Primary Carcinoma Of The Extrahepatic Biliary Ducts

Lawrence E. Permen

E. Bert McCollum
PRIMARY CARCINOMA OF THE EXTRAHEPATIC BILIARY DUCTS

LAWRENCE E. PERMEN, M.D.,* AND E. BERT MCCOLLUM, M.D.**

Nineteen cases of primary malignancy of the extrahepatic bile ducts studied during the ten year period from January, 1952, through December, 1961, form the basis of this report. Only carcinoma of the extrahepatic bile ducts which has been proved by biopsy, surgical specimen, or post-mortem examination, will receive consideration. Lesions of the gallbladder and ampulla of Vater will not be included in this series.

INCIDENCE

Primary carcinoma of the extrahepatic bile ducts is a relatively rare disease. The autopsy incidence ranges from 0.012% (Bolli, C.) as cited by Sako21 to 0.85% (Von Berencsy) as quoted by Mohardt17 (Table I).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. W. McLaughlin15</td>
<td>1933</td>
<td>0.07</td>
</tr>
<tr>
<td>C. F. Iltingworth10</td>
<td>1935</td>
<td>0.33</td>
</tr>
<tr>
<td>K. I. Masuda13</td>
<td>1935</td>
<td>0.45</td>
</tr>
<tr>
<td>I. R. Jankelson11</td>
<td>1937</td>
<td>0.27</td>
</tr>
<tr>
<td>J. H. Mohardt (Von Berencsy)17</td>
<td>1939</td>
<td>0.85</td>
</tr>
<tr>
<td>J. C. Dick2</td>
<td>1939</td>
<td>0.42</td>
</tr>
<tr>
<td>M. S. Kirshbaum12</td>
<td>1941</td>
<td>0.46</td>
</tr>
<tr>
<td>K. Sako (C. Bolli)21</td>
<td>1946</td>
<td>0.012</td>
</tr>
<tr>
<td>H. A. Nebling18</td>
<td>1949</td>
<td>0.26</td>
</tr>
<tr>
<td>I. S. Goldenberg7</td>
<td>1953</td>
<td>0.40</td>
</tr>
<tr>
<td>K. Sako 21</td>
<td>1957</td>
<td>0.38</td>
</tr>
<tr>
<td>Authors' Series</td>
<td>1962</td>
<td>0.54</td>
</tr>
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</table>

Nineteen cases of carcinoma of the extrahepatic bile ducts constitute 0.54 per cent of all post-mortem examinations, while the surgical incidence is 0.01 per cent of 184,672 operations.

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SEX DISTRIBUTION AND AGE

The sex ratio according to Sako\textsuperscript{21} was in the proportion of three men to two women in 433 cases reported in the world literature from 1935 to 1954. In accordance with this proportion, Lippman's\textsuperscript{14} study of 20 patients was comprised of 12 men and 8 women. In contrast to this, Brown\textsuperscript{1} found a ratio of 3:4, 27 men and 35 women.

The ages of the patients ranged from 34 to 91 years with an average of 60.3 years in Lippman's\textsuperscript{14} review. Brown states that most of his 62 patients were in the 50 to 70 year age groups.

The ages ranged from 51.3 years to 80 years in our series, with an average of 62.7 years. The average for men was 62.4 years and for women 63.0 years. In the 50 to 59 year group, we had five men, three women; in the 60 to 69 year group, three men, four women; in the 70 to 79 year group, two men, one woman; in the 80 to 89 year group, one man.

ETIOLOGY

The cause of this disease is obscure since the specific etiologic factor of cancer remains an enigma. The predisposing influence of gallstones, mentioned in reports of carcinoma of the gallbladder, is less well established for carcinoma of the bile ducts. Their presence has been variously reported from 20.2 per cent\textsuperscript{22} to 57 per cent\textsuperscript{19} of cases.

