

# THE PRESENT STATUS OF CARCINOMA OF THE GALLBLADDER

## A STUDY OF THIRTY-FOUR CLINICAL CASES

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IN PRESENTING a communication on carcinoma of the gallbladder, the author is inclined to agree with Boyce and McFetridge,<sup>1</sup> who stated that at the present time there is little or no excuse for the publication of a small series of cases. However, when these cases were reviewed, and it was found that only one out of 34 was cured, and that a correct preoperative diagnosis was made in only four cases, it appeared that the condition deserved continued study.

There is disagreement regarding the incidence of carcinoma of the gallbladder. Since very few cases are cured, we should be able to obtain an idea of the prevalence from the Bureau of Census mortality statistics. There is difficulty, however, because in these statistics all carcinomata of the biliary tract are grouped together. Graham,<sup>2</sup> in 1931, noted that carcinoma of the gallbladder and liver accounted for almost 10 per cent of all deaths from carcinoma in 1926, and he felt that most of these were primary in the gallbladder. This assumption demands scrutiny. Judd and Gray<sup>3</sup> studied 312 cases of carcinoma of the gallbladder and ducts, and found that approximately one-half of the cases occurred in men, and one-fourth of those in women were primary in the ducts. In addition, a small number of malignancies of the liver are primary liver-cell carcinomata. In a recent study,<sup>4</sup> 16 malignant hepatomata, seven cholangiomata, and six primary tumors of the extrahepatic ducts were noted in 6,050 autopsies; carcinoma of the gallbladder was, however, encountered in only 11 cases.

The mortality statistics for 1936<sup>5</sup> indicate that 65,545 males and 77,068 females died from all forms of cancer, a total of 142,613; 4,490 men and 5,935 women died of malignancy of the biliary tract, a total of 10,420; which is approximately 7 per cent of all cancer deaths. If we accept the proportions of gallbladder and duct carcinoma of Judd and Gray as being representative, 3,729 of the cases of biliary tract malignancy would be considered as duct carcinoma, leaving 6,691 cases, of which some are primary liver-cell tumors. It would seem reasonable to estimate that about 6,500 persons in the United States died of primary carcinoma of the gallbladder in 1936. This is 4.5 per cent of the total malignancy deaths, or about one-half the percentage estimated by Graham for 1926. This difference is due to the fact that total cancer deaths increased more than 40 per cent during the ten-year period, while carcinoma of the biliary tract increased less than 10 per cent, and deductions were made for duct and primary liver carcinoma.

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The disease is not found very frequently in operations upon the biliary tract. Boyce and McFetridge collected 35,054 operations upon the gallbladder from the literature, and in these there were 393 cases of carcinoma of it, an incidence of 1.12 per cent. A higher incidence is noted in individual series of cases. Cooper<sup>6</sup> had 48 cases in 1,500 operations, or 3 per cent. In women with cholelithiasis, the disease is more common. Lentze<sup>7</sup> found it in 4.3 per cent of cases, and Graham in 8.5 per cent. The incidence in autopsy material was 0.33 per cent in 13,034 autopsies collected by Boyce and McFetridge, and 0.61 per cent in 2,941 autopsies in Cooper's series.

*Clinical Phenomena.*—As stated in the opening paragraph, one of the purposes of this analysis was an attempt to clarify the picture of carcinoma of the gallbladder, so that a greater percentage of correct preoperative diagnoses could be made. It will be readily admitted that greater success in diagnosis may not affect the end-results; indeed, overemphasis of gallbladder malignancy as a diagnostic possibility might cause surgery to be withheld in certain cases of jaundice of benign origin. However, from other standpoints, more accurate diagnosis is desirable. Therefore, the clinical picture of the disease, as it appears from this series, will be presented and compared with the reports of others.

*Age, Race, and Sex.*—Carcinoma of the gallbladder is a disease of the "cancer age." The youngest case was 46, the oldest 82. Eighty per cent of cases of carcinoma of the gallbladder will be over 50 years of age, and, with rare exceptions, the others will be in the late forties. Cooper reported the condition in a patient 28 years of age, which is the youngest in the recent literature (Table I).

TABLE I  
AGE DISTRIBUTION

Age Group	No. of Cases	Per Cent
46-49 years.....	4	12
50-59 years.....	10	29
60-69 years.....	13	38
70-79 years.....	6	18
80-82 years.....	1	3

There were 23 females and 11 males in this series, a ratio of 2:1. Others, such as Finsterer<sup>8</sup> and Illingworth,<sup>9</sup> have reported ratios as high as 4:1. The ratio usually given in this country is 3:1. With regard to race, all of the cases in this series were white, but two recent reports,<sup>1,9</sup> indicate that the disease is not infrequently seen among the Negroes of the South.

