CARCINOMA OF THE PERIPAPILLARY PORTION OF THE DUODENUM

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PART TWO

Age and Sex Incidence.—In this series of 222 cases, there were 139 males (five Negroes), varying in age from 15 to 81, an average age of about 53.4, and 83 females, varying in age from 24 to 82, an average age of 55.3. It was surprising to find a relatively large number of comparatively young individuals in this group. There were six males, age 15, 16, 18, 34, 34 and 34, respectively, and seven women, age 24, 29, 32, 33, 33, 34 and 36, respectively.

It is practically impossible to make an accurate estimate of the true incidence of carcinoma of the peripapillary region of the duodenum from the statistical analyses of the cases that have been reported, predicated upon the requirements for their acceptance, as set forth in the present communication. Owing to the impulse to report new studies of this unusual condition, one finds the literature cluttered up with many case reports that are not genuine examples, and the misinformation thus established is propagated in succeeding reports. Our own cases were selected as carefully as possible, and a number of additional cases, listed under the diagnosis of carcinoma of the duodenum, from the records of the Philadelphia General Hospital were rejected because we were not personally satisfied with the interpretation of the clinical and pathologic findings. Many authors have repeatedly stated that the second portion of the duodenum undergoes malignant transformation far more frequently than the other segments. In general, this is true if it applies to all the epithelial structures comprising the papilla of Vater, that is, the intestinal mucous membrane, terminal common bile and pancreatic ducts and ampulla of Vater. As shown above, however, even after the most painstaking review and study of the anatomic specimen, including microscopic examination, it is frequently impossible to determine the exact source of the neoplasm. Until more and better information is obtainable, it will be impossible to affirm or deny the belief that the intestinal mucosa of the second portion of the duodenum (peripapillary region) is the segment most susceptible to cancer. It is,

likewise, futile to compare the incidence of duodenal carcinoma with that of the rest of the small intestine.

Fourteen cases (13 of our own, and one reported by Boston and Jodzis) were observed at the Philadelphia General Hospital among 22,152 autopsies, from January 1, 1920, to December 31, 1936, and of these, 2,687 showed carcinoma, an incidence of 0.063 per cent of all autopsies, and 0.52 per cent of all carcinomata. Four cases (one of which has been reported elsewhere) from the Jefferson Hospital, from the findings in 4,154 autopsies, among which were 352 carcinomata, give an incidence of 0.096 per cent of all autopsies, and 1.13 per cent of all carcinomata.

Anatomy of Papilla of Vater.—The major duodenal papilla is situated in the medial aspect of the descending portion of the duodenum, 7 to 10 cm. from the pylorus. The undistended papilla is 5 Mm. in length. Above it is often a hood-like fold (*valvula connivens*) and below it a variable fold or frenum which forms a continuation of the plica longitudinalis. Its structure is essentially that of the duodenum with the ampulla of Vater passing through its center. The duodenal surface is covered by mucous membrane containing villi and glands of Lieberkühn and is continuous with that of the intestine. The submucosa consists of firm connective tissue in which Brunner's glands are dispersed with greater frequency than is usually indicated. For the detailed description of the external surface of the papilla with its relation to the surrounding intestinal musculature, together with the relation of the terminal portions of the common and pancreatic ducts, the reader is referred to a recent description by Dardinski.

The results obtained, with regard to the presence of an ampulla and the point of termination of the common and pancreatic ducts, vary. A true ampulla, in the sense of a small pouch or sacculation lying within the papilla, according to Letulle and Nattan-Larrier, is present in only one-third to one-fourth of all individuals. Holzapfel, in a study of 50 cases, found that the common and pancreatic ducts entered separately into the papilla in 30 cases, had a common entrance into the papilla in ten cases, entered separately into two papillae in nine, and in one, the union of the two ducts took place in the papilla itself. Dardinski states that true ampulla dilatation, within the papilla, is present only in those cases in which the two ducts unite 5 Mm., or more, from the outlet. In the remainder, both ducts are separated by a thin membrane formed by the adjacent walls of the pancreatic and common ducts which extends from the base of the papilla to the point where they unite. His results, based on a study of 100 cases, were as follows: 51 cases, both ducts emptied separately into the tip of the papilla. In 12 cases, both ducts united in the papilla 1 Mm. from its outlet, in five cases, 2 Mm. from its outlet, in 12 cases 3 Mm. from its outlet, in 10 cases, 4 Mm. from its outlet, in four cases, 5 Mm. from its outlet and in four cases, 1 cm. from its outlet. In one case, both ducts emptied separately into the intestine, and in another case, the pancreatic duct passed through the major papilla and the common

duct passed through a slit-like opening in the wall of the intestine 1 cm. below the tip of the papilla.

The intraduodenal portion of the common duct is composed of numerous longitudinal folds 2 to 3 Mm. in length and from 2 to 3 Mm. in width. The tip, or end, of one fold fuses with the tip, or side, of another fold forming by this union pockets or cavities around the entire inner surface of the papilla. In the final 1 to 2 Mm. of the papilla there is no fusion of these folds—on the contrary they hang free. The intrapapillary portion of the pancreatic duct contains similar folds, smaller in size but not as prominent, and they do not form pockets as described above. Such a complicated arrangement is not abnormal or the result of inflammatory adhesions but is present throughout life.

(I) Primary Carcinoma of the Ampulla of Vater.—Many cases are described in the literature, purported to be examples of primary carcinoma of the ampulla of Vater, but none of these fulfilled the rigid specifications set up for cancer of this origin. Case 15 presents the clinical record and protocol of an autopsy performed upon a subject who died of obstructive jaundice, incident to a small malignant polyp originating from the mucous membrane of the ampulla of Vater. The growth permeated the surrounding pancreas and muscular wall of the duodenum, but so far as we could determine it did not involve the surface epithelium of the intestinal mucosa or of the common bile or pancreatic ducts. This case is, therefore, presented as an original example of primary carcinoma of the ampulla of Vater.

(II) Primary Carcinoma of the Terminal Duct of Wirsung.—We have classified three cases from the literature in this group but have had no personal experience with this type of lesion. In Letulle and Verliac's case, the papilla of Vater was apparently normal. The pancreatic duct was considerably distended and a probe introduced into it did not pass into the ampulla of Vater, at which point the duct was completely obstructed. The terminal portion of the common bile duct was extremely narrow but still permeable, as a sound could be passed into it; the stenosis was partial and parietal, being situated 3 Mm. above the orifice of the ampulla of Vater at a point corresponding precisely to the obstruction in the duct of Wirsung. The gallbladder and bile ducts were markedly distended and the liver showed the typical effects of biliary stasis. The pancreas was firm, indurated and markedly atrophied. In Carnot and Harvier's case, the papilla of Vater appeared as a voluminous pedunculated mass the size of an ordinary lymph node, with numerous fine villous projections appearing through its orifice. A longitudinal section through the ampulla of Vater showed deviation of the common bile duct which was completely flattened but not entirely obliterated and was not involved by the new growth. The duct of Wirsung was markedly dilated and contained a firm, whitish, neoplastic mass, the size of a pea, taking origin from its inferior wall and extending into the wall of the duodenum to form a small indurated plaque immediately beneath the papilla of Vater. Numerous villous projections on the surface of the duct extended through the orifice of

the papilla into the duodenum. The cystic duct in its terminal portion was compressed by two enlarged lymph nodes. The gallbladder was dilated and pyriform; the extrahepatic and intrahepatic bile ducts were dilated; the liver showing the characteristic changes of biliary stasis and the pancreas appearing normal in consistency. In Hadfield's case, the biliary papilla was enlarged, prominent, and projected for 1 cm. into the lumen of the duodenum. A catheter was easily passed into its orifice for a distance of about 1 cm., where it met with an obstruction. The ampulla of Vater was exposed, and projecting into it was a white, firm spherical new growth, 1.5 cm. in diameter, arising by a broad base of attachment from the posterior wall of the pancreatic duct. The neoplasm half filled the ampulla, which appeared dilated, but its mucous membrane was not infiltrated. The common bile duct was deviated to one side by pressure of the primary neoplasm. The biliary and pancreatic ducts were widely distended. The regional lymph nodes were enlarged, fixed and secondarily involved. The pancreas was moderately firm and atrophic and the liver showed a mild biliary cirrhosis. Microscopically, all three cases were adenocarcinoma with anaplasia a pronounced feature in the last case.

(III) Primary Carcinoma of the Terminal Common Bile Duct.—The cases included under this heading will be considered in a separate communication dealing with primary carcinoma of the extrahepatic bile ducts. A brief summary of the morbid anatomy of this lesion is presented here for the sake of completeness, but these cases are omitted from the analysis in the clinical and statistical sections of this paper. Of 21 cases of primary carcinoma of the common bile duct, seven were located in the terminal segment of the duct. In one case, a small, round, firm, whitish mass, the size of a cherry stone, was implanted on an indurated base, at the point where the common duct entered the wall of the duodenum. In another case, the duct was normal for a distance of 2 cm. from the apex of the papilla of Vater, and then for a distance of 8 to 10 cm. it showed multiple, soft, vegetating tumor nodules, varying from the size of a pea to that of a small hazel-nut, with the mucosa in the intervals thickened, and hyperemic but not ulcerated. In five cases, the neoplasm formed a diffuse, firm, grayish or yellowish, stenosing type of growth usually 1 to 2 cm. in length and 4 to 5 Mm. in thickness. There were metastases in the regional lymph nodes and liver, and extension into the head of the pancreas in one case each.

(IV) Primary Carcinoma of the Intestinal Mucous Membrane Covering the Papilla of Vater.—Many authors have a tendency to derive neoplasms of the peripapillary region of the duodenum from the duodenal mucosa, but few offer any real proof for holding this belief. The intestinal mucous membrane was apparently the source of the neoplasm in three cases. In Borelius' Case 4, the papilla of Vater projected 1 cm. into the lumen of the intestine as a fine reddish-brown navel-like structure 0.5 cm. in diameter, villous on the surface. The mucous membrane of the common bile and pancreatic ducts was smooth and without noticeable change, although the primary neoplasm formed a papillary crown around the orifice of the former

and partially compressed the latter. Metastatic lesions were present in the liver. In Le Noir and Courcoux's case, a small villous tumor of the ampulla (papilla?) formed an oblong projection on the intestinal mucosa resulting in complete obstruction of the common bile and pancreatic ducts which were markedly dilated. Microscopically, the mucosa of both ducts was normal and the authors concluded that the neoplasm originated in the duodenal mucosa. In Countryman's case, the second portion of the duodenum was occupied by a cauliflower-like growth 12 cm. in length with its widest portion at the level of the papilla of Vater, where it encircled half the circumference of the bowel. The margins were raised and wavy and the tissue in the center was friable and grayish-pink. The common bile and pancreatic ducts opened separately through small orifices into the duodenum, 2 cm. below the papilla and, although they were both dilated above, their mucous linings were everywhere smooth. The terminal 1.75 cm. of the common bile duct was surrounded by the neoplasm, and metastatic lesions were present in the peripancreatic, periductal, perirenal and gastric lymph nodes and in the thoracic duct, liver, pancreas and lungs. Microscopically, an abrupt change from the normal duodenal mucosa to neoplasia was observed.

℮ (V) Carcinoma Involving All the Epithelial Structures of the Papilla of Vater Under Groups I, II, III and IV.—A large majority of all cases of carcinoma of the peripapillary region of the duodenum fall into this large indeterminate group. Since, as stated previously, the structures comprising this region are of small size, complex in arrangement, and variable in their anatomic relationships, the primary site of neoplasms arising anywhere in this area is quickly obscured owing to spread to adjacent tissues. This early involvement of adjacent tissues depends chiefly upon the close anatomic relationships of the structures in this region rather than rapid neoplastic proliferation, thus precluding the classification of these growths on any basis other than extent of involvement at the time of observation, as was done in the preceding groups. It is also difficult to make allowances for anatomic anomalies, since with extensive tumor formation and ulceration, variation or even absence of structure cannot be definitely ascribed either to congenital defect or neoplastic compression or destruction. Judging from the statistical data regarding the incidence of occurrence of an ampulla of Vater, it is reasonable to suppose that it was anatomically absent in a certain proportion of these cases. The fact, however, that descriptions of it were frequently lacking in the reports does not materially affect the proposed classification of these tumors. In no case was the intestinal mucous membrane of the duodenum indubitably shown to be free of neoplasm, and in the majority it was definitely proved to be involved.