Many interesting, but as yet unsubstantiated, contributory factors have been suggested for the pathogenesis:

1. Carcinogenic action of cholic acid in susceptible persons\textsuperscript{2} or its conversion to a derivative, methylcholanthrene.\textsuperscript{6}
2. Precancerous inflammatory proliferation of the ductal accessory glands.\textsuperscript{8}
3. Carcinoma originating from previous ulceration of the bile ducts.\textsuperscript{20}
4. Malignant changes from a benign papilloma.\textsuperscript{2}
5. Pre-existing cholecystitis.\textsuperscript{10}
6. Giardia lamblia infestations (Grott, cited by Brown, 1961).\textsuperscript{1}
7. Radio-active salts in a small proportion of gallstones.\textsuperscript{12}
8. Embryonic rests.\textsuperscript{16}

PATHOLOGY

GROSS: The tumor may be a (a) nodule, (b) papillary tumor, (c) annular stricture, (d) diffuse infiltrating growth, or (e) large, poorly defined lesion. There does not seem to be an affinity of any type of tumor for a certain segment of the biliary tree. Most frequently it is a firm, tan colored nodule encroaching upon the ductal lumen. The duct may be partially or completely obstructed, with moderate to extreme
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dilatation of the proximal ducts. Rarely, the lesion is papillary, which by ball valve action and/or necrosis and hemorrhage (to which it is prone). may produce intermittent occlusion, with resulting intermittent jaundice.

The scirrhouS adenocarcinoma is a hard, infiltrating lesion that may be mistaken for an inflammatory condition. In one instance, an exploratory laparotomy was performed which appeared to reveal an inflammatory lesion. The pathologist reported fibrosis and chronic inflammation of the common bile duct, concluding that the lesion was sclerosing cholangitis. At post-mortem examination, however, it proved to be scirrhouS carcinoma, grade III, of the common bile duct.

MICROSCOPIC: Confusion in the nomenclature of these neoplasms has prompted one author to classify them as adenocarcinoma or squamous cell carcinoma, modified by the adjectives, scirrhouS, simplex, medullary, papillary, solidum, mucous, cylindrical cell, or undifferentiated for the former, and hornifying or nonhornifying for the latter. On histologic examination these tumors are found to be composed of glandular structures lined by cuboidal to columnar cells that may or may not be mucin-secretino. The epithelial proliferation is accompanied by fibrous stroma. Mitotic figures are seen infrequently in the scirrhouS carcinomata but frequently in the undifferentiated tumors. There is wide variation in the size of acini, the scirrhouS type having many small ones, while other types of adenocarcinoma demonstrate large acini.

SITE: One can usually determine the origin of the primary tumor at necropsy. In two cases the exact primary site of the tumor was impossible to determine with certainty because of invasion into adjacent tissues. The most common site of primary tumor is the common bile duct. Less frequently are (a) the junction of the common hepatic, cystic, and common bile ducts, and (b) the hepatic ducts. Cystic duct malignancy is the least common. The figures of various authors concerning the site distribution of tumors are shown in Table II.

SPREAD: These tumors extend and spread by direct extension, lymphatic permeation, and rarely by hematogenous dissemination. The most common microscopical evidence of spread is local infiltration of the choledochal wall, apparently following lymphatic spaces. Thorbjarnarson reported 13 of 31 cases with ductal infiltration, transforming

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Cases</th>
<th>Common Bile Duct</th>
<th>Junction of 3 Ducts</th>
<th>Hepatic Ducts</th>
<th>Cystic Duct</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>K. Sako21</td>
<td>570</td>
<td>203</td>
<td>137</td>
<td>126</td>
<td>34</td>
<td>70</td>
</tr>
<tr>
<td>D. B. Brown1</td>
<td>62</td>
<td>26</td>
<td>12</td>
<td>20</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>M. S. Kirshbaum12</td>
<td>52</td>
<td>32</td>
<td>0</td>
<td>13</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>C. W. McLaughlin15 (Renshaw)</td>
<td>20</td>
<td>14</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F. Glen3</td>
<td>18</td>
<td>9</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Authors' Series</td>
<td>19</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
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</table>
the ducts into hard, rigid tubes. Early direct extension to the liver may occur because of the close proximity of the hepatic ducts to this organ. Similarly, the pancreas was commonly affected by direct extension from neoplasms just above the ampulla of Vater. Frequent invasion of nerves has been reported.

Stewart and others have reported metastases most commonly to the liver and regional lymph nodes. Extension to other intra-abdominal organs is frequent, but the incidence of distribution is inconstant. Of ten cases with post-mortem examinations, all were found to have metastatic disease. Two cases exhibited extra-abdominal spread, one with metastases to the lung and iliac lymph nodes, the other with involvement of the mediastinal and peribronchial lymphatics.