*History.*—The disease begins rather acutely in many cases. Forty-one per cent of the patients stated that the present illness was of less than one month's duration; 32 per cent gave one to three months; 12 per cent, three to six months; and three had been sick for more than six months. Seventeen patients, half of the series, had symptoms suggesting benign biliary disease which antedated the present illness from one to 25 years.

The most frequent chief complaint was pain in the upper quadrant (11 patients, 32 per cent). Six listed jaundice, and four, abdominal distress. Others were chiefly concerned with nausea, pain in the back, belching, tumor, anorexia, constipation, and indigestion. Pain was an almost constant symptom, being present in 30 cases (88 per cent). This was in the right upper quadrant in 15 cases (44 per cent), and epigastrium in 11 cases (32 per cent). Two patients complained of generalized abdominal pain, two had pain in the back and right side, and four did not have pain. Twenty-one patients (62 per cent) had nausea, and 18 (53 per cent) vomited. Slightly more than half of the cases were jaundiced. Weight loss was not prominent, since only 13, or 38 per cent, had lost ten pounds or more. Cooper found weight loss in 95 per cent of his cases, while others<sup>10, 11</sup> reported that half of their patients had lost weight.

*Physical Findings.*—The findings with regard to tenderness are shown in Table II. It should be noted that 41 per cent of the cases did not have tenderness, and if tenderness was present, it was usually in the right upper quadrant. A tumor in the region of the gallbladder was palpable in 12 cases, or 35 per cent. Most of the authors quoted in this paper found a tumor present in slightly more than half of the cases. In our series, the liver was palpable in 16 cases (47 per cent). This is in accord with the experience of other writers.

TABLE II  
LOCATION OF TENDERNESS

	No. of Cases	Per Cent
Right upper quadrant.....	16	47
No tenderness.....	14	41
Epigastrium.....	2	6
General.....	2	6

*Laboratory Data.*—The rarity of marked anemia in carcinoma of the gallbladder has been noted by others. Judd and Baumgartner<sup>12</sup> studied 56 cases, and found only five with a hemoglobin less than 70 per cent. The average was 73 per cent. This was felt to be within the normal limits. Twenty-nine of the cases in this series had a hemoglobin recorded. Of these, 18, or 62 per cent, had values above 80 per cent, and seven had values between 70 and 79 per cent. In other words, over 85 per cent of the cases did not have a well-marked anemia. The Wassermann test was recorded in 31 cases. It was negative in all except the one five-year survival. Leukocyte counts were recorded in 30 cases. Seventeen of these were normal, 12 were between 10,000 and 15,000, and there was one extremely high count of 25,000. The bromsulphalein test was done for only two patients. These showed 55 per cent and 25 per cent retention, respectively, of the dye in 30 minutes, and, subsequently, extension to the liver was noted. Diagnostic transduodenal biliary drainage was done in 16 cases. This was reported as normal in six cases, negative for bile in four cases, no "B" bile in two

cases, positive for crystals suggesting cholelithiasis in three cases, and scant bile was obtained in one case. These findings were of no assistance in making the diagnosis of malignancy. Since gallbladder bile ("B" bile) was obtained in nine cases out of 16, or more than half, it seems possible that a careful histologic investigation of the bile for malignant cells might be worth while.

*Roentgenologic Diagnosis.*—Cholecystograms were made in nine cases. All of these showed nonfilling of the gallbladder, and only one roentgenogram showed positive stones. Kirklin,<sup>13</sup> in reporting his experience in the cholecystographic diagnosis of neoplasms of the gallbladder, stated that he was able to diagnose papilloma and adenoma with considerable accuracy, but had not yet made a diagnosis of carcinoma of the gallbladder. He reviewed the roentgenograms on 16 cases of proven carcinoma of the gallbladder, and found that 14 of these gave no shadow of the dye, half showed positive stones, one showed stones with, however, good function, and one had a normal cholecystogram. Cooper reported a similar experience. Rarely, carcinoma of the gallbladder may be strongly suspected, when the barium meal or enema demonstrates a fistulous connection between the gallbladder and the stomach or colon. Two such cases, with correct preoperative diagnoses, were described by Spitzenberger.<sup>14</sup> In summary, we may say that a nonfilling gallbladder, with or without positive stone shadows, is to be expected in carcinoma of the gallbladder.