One hundred and eighty-two cases (168 from the literature and our Cases 1 to 14) were classified under this heading. The duodenal neoplasms in this group varied in size from small, barely perceptible, localized thickenings or plaques of the mucous membrane of the papilla of Vater to a large cancerous mass 12 cm. in length spread throughout the second and into the adjacent first

and third portions of the duodenum. Between these extremes there were many variations.

The tumor was well limited to the papilla of Vater and not ulcerated in 103 cases. More than a third of these were described as vegetating, papillary or cauliflower-like, usually firm and inelastic and less frequently soft and friable. The majority varied in size from that of a pea to a pigeon's egg and three attained the dimensions of a small apple. At least one or more measurements were accurately stated in 22 cases, the average growth being 1.8x1.3x 1.3 cm., and the largest, 3 to 4 cm. in length. In many instances these limited growths formed a cylindrical or conical mass projecting into the lumen of the duodenum, sometimes freely movable or firmly fixed to the duodenal wall by a broad pedicle. In one case, the papilla was described as everted, in a manner not unlike that with stone impaction. The tumor masses were colored varying shades of white, gray and red, and cut section occasionally revealed small, yellowish, necrotic areas.

In 22 additional cases, in which the tumor was not ulcerated, there was extension on to the surface of the duodenum beyond the limits of the papilla. The latter structure under these circumstances was either displaced or its identity occasionally lost. At least one dimension was accurately stated in 16 of these diffuse growths, the average being 4.9x4.2x1.5 cm. The tumors were varying shades of gray, white, yellow and red, hard or soft, nodular or villous-like. Five were stenotic, four annular, and in three cases the lumen of the duodenum was almost entirely filled by a large fungating growth. Occasionally, the greatest dimension of the growth was in the transverse axis of the bowel causing distortion of the plicae, and in one instance resembling an enormous *valvula connivens*. Involvement of the wall of the duodenum was variable in extent. The tumor appeared superficial in some cases, extended deeply even into the head of the pancreas in others, and in one, formed a neoplastic mass on the serosa. Raviart and Lorthois' case exhibited two small tumors, one confined to the papilla of Vater and another 2 cm. below, apparently limited to the intestinal mucous membrane.

The proliferation and local spread of the neoplasm is obviously slow and indolent in many cases and its beginning inconspicuous. From the following, it may be concluded that, although with symptoms severe enough to call for surgical interference, the primary neoplasm may be actually undetectable by direct inspection and palpation. Observations on rapidity of growth were made in six cases. In Abell's Case 2, the papilla of Vater was everted into the lumen of the intestine in a manner not unlike that with stone impaction, and a biopsy was taken. At the second operation, 31 months later, a tumor mass 3.5 cm. in diameter involved the duodenum and pancreas. In Case 3, reported by the same author, the papilla formed a well defined projection 0.6 cm. in diameter, and, 10 weeks later, the growth measured 1.9x1.6x1.2 cm. In Santero's Case 1, the tumor at first measured 2x1.5 cm. and, 17 months later, a recurring mass 5x2.5 cm. was excised. Harbin, Harbin and Harbin stated that the tumor mass in the duodenum in their case was only

slightly larger two and one-half months after their initial observation. In Mateer and Hartman's case, a small mass of tissue was found in the region of the papilla and at autopsy, 22 months later, a papillomatous tumor, 4 cm. in diameter and elevated 2 cm., completely filled the lumen of the duodenum. Pemberton inspected the tumor in his case on three different occasions. Exploration of the duodenum at the first operation revealed nothing abnormal; three months later, a soft nodule 2.5x1.5 cm. was excised and at the third operation, 20 months later, a firm mass 10x12 cm. in diameter involved the second portion of the duodenum.

Ulceration occurred in 57 cases. The ulcer in 31 cases was fairly well limited to the enlarged papilla; in 22 of these it was quite small, superficial, and usually situated at the apex of the papilla, while in the remaining nine cases the ulcer varied in size up to 2 cm. in diameter, as a result of which the papilla was practically destroyed. In 26 cases there was ulceration well beyond the limits of the papilla, varying in size from 2 to 12 cm., the average of 12 stated measurements being about 4 cm. The papilla was completely destroyed in six of these cases, the terminal ends of the common and pancreatic ducts opening separately into the base of the ulcer. In one case the lower end of the common bile duct was laid bare for a distance of 1 cm. In three instances the papilla persisted in the center of an ulcer as a raw fungiform or mushroom-like, pea-sized projection. In a few, only one side or a portion of the papilla was destroyed. Some ulcers were centrally depressed and crater-like, with extension downward into the pancreas in two cases. The base was variously described as gray-yellow, pink, or green, black, shaggy, irregular, granular or worm-eaten, and firm, resistant, indurated or cartilaginous. The margins were usually firm and indurated, undermined in two cases, raised and rolled in eight, while in seven, the edges blended abruptly with the adjacent duodenal mucosa.

A statement regarding examination of the ampulla of Vater was made in 17 cases. This structure appeared to be congenitally absent in four cases, and in several others its presence or absence was difficult to establish owing to extensive ulceration and destruction of the papilla, the bile and pancreatic ducts under these circumstances opening separately into the base of ulcers as noted above. In six cases there was a neoplastic change on the surface of the ampulla varying from slight thickening of the mucous membrane to definite polypoid masses the size of a split-pea or larger, and in two, ulceration was also present. Almost complete obstruction or obliteration of the ampulla occurred in six cases. Occasionally small tumor masses projected through its orifice and were visible in the duodenum.

Biliary obstruction of some degree was present in all but four cases. Obstruction was complete in 44 cases, that is, the common duct was impervious to the passage of a sound, and pressure upon the gallbladder failed to elicit a flow of bile into the duodenum. Partial obstruction was said to exist in 28 cases. In the remainder, no statement was made regarding this feature. Jaundice may come and go in this condition and at least one mechanism involved

in spontaneous relief of obstruction is illustrated by Descos and Bériel's patient, in whom jaundice disappeared as the result of extensive ulceration of the papilla of Vater. Other mechanisms include increasing bile pressure sufficient to overcome the obstacle and absorption of inflammatory exudates and edema which may close the terminal orifice of the common bile duct. The four cases in which there was no biliary stasis or bile duct dilatation are of particular interest and are discussed below.

Common duct obstruction usually developed in the intramural segment due either to neoplastic stricture or to tumor growth within the lumen. Biliary stasis was further accentuated in a few cases by pressure of the primary duodenal tumor, metastatic growths in the pancreas or regional lymph nodes or by biliary calculi. In 43 cases the mucous surface of the terminal end of the common duct showed one or more elevated projections varying from slight granular excrescences to nodules or polypoid masses measuring as much as 2.4x1.5 cm. These were yellow, gray, friable, and occasionally ulcerated, in rare instances extending through the orifice of the duct into the lumen of the intestine. The annular neoplastic stricture, responsible for most cases of obstruction, is exemplified in the cases of Hultgren and Santero. In the former, the common duct, for a distance of 1 cm. from its point of exit into the intestine, was narrowed by an annular, infiltrating tumor mass, hard, sclerotic, grayish-white and 2 Mm. thick. In Santero's case, the terminal end of the duct was represented by a fibrous cord measuring 1x1 cm.

Dilatation of the common bile duct began, as a rule, well down in its terminal portion, 1 cm. or less from the apex of the papilla. In those cases, however, in which obstruction was due to a pancreatic lesion or cancerous lymph nodes, the point of constriction and of dilatation was correspondingly higher. The degree of distention of the common duct varied depending on the degree of obstruction, measuring 5 to 8 cm. in circumference with complete obstruction. The fluid content was dark brown, green, yellow, clear or white and thick, tarry, mucoid or watery. White bile was noted in nine cases, obstruction being apparently complete in all.

Common duct calculi occurred in seven cases, being multiple in five, and varied in size from fine sand or gravel to a spherical stone 5 cm. in diameter. Obstruction was not attributed solely to gallstones in any case. In a few instances the duct showed evidences of previous inflammation and thickening, and in one case (Murgoci) there was a bronchobiliary fistula with stones in the lung. In two cases, although stones were found in the common duct at autopsy, these were not palpated at previous operation and the gallbladder was free of calculi.

Obstruction of the duct of Wirsung was complete in 11 cases, definitely incomplete in 17 and probably incomplete in 37, while in 13 cases it was apparently unaffected. The duct of Santorini was obstructed and dilated in two cases and was said to be normal in three others. The exact mechanism by which obstruction of the duct of Wirsung was effected was not always clearly stated. It was probably most frequently brought about by compression

of the intraduodenal segment of the duct by the primary tumor or by secondary deposits in the pancreas. In two cases, however, obstruction was effected by occlusion of the orifice of the duct of Wirsung by tumor masses on the mucous surface. Proximal to the obstruction, the duct of Wirsung measured as much as 4.7 cm. in circumference in the head of the pancreas. The ductal dilatation extended into the finest ramifications and gave the organ a pitted honeycombed appearance with the formation of multiple cystic cavities 1 to 2 cm. in diameter. In a few cases, the pancreas was converted into a longitudinal cystic mass with the duct measuring as much as 1.8 cm. in circumference in its most distal portion, the residual parenchyma forming a thin mantle 1 to 6 Mm. thick. The ductal contents were pale, watery, clear, mucoid and sometimes black, yellow and green. Concretions were present in the pancreatic duct radicles in a single instance (Cade). In only one instance, apparently, was it possible to state that the common and pancreatic ducts were converted into a common communicating channel (Murgoci). Even in the cases in which the contents of the pancreatic duct were colored, it is doubtful that this was due to reflux of bile.

The pancreas was described in 117 cases, and in 25 of these it appeared normal. The pancreas was firm, indurated and fibrotic in 48 cases, in many atrophic and in a few enlarged. Abscesses were present in five cases and areas of fat necrosis in six, three of which followed celiotomy. Secondary neoplastic invasion of the pancreas occurred in 34 cases. Occasionally an ulcerated primary lesion in the duodenum extended downward into the pancreas and in a few, a well defined tumor mass was noted, but in the majority no further description of these secondary deposits was made. In Cohen and Colp's Case 4, an accessory pancreas, the size of a half dollar, in the anterior wall of the duodenum, showed neoplastic involvement microscopically, although the pancreas proper was normal.

The hepatic changes, where noted, resembled, for the most part, those already described as characteristic of obstructive jaundice (Lieber and Stewart). Since the condition of peripapillary carcinoma of the duodenum lasts for a variable period of time and jaundice appears and disappears alternatingly, the hepatic damage sustained is frequently severe. The liver was, therefore, usually enlarged, although sometimes unchanged or even diminished in size and the surface occasionally finely or coarsely nodular but usually smooth and tense. The cut surface was deeply bile-stained and the intrahepatic ducts were distended frequently with white bile. Biliary cirrhosis was present in 32 cases and in several of these the hepatic damage was severe.

Various operative procedures were performed upon the biliary passages for reestablishment of biliary flow into the gastro-intestinal tract or the external drainage of bile. However, postoperative studies of the liver were not carried out to determine the immediate functional and morphologic effects of biliary decompression upon the hepatic parenchyma. Likewise little or no attention was paid to the more remote effects of cholecysto-enterostomy or cholecystogastrostomy upon the biliary ducts and connective tissue within the

liver. In three of our patients who were subjected to cholecystogastrostomy or cholecystoduodenostomy, the gallbladder was distended with blood clots, which obviously formed a barrier to biliary drainage. One patient died nine days after operation without abatement of the jaundice and at autopsy the liver showed the characteristic changes of total biliary stasis. Similar hepatic changes were noted in the second patient dying one day postoperatively. The third patient died five days after operation, with increase of jaundice clinically, and the liver showed marked degeneration and necrosis similar in extent and distribution to that described by us following decompression in pancreatic carcinoma (Stewart and Lieber). Multiple small abscesses were present in the liver in 11 cases, occasionally distributed along the branches of the portal vein or small intrahepatic biliary ducts which occasionally also showed cholangeitis. In two cases, suppurative lesions of the liver followed eight to ten months respectively after cholecystogastrostomy. Among the more unusual findings were an echinococcus cyst, calculi in the intrahepatic ducts and spontaneous rupture of the liver, one case each. The ruptured liver occurred in the presence of extensive metastases to this organ, which weighed 3,970 Gm., and death was attributed to a massive intraperitoneal hemorrhage of 2,500 cc. In Murgoci's case there were pericholecystic, subphrenic and hepatic abscesses and a bronchobiliary fistula which extended through the diaphragm into a cavity in the lower lobe of the right lung which contained inspissated bile and gallstones; this cavity in turn communicated with a bronchus. In Ely's case, the left kidney was enclosed in an irregular cavity traced to the edge of the left lobe of the liver where it was found continuous with the ruptured extremity of a dilated bile duct. There was no peritonitis in Ely's case, as the fistulous sac lay entirely behind the peritoneum.