ASSOCIATED PATHOLOGY: In addition to metastatic disease, the liver showed changes secondary to obstruction and inflammation. Biliary hepatitis was seen in six necropsy cases, hepatic abscesses in three, biliary cirrhosis in one, and cholangitis in another. There were seven instances of cholecystitis and/or cholelithiasis.

The changes found in the pancreas were chronic pancreatitis (four cases), and interstitial fibrosis of the pancreas (two cases). Excessive levels of bilirubin and bile salts resulted in cholemic nephrosis in four cases.

Other complications, mentioned by Kirshbaum, include perforation, pericholecystic abscess, and biliary peritonitis.

CLINICAL PICTURE

The diagnosis of extrahepatic biliary duct cancer was established in 19 patients. Nine of these were found at operation only; eight at surgery and later confirmed by post-mortem examination; and two at necropsy only.

SYMPTOMS: The clinical picture of this disease is similar to other lesions which produce an obstructive type of jaundice. Although no diagnostic criteria can be suggested, the symptomatology may be of some aid in making the correct diagnosis.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Patients</th>
<th>Signs</th>
<th>No. of Patients</th>
</tr>
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<tbody>
<tr>
<td>Jaundice</td>
<td>18</td>
<td>Acholic Stools</td>
<td>18</td>
</tr>
<tr>
<td>Pain</td>
<td>14</td>
<td>Dark Urine</td>
<td>17</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>14</td>
<td>Pulpable Liver</td>
<td>16</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12</td>
<td>Mass RUQ, ? Gallbladder</td>
<td>9</td>
</tr>
<tr>
<td>Pruritis</td>
<td>11</td>
<td>Tender Abdomen</td>
<td>8</td>
</tr>
<tr>
<td>Vague Abdominal Distress</td>
<td>9</td>
<td>Grossly Bloody Stool</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td>Dehydration</td>
<td>4</td>
</tr>
<tr>
<td>Weakness</td>
<td>4</td>
<td>Ascites</td>
<td>4</td>
</tr>
<tr>
<td>Chills/Fever</td>
<td>4</td>
<td>Cachexia</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>Distension</td>
<td>2</td>
</tr>
</tbody>
</table>
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The major symptoms noted were jaundice, pain, weight loss, anorexia, and pruritis. Other symptoms may include vague gastrointestinal distress, vomiting, chills, fever, and diarrhea (Table III).

Jaundice, present in 18 cases (95 per cent), developed rapidly and progressively in all cases but one, in which the jaundice was intermittent. The patient who did not have jaundice on admission was a 67 year old woman, who complained of back pain, fatigue, anorexia, and weight loss. Examination revealed a cachectic woman with a tender abdomen and a right upper quadrant abdominal mass. At necropsy the primary lesion was discovered in the cystic duct.

Pain was present in 14 cases (74 per cent) and described variously as dull, aching, or boring in character. It was right upper quadrant in four, epigastric in three, and substernal in one. In one the pain radiated to the right shoulder. Brown studied 39 cases regarding the time incidence of pain and jaundice. The pain developed before jaundice in 31 patients and afterwards in eight. In 14 cases the onset of jaundice was delayed by a month or more. The pain may be a result of gallstones, biliary duct distension proximal to the obstruction, stretching of the liver capsule, or invasion of surrounding nerves.

Weight loss was as frequent as pain (14 cases). An average weight loss of 26 pounds during four months prior to admission was noted by one observer. This is probably a result of nausea (ten patients) and anorexia (12 patients) rather than cancer cachexia.

Generalized pruritis was seen in 11 patients, three of whom expressed it as a chief complaint.

In nine of the group, there was vague abdominal distress, dyspepsia, sense of fullness, and flatulence described by the patients as “indigestion”, “bloating”, or “gas”.

Weakness (four cases) and chills or fever (four cases) were also noted. Fever was probably due primarily to superimposed infection within the obstructed ductal system rather than cancer.

The time interval from the first symptom to the first hospital admission varied from two weeks (three patients) to two years (one patient), with an average time interval of 2.3 months.

FINDINGS: Most patients noticed acholic stools (18) and dark urine (17).

Hepatomegaly was found in 16 patients (84 per cent) and was usually nontender. The liver edge usually extended four or five centimeters below the right costal margin in the midclavicular line. The greatest hepatic enlargement, palpated ten centimeters below the right costal margin, was found in a woman with a lesion involving the tripartite junction.