Judd and Baumgartner suggested that cases of carcinoma of the gallbladder may be divided roughly into three groups: Group I, consisting of those cases with a history of colic or other symptoms of benign biliary disease for several years, with superimposed symptoms and signs of malignancy, namely, constant pain, loss of weight, anorexia, and the appearance of tumor; Group II, containing those cases which simulate benign biliary disease until operation; Group III, containing those cases in which there is a rather sudden onset of the malignant phase, sometimes without definite indication that the disease is in the gallbladder. The cases in this series were allocated in these categories, and compared with the series of Judd and Baumgartner (Table III).

TABLE III  
PERCENTAGE OF CASES IN THE THREE CLINICAL GROUPS

	Judd and Baumgartner <sup>12</sup>	This Series
Group I.....	70%	26%
Group II.....	22%	44%
Group III.....	9%	29%

The preoperative diagnoses in the 34 cases of this series are shown in Table IV.

*Discussion of the Clinical Picture.*—It is difficult to set up diagnostic criteria for carcinoma of the gallbladder. From the above study, a typical case might be described as follows: The patient, female, about age 60, states

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TABLE IV  
PREOPERATIVE DIAGNOSES

Diagnosis	No. of Cases	Per Cent
Cholecystitis.....	12	35
Carcinoma of pancreas or ducts.....	9	26
Carcinoma of gallbladder.....	4	12
Carcinoma of liver.....	2	6
Common duct stone.....	2	6
Cirrhosis of liver.....	2	6
Intestinal obstruction.....	2	6
Carcinoma of stomach.....	1	3

that her trouble began about a month previously, but as likely as not, she has had biliary colic for a number of years. She complains of pain in the right upper quadrant which is steady and severe. She is apt to have nausea and vomiting. She may or may not be jaundiced. There is little if any weight loss, and she is not anemic. She probably has tenderness in the right upper quadrant, and the chances are even that a tumor, as well as the liver, is palpable. Cholecystograms show nonfilling of the gallbladder, with or without stone shadows. Other gastro-intestinal studies are negative.

This picture will fit many cases of benign biliary disease or cancer in organs other than the gallbladder. In making the differential diagnosis, the following points might be stressed: Advanced age, steady pain, tumor (particularly if it is not tender), weight loss, absence of leukocytosis, and a persistent downhill course point toward malignancy rather than an inflammatory condition.

The treatment of the cases in this series is indicated in Table V. In three of the cases in which cholecystectomy was performed, carcinoma was not suspected at the time of the operation. Therefore, a deliberate attempt to

TABLE V  
OPERATIVE PROCEDURES

	No. of Cases	Per Cent
Exploration and biopsy.....	23	68
Cholecystectomy.....	6	19
Cholecystectomy and implantation of radium.....	3	9
Cholecystostomy.....	1	3
No operation (autopsy).....	1	3

remove the carcinoma was made in only six cases, or 18 per cent. These cases all died. The malignancy in the gallbladder of the one five-year survival in this series was not suspected until the routine histologic examination was made. Others have performed cholecystectomy more often. This was done 16 times in 48 cases in Cooper's series. He could report only one patient alive after two years. Judd and Gray had 59 cholecystectomies in 212 cases, and palliative procedures as follows: Cholecystostomy in 42, some type of anastomosis in 27.

A radical operation for carcinoma of the gallbladder has been suggested by several authors. Gray<sup>15</sup> described a method of removing the

gallbladder together with a portion of the liver, using the electrocautery. His one case recovered from the operation, but the end-result was not stated. Finsterer had one survival in 46 cases, in which instance he performed a resection of the contiguous portion of the liver. Microscopic sections on his case showed that carcinoma had invaded the full thickness of the gallbladder wall, but had not actually penetrated the liver substance. He advised partial hepatectomy, if carcinoma is suspected at the time of the operation. Another single case report is that of Aiga,<sup>16</sup> who removed the gallbladder, a portion of the common duct, and a large mass of necrotic tumor tissue from the common duct. The patient was alive after seven and one-half years.

In this series, the duration of life after operation was as follows: Less than one month, 18 cases; one to three months, five cases; three to six months, five cases; six months to one year, two cases; one to three years, three cases. One case is well and asymptomatic after five years.

*Pathology.*—Gallstones were frequent. They were present in 20 out of 23 gallbladders which were opened, an incidence of 87 per cent. Judd and Gray found 64.6 per cent, and Cooper found 79 per cent.