The gallbladder was variably distended in 131 cases, contracted or not distended in 12 and no mention of this feature was made in six, while in 33 there was no note regarding this viscus. The distention varied from slight to enormous. In the majority of cases the gallbladder was greatly distended measuring from 12 to 17 cm. in length and 6 to 10 cm. in width. Upwards of 1,500 cc. of fluid were obtained by incising the gallbladder. The fluid was described as clear, mucoid, colorless or white in 20 cases, pale green or thick and tarry in 13, and purulent in five. In a few others the bile was said to contain grumous mud-like material. In several cases the gallbladder was distended with blood following operation and in at least one case this phenomenon developed spontaneously.

Gallstones were present in the gallbladder in 25 cases, in three of which they were also present in the bile ducts. In four other cases in which stones were found in the common bile duct, none was found in the gallbladder. In Whipple, Parsons and Mullins' Case 2, the gallbladder, at autopsy, was dilated and contained numerous soft stones although it had been free of stones nine months previously when a cholecystogastrostomy was performed. Perforation of the gallbladder occurred in three cases, one of which showed suppurative cholecystitis and another an impacted stone in the cystic duct. A spon-

taneous cholecystocolic fistula was found in Fischel's case. Inflammatory stricture of the cystic duct was noted in a few instances. Pericholecystic adhesions were present in 18 cases.

Among 22,152 autopsies, performed at the Philadelphia General Hospital, gallstones were found in 1,956, or 8.83 per cent. In the present series of 182 cases, stones were present in 29, or 15.9 per cent. This high figure may be of some significance, implying that stones are a predisposing factor in the etiology of cancer in these patients. Of the 1,956 cases of gallstones at the Philadelphia General Hospital, 79 had stones in the common bile duct, an incidence of 4.04 per cent, as contrasted with seven of the 29 present cases, or 24.1 per cent with common duct stones. This high incidence of common duct stones is partly due to the greater facility with which stones may migrate from the gallbladder into distended bile ducts in the presence of biliary obstruction.

Peritoneal effusions were noted in 41 cases, and varied from a slight excess up to eight liters of fluid in one instance. The fluid contained bile in 22 cases, blood in nine, five of which occurred postoperatively, and pus in five. Peritonitis was present in 13 cases, in five of which the inflammatory change was localized to the region of the gallbladder while another was associated with a spontaneous bronchobiliary fistula. Inflammatory peritoneal adhesions were present in 39 cases, occurring postoperatively in five. In order of frequency the organs involved by adhesions were gallbladder, intestines, liver, pancreas and stomach. At times the biliary passages were completely buried in dense adhesions and were almost impossible to identify at operation.

Extension and metastases of the primary neoplasm occurred in at least 79 cases (43.6 per cent). This is a highly conservative figure, when it is considered that in 51 cases examination was limited to biopsy material and surgical specimens only, and a few autopsies were incomplete. A definitely negative statement regarding neoplastic spread was made in only 31 cases, while in 41 additional cases no comment was made. Direct extension into the head of the pancreas occurred in 34 cases and was questionably present in two others. There were metastases to the regional lymph nodes in 36 cases —liver, 31; lungs, two; perirenal lymph nodes, two; and the following one each, left kidney, gallbladder, thoracic duct and left supraclavicular, peribronchial and gastric lymph nodes. Implantation metastases were observed in the peritoneum in two cases. The most extensive secondary deposits were present in Butz's case, being observed in the right lung, left pleura, liver, pancreas and left supraclavicular, bronchial and retroperitoneal lymph nodes.

Histology.—All but four of the 182 cases in this series were glandular carcinomata. The exceptions were three adenosquamous (Mateer and Hartman, Case 5; Hoffman and Pack, Case 8, and Lieber, Stewart and Morgan), and one squamous cell carcinoma (Cohen and Colp, Case 5). In approximately half the cases no other histologic details were given aside from the designation of glandular carcinoma. Acinar structures were present in the majority of the remainder and were usually fairly regular, although in a

few they were branching, elongated or otherwise imperfect, and in six instances markedly dilated to form microcysts. The acini were lined by single and in a few instances by multiple layers of cylindrical, columnar or cuboidal cells which, in 31 cases, formed papillary infoldings or projections. The atypical cells grew solidly in clumps, strands, cords or nests in 39 cases, and in five of these acini were definitely absent. Some degree of irregularity in size, shape and staining of the cells occurred in 37 cases, and in a few the cells were described as embryonic or anaplastic. Mitotic figures were observed in 25 cases but were numerous in only a few. Considerable quantities of mucinous material occurred in and between the cells and acini in seven cases, two of which were designated as mucoid or colloid carcinoma and another as medullary carcinoma. The lumens of the acini occasionally contained desquamated cells, débris, small amounts of mucin and leukocytes. The connective tissue stroma, varying in cellularity and usually infiltrated with inflammatory cells, was abundant in 24 cases and scanty in 12. Areas of necrosis were noted in eight cases, miliary abscesses in one, and perivascular and perineural infiltration of tumor cells in another.

Several authors expressed an opinion regarding the origin of the neoplasm in their case, these views being advanced much more frequently in the earlier reports than in the more recent ones. Thus the tumor was stated as having been derived from the duodenal mucous membrane in 31 cases, from the common bile duct in four, from the common bile duct, pancreatic duct or duodenum in two, and from the following in one each—common bile or pancreatic ducts, ampulla of Vater, common duct or ampulla of Vater and Brunner's glands. The reasons given for deriving the tumor from one or another of the structures just listed were wholly inadequate and in our opinion do not influence its classification in the group of carcinomata involving all the epithelial structures comprising the papilla of Vater as in Groups I, II, III and IV, described above.

VI Carcinoma Involving the Epithelial Structures Comprising the Papilla of Vater Exclusive of the Intestinal Mucous Membrane.—Thirty-one cases from the literature were included in this group as examples of neoplastic involvement of the combined terminal common bile duct and duct of Wirsung together with the ampulla of Vater, if present. Our Cases 16 and 17 are examples of this type of lesion. The duodenal mucous membrane covering the papilla of Vater was free of tumor in all instances and can, therefore, be dismissed as a source of origin for these growths. Otherwise, however, the primary source remains obscure.

The duodenum, opened at celiotomy or at autopsy, showed an unusually prominent papilla of Vater which projected forward as a cylindroconical body into the lumen of the bowel. It varied in size from that of a cherry to a plum, the largest stated diameter being 3 cm. The papilla was usually firm and resistant and the mucous membrane covering it was smooth, not thickened and usually freely movable. The orifice was patent in all instances and appeared dilated and stretched in a few. Just beyond the orifice, however, a

sound usually met with resistance, obstruction being complete in nine cases and incomplete in 24. It was demonstrated in one case that obstruction was due to pressure and kinking rather than to invasion and obliteration of the lumen by neoplasm. In eight instances, the tumor was believed to emanate from the wall of the ampulla of Vater but in each of these the common bile duct or duct of Wirsung, or both, showed associated neoplastic changes on the surface.

The common bile duct in its lower few to 30 Mm. was regularly thickened. This thickening was usually attributed in the reports to an annular, grayish-white, indurated, firm or occasionally friable growth often barely perceptible but at other times measuring 2 cm. in diameter. Elevated tumor excrescences studded the mucous surface in 15 cases, five of which were distinctly papillary, villous or mulberry-like while seven were localized and pea-sized. Ulceration occurred in four cases. Proximal to the obstruction, the biliary ducts were maximally distended up to a circumference of 10 cm., the ductal contents being colorless in two instances. Gallstones were present in the gallbladder in two cases and in the cystic and common bile ducts in one case each.

The duct of Wirsung was obstructed in 15 cases, not obstructed in three, and no mention of this feature was made in the remainder. The pancreas was reported as normal or unaffected in eight cases. The exact site of obstruction of the duct was localized in only five cases, occurring definitely at the ampulla in three, while in the others the tumor had propagated backwards 2 cm. along the lumen. In three cases the orifice was completely effaced. Proximal to the obstruction, the intrapancreatic ducts were maximally dilated and occasionally contained blood or blood-stained fluid. The parenchymatous tissue usually showed chronic inflammatory changes and atrophy and fat necroses were present in two cases.

Some degree of biliary stasis existed in all the cases in this group. In three cases the hepatic changes showed well advanced biliary cirrhosis, the liver being small and contracted, with a granular surface. Suppurative cholangeitis and hepatic abscesses were present in two cases. Distention of the gallbladder was regularly observed and sometimes the viscus measured 30 cm. in length. Suppurative cholecystitis was associated with cholecystoenterostomy in one case, gallstones in another, and ulceration in two cases, one of which perforated. Stones were present in the gallbladder in two cases. Dilatation of the stomach and proximal duodenum was rarely encountered. Adhesions between the gallbladder and neighboring structures were present in four cases, in one to the spleen. Diffuse fibrinous peritonitis occurred in three cases, hemorrhagic peritoneal effusion in four, and biliary effusion in three, one of which followed perforation of the gallbladder.

Extension and metastases of the primary neoplasm occurred in nine cases, to the regional lymph nodes (five), pancreas (six), liver (four) and lung (one).

Histology.—All the cases in this series were glandular carcinomata. Acini were described in 27 cases, and there was little or no tendency for the tumor

cells to form strands, clumps, nests or cords. The atypical tumor cells were essentially cylindrical, columnar or cuboidal in type, and in ten cases, variation in size, shape and staining of slight degree occurred, but anaplastic features were not marked in any instance. Mitotic figures were numerous in only one case. The stroma varied from scanty to abundant, and areas of necrosis were occasionally observed. The tumor cells permeated the surrounding duodenal musculature and nerve fibers invading the submucosa of the intestine in four instances.

Clinical Features.—Early recognition of carcinoma of the peripapillary portion of the duodenum depends upon a careful, critical evaluation of the symptoms. For this reason, the clinical features are analyzed at some length.

Onset.—Of the 222 cases in this series, the onset was acute in 178, gradual in 29, and at first gradual and then acute in 15.

Symptoms occurring with the acute onset were: Jaundice (126), pain (71), loss of weight (40), loss of strength (36), anorexia (31), vomiting (21), fever (14), nausea (13), constipation (13), diarrhea (10), chills (8), a sense of pressure or weight in the abdomen (8), and infrequently, dyspepsia, epigastric distress, sour eructations, flatulency and abdominal distention. Symptoms occurring after the onset were: Jaundice (47), pain (27), vomiting (24), anorexia (18), abdominal distention (16), diarrhea (14), and infrequently, nausea, constipation, a sense of weight or pressure in the abdomen, flatulency, sour eructations and dyspepsia.

Symptoms occurring with the gradual onset were: Pain (12), anorexia (10), loss of weight and strength (11), a sense of weight or pressure in the abdomen (8), jaundice (6), vomiting (5), diarrhea (4), and less frequently, fever, abdominal distention, flatulency, dyspepsia, constipation and sour eructations. Later manifestations were: Jaundice (24), pain (12), fever (8), loss of weight and strength (7), vomiting (5), and less frequently, abdominal distention, flatulency, a sense of weight or pressure in the abdomen, anorexia, constipation and diarrhea.

In the group of cases with a gradual onset, followed later by an acute phase, the symptoms with the gradual onset were loss of weight and strength (7), pain (5), jaundice (3), a sense of weight or pressure in the abdomen (3), vomiting (2), and constipation, abdominal distention, dyspepsia, nausea and malaise (one each). Symptoms with the acute phase were: Jaundice (10), vomiting (4), pain (3), and chills and fever (2). Later manifestations were: Chills and fever (5), jaundice (2), pain (2), and vomiting, diarrhea and hiccoughs (one each).