A right upper quadrant abdominal mass, which clinically might have been a distended gallbladder or tumor, was discovered in 47 per cent of cases. Tenderness
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on palpation of the abdomen was noted in eight cases: two with fever and abdominal tenderness both, and six with tenderness but without fever.

Six patients had grossly bloody stools; in addition, two cases that did not have the latter, demonstrated stools positive for occult blood.

Of eight patients who had ascites (four cases) or dehydration (four cases), two had both of these findings. Three patients showed cachexia and only two had abdominal distension.

DIFFERENTIAL DIAGNOSIS

The recognition of this condition is difficult, clinically, and even occasionally at abdominal exploration. Carcinoma of the ampulla of Vater or head of the pancreas can present identically as carcinoma of the extrahepatic biliary ducts. An impacted gallstone could produce the same clinical picture. Even after laparotomy, the diagnosis may be made incorrectly. Of 17 cases in which an exploratory procedure was performed, two were thought to be carcinoma of the head of the pancreas. At post-mortem examination, however, the true nature of the lesions became apparent. One case was cancer of the common bile duct with metastasis to the pancreas; the other, cancer of the distal end of the common bile duct with widespread metastases.

The correct diagnosis was made preoperatively in only two patients, and listed as a possibility in two others. The preoperative diagnoses made, in order of frequency, were carcinoma of the head of the pancreas, cholecystitis and/or cholelithiasis, hepatitis, carcinoma of the ampulla of Vater, and carcinoma of the stomach with metastatic disease.

LABORATORY DATA

Laboratory tests revealed biliary tract obstruction in all cases, and secondary hepatocellular disease in almost half.

The serum bilirubin was determined in 17 cases preoperatively, and in all patients was moderately to markedly elevated. The level of concentration ranged from 4.6 to 42.0 milligrams per hundred milliliters. A serum bilirubin value was not obtained in two cases. One of these had an icterus index of 101 units; the other an alkaline phosphatase of 7.7 Bodansky units. Bilirubinuria was present in all cases.

Some degree of parenchymal liver damage was suggested in most patients. Six of ten patients tested demonstrated elevated serum cholesterol, nine of fourteen a positive cephalin-cholesterol flocculation test, and nine of twelve hypoalbuminemia. Two or more of these tests were positive in nine patients. Prothrombin activity was normal in two patients, but ranged from 39 to 94 with an average of 72 per cent of normal for the remaining 17 patients.

Hemoglobin values of less than 12 grams per hundred milliliters were observed in six patients. Serum amylase studies were always negative. The nonprotein nitrogen
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or blood urea nitrogen levels were abnormal in nine of sixteen patients tested. This observation has not been previously reported.

Papanicolaou cytology studies on duodenal aspirate have not been found to be diagnostically helpful.²

RADIOLOGICAL FINDINGS

Hodes⁴ described duodenal impressions in the immediate post-bulbar region or in the bulb itself, produced by dilated common bile ducts. It was also noticed that there was disordered motor function of the second part of the duodenum, with limited or even absence of peristalsis. Changes in the duodenal mucosal pattern may be seen when the duodenum is infiltrated by neoplasm.

Examination of the biliary ducts by conventional oral and intravenous cholecystocholangiography has proved to be of little value in the diagnosis of carcinoma of the extrahepatic bile ducts.³ A newer radiographic technique is percutaneous cholangiography. This was performed in a 66 year old woman by percutaneous injection of the right hepatic duct (case 2).

Percutaneous transhepatic cholangiography is an alternate means of investigation, favored by Evans et al⁵, but has the same danger as the other method, namely internal bleeding if a blood vessel is punctured, and bile peritonitis if there is leakage of bile into the peritoneal cavity.

TREATMENT AND RESULTS

The surgical management of these patients is difficult, and the reported results are poor, with the exception of an occasional long survival following a palliative procedure.⁵,⁷,₁⁸,₂² Most of these cases were inoperable at surgery; a satisfactory cancer operation was rarely possible. In view of the results of any type of surgery, all present procedures should be considered palliative.

Seventeen patients were subjected to an exploratory operation, and two died without one. Four patients had such extensive disease that not even palliation was possible.