With regard to the type of tumor, 28 were classified as adenocarcinoma (82 per cent); five were of the squamous variety (15 per cent); and one was mixed. The squamous cell variety was encountered more frequently than usual. Judd and Baumgartner found only three such tumors in 55 cases, and Cooper found only one in 48 cases. The various theories to explain the presence of squamous cell epithelium in this location have been discussed by Rabinovitch and Kieffer.<sup>17</sup> The tumor had extended into the liver in 15 cases, into the common duct in four cases, the liver and common duct in four cases, the stomach in three cases, and the colon in one. There were metastases to the regional lymph nodes in six cases. In 11 autopsies, metastasis to the lungs was found only once. Occasionally, a lung tumor may be due to an unsuspected primary growth in the gallbladder, as in the case reported by Foggie and Tudhope.<sup>18</sup>

*Prophylaxis.*—Since treatment for established carcinoma of the gallbladder has given such poor results, it has been repeatedly suggested that gallbladders with stones should be removed prophylactically. In 1931, Graham stated: "It would seem reasonable to conclude that at least 4 to 5 per cent of women of the cancer age who have stones, will develop carcinoma of the gallbladder. This would be much more than the operative mortality rate of 1 to 3 per cent." Even if the danger of loss of life from carcinoma of the gallbladder were the same or less than the danger from the operative procedure, cholecystectomy is indicated in the absence of symptoms because of the danger of complications other than malignancy. There should be more reports of series of cases like that of Jaguttis.<sup>19</sup> He followed 114 cases of cholelithiasis which were treated conservatively for ten to 25 years. Five developed carcinoma of the gallbladder, 13 died of cholecystic disease, 25 were operated upon for complications, four of which died. This report considers mortality only, and does not take into account the suffering which probably accompanied the cholelithiasis in some of the survivals.

*Status of Experimental Work in Carcinoma of the Gallbladder.*—It is generally thought that gallstones cause cancer from irritation, since they are found in 70 to 100 per cent of cases. However, the experimental proof of this causal relationship is lacking. In 1931, Burrows<sup>20</sup> gave a summary of the experimental work up to that time. He reviewed the work of Kazama, Leitch,<sup>21</sup> Clemente, Delbert and Goddard, Petrov and Krotkina, and Gioia. This experimental work consisted of the introduction of various foreign bodies, especially human gallstones, into the gallbladders of experimental animals. Instances of carcinoma were reported as having developed in several animals, but the results have been discredited for various reasons. For instance, the work of Leitch is often quoted, but his paper was in the nature of a preliminary report, and part of his animals were still alive at the time of his publication. A final report did not appear. After seeing the reproductions of his photomicrographs, one would agree with Creighton,<sup>22</sup> who stated: "The conclusion, I think, from Dr. Leitch's experiments on the gallbladder should be that the guinea-pig is peculiarly apt to develop these epitheliated tubes in the interstices of the chronic inflammatory reaction. To judge from the few details and the low power photomicrographs, they lacked the large nuclei and the deep chromatinization of true cancer, and until further advised, I should hold the results in the same ambiguity as Dr. Leitch holds the Japanese guinea-pig experiments" (Kazama).

Petrov and Krotkina reported, in 1928, that they could not reproduce carcinoma of the gallbladder in the guinea-pig, by the introduction of foreign bodies, but in 1933, they<sup>23</sup> reported success. Nineteen guinea-pigs were used. Small glass tubes containing a microgram of radium were inserted into the gallbladders of 12 animals, and seven controls had empty glass tubes inserted. They were trying to confirm the work of Barlow, who had presented evidence that cancer of the gallbladder was due to the radioactivity of gallstones. They reported that carcinoma developed in two animals in each group. Three of the animals were said to have had multiple metastases, and died of cancer. The fourth was operated upon at the end of the experimental period, and a carcinoma of the common duct was found. However, these authors did not choose to publish photomicrographs of the tumor tissue, but submitted drawings instead. Hence, it can be stated that at the present time, experimental proof that gallstones cause cancer is lacking.

However, even though an etiologic relationship is not proved, or even if it is disproved, it is well established that the two conditions occur together, and if cholelithiasis is not the cause of cancer, it may be, at least, a warning sign.

#### SUMMARY

- (1) The present incidence of carcinoma of the gallbladder is discussed.
- (2) Thirty-four cases of carcinoma of the gallbladder are analyzed with respect to clinical picture and pathologic findings.
- (3) The question of prophylactic cholecystectomy in cholelithiasis is discussed.

(4) The difficulty in diagnosis and comparatively hopeless prognosis in evident cases is stressed.

(5) The present status of experimental work on carcinoma of the gallbladder is summarized.

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