Jaundice.—Jaundice was a symptom in all but four of the 222 cases. It occurred with the onset of the condition in 136 cases and later in 82. In the latter cases, the time interval, from the onset to the appearance of jaundice, varied from a few days to four years, averaging three to five months. The antedating symptoms were malaise, feebleness, vomiting, chills and fever, dyspepsia, abdominal soreness, pain, diarrhea and constipation. Infrequently, cutaneous icterus was preceded by pruritis, dark urine or colorless stools. A

few patients gave an antecedent history, the symptoms of which merged with those of the condition under discussion. In Cabot's case, for example, the patient complained of pain in the epigastrium, jaundice, vomiting and chills beginning four years before, the last attack occurring two months before admission to the hospital. In our Case 2, painful attacks of jaundice occurred respectively five years and two years before her last admission with the same symptoms, and each of these was relieved by operation. In our Case 6, there was a history of painless jaundice for a week or ten days on two occasions, one and three years previously.

There was a single attack of jaundice in 186 cases, the icteric tint of the skin never completely disappearing except following surgical intervention. It was marked and fairly constant in 38 cases, in most of which it was of relatively brief duration (one to two months), although one patient showed constant deep jaundice for 12 months without apparent abatement. In 22 cases, the jaundice, although continuous, varied in intensity and occurred at all phases of the condition, early and late. In some cases, sustained jaundice could be accounted for in part by the presence of biliary tract infection and, in at least five cases with jaundice of long duration, stones in the common duct or gallbladder may have been responsible for the variation in the intensity of this symptom. The duration of the jaundice in the cases with a single attack, where the time was accurately stated, varied from a few days to 21 months, being less than one month in 16 cases, one month in 33, two months in 36, three months in 25, four to six months in 42, seven to 12 months in 21, and four, 13, 16, 18 and 21 months, respectively, in one case each.

Multiple attacks of jaundice occurred prior to surgical treatment in 32 cases with two attacks in 17 cases, three attacks in five, four attacks in two, and in eight cases the number of attacks were not stated, although there were at least two. The duration of the individual attacks varied from a few days to nine months, being less than a month in six cases, one month in 10, two months in 5, three months in 4, six months in 2, and seven, eight, nine and 12 months respectively in one case each. The intervals between attacks of jaundice varied from one week to 18 months, being less than a month in 2 cases, one month in 10, two months in 7, six months in 3 and seven, eight, 12 and 18 months respectively in one case each. The total duration, that is, the sum of all the individual attacks and the intervals between them, was as follows: Thirteen were fairly evenly distributed over the first nine months; six occurred between the first and second years; and one each occurred at 27 and 48 months, respectively.

Jaundice occurred as the only symptom in 14 cases, and in 22 others, it occurred in association solely with diarrhea, constipation, loss of weight, loss of strength or chills and fever. Pain was associated with jaundice at the onset of the condition in 54 cases, preceded the appearance of jaundice in 48 and occurred later in 30 cases. Fever, frequently accompanied by chills, occurred in 74 cases, with the onset of jaundice in 16, and after the appearance of jaundice in 56, while in two cases, the exact time of occurrence was not

stated. The fever was sometimes described as irregular, intermittent, septic or low grade. The temperature varied from 100° F. to 102° F., occasionally rising to higher levels terminally.

Jaundice first appeared as a symptom after admission to the hospital in eight cases. In Pozzi's Case 2, for example, the patient developed pain and jaundice while convalescing from bronchopneumonia. Pemberton's patient complained of attacks of pain for two years with loss of 30 pounds in weight, unexplained even after exploratory celiotomy. Two months later, pruritis, followed gradually by jaundice, appeared and a second celiotomy a month later revealed complete obstruction of the common bile duct due to a carcinoma of the papilla of Vater.

Jaundice was never a symptom in four cases which are cited rather fully. Mauclaire and Durrieux's patient complained of violent colicky pains in the epigastrium and hypogastrium, infrequent vomiting and obstipation for 12 days. At autopsy there was an ulcerated, markedly stenotic cancer occupying three-quarters of the circumference of the duodenum, extremely firm and measuring 7 to 8 Mm. in length and 1 cm. in width. The papilla of Vater, although not definitely identified, appeared to correspond to the seat of the cancer but the bile ducts were not obstructed. Lannois and Courmont's patient complained of difficulty in swallowing solid foods, diarrhea and loss of appetite, weight and strength for four and one-half months. One month before admission to the hospital he could no longer swallow food without promptly vomiting. At no time was there a complaint of pain or icterus but obstinate constipation developed terminally. At autopsy, a firm tumor 4x2 cm. completely obstructed the inferior portion of the esophagus, histologically a squamous cell carcinoma; at the level of the papilla of Vater was found a second, reddish-white, mushroom-like, soft tumor, the size of a five franc piece. The papilla of Vater was eccentrically placed to the right and in front of the tumor. A probe easily passed into the common bile duct without meeting an obstruction. Histologically, the duodenal tumor was a cylindrical cell adenocarcinoma.

Del Valle and Brachetto-Brian's patient complained of pain two to three hours after meals and occasionally during the night. The pain radiated to the "pancreaticoduodenal area of Chauffard" and occasionally to the right shoulder blade. The first attack appeared one year before admission to the hospital. The attacks recurred more frequently and with greater intensity. A clinical diagnosis of pyloric ulcer and cholecystitis was made. At celiotomy, the antrum of the stomach and pylorus revealed no ulcer or neoplasm. The gallbladder and bile ducts were enormously distended and an indurated area was palpated in the second portion of the duodenum, which was opened. An oval shaped, firm tumor 3x1x0.3 cm. with firm borders and without ulceration was found, the major papilla forming the superior extremity of the tumor. In Hoffman and Pack's Case 3, the complaints were pain in the abdomen, anorexia, loss of weight and strength, constipation and marked distention after eating, but jaundice was not mentioned. Autopsy revealed an annular,

polypoid carcinoma surrounding the papilla of Vater and extending for 6 cm. along the lumen of the duodenum which was partly obstructed. There was no record of examination of the biliary passages in this case.

The duodenal contents were examined 44 times in 15 patients. Bile was recovered in nine patients examined, and was always absent in six patients, indicating the complete nature of the obstruction. In three patients, bile was detected on the first examination but disappeared subsequently. Interesting information may be obtained by citing some of the cases in which the duodenal contents were repeatedly examined. In Carnot and Libert's patient, the icterus began to recede several days after admission to the hospital and finally disappeared, the duodenal contents at this time showing the presence of bile and pancreatic ferments. Two weeks later, there was an absence of bile but pancreatic ferments and blood were present; the examination was repeated again several weeks later with the same results. In Bérard, Mallet-Guy and Croizat's case, bile was detected in the duodenal contents, and, although at operation the degree of biliary obstruction was minimal, evidences of biliary infection existed which probably accounted for the clinical jaundice. In Crohn's Case 3, the onset was with jaundice which cleared during hospitalization, at which time duodenal intubation yielded an abundance of thick, mucoid bile and active pancreatic ferments. On the second admission to the hospital, jaundice was marked and the duodenal contents showed complete absence of bile and a diminution in pancreatic ferments. At autopsy, there was apparently complete obstruction of the pancreatic duct. It is obvious that in certain cases jaundice may be marked clinically and yet bile is detected in the duodenal contents, the icterus being accentuated probably by biliary tract infection or stone. Einhorn and Stetten's case illustrates the fact that although marked biliary obstruction with considerable dilatation of the ducts obtain, yet jaundice may not be recognized clinically. During the entire course of illness in their patient, there was nearly total absence of jaundice except for a transient, slight attack at the inception which subsided after cholecystectomy, despite persistency of the lesion at the papilla of Vater. This the authors accounted for on the basis that the tumor was ulcerative in type and not actually obstructive in character. During a period of two weeks in the latter part of the patient's illness, daily biliary drainage yielded a free flow of bile. A few days after the last drainage, celiotomy revealed a markedly distended common bile duct through which a probe was passed with considerable difficulty.

Pain.—This symptom was present in 132 cases in this series and was absent in 59, no mention of it being made in the remainder. At least nine of the patients, not complaining of definite abdominal pain, did have vague dyspepsia, distress or discomfort, sometimes after meals. In several other patients, vague symptoms of this type preceded the actual onset of pain.

Epigastric pain was manifested in 55 cases, and in 19 of these there was associated pain in the right upper abdominal quadrant. Radiation occurred to one or both shoulders in nine cases, lumbar region nine, and hypogastrium

three. In one case, pain began in the epigastrium and radiated to the right hypochondrium, right iliac fossa and backward to the right shoulder, accompanied by a sense of constriction.

In 36 cases, pain began in the right hypochondrium and radiated to the back in seven, right shoulder in three and right upper arm and right chest in one each. While pain usually began in the two situations mentioned above, in a few cases it began elsewhere, namely, the lumbar region in six cases, the entire abdomen in four, the lower abdomen in two, and substernal region in one. In three of these cases, the pain radiated either to the abdomen, chest, gallbladder region or left arm.

There were few other details regarding pain but it appeared to be intermittent in 50 cases and continuous in 10. The intensity was severe in 40 cases and slight in 10. It was accentuated by food and occurred from one-half to several hours after eating in 20 cases, but in three, there was no relation to food. Di Giovine described the pain in his patient as tolerable, paroxysmal, variable in duration and was referred, at times, to the right shoulder and at other times to the right hypochondrium. Abdominal tenderness was associated with pain in 61 cases, occurred independently of pain in 29, and in association with pain and rigidity in 10. Rigidity alone occurred in two cases and in association with pain in three. Pain was relieved by vomiting in five cases. Nineteen patients complained of a sensation of weight or pressure in the abdomen and in several of these there was no pain. In a few cases, pain was a transient symptom at the onset and in one case, it disappeared with the advent of jaundice. Practically none of the authors emphasized the nocturnal occurrence of pain.

Vomiting.—This occurred with the onset of the condition in 28 cases, later in 34, and was absent in 46. It was intermittent in 23 cases and in a few instances, it became incessant terminally. In seven cases, it occurred after meals. Vomiting was associated with nausea in nine cases, and nausea occurred independently of vomiting in 17. Blood and bile were present in the vomitus in five cases each. Vomiting was associated with jaundice in 20 cases and with pain in 23, the three symptoms occurring simultaneously in eight cases. Vomiting preceded the appearance of jaundice in 20 cases and of pain in eight. It followed the appearance of jaundice in 21 cases and of pain in 20.

Examination of the vomitus, or material obtained for gastric analysis, was made in 27 cases. Free hydrochloric acid was absent in five cases, and in the remainder it varied from 17 to 58, while the total acidity varied from 9 to 90. Blood was present in four specimens and bile in five.

Diarrhea and Constipation.—Diarrhea occurred early in 20 cases and late in 19, while constipation occurred early in 23 and late in 19. The two occurred early in association in four cases, and late in two cases, while diarrhea was preceded by constipation in three cases and followed by constipation in one. One case of diarrhea lasted for eight months. Of the 39 cases with diarrhea, nine showed evidences of obstruction of the pancreatic duct at autopsy.

The stools were pale, gray, clay-colored, white or colorless in 129 cases, and were brown in four cases, in all of which jaundice was clinically present for a week or longer. Blood was present in the stools in 42 cases, and in a few of these the stools were black, massive hemorrhage occurring as a terminal feature in one case. Most of the reports on the occurrence of melena have been published since 1912. Neutral fats were variably increased in 15 cases and fatty acids in 8. The stools were described as fetid in 10 cases.

Physical Examination.—A mass was palpable in the abdomen in 14 cases, but only in four of these could it possibly be ascribed to the primary neoplasm. In Le Blanc's case, a small mass was palpable to the left of the umbilicus and was thought to be an enlarged lymph node. At autopsy there was no enlargement or metastases in the lymph nodes but a mass was found involving the terminal common bile duct, the papilla of Vater and the head of the pancreas. In Doberauer's case, a hazel-nut-sized mass could be rolled under the examining finger, and was situated deep in the region of the duodenum. Celiotomy revealed a hazel-nut-sized tumor of the common bile duct near the duodenum. In Mateer and Hartman's Case 2, a very hard, nodular, circumscribed, slightly movable, nontender mass, the size of a lemon, was palpable to the right of the midline, in the lower epigastrium. It was not connected with the liver and did not move with respiration. At autopsy, a large papillomatous tumor 4 cm. in diameter and elevated 2 cm. above the adjacent duodenal mucosa, surrounded the papilla of Vater and completely filled the lumen of the duodenum. There were metastases to the regional, mesenteric and retroperitoneal nodes. In Hoffman and Pack's Case 11, a hard mass, slightly movable, especially with respiration, and 5 cm. in diameter, was palpable in the epigastrium slightly to the right of the midline. Celiotomy revealed a neoplasm 8 cm. in diameter surrounding the papilla of Vater.