A bypass procedure was performed in six patients, accomplished by (a) anastomosing the gallbladder to the jejunum (two cases), or the bile duct to the duodenum (one case) and (b) providing external drainage from the gallbladder (two cases) or common bile duct (two cases) by means of a T-tube or catheter. In several cases the ductal lumen of the common bile duct and hepatic ducts were solidly filled with malignancy, necessitating the creation of a passageway through the tumor in order to provide space for a drainage tube.

Cholecystectomy and choledochostomy were performed in two patients. Radical pancreaticoduodenectomy was undertaken in four patients, two of whom died post-operatively.
Table IV summarizes the results of treatment in 19 cases. Although it is evident that only palliative measures can be offered to some patients at this time, relief of jaundice, pruritis, and other symptoms with some prolongation of life is occasionally possible.

ADDENDUM

CASE REPORTS

CASE 1 (S.A.) — A 65 year old white woman, was admitted on March 30, 1960, with a two year history of intermittent, dull, right epigastric pain, which was associated with nausea, vomiting, and sour eructations. About two months prior to admission she first noticed jaundice, generalized pruritis, and "cream-like" stools. The epigastric pain became severe, with radiation to the back, during the week before admission.

She was weak, restless, dehydrated, and jaundiced. Blood pressure was 60/40, pulse 98 and thready, and oral temperature 95.2°F. The left epigastric region was tender to palpation. The liver, palpable seven centimeters below the right costal margin, was slightly tender. A small, hard mass, thought to be a distended gallbladder, was palpable in the right upper abdominal quadrant.

The clinical diagnosis was obstructive jaundice secondary to carcinoma of the extrahepatic bile ducts or gallbladder.

Red blood cell count was 5,100,000, hemoglobin 16.8 grams per one hundred milliliters of blood, and hematocrit 49 volumes per cent. Urine contained four plus albumin, a trace of sugar, occasional white blood cells, red blood cells, bacteria, and casts. Bile and urobilinogen were present.

Table IV

Results of Symptomatic, Palliative, and Radical Treatment in 19 Cases of Carcinoma of the Extrahepatic Bile Ducts.

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>CASES</th>
<th>SURVIVAL AFTER OPERATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Symptomatic Treatment or Palliative Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. No laparotomy</td>
<td>2</td>
<td>24 months after first symptom</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after first symptom</td>
</tr>
<tr>
<td>2. Laparotomy only</td>
<td>4</td>
<td>1.7 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 days</td>
</tr>
<tr>
<td>3. Cholecystojejunostomy</td>
<td>2</td>
<td>10.2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 days</td>
</tr>
<tr>
<td>4. Choledochostomy</td>
<td>2</td>
<td>57.0 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.7 months</td>
</tr>
<tr>
<td>5. Choledochoduodenostomy</td>
<td>1</td>
<td>2.5 months</td>
</tr>
<tr>
<td>6. Cholecystostomy</td>
<td>2</td>
<td>1.5 months</td>
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<td></td>
<td></td>
<td>1.3 months</td>
</tr>
<tr>
<td>B. Radical Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Cholecystectomy and choledochostomy</td>
<td>2</td>
<td>13.8 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lost to follow-up study</td>
</tr>
<tr>
<td>2. Whipple procedure</td>
<td>4</td>
<td>46.1 months</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
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<td></td>
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<td>9 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 day</td>
</tr>
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</table>

174
ogen were also present in the urine. Prothrombin activity was 83 per cent of normal, and quantitative bilirubin 31.6 milligrams. After rehydration with intravenous fluids, the red blood cell count and hemoglobin were 4,340,000 and 14.6 grams per cent respectively.

Roentgenographic examination of the chest revealed plate-like atelectasis at the right lung base due to elevation of the right hemidiaphragm.

The following day the oral temperature spiked to 103°F, and it was realized that the patient was anuric. In spite of vigorous medical therapy, the patient remained anuric with a nonprotein nitrogen of 150 milligrams. On the fourth hospital day the patient became comatose and expired.

Necropsy findings: The abdominal cavity contained 300 milliliters of green-brown stained fluid. Secondary newgrowth and peritoneal adhesions were observed involving the hepatic flexure of the colon, gallbladder, and transverse colon. All abdominal organs had a green hue. The retroperitoneal lymph nodes were enlarged and some were partially replaced by newgrowth.

The liver weighed 2,300 grams and was deeply bile tinged. Approximately 25 per cent of the cut surface was replaced by variously sized light gray, umbilicated nodules. The biliary radicles were dilated.

The gallbladder was filled with brown, viscid bile and over 60 hard, dark green calculi. The distal common bile duct was totally obstructed by newgrowth; the cystic and proximal common bile ducts were markedly dilated and contained green-brown liquid.

Microscopic diagnoses were (a) primary adenocarcinoma of the common bile duct (Figure 1) with invasion of the second part of the duodenum, head of pancreas, cystic duct, gallbladder, and metastases to the liver, retroperitoneal lymph nodes, stomach, and right adrenal gland, (b) chronic cholecystitis and cholelithiasis, (c) marked chronic biliary hepatitis, and (d) chronic interstitial fibrosis of the head of the pancreas.

CASE 2 (C.T.) — A 66 year old white woman was admitted on March 28, 1957, with jaundice, light-colored stools, dark urine, and weight loss for three weeks, and pruritis for two weeks prior to admission.

Figure 1

(Case 1). Photomicrograph showing adenocarcinoma of the common bile duct with distorted neoplastic glands lined by small cells with hyperchromatic nuclei; the stroma is permeated by many anaplastic cells.
(Case 2). Percutaneous cholangiogram demonstrating a diffusely narrowed, irregular common bile duct with extension of the neoplasm into both hepatic ducts and marked retrograde dilatation of the ductal system more distally.

Figure 3
Site of percutaneous injection and operative findings in case two.
The patient was well developed, obese, and icteric. Blood pressure was 115/60, pulse 100, and oral temperature 98°F. Multiple purpuric areas were present on the body and extremities. The liver edge was five fingerbreadths below the right costal margin and nodular. No abdominal masses were evident.

Clinical impression was carcinoma of the pancreas with liver metastases.

Bile and one plus albumin were found in the urine. The erythrocyte count was 3,980,000 per cubic millimeter, hemoglobin 13.2 grams per cent, and leukocyte count 15,500 per cubic millimeter, with 91 per cent polymorphonuclear leukocytes and 9 per cent lymphocytes. Sedimentation rate was 50 millimeters per hour. Prothrombin activity was 77 per cent of normal. Quantitative Van den Bergh was 19.8 milligrams, icterus index 105 units, alkaline phosphatase 13.1 Bodansky units, and cephalin-floculation three plus. Total serum proteins were 6.6 grams per cent, with albumin 4.0, and globulin 2.6 grams per 100 milliliters of blood. Nonprotein nitrogen was 31 milligrams.

On April 12, 1957, percutaneous cholangiography demonstrated a diffusely narrowed, irregular common bile duct with extension into the hepatic ducts. There was no displacement of the duct system or hepatic radicles. (Figures 2 and 3).

At exploratory laparotomy on April 13, 1957, a diffuse carcinoma of the common bile duct with extension into the cystic duct, gallbladder, and hepatic ducts was found. (Figure 3.) Numerous adhesions were present between the omentum and gallbladder, which was hard and replaced by newgrowth. Attempts at intrahepatic cannulization of the liver radicles were unsuccessful.

Two days postoperatively the patient became apathetic, with fetor hepaticus and hyperventilation. She recovered and was discharged April 25, 1957.

The patient was readmitted three days later, with a history of serous fluid drainage from the abdominal incision, diarrhea, and abdominal distension. She was confused, lethargic, and severely jaundiced. Ascites and tremors of the extremities were apparent. The patient expired on April 30, 1957.

The gross findings at necropsy were identical to those found at surgery. Microscopic diagnoses were (a) carcinoma of the common bile duct (Figure 4) with metastases to the

**Figure 4**

(Case 2). Photomicrograph demonstrating adenocarcinoma of the common bile duct with a papillary architecture. The underlying stroma exhibits invasion by clusters of tumor cells and small neoplastic glands.
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gallbladder, liver, porta hepatis, peritoneum, periaortic, internal mammary, mediastinal, and peribronchial lymph nodes, and (b) cholemic nephrosis.

CASE 3 (C.M.) — A 63 year old white man, was admitted on July 27, 1959, with complaints of epigastric distress and abdominal pain for two months; anorexia, nausea, eructations, and 27 pound loss over the past six weeks; and abdominal distension and obstipation for five weeks. The stools had become pale, the urine dark, and skin jaundiced, beginning four weeks prior to admission.

The patient appeared dehydrated, jaundiced, and cachectic. Blood pressure was 130/80, pulse 76, and oral temperature 99°F. The abdomen was distended and a positive fluid wave was elicited. The liver, four centimeters below the right costal margin, was nontender.

Clinical impression was carcinoma of the head of the pancreas.

Red blood cell count was 3.36 million per cubic millimeter, hemoglobin 12.5 grams per 100 milliliters, and prothrombin activity 44 per cent of normal. Bile, urobilinogen, and two plus albumin were found in the urine. The alkaline phosphatase was 43.3 Bodansky units, quantitative serum bilirubin 9.7 milligrams, and cephalin-flocculation three plus.

Blood urea nitrogen was 12 milligrams, cholesterol 205 milligrams, serum albumin 3.2 grams, and globulin 2.8 grams. Occult blood was present in the stool. Serum amylase was 144 units. Intravenous pyelography was negative.

On August 8, 1959, an exploratory laparotomy revealed the presence of one liter of bile stained ascitic fluid within the peritoneal cavity. A large mass was palpated in the head of the pancreas; the gallbladder was distended. The operative diagnosis was carcinoma of the head of the pancreas, and a cholecystojejunostomy was performed.

On the succeeding day, the patient vomited 1000 milliliters of coffee colored fluid and passed a black stool. He was dyspneic, and wheezing and moist rales became audible. The patient expired on August 10, 1959.

Necropsy findings: The abdomen contained 700 milliliters of straw colored fluid. There were several nodules of new growth in the omentum and celiac lymph nodes. The gastrointestinal tract contained dark red fluid blood.

Figure 5
(Case 3). Photomicrograph showing adenocarcinoma of the common bile duct. The carcinomatous glands are lined with low columnar cells having variable sized hyperchromatic nuclei; stromal invasion by neoplastic cells is evident.

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The liver, weighing 2,050 grams, exhibited numerous gray, hard umbilicated nodules of new growth. The remaining parenchyma was yellow-green in color. The bile ducts were dilated. Subserosal nodules were present on the posterior surface of the stomach.

Microscopical diagnosis was (a) adenocarcinoma of the common bile duct (Figure 5) with metastases to the liver, celiac lymph nodes, omentum, and posterior stomach wall, (b) chronic biliary hepatitis, (c) interstitial fibrosis of the head of the pancreas, and (d) chronic cholecystitis.

CASE 4 (A.L.) — A 51 year old white man, was admitted on October 28, 1958, with jaundice, dark urine, acholic stools, and vague lumbar pain for two weeks prior to admission.

The patient, well nourished but deeply jaundiced, had an ill-defined mass palpable in the right upper abdominal quadrant. The clinical impression was carcinoma of the head of the pancreas.

Red blood cell count was 3.78 million, white blood cell count 4,900 per cubic millimeter. Prothrombin activity was normal, serum cholesterol 420 milligrams, and quantitative bilirubin 12.4 milligrams. Nonprotein nitrogen was 28 milligrams, and the stool was positive for occult blood.

Radiographic studies indicated a nonfunctioning gallbladder and a small duodenal ulcer.

On November 4, 1958, an exploratory laparotomy revealed a stony hard mass filling the entire common bile duct, extending into both hepatic ducts. Operative diagnosis was carcinoma of the common bile duct, and a choledochostomy was undertaken.

The pathologic diagnosis was fibrosis and chronic inflammation of the common bile duct. The patient was discharged on December 11, 1958.

Extreme weakness, numbness of the extremities, and anorexia were the symptoms on the first readmission, December 16, 1959. The liver was palpated just below the right costal margin.

Twelve days later the patient was re-explored, and a cholecystostomy was done. Again, the pathologic diagnosis was chronic inflammation, and the patient was discharged January 24, 1960.

Figure 6
(Case 4). Photomicrograph showing adenocarcinoma of the common bile duct with a papillomatous pattern of well differentiated columnar epithelial cells.
Necropsy findings: (a) adenocarcinoma of the common bile duct (Figure 6) with local extension, (b) biliary cirrhosis with multiple liver abscesses, (c) chronic pancreatitis, and (d) cholemic nephrosis.

CASE 5 (R.B.) — A 53 year old white man, was admitted on January 24, 1960 with a three week history of intermittent epigastric distress, usually following meals. For only a week prior to admission, he had jaundice, pruritis, dark urine, and clay-colored stools. Four days before admission he had a temperature of 102°F, lasting only one night.

The patient was well developed but markedly icteric. Blood pressure was 140/80, and pulse 88. The liver edge was just palpable below the right costal margin. Clinical impression was obstructive jaundice secondary to gallstones.

Erythrocyte count was 4,240,000 per cubic millimeter, hemoglobin 14.5 grams per 100 milliliters, and leukocyte count 10,000 per cubic millimeters with 67 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes, 6 per cent monocytes, and 2 per cent eosinophils. Alkaline phosphatase was 14.2 Bodansky units, quantitative bilirubin 8.0 milligrams, and prothrombin activity 82 per cent of normal. Serum cholesterol was 209 milligrams, serum albumin 4.8 grams, and serum globulin 3.3 grams. Urine was positive for bile and the stool for occult blood.

On February 3, 1960 exploratory laparotomy disclosed carcinoma of the common bile duct; cholecystectomy and choledochostomy were performed. The patient recovered and was discharged February 22, 1960.

On subsequent readmissions, the patient was treated with external irradiation and 5-Fluorouracil. He succumbed on March 26, 1961.
Necropsy findings: The liver, green-brown in color and weighing 3,200 grams, was diffusely studded with abscesses. The bile duct system was dilated. The kidneys were dark green in color.

Microscopical diagnoses were (a) adenocarcinoma of the common bile duct (Figure 7), (b) chronic biliary hepatitis, (c) multiple liver abscesses, and (d) cholemic nephrosis.

**SUMMARY**

Nineteen cases of primary extrahepatic bile duct carcinoma are reported.

The reported autopsy incidence varies from 0.012 to 0.85 per cent. Our autopsy incidence was 0.54 per cent.

The sex incidence was 2.8:2, 11 men and 8 women.

The patients' ages ranged from 51.3 to 80 years with an average of 62.7 years.

The etiology is unknown; the presence of gallstones has not been proven to be a predisposing factor.

The tumor may be a (a) nodule, (b) papillary tumor, (c) annular stricture, (d) diffuse infiltrating growth, or (e) large, poorly defined tumor. It has been classified histologically into two groups, adenocarcinoma and squamous cell carcinoma.

The most common site of the primary tumor is the common bile duct, less frequently (a) the junction of the common hepatic, cystic, and common bile ducts, and (b) the hepatic ducts. Cystic duct malignancy is the least common.

Metastases occur most commonly in the liver and regional lymph nodes. Of ten post-mortem cases, all had metastatic disease and two exhibited extra-abdominal spread.

Biliary hepatitis, hepatic abscesses, biliary cirrhosis, cholangitis, chronic pancreatitis, interstitial fibrosis of the pancreas, and cholemic nephrosis were the associated diseases observed, in addition to metastases.

The clinical picture is similar to other lesions producing obstructive jaundice. The symptoms, in order of frequency were: jaundice, pain, weight loss, anorexia, pruritus, vague gastrointestinal distress, vomiting, chills, fever, and diarrhea.

Physical findings were acholic stools, dark urine, hepatomegaly, right upper quadrant abdominal mass, abdominal tenderness, bloody stools, ascites, dehydration, cachexia, and abdominal distension, in this order.

The recognition of this disease is difficult; the preoperative diagnosis was made only twice and suggested as a possibility in two others. The most frequent diagnoses made preoperatively were carcinoma of the head of the pancreas, cholecystitis, and/or
cholelithiasis, hepatitis, carcinoma of the ampulla of Vater, and carcinoma of the stomach with metastatic disease.

Laboratory tests revealed biliary tract obstruction in all cases, and secondary hepatocellular disease in almost half. All patients tested demonstrated elevated serum bilirubin and alkaline phosphatase levels; some had elevated serum cholesterol, positive cephalin-flocculation tests, and/or hypoalbuminemia.

Examination of the bile ducts by oral or intravenous cholecystocholangiography was of little value, but precutaneous cholangiography was found to be a valuable adjunct in the diagnosis of the lesion.

Most patients were inoperable at surgery; only four were operated for "cure". The surgical procedures performed were cholecystectomy with choledochostomy, cholecystostomy, and radical pancreaticoduodenectomy.

Since the results of all forms of surgery are poor, all present procedures should be considered palliative.

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