occlusion of the stoma following these anastomotic operations is the important factor in determining whether the complication of cholangeitis will follow. He reports a case which it is of sufficient interest to review briefly.

The patient, a white male aged fifty-four, was admitted to the University of Minnesota Hospital, complaining of painless jaundice of three months’ duration, anorexia, loss of strength, and loss of weight. Physical examination showed moderate emaciation, a deep jaundice, an enlarged liver, and a palpable gallbladder. A cholecystoduodenostomy was done for a carcinoma of the head of the pancreas. The patient was relieved of symptoms for six months, after which he developed chills and fever, accompanied by a slight jaundice. Two months later he was re-admitted to the hospital and during a period of observation showed a daily range of fever from 99° to as high as 104°. After drainage of the hepatic ducts there was an immediate drop in temperature to a normal level. Later, attempts to anastomose the hepatic ducts to the duodenum and to the pyloric end of the stomach were unsuccessful and the patient died fifteen months after the initial cholecystoduodenostomy. Post-mortem examination showed the gallbladder to be buried in a bed of fibrous adhesions, the cystic duct practically obliterated, and the stoma of the anastomosis considerably narrowed.

In the autopsy series of the Department of Pathology of the University of Minnesota are 13 cases in which anastomoses were made between the gallbladder and the gastro-intestinal tract. In 12 of these cases an anastomosis was made between the gallbladder and duodenum or pyloric end of the stomach. In one case the anastomosis was to the colon.

Bell states that in obstructive jaundice the degree of hepatic change depends upon the duration and completeness of the obstruction. At first there are pigmentation, atrophy, and necrosis of the centers of the lobules, dilatation of the bile capillaries, frequently with rupture and portal leukocytic infiltration. Thereafter there is a gradual increase in the amount of portal connective tissue with evidence of regeneration of hepatic cells. The portal infiltration in obstructive jaundice is usually of round cells. Therefore, in the single microscopic sections of the liver studied for evidence of cholangeitis, only in those cases in which definite polymorphonuclear leukocytes were seen in or about the duct system was a diagnosis of suppurative cholangeitis made. In 4 cases there was definite evidence of suppurative cholangeitis, which in one instance had gone on to abscess formation. It is of interest to note that in one case in which a definite clinical cholangeitis was relieved by surgical drainage of the ducts, the microscopic sections of the liver at autopsy showed no more hepatic change than a normal liver at that age.
Fig. 2. Microscopic sections showing cholangitis following cholecyst-enterostomy, from autopsy specimens

A. Twenty days after operation. B. Thirty days after operation. C. Thirty-four days after operation. D. Two-hundred and ten days after operation.
The sections showing cholangitis in this series were taken from livers at autopsy 20, 30, 34 and 210 days after cholecystenterostomy (Fig. 2). In one case the data were sufficient to determine that there was no clinical evidence of cholangitis present. It is therefore evident that cholangitis is not an uncommon complication following anastomosis between the biliary and gastro-intestinal tracts and that cholangitis may be present without presenting the typical clinical picture.

**Fig. 3. Section Taken at Autopsy, Four Hundred and Thirty-Four Days After Cholecystenterostomy**

A definite cholangitis had been relieved by drainage nine months previously. Section shows normal liver cells with some portal infiltration.

**Summary**

1. Primary carcinoma of the pancreas represents 1 to 2 per cent of all carcinomas.
2. It is a disease having its maximum incidence in the 5th and 6th decades.
3. Males are twice as frequently affected as females.
4. The head of the pancreas is the site of predilection, being affected in about 60 per cent of cases.
5. The most prominent characteristics of the disease are rapid cachexia, pain, jaundice, and enlargement of the liver.
6. Surgical intervention offers the best means of palliation in cholecystenterostomy; radical excision of the tumor may prove to be of some value when done in stages.

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