In seven cases a mass was palpated in the right epigastrium or hypochondrium and was probably due, as disclosed at autopsy, to secondary neoplastic deposits in the regional and pancreatic lymph nodes in four, in one of which there was also a large infiltrating mass in the head of the pancreas, and to metastatic nodules in the liver in two cases. The right kidney in Mauclaire and Durrieux's case was palpable as a firm irregular mass. In Hunt and Budd's patient, a large cystic mass occupying the entire left upper quadrant of the abdomen was interpreted as due to a hydronephrotic left kidney; which autopsy confirmed. In Hoffman and Pack's Case 3, a movable, irregular mass the size of an orange was palpable in the region of the right kidney; examination of the kidneys was not mentioned in the autopsy report. A hard mass was palpable in the epigastrium to the right of the vertebral column in Rutishauser's Case 6; this case was complicated by a diaphragmatic hernia, a lumpy mass in the omentum and metastatic lesions in the regional lymph nodes in addition to the primary neoplastic ulcer measuring 5.5 cm. to 6 cm.

The liver was palpably enlarged in 173 cases; sometimes it extended to the umbilicus and in several it was definitely nodular. The gallbladder was palpably distended in 110 cases, and in one instance it reached the level of the

anterosuperior iliac spine. Tenderness was present in 90 cases, with associated abdominal rigidity in 12. Abdominal distention was noted in 26 cases, usually late in the condition, and signs of ascites were elicited in 24 cases. Dilatation of the stomach was found in two cases, in one of which the lower border of the viscus was situated two fingers' breadth above the symphysis pubis. Several enlarged lymph nodes were palpable above the left clavicle in one case, and in the right supraclavicular group in another.

Laboratory Data.—Blood examinations were carried out in 72 cases. A varying grade of anemia was present in 48 instances, the red cell count varying from two to below four million per cm. Hemoglobin estimations varied from 51 to 88 per cent in 19 cases, and in four others the hemoglobin was 25, 28, 32 and 39 per cent, respectively. In the majority of instances the color index was correspondingly low but in 12 cases it varied from 0.9 to 1.3. Although a slight leukocytosis was the rule, the white blood cell count was within normal limits in a few cases and in one there was a slight leukopenia. With jaundice present, the danger from hemorrhage increases and the determination of the circulating bilirubin and estimation of the bleeding and coagulation time should be carried out routinely throughout the course of illness of these patients. The bleeding and coagulation times were estimated in only a few instances, being slightly prolonged in one case and markedly prolonged, to four hours, in another. The Wassermann reaction on the blood serum was positive in six cases. The van den Bergh reaction on the blood serum was described as directly positive in 21 cases, direct and indirect positive in three and delayed and biphasic in one. Quantitative van den Bergh estimations varied from 6.8 to 70 mg. per 100 cc. of blood in 18 cases, with an average of about 20 mg. The icterus index varied from 12 to 280 in 17 determinations, with about 120 as an average. Tests of liver function with bromsulphthalein (2 mg. dosage) in the presence of jaundice showed varying impairment, from slight to 100 per cent retention in 30 minutes in the seven cases examined.

The blood sugar determinations were within normal limits except in five cases showing 134, 150, 160, 250 and 318 mg. per cent respectively. It is interesting that in each of these cases the pancreas was markedly affected. In Meyer and Rosenberg's Case 1, the pancreatic duct was distended with almost clear fluid, probably the result of extension of the primary tumor into the head of the pancreas, and cut section of the organ showed that hardly any pancreatic tissue remained. In Mateer and Hartman's case, there was a chronic pancreatitis and no other mention was made of this organ. The reader is referred to the protocols of our Cases 3, 7 and 13 for the detailed pancreatic changes. In each of these, the pancreatic duct was obstructed and the parenchyma markedly atrophied with extensive fibrosis and chronic inflammatory changes. Blood amylase estimations were carried out in Whipple, Parsons and Mullin's Cases 2 and 3. In the former, the blood amylase was 5.8 prior to the first operation and 11.4 after the third operation eight months later. In the latter, the blood amylase was 40, 13 days after the first opera-

tion, 44, the day after the second operation, remaining below 20 on the succeeding days and rising to 72, 46 days later.

Retention of nitrogenous products in the blood occurred in ten cases, the urea varying from 16 to 220 mg. per cent and the creatinine being correspondingly high, reaching in one instance to 17.2 mg. per cent. Of two of our cases with high nonprotein-nitrogen readings, one showed uremic manifestations clinically, and deep renal pigmentation at autopsy, and the other showed renal arteriosclerosis and marked nephrosis. Blood cholesterol studies were carried out in four cases, values of 225 and 1500 mg. per cent being obtained, the blood cholesterol remaining consistently above 1,000 in one case. Studies of the fibrinogen of the blood were reported in one case in which it varied from 0.64 to 0.9 in five examinations.

Uranalyses.—There was no case in this series in which bile was reported absent from the urine. In a few cases there was no mention of this feature and in the four patients who did not exhibit jaundice clinically, the test for biliary pigments in the urine was apparently not performed. A trace of albumin was detected in 47 cases and in another, large amounts were present. Urobilin was present in 11 cases. The urine was free of sugar in all but two cases examined. A few patients showed the presence of albumin, casts, red blood cells and leukocytes in the urine, which seemed to indicate the presence of nephritis.

Duodenal Analyses.—The duodenal contents were examined 44 times in 15 cases, and bile was detected in nine patients and was always absent in six others. Pancreatic ferments were detected in six cases and were absent in three. In three of the patients, the pancreatic ferments were present in small amounts and in one of these they had disappeared at a second examination. Blood was present in three specimens and many pus cells in two. The diminution or total absence of pancreatic ferments in the duodenal contents could be accounted for by partial or complete obstruction of the duct of Wirsung as proved at autopsy.

Roentgenologic Studies.—The inexactness of roentgenologic diagnosis of carcinoma of the duodenum has been the subject of considerable discussion for many years. We have emphasized, elsewhere (Stewart and Lieber), that with vague and inconstant symptoms occurring early in the course of the disease, the roentgenologic examinations are of value chiefly in ruling out primary tumors in other locations such as the stomach, colon and gallbladder. Roentgenologic studies were carried out in 60 cases, in 11 of which only a "scout" roentgenogram of the abdomen was taken. The presence of a lesion in the region of the papilla of Vater was recognized roentgenographically in 16 cases. A brief analysis of each of these cases is presented comparing the roentgenographic findings with the gross anatomic specimen as disclosed at operation or autopsy.

Propping's patient showed a continual duodenal deformity, and at celiotomy a prominent cherry-sized tumor was found localized to the papilla of Vater. In Abell's Case 2, a tumor of the papilla of Vater was proved by

operation and a cholecystoduodenostomy performed; two and two-thirds years later, roentgenologic examination showed marked deformity and obstruction in the second portion of the duodenum. Celiotomy at this time revealed a rounded, firm, fixed mass, 7.7 cm. in diameter, involving the duodenum and pancreas. In Meyer and Rosenberg's Case 1, a defective duodenal bulb was noted, and autopsy showed an irregular, annular ulcerated tumor at the site of the papilla with extension into the underlying pancreas. In Mateer and Hartman's Case 2, the persistent filling defect observed in the second portion of the duodenum was due to the presence of a peripapillary nodule 4x2 cm. In Lauwer's Case 1, the superior segment of the second portion of the duodenum showed peristaltic movements in the vertical position but in the ventral position, interruption of the duodenal shadow was noted; at celiotomy, the papilla of Vater was occupied by a tumor the size of a strawberry. Swenson and Levin's patient showed, at the first examination, very obvious alterations of duodenal mucosal patterns. A second examination about a year later showed a filling defect in the second portion of the duodenum; autopsy revealed a mushroom-like growth measuring 6.5x7 cm. with the papilla of Vater almost in its center, and the surrounding plicae were distorted.

In the case reported by Harbin, Harbin and Harbin, fluoroscopic examination revealed a moderately dilated but otherwise negative stomach; a constant filling defect occurred in the distal part of the first portion of the duodenum, the proximal segment was dilated and showed rather pronounced peristalsis. Only a small amount of barium passed by the obstruction, two-thirds of the meal remaining in the stomach at the end of 24 hours. At autopsy, three months later, an annular, stenosing, papillomatous tumor attached to the first segment of the second portion of the duodenum almost completely occluded the lumen of the gut. In Doub and Jones' case the stomach was negative; the lumen of the second portion of the duodenum was irregular and displaced somewhat laterally and there was a pressure defect in the cap. The duodenum emptied slowly and no peristaltic waves were seen. There was 15 per cent retention in the stomach at the end of six hours. Autopsy revealed a carcinoma of the papilla of Vater but the exact size of the lesion was not stated. Bérard, Mallet-Guy and Croizat's case is especially interesting. These authors stated that injected lipiodol did not pass into the duodenum; the common bile duct appeared constricted and the rough outline of the sphincter could be made out. Stereoscopic examinations made 15 and 25 minutes later confirmed the radioscopic findings and showed that the common bile duct, 2 cm. in diameter, ended in a sort of point having the appearance of a notch of its external wall. This notch was noted exactly at the site of the ampulla of Vater, and their description was well borne out in the illustrations accompanying their article. At celiotomy a well limited cherry-sized tumor of the ampulla of Vater was found corresponding precisely to the image seen in the lipiodol radiograph.

In Hoffman and Pack's Case 3, there was a filling defect in the prepyloric segment of the stomach and evidence of upward displacement of the duo-

denum and pressure on the greater curvature of the gastric antrum, with filling defects in the stomach and duodenum. Some evidence of infiltration of the pylorus and in the descending duodenum was noted, and there was marked retention of barium after six hours. These findings were interpreted as probably due to a tumor of the head of the pancreas. Autopsy revealed an annular, polypoid tumor surrounding the papilla of Vater and extending for 6 cm. along the lumen of the duodenum, partly obstructing it. In Case 11 by the same authors, there was irregularity of the second portion of the duodenum which curved far out to the right. In the middle of the first portion of the duodenum, a persistent fleck of barium was noted which was still present six hours later and was interpreted as due to a perforating ulcer of the inferior horizontal portion of the duodenum. Celiotomy disclosed a tumor, 8 cm. in diameter, surrounding the papilla of Vater. In Case 12 by these authors, the stomach was normal. The duodenal cap was greatly enlarged, triangular and regular in outline. The descending portion of the duodenum was irregular and narrowed with retention of barium for more than 24 hours. These findings were interpreted as due to a duodenal diverticulum with partial obstruction and possible carcinoma of the head of the pancreas. Autopsy showed a polypoid tumor surrounding the papilla of Vater but the size of the lesion was not stated. In their Case 16, there was no evidence of ulcer or cancer in the stomach. The second portion of the duodenum, however, showed some deformity considered due to adhesions. Celiotomy disclosed a small, soft, friable mass on the posterior surface of the duodenum close to the papilla. In Cabot's Case 23282, several roentgenologic studies, made two months after the onset of the illness, were all negative. These studies were repeated two months later and showed the stomach slightly displaced to the left and a pressure defect near the tip of the duodenal cap. In the upright position, it was possible to bring only a small amount of barium into the duodenum, and in the horizontal position the duodenum was obscured by the barium filled colon. Reexamination of the duodenum showed a pressure defect at the beginning of the descending duodenum. At celiotomy, the stomach was found adherent to the liver, and with the separation of these adhesions an old perforated pyloric ulcer was uncovered. The autopsy disclosed an ulcerated tumor 3x1.5x0.2 cm. in the region of the papilla of Vater. The roentgenograms were then reexamined, and below the defect in the duodenum a slight irregularity was noted on the medial aspect of the descending duodenum which did not seem to be very constant during the examination, but seemed very definite at this time. There had been an area of rigidity about 3 cm. in diameter along the medial aspect of the descending duodenum where it joined the third portion. On one film, a crater was visible in this area creating the impression of a centrally ulcerated lesion which protruded into the duodenum from its medial aspect. In our Case 15, the stomach and duodenum appeared to be normal, but there was widening of the duodenal loop and considerable stasis in the second and third portions of the duodenum. At autopsy, there was moderate distention of the stomach and proximal half

of the duodenum. The papilla of Vater consisted of a smooth, fluctuant nodule projecting 1 cm. into the lumen of the duodenum, and the immediately surrounding tissue was firm. In our Case 17, there was slight broadening of the duodenal curve with delay in the passage of barium through the second and third portions of the duodenum interpreted as due to some enlargement of the pancreas. At autopsy, the papilla of Vater was enlarged and formed a tumor mass 2.2x1.5 cm.

In summarizing the data from these 16 cases, all the lesions, except Cabot's case, were nodular or polypoid and elevated; six measured 2 to 4 cm. in diameter and four measured 6, 7, 7.7 and 8 cm., respectively. The dimensions of the lesions in the other six cases were not recorded. On the other hand, in the 33 cases in which no lesion of the gastro-intestinal tract was visualized, analysis of the postmortem data showed that the primary neoplasm consisted of a nodule 2 cm. or less in diameter in 18 cases, an ulcer 2 cm. or less in diameter in 7, a nodule 3 to 4 cm. in diameter in 5 and 6 cm. in 1, and an ulcer 3 to 4 cm. in diameter in 7.

Gastric retention was correctly recognized roentgenologically in three cases and gastric dilatation in five. Extrinsic lesions resulting in gastric or duodenal deformities were observed in four cases, due to adhesions in one and cancerous lymph nodes in three. In another case, suggesting the presence of an extrinsic lesion, none was demonstrated at autopsy. A roentgenographic diagnosis of carcinoma of the head of the pancreas, without reasons therefore, was made in one case, but at autopsy this organ showed no visible change. A healed ulcer was, in two instances, correctly visualized in the duodenal bulb, but in four others, suspected lesions of the pylorus or duodenal bulb were not confirmed at autopsy. In two cases, the duodenal bulb was widened, in one of which the pancreas as enlarged and cancerous while in the other it was unchanged. The gallbladder was visualized in two cases but it was not visualized in several others, in all but one of which obstructive jaundice was present, the exception showing calculous cholecystitis.

Diagnosis.—A correct clinical diagnosis was made in 39 cases, in which a tumor was suspected in the common bile duct, ampulla of Vater, papilla of Vater or duodenum. In 62 cases, one or more of the following diagnoses were made: Carcinoma of the head of the pancreas (25); calculous choledochitis (14); calculous cholecystitis (10); obstruction of the bile ducts (12); carcinoma of the stomach (6); carcinoma of the liver (5); cholangeitis (4); cholecystitis (3); carcinoma of the gallbladder (3); and in one case each, catarrhal icterus, carcinoma of the pancreatic duct, ulcer of the ampulla of Vater, ulcer of the duodenum, pyloric ulcer, primary anemia, syphilitic hepatitis, intestinal obstruction due to volvulus or intussusception, neoplasm, chronic nephritis, echinococcus cysts of liver and metallic poisoning. No clinical diagnoses were reported in the remaining cases.

A correct surgical diagnosis of carcinoma of the ampulla or papilla of Vater, duodenum or common bile duct was made in 83 of the 122 cases subjected to operation. In eight additional cases, the diagnosis was correctly made

at a second operation. In 22 cases, one or more of the following diagnoses were made: Tumor of the pancreas (12); calculous cholecystitis (4); noncalculous obstruction of the common bile duct (2); and in one case each, stone in the common bile duct, pyloric ulcer, a mass adjacent to the head of the pancreas and tuberculosis of the papilla of Vater.

Treatment.—The treatment of peripapillary carcinoma of the duodenum has been symptomatic, palliative or directed toward a cure. Radiation therapy was employed in three cases. In Upcott's case, a transduodenal excision of the primary tumor and cholecystostomy were performed, and five days later 5 mg. of radium were inserted and left in place for six hours, this procedure being repeated the following day for four hours. The patient was discharged from the hospital nine days later; no further notes as to his subsequent course were recorded. In Abell's Case 3, cholecystostomy was performed first, then biopsy and cholecystoduodenostomy two months later and, at a third operation, two and one-half months later, 25 mg. of radium were applied to the primary neoplasm in the duodenum for 12 hours. The patient subsequently gained 55 pounds (25 Kg.) in weight but never experienced complete relief from digestive discomfort. He lived for 20 months, however, despite clinical evidences of metastases. Muller's patient received lead intravenously followed by deep roentgenotherapy about three and one-quarter years after the first operation, and five months after the third operation. Death ensued approximately one and one-half years later, or a total of four years and eight months after the first operation, there being clinical evidences of metastases at that time.

Celiotomy was performed in 122 cases, in 86 of which the presence of a tumor in the region of the papilla of Vater was detected by means of external palpation of the duodenum in 59 instances, by opening the common duct and attempting to pass a sound which met with an obstruction in 10, whereas, in 16, the method of recognition was not stated, although it was possible to tell from the description that the lesion was directly inspected by opening the duodenum in 14 of these. In eight of these cases, the tumor, unrecognized at the first operation, was detected at a subsequent operation. Some of the tumors palpated were quite small, being only the size of a pea or lentil. Walters cleverly detected an inconspicuous lesion of the papilla of Vater which would have been disregarded except for the fact that the gallbladder was distended and the possibility of an ulcerating lesion of the papilla suspected as a cause of the intestinal hemorrhage. In 25 cases, the primary tumor went unrecognized at operation, even though it measured in many cases 2 to 3 cm. in diameter and in one, 5 cm. In one case, the tumor was missed at each of three operations. In seven cases, a malignant lesion was thought to be present in the head of the pancreas but this was not substantiated at autopsy. In another case, although a sound introduced into the common duct was arrested lower down, the neoplastic nature of the obstruction was not appreciated. In several cases, the primary tumor was mistaken for a gallstone. In one case in which a biopsy was obtained, an incorrect histologic diagnosis of

tuberculosis was submitted. Other findings were infrequently mentioned. Metastases or extension of the neoplasm was noted in 11 cases, in the regional lymph nodes in all, in the pancreas in two, and in the kidney in one. The peritoneal cavity contained ascitic fluid in four cases. Evidences of cholecystitis were present in 12 cases, in most of which there were pericholecystic adhesions. The gallbladder contained pus and bacteria in a few, and gallstones in eight cases, while of three cases, stones were encountered in the common bile duct in all and in the cystic duct in one.

The operative procedures employed, and the results obtained by the various authors are indicated in Table I. Excision was performed in 57 cases, at the first operation in 47, at the second operation in 10, and in two cases it was attempted at both operations. It was the sole procedure in 15 cases, while in the others it was performed in association with one or more of the following: Anastomosis between the biliary and gastro-intestinal tracts in 26 cases; drainage of the biliary tract in 20; implantation of the pancreatic duct into the duodenum in 8; gastro-enterostomy in 10; cholecystectomy in 5; biopsy in 2; and in one case each, pyloroplasty, pancreaticostomy, duodenoduodenostomy, appendicectomy, implantation of pancreatic duct into common bile duct, insertion of radium and drainage of abdomen.

Of 65 cases, in which the primary neoplasm was not excised, one or more of the following procedures were employed: Drainage of the biliary tract (29); some anastomosis between the biliary and gastro-intestinal tracts (28); biopsy (9); gastro-enterostomy (8); cholecystectomy (7); exploratory (6); and in one each, appendicectomy, drainage of the pancreatic duct, duodenostomy and insertion of radium into the primary neoplasm.

Cholecystectomy was performed in 12 cases, in all of which biliary obstruction was present, and in five, some evidence of inflammation such as adhesions or stones was noted. There was generally no assignable reason stated for this procedure, although in one the primary lesion was mistaken for an impacted stone in the common bile duct, and cholecystectomy was carried out apparently with this idea. In one patient, this procedure was instituted despite the fact that metastatic nodules were present in the liver. In a few, the true nature of the condition was, unfortunately, not appreciated until after the gallbladder had been removed, whereupon, appropriate surgical measures were then instituted. In three cases, simple cholecystectomy was, curiously enough, followed by disappearance of jaundice. This may probably have been coincidental, for the spontaneous disappearance of this symptom occurred in several other instances both with and without surgery. It is, of course, evident that the removal of the gallbladder in these cases does away with a useful viscus for establishing a biliary anastomosis with the gastro-intestinal tract, and, therefore, this procedure may result in real embarrassment under these circumstances.

Little or no reference was made, generally, to the clinical state of the patient after operation. Even so important a feature as the persistence or disappearance of icterus was not commented upon in 31 cases in which sur-

TABLE I

RESULTS IN CASES IN WHICH OPERATION WAS PERFORMED

Year	Author	Operation	Result
1889	Ely	Cholecystostomy	Died 5 days after oper.
1893	Hesper	Cholecystostomy	Died 3 wks. after oper.
1893	Weir	3/8/93: Cholecystostomy; drainage of pancreatic duct	Died 10 days after first oper.
		3/18/93: Cholecystojejunostomy	Died 2 hrs. after second oper.
1900	Butz	11/30/98: Cholecystoduodenostomy	Died 19 mos. after first oper.
		2/20/00: Gastro-enterostomy	Died 5 mos. after second oper.
1900	Dobbertin	Partial cholecystectomy; cholecystostomy	Died 3½ mos. after first oper.
		3¼ mos. later: Cholecysto-enterostomy	Died 8 days after second oper.
1901	Schüller, Case 1	Transduodenal excision; cholecystostomy	Died 5 days after oper.
	Case 2	Cholecysto-enterostomy	Died 12 days after oper.
1901	Rixford	10/22/01: Transduodenal excision; cholecystostomy	Operative recovery
		11/21/01: Transduodenal excision; choledochoduodenostomy	Operative recovery
		7/?/02: Cholecysto-enterostomy	Died 4 mos. after third oper., 13 mos. after first and 12 mos. after second oper.
1901	Mayo	11/3/00: Cholecystostomy	Operative recovery
		1/3/01: Transduodenal excision	Operative recovery
		7/7/02: Cholecystoduodenostomy	Operative recovery; discharged, 20 mos. after first, and 17¼ mos. after second oper.
1902	Scheuer	2/?/00: Cholecystostomy	Died 10 mos. after first oper.
		?/?/00: Exploratory	Operative recovery; discharged
1902	Miodowski, Case 4	Cholecystostomy	Died 1 day after oper.
1902	Hagen	Cholecystoduodenostomy; gastro-enterostomy	Died several hours later
1903	Cornil and Chevassu	Cholecysto-enterostomy	Died 9 days after oper.
1904	Klotz	Exploratory	Died 1 mo. after oper.
1906	Carnot and Harvier	Cholecystostomy	Died several days after oper.; peritonitis
1906	Arnsperger, Case 25	Cholecystostomy	Died 13 days after oper.
	Case 28	Transduodenal excision	Died 2 days after oper.
1907	Verhoogen	Transduodenal excision	Died 11 days after oper.
1908	Devic and Savy	Gastro-enterostomy	Died 36 hrs. after oper.
1909	Körte, Case 32	Transduodenal excision	Living and well 46 mos. after oper.

TABLE I—*Continued*

Year	Author	Operation	Result
1910	Navarro	Transduodenal excision; choledochoduodenostomy	Operative recovery; discharged
1910	Koerber, Case 1	Cholecystojejunostomy	Died 3 days after oper.
	Case 2	Cholecysto-enterostomy	Died 5 days after oper.
1910	Doberauer	Transduodenal excision; cholecystoenterostomy	Died 3 mos. after oper.
1910	Cuneo	Transduodenal excision; choledochoduodenostomy	Died 5 days after oper.
1910	Oehler	Transduodenal excision; cholecystostomy	Living and well 5 wks. after oper.
1912	Upcott, Case 2	5/3/12: Transduodenal excision; cholecystostomy	Operative recovery
		5/14/12: 5 mg. radium inserted into cystic duct for 6 hrs. Same procedure next day.	Operative recovery; discharged
1912	Kausch, Case 2	6/15/09: Cholecysto-enterostomy	Operative recovery
		8/21/09: Radical resection of 11 cm. of duodenum	Operative recovery
		5/25/10: Cholecystostomy	Died 1 day after third oper.; hemorrhage, 11½ mos. after first oper. and 9 mos. after second oper.
	Case 1	Cholecystojejunostomy; duodenotomy	Died 4 days after oper.
1912	Oppenheimer	Transduodenal excision; gastro-enterostomy	Living and well 7 mos. after oper.
1912	Lenormant	Cholecystectomy; choledochostomy	Died 7 days after oper.
1913	Pollet	Biopsy; choledochostomy	Died 8 days after oper.
1914	Crohn, Case 2	Cholecystostomy	Died several hrs. later; shock
	Case 3	Cholecystostomy	Died 1 day after oper.; shock
1914	Zuccola, Case 2	Cholecystostomy	Died 39 days after oper.
1914	Docq and van Bever	Transduodenal excision	Died 4 days after oper.
1917	Pétren, Case 56	Cholecystoduodenostomy; choledochostomy	Died 5 days after oper.
1918	Anschütz	Transduodenal excision; gastro-enterostomy; cholecystostomy	Operative recovery; discharged
1919	Oliani	Transduodenal excision	Living and well 1 mo. after oper.
1919	Schüssler, Case 3 in text.	Cholecystostomy; transduodenal excision; choledochoduodenostomy; gastro-enterostomy	Living and well 4 mos. after oper.
1920	McGuire and Cornish, Case 1	Cholecystostomy	Died 3 hrs. after oper.

TABLE I—*Continued*

Year	Author	Operation	Result
1921	Pallin, Case 1	Transduodenal excision; cholecystostomy; choledochostomy	Died 8 hrs. after oper.; pneumonia; intestinal hemorrhage
	Case 2	Transduodenal excision; cholecystectomy	Died 2 days after oper.; intestinal hemorrhage
	Case 3	Transduodenal excision	Died 3 days after oper.
1921	Carnot and Libert	Cholecystogastrostomy	Died 16 days after oper.
1921	Propping	Transduodenal excision	Living and well 13 mos. after oper.
1921	Lewis	Transduodenal excision; cholecystostomy	Living and well 4 mos. after oper.
1922	Brütt, Case 6	Transduodenal excision	Living and well 9 mos. after oper.
	Case 7	Transduodenal excision	Living and well 18 mos. after oper.
1922	Kleinschmidt, Case 1	Transduodenal excision; cholecystectomy; choledochotomy	Died 8 days after oper.; peritonitis
	Case 2	Tranduodenal excision; cholecystectomy; choledochostomy; implantation of pancreatic duct into duodenum; drainage of hepatic duct	Living and well 6 yrs. after oper.
1922	Tenani	8/?/18: Cholecystoenterostomy	Operative recovery
		9/?/18: Transduodenal excision	Living and well 4 mos. after second oper., 5 mos. after first oper.
1923	Hartmann	Choledochostomy	Died 8 days after oper.
1923	Angeli	Exploratory	Died 12 days after oper.
1923	Pozzi, Case 2	Transduodenal excision; cholecystogastrostomy; choledochotomy	Died 6 days after oper.; peritonitis
	Case 3	Transduodenal excision	Living and well 1 mo. after oper.
1923	Prat, Case 1	Exploratory	Died 25 days after oper.
1924	Pozzi, Case 1	Transduodenal excision; cholecystogastrostomy; choledochotomy	Operative recovery
1924	Abell, Case 3	5/?/20: Biopsy; cholecystoduodenostomy	Operative recovery
		1/?/23: Gastro-enterostomy	Living and well 10 mos. after second oper., 42 mos. after first oper.
1924	Chiray, Benda and Milchovitch	Cholecystostomy	Died 2 days after oper.
1924	Einhorn and Stetten	6/16/23: Cholecystectomy; appendicectomy	Operative recovery
		11/2/23: Biopsy; choledochostomy	Died 1 mo. after second oper.; septicemia, 5 mos. after first oper.

TABLE I—*Continued*

Year	Author	Operation	Result
1925	Konjetzny	Transduodenal excision; implantation of pancreatic duct into duodenum	Living and well 3 wks. after oper.
1925	Hadfield	Cholecystogastrostomy	Died 4 days after oper.
1926	Hingst, Case 1	Cholecystoduodenostomy	Died 5 yrs. after oper.; diabetic coma
	Case 2	Cholecystectomy; cholecystostomy	Died 12 hrs. after oper.
	Case 3	Drainage of hepatic duct	Died 7 days after oper.
1926	Cabot, Case 12063	Cholecystostomy	Died 4 days after oper.
1926	Garcia Lagos, Ugón, and Dominiquez	Transduodenal excision	Died 16 hrs. after oper.
1927	Clar	1/20/22: Transduodenal excision	Operative recovery
		2/6/22: Cholecystectomy	Living and well 5 yrs. after second oper., 5 yrs. 2 mos. after first oper.
1927	Fulde	Transduodenal excision	Living and well 2 yrs. after oper.
1927	Savinych, Case 2	Transduodenal excision; choledochoduodenostomy; implantation of pancreatic duct into common duct	Died 5 days after oper.
1927	Cohen and Colp, Case 1	Transduodenal excision	Died 10 hrs. after oper.
	Case 2	Transduodenal excision; choledochostomy	Died 5 days after oper.
	Case 4	Cholecystectomy; choledochostomy; duodenostomy	Died 19 days after oper.
	Case 5	Cholecystostomy; choledochostomy	Died 8 hrs. after oper.
	Case 8	Transduodenal excision; cholecystoduodenostomy; gastrojejunostomy	Died 4 days after oper.
1927	Del Valle and Brachetto-Brian	Transduodenal excision; cholecystectomy; appendicectomy; drainage of hepatic duct	Operative recovery; discharged
1928	Llambías, Brachetto-Brian and Orosco	Cholecysto-enterostomy	Died 3 days after oper.
1928	Busch	Transduodenal excision	?
1928	Dewis and Morse	Cholecystostomy	Died immediately after oper.
1928	Boston and Jodzis	Exploratory	Died on operating table
1929	Countryman	Cholecystectomy	Died 5 mos. after oper.
1929	Jermain	Cholecysto-enterostomy	Died 4 days after oper.
1931	Muller and Rademaker	5/20/24: Transduodenal excision; choledochoduodenostomy	Operative recovery
		8/17/26: Cholecystoduodenostomy	Operative recovery

TABLE I—*Continued*

Year	Author	Operation	Result
	Muller and Rademaker..	3/11/27: Gastro-enterostomy	Died 22 mos. after third oper., 4 yrs. 8 mos. after first oper., and 2 yrs. 5 mos. after second oper.
1931	Ross and Davie.....	Cholecystostomy	Died 5 days after oper.
1932	Godfrey and Sappington	Exploratory	Died 8 mos. after oper.
1932	Mateer and Hartman,	6/?/28: Cholecystectomy	Operative recovery
	Case 2.....	7/?/29: Transduodenal excision; biopsy; choledochoduodenostomy	Died 22 mos. after second oper., 35 mos. after first oper.
	Case 5.....	Cholecystostomy	Died 2 mos. after oper.
1932	Walters.....	Transduodenal excision; choledochoduodenostomy; pyloroplasty	Living and well 28 days after oper.
1932	Pemberton.....	10/8/24: Exploratory	Died 26 mos. after first oper.
		1/?/25: Transduodenal excision; choledochoduodenostomy; implantation of pancreatic duct into duodenum	Died 20 mos. after second oper.
		9/20/26: Exploratory	Died 6 mos. after third oper.
1932	Judd.....	11/1/28: Cholecystostomy; choledochostomy	Operative recovery
		12/21/28: Transduodenal excision	Operative recovery
		9/9/29: Cholecystogastrostomy	Operative recovery
		4/26/31: Gastro-enterostomy	Living and well 2 weeks after fourth oper., 30½ mos. after first, 29½ mos. after second and 20 mos. after third opers.
1933	Goldberg	Cholecystoduodenostomy	Died on operating table
1933	Bérard, Mallet-Guy and Croizat	12/17/31: Cholecystostomy; choledochostomy	Operative recovery
		2/13/32: Biopsy; choledochoduodenostomy	Living and well 4 mos. after second oper., 6 mos. after first oper.
1933	Cabot, Case 19191.....	Cholecystogastrostomy	Died 36 hrs. after oper.
1933	Lauwers, Case 1.....	Transduodenal excision; cholecysto-enterostomy	Living and well 46 mos. after oper.
	Case 2.....	Transduodenal excision; cholecysto-enterostomy	Living and well 9 mos. after oper.
1933	Potter.....	Transduodenal excision; implantation of common and pancreatic ducts into duodenum; drainage of common and pancreatic ducts	Living and well 11 mo. after oper.
1934	Santero Case 1.....	10/10/27: Transduodenal excision; choledochoduodenostomy	Operative recovery

TABLE I—*Continued*

Year	Author	Operation	Result
	Santero Case I (*Cont.*)..	3/16/29: Transduodenal excision; implantation of common and pancreatic ducts into duodenum	Died 5 mos. after second oper., 22 mos. after first oper.
	Case 2.....	7/21/28: Transduodenal excision; implantation of common and pancreatic ducts into duodenum	Operative recovery
		10/30/29: Cholecystostomy	Died 4 mos. after second oper., 19 mos. after first oper.
1934	Harbin, Harbin and Harbin	2/?/32: Cholecystoduodenostomy	Operative recovery
		5/?/32: Gastro-enterostomy	Died 9 days after second oper.; pneumonia, 2¾ mos. after first oper.
1934	Swenson and Levin.....	Cholecystostomy	Died 3 days after oper.
1935	Hunt and Budd.....	Transduodenal excision; implantation of common and pancreatic ducts into duodenum; cholecystostomy	Living and well 3 mos. after oper.
1935	Whipple, Parsons and Mullins, Case 1	3/16/34:Choledochoduodenostomy; cholecystostomy	Operative recovery
		5/17/34: Transduodenal excision; pancreaticoenterostomy	Died 30 hrs. after second oper., 1½ mos. after first oper.
	Case 2.....	7/18/34: Cholecystogastrostomy	Operation recovery
		8/21/34: Transduodenal excision; biopsy; duodenoduodenostomy	Operative recovery
		8/29/34: Gastro-enterostomy	Died 7½ mos. after third oper., 9 mos. after first, and 8 mos. after second oper.
	Case 3.....	1/25/35: Gastro-enterostomy; cholecystogastrostomy	Operative recovery
		2/7/35: Transduodenal excision	Operative recovery
		3/25/35: Drainage of abdomen	Living and well 4½ mos. after third oper., 6½ mos. after first oper.
1936	Doub and Jones, Case 2..	Exploratory	Died 7 days after oper.; intestinal hemorrhage
1936	Koch, Case 2.....	Cholecysto-enterostomy	Died a few days after oper.
1937	Geisthövel, Case I 1.....	Transduodenal excision; choledochoduodenostomy; cholecystoduodenostomy	Living and well 6 mos. after oper.

TABLE I—*Continued*

Year	Author	Operation	Result
	Geisthövel, Case II 1	Choledochoduodenostomy	Died 1 day after oper.; hemorrhage
	Case II 8	Cholecystojejunostomy	Died 4 days after oper.
1937	Cabot, Case 23282	Cholecysto-enterostomy; pyloroplasty	Died 4 days after oper.
1937	Hoffman and Pack, Case 3	Duodenotomy; biopsy	Died 11 days after oper.; bronchopneumonia
	Case 11	Duodenotomy, biopsy; gastro-enterostomy; cholecystogastrostomy	Operative recovery
	Case 12	Duodenotomy; biopsy; cholecystostomy	Died 7 days after oper.; bronchopneumonia
	Case 15	4/?/35: Cholecystostomy	Operative recovery
		5/?/35: Duodenotomy; biopsy	Died 3½ mos. after second oper., 4½ mos. after first oper.
	Case 16	Choledochostomy	Operative recovery
		Transduodenal excision, one month later	Died 6 hrs. after second oper., 1 mo. after first oper.
1937	Lieber, Stewart and Morgan	Cholecystogastrostomy	Died 1 day after oper.; hemorrhage
1937	Lieber, Stewart and Lund, Case 1	Cholecystogastrostomy	Died 5 days after oper.
	Case 3	8/29/32: Cholecystectomy	Operative recovery
		12/19/32: Duodenostomy; removal of fistulous tract	Died 18 mos. after second oper., 22 mos. after first oper.
	Case 7	Cholecystoduodenostomy	Died 9 days after oper.
	Case 17	Cholecystogastrostomy; gastrojejunostomy; jejunojejunostomy	Died 3 days after oper.

gical procedures were instituted, designed for the reestablishment of biliary flow. In 39 cases, however, jaundice cleared postoperatively; in one it remained unaffected; in three it increased in intensity; and in 11 it recurred. The time of disappearance of icterus was mentioned in only three cases, being 11 and 15 days and one and one-half months, respectively. Other symptoms noted after various types of operative procedures were pain in 13 cases, chills and fever in 9, vomiting in 7, loss of weight in 8, indigestion in 3 and in one each, nausea, diarrhea and anorexia. In some patients, one or more of these symptoms reappeared together, and frequently served as indications for multiple operations. An analysis of the cause of these symptoms revealed some interesting data. The recurrence of jaundice postoperatively was apparently due to spontaneous closure of the anastomosis between the biliary and gastrointestinal tract in five cases and to biliary tract infection following instrumentation immediately in two and more remotely after excision and anastomosis in three. Symptoms of intestinal obstruction were noted in three cases in which growth of the local lesion produced obstruction of the lumen of the

duodenum, even though relatively wide excision with reimplantation of the ducts had been previously performed in two of these. Recurrence of the tumor and local infiltration no doubt partially accounted for recurrent symptoms, especially pain as in five other cases. White stools in one case and diarrhea in another were ascribed to the absence of pancreatic secretion from the intestine as a result of recurrence of the growth in one, and almost total atrophy of the pancreas in another.

There was a positive, ultimate mortality rate of about 72 per cent, but this figure would undoubtedly be higher if follow-up studies had been more complete. The period of postoperative survival was not specified in a number of instances in which only palliative operations were performed. There were 60 patients who died during the first 13 postoperative days, and one each on the sixteenth and twenty-fifth postoperative days, respectively, thus emphasizing what poor operative risks these patients are. This high surgical mortality can be attributed, in large part, to the magnitude of the surgical procedures in critically ill patients with biliary stasis, chronic hemorrhage, anemia, dehydration and sometimes intestinal obstruction and varying degrees of starvation. Analyzing the data from the view of the postoperative survival alone, it appears that despite the marked difference in pre- and postoperative treatment, the surgeons of to-day are having no better immediate success in operating upon these patients than they had 25 to 50 years ago. No doubt, this can partly be ascribed to the fact that many more patients who are poor risks are now being treated surgically.

Longer periods of survival were recorded in 23 cases, in which the patients died in from one to 60 months, while in 31 additional cases, the patients survived varying periods of time from one to 72 months after which, however, they were not followed. Thus survival periods of six years were reported in one case, of five years in two cases, of four years in two cases, of three years in one case, of two years in five cases, of one year in six cases and of less than a year in the remainder. It is interesting that two patients, followed for 56 and 60 months, respectively, after operation, ultimately died of recurrent carcinoma with metastases as proved by autopsy, while in Kleinschmidt's case, the last clinical examination made six years after operation showed no evidence of recurrence.

Taken as a whole, the patients who survived the immediate effects of operation lived for a total average of two years after the onset of the condition, and a little more than half of these were reported as still alive at the end of this period. A comparison of the preoperative period of illness in the patients who died with those who were reported as still alive and well showed that the former group were ill for an average of about seven months before surgery was instituted, whereas the latter were ill for an average of only two months, thus illustrating, conclusively, the importance of early diagnosis and early treatment. The patients who lived for less than one month postoperatively were ill for an average of about six months before operation.

Carrying the analysis still further some interesting features come to light. Of 51 patients subjected to some type of palliative procedure only for the relief of obstructive jaundice, 39 died during the first 19 days postoperatively; nine survived for one to 60 months, an average of 19 months; and three were still living at the end of four, four and one-half, and 42 months, respectively. Of 57 patients, in whom the primary growth was resected either alone or in combination with other surgical procedures, 17 died in the first two weeks postoperatively; ten died in from two to 22 months, an average of 11 months, and the remaining 30 were still living one to 72 months later, an average of about 14 months. Of nine patients, in whom resection was preceded by some operation for the relief of obstructive jaundice, there were no immediate postoperative deaths at the time of the resection, and four of the patients died at the end of 11 months on the average, while five were still alive at the end of ten months on an average. Of the 25 patients subjected to two or more operations, the immediate postoperative mortality was five at the second operation.

Many difficulties may be encountered in carrying out surgical treatment, as a review of the clinical and the morbid anatomic findings in the present series indicates. The patients were as a rule deeply jaundiced, undernourished, asthenic and had varying degrees of liver damage. The tumor was not limited to a single structure, but directly or indirectly involved adjacent tissues of equal importance to the human economy. Extension or metastases from the primary lesion occurred in at least 45 per cent of the cases in this series, and of 122 patients subjected to celiotomy, extension or metastases were found in about 11 per cent. Obviously, the surgical measures employed in any individual case must depend upon the general condition of the patient, the character and extent of the primary lesion, the presence of extension or metastases and on the degree of biliary, pancreatic and duodenal obstruction. We are entirely in accord with the views expressed by Whipple, Parsons and Mullins on the surgical treatment in these cases. Greater efforts must be expended in reducing the high, immediate postoperative mortality, and the most satisfactory results can be expected only if surgery is resorted to very early in the condition. Jaundice is usually an early symptom, and in patients in the fifth to the eighth decade of life it should always suggest the possibility of carcinoma in the region of the papilla of Vater. Exploratory duodenotomy and direct inspection of the region about the papilla of Vater is to be emphasized, for the primary lesion may be quite small and otherwise escape detection. The prompt appearance of symptoms at the onset, the absence of metastases in many patients observed at celiotomy in the early stages of the condition, and the unusual longevity shown in several cases should favor the successful eradication of the neoplastic process if adequate preparation and wide excision are carried out.

Ninety-seven of the 100 patients not subjected to surgery lived from two weeks to 28 months, or an average of 6.63 months. The period of survival was two weeks to one month (7); about two months (17); three months

(15); four months (9); five months (7); six months (6); seven months (5); eight months (3); nine months (3); ten months (4); 11 months (4); 12 months (7); 17 months (2); 22 months (3); 26 months (2); and 13, 24 and 28 months (one each). In three cases the period of survival was not stated.

SUMMARY

(1) A clinical and pathologic study of carcinoma of the peripapillary region of the duodenum is presented, based upon 17 new cases and 205 reported in the literature.

(2) These cases have been classified as follows:

(I) Primary carcinoma of the ampulla of Vater (one case).

(II) Primary carcinoma of the terminal duct of Wirsung (three cases).

(III) Primary carcinoma of the terminal common bile duct (seven cases omitted from the present analysis).

(IV) Primary carcinoma of the intestinal mucous membrane covering the papilla of Vater (three cases).

(V) Carcinoma involving all the epithelial structures of the papilla of Vater under Groups I, II, III and IV (182 cases).

(VI) Carcinoma involving all the epithelial structures comprising the papilla of Vater, as before, exclusive of the intestinal mucous membrane (33 cases).

(3) Thirteen of our cases and one from the literature, totaling 14 in all, were found in 22,152 autopsies (0.063 per cent), and three cases in 4,154 autopsies (0.096 per cent).

(4) The average age was about 54.4 years, 139 patients being men and 83 being women. Thirteen cases (5.9 per cent) occurred in young individuals, between 15 to 34 years of age.

(5) The onset was acute in about 80 per cent of cases and gradual in 20 per cent. The principal symptoms and signs, irrespective of the mode of onset, were jaundice, pain, loss of weight and strength, anorexia, fever, vomiting, constipation, diarrhea and a sense of weight and pressure in the abdomen. Other less common symptoms were dyspepsia, epigastric distress, flatulency, abdominal distention, nausea and chills. Jaundice was a symptom in 98.2 per cent of the cases, pain in 59.4 per cent, and both were associated at the onset of the condition in 24.3 per cent. Fever, sometimes accompanied by chills, occurred in 33.3 per cent of cases, usually late in the condition. A mass was palpable clinically in the region of the primary tumor in only four cases. The liver was palpably enlarged in 77.9 per cent of cases and the gallbladder in 49.9 per cent. A moderate grade of anemia was the rule in these patients. The duodenal contents contained bile in nine of 15 cases, pancreatic ferments in six and blood in three. The stools were usually clay-colored or colorless and contained blood in 18.9 per cent of cases examined, and occasionally an increase in neutral fats and fatty acids.

(6) A correct preoperative diagnosis was made in approximately 17.1 per cent of cases. The presence of a lesion in the region of the papilla of

Vater was recognized roentgenographically in 16 or 60 cases examined (26.6 per cent). At celiotomy, a correct surgical diagnosis was made in approximately 68 per cent of 122 cases.

(7) The primary neoplasm in Group V (carcinoma involving all the epithelial structures comprising the papilla of Vater) was usually hazel-nut in size and well limited to the papilla of Vater in 73.9 per cent of the 182 cases; and in the remainder, the neoplastic tissue extended into and along the duodenum for varying distances up to 12 cm. in length, the growths averaging 4.5 cm. in length. More than one-third of these tumors were vegetating, papillary or cauliflower-like and rarely filled the lumen of the duodenum. Ulceration of the primary neoplasm was present in 31.3 per cent of cases. Some degree of obstructive jaundice due to involvement of the terminal end of the common bile duct occurred in all but four cases. The terminal end of the pancreatic duct was obstructed in 83.3 per cent of cases in which this structure was examined. Metastases or extension of the primary tumor to adjacent structures occurred in at least 43 per cent of cases. All but four of the neoplasms in this group were of the glandular variety; the exceptions were three cases of adenosquamous cell carcinoma and one of squamous cell carcinoma.

(8) The primary neoplasm in Group VI (carcinoma involving all the epithelial structures comprising the papilla of Vater except the intestinal mucous membrane covering it) was usually the size of a cherry, the papilla projecting forward as a cylindro-conical body into the lumen of the bowel with the mucous membrane covering it smooth, not thickened and usually freely movable. The terminal end of the common bile duct was regularly thickened by an annular growth, grayish-white, usually hard, indurated and measuring as much as 2 cm. in diameter. Elevated tumor nodules studded the mucous surface of the duct in 45.7 per cent, and ulceration of the surface occurred in 12.1 per cent of the 33 cases in this group. The terminal end of the pancreatic duct was obstructed in 83.3 per cent of the 18 cases in which this structure was examined. Metastases and extension of the primary neoplasm occurred in at least 27 per cent of cases. All the cases in this group were glandular carcinomata.

(9) Contrasting the pathologic features of Groups V and VI, certain essential differences were noted. In the latter group, the tumors were consistently smaller and well differentiated histologically, with less anaplasia, all being examples of adenocarcinoma with little or no tendency for the cells to grow in strands, clumps or nests; and mitoses were numerous in only a single case. Metastases and extension of the primary tumor occurred in 27 per cent of the cases of this group as compared with 43 per cent in Group V, and in the former, the intestinal mucous membrane showed no involvement.

(10) Ninety-seven of the 100 patients, treated medically and not subjected to surgery, died on an average of 6.63 months after the onset of the illness.

(11) Surgical therapy was instituted in 122 cases. There was an ultimate mortality rate of 72 per cent but this figure would undoubtedly have been

higher had the follow-up studies been more complete. The operative mortality was 50.6 per cent. Of 51 patients subjected to some type of palliative procedure only for the relief of obstructive jaundice, the operative mortality was 78.4 per cent. Of 57 patients, in whom the primary growth was resected either alone or in combination with other surgical procedures, the operative mortality was 30 per cent. The patients who succumbed immediately postoperatively were ill for an average of six months before operation. Other patients who were operated upon and who survived the immediate postoperative effects lived for a total average of two years after the onset of the condition, and a little more than one-half of these were reported as still alive at the end of this period; of this group, those who died were ill for an average of seven months before operation, whereas those reported as still surviving were ill for an average of only two months before operation. These figures emphasize the importance of early diagnosis and early surgical treatment.

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