

CARCINOMA OF THE GALLBLADDER A CLINICAL AND PATHOLOGIC ANALYSIS OF FIFTY CASES*

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WELL DOCUMENTED PAPERS on the subject of carcinoma of the gallbladder very properly emphasize the grave prognosis of this disease. It seems justifiable, therefore, to continue to analyze large series of cases in the hope that a more effective approach in its treatment may be devised.

The present report is concerned with 50 cases of carcinoma of the gallbladder among which 15 patients died without operation but were examined at autopsy; 15 had operations upon their biliary tract and then later came to autopsy; and 20 had operations with the removal of tissue for pathologic examination but no autopsy examinations. Thirty of the cases represent the total number of instances in which cancer of the gallbladder was found in a series of 8808 autopsies performed at the Pathological Institute, McGill University, and 35 of the cases were comprised in a series of 3000 consecutive operations on the biliary tract performed at the Royal Victoria Hospital, Montreal, during the period 1926 to 1948. Thus, the incidence of carcinoma of the gallbladder is 0.34 per cent in the autopsy series and 1.16 per cent in the surgical series. The frequency of occurrence of this type of cancer in the present series as compared with the incidence reported in other communications is shown in Table I.

An analysis of Table I also shows clearly that the disease has a marked tendency to occur more frequently in women than in men. Ewing⁶ states that carcinoma of the gallbladder is four to five times as frequent in females as in males. The figures of Willis²⁷ would indicate that women are affected more frequently than men, in a ratio of three or four to one. In the series reported here there were 36 females and 14 males.

Cancer of the gallbladder is also essentially a disease of the older age group, occurring nearly always after the age of 50. A moderate number of cases have been reported in relatively young persons and in Biering's recent report¹ the patient was a 13-year-old girl. Moxon¹⁶ is often cited as having reported a case in which the patient was four years old. He is misquoted, for in his original paper he did not give the patient's age, but in fact, described his occupation as that of a brushmaker. None of the patients in the series of this paper was under 40 years of age. The oldest was 85 years (Table II).

Gallstones were present in 82 per cent of the total cases. No mention was made of their presence or absence in 16 per cent, and in one case, 2 per

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cent, it was definitely stated that none could be found. These figures approximate closely those reported in the literature (Table III).

TABLE I.

	Number of Autopsies	Incidence (Per Cent)	Number of Operations on Biliary Tract	Incidence (Per Cent)	Total Number of Cases	
					Female	Male
Finney ⁷	1,192	1.5	16	2
Warren and Balch ²⁶	1,528	1.96
Vadheim, Gray, and Dockerty ²⁴	33,500	0.87
Hochberg and Kogut ⁹	1,074	0.36	1,078	2.5	25	6
Jankelson ¹¹	11,400	0.42	28	20
Cooper ⁴	2,941	0.61	1,500	3.0
Author's series.....	8,808	0.34	3,000	1.16	36	14
Total.....	24,223	0.41	41,798	1.07	105	42

ETIOLOGY

The etiology of cancer of the gallbladder is unknown. The frequent association of stones with cancer of the gallbladder has been taken as evidence that cholelithiasis is the predisposing factor in its development. Support for this view is derived in part from the studies of Kazama¹³ in 1922, and Leitch¹⁴

TABLE II.—Number of Cases.

Age (Years)	Liebowitz ¹⁵	Finney ⁷	Sainburg ¹⁹	Author's Series	Total
30-39	1	..	1
40-49	3	1	8	9	21
50-59	8	3	29	18	58
60-69	7	6	30	12	55
70-79	8	7	6	10	31
80-89	2	1	1	1	5
Average age	64.1	67.4	60.1	59.1	61.3

in 1924, both of whom inserted hard foreign bodies, including gallstones removed from human beings, in the gallbladders of guinea pigs. They reported that 26 of 98, and eight of 35 animals, respectively, developed carcinoma of that organ. These experiments were fully reviewed by Burrows^{2, 3} who also carried out experiments with gallstones (human) and with pellets, some

TABLE III.—Incidence of Stones in Cancerous Gallbladders.

	Percentage
Judd and Gray ¹²	64.6
Shelley and Ross ²¹	73.7
Hochberg and Kogut ⁹	76.0
Illingworth ¹⁰	81.5
Warren and Balch ²⁶	88.0
Author's series.....	82.0

containing cholesterol, others dibenzanthracene, and still others, fat. He obtained inflammatory proliferations of a benign type, but no tumors. He concluded that this had been the case also with the results of the earlier workers. Creighton⁵ is of the same opinion, that the changes described by

Kazama and Leitch were merely those of inflammatory hyperplasia. Willis,²⁷ in his discussion of Burrows' work, further pointed out that the guinea pig is an animal which seldom develops spontaneous tumors and which is also refractory to the experimental production of skin tumors. Petrov and Krotkina¹⁷ have recently reopened the discussion. They reported experiments on 100 animals in which five cases of carcinoma resulted from the introduction of foreign bodies into the gallbladder. Fifty-one of the 100 guinea pigs survived 14 months or longer. In five of these 51 animals, after 14 to 39 months, there was found an epithelial proliferation of the gallbladder wall with characteristics of malignant growth, including local invasion and distant metastases. Gallstones were used as the foreign body in four of the surviving 51 animals. None of these developed cancer. In eight other subjects the foreign body was a glass tube containing one gamma of radium. Two of these animals developed malignant tumors. Ten sterile glass tubes, each measuring 16 by 2 mm., were placed in each gallbladder of the remaining 39 guinea pigs. Petrov and Krotkina were aware of the work of Kazama and Leitch, and of the criticism directed toward these earlier workers, and although they attempted to perform a more carefully controlled experiment, it would appear that they invalidated their results to some extent by using a radioactive material as one of the test substances.

Both Graham⁸ and Sainburg and Garlock¹⁹ feel that the published statistics and experimental data are convincing enough to accept as fact that cholelithiasis is the most important precursor of carcinoma and go on to advocate cholecystectomy as a prophylaxis against the development of cancer. Sainburg and Garlock, in particular, argue that the mortality due to malignant transformation, in addition to the other frequently fatal complications of cholelithiasis, impose an obligation to remove all calculous gallbladders, in the absence of surgical contraindications. They cite the mortality figure of 1.6 per cent following cholecystectomy reported by the Mayo Clinic,²⁵ the 1.5 per cent of Graham,⁸ and the 0.6 per cent mortality rate in 346 cholecystectomies performed during 1946 at the Mount Sinai Hospital.¹⁹

Warren and Balch,²⁶ writing in 1940, thought otherwise. It was their belief that although simple cholecystectomy carried a mortality not greater than 2 per cent, it was not enough lower than the risk of carcinoma, 1 to 2.5 per cent, to say flatly that cholecystectomy should be performed in all cases of stones for that reason alone. They estimated that the policy advocated by Graham and others would involve performing cholecystectomies on 25 to 50 per cent of the female population over 60 years of age.

One concludes from the conflicting experimental results reported above that further attempts to produce cancer of the gallbladder should be made, particularly on other species of animals. Since the exact etiology of carcinoma of the gallbladder is as yet unknown, and since the mortality figures for cholecystectomy and the incidence of cancer of the gallbladder vary slightly from clinic to clinic, the value of cholecystectomy solely as a prophylaxis against the development of cancer in that organ remains a personal decision.

CLINICAL FEATURES

A striking fact which becomes immediately apparent upon reviewing the clinical histories of the 50 cases in this report was that 66 per cent of the patients experienced the initial onset of their illness six months or less prior to their entry into the hospital. Before that time they had enjoyed relatively good health. Warren,²⁶ Seide and Geller,²⁰ and Jankelson¹¹ have all remarked on this same point, each reporting approximately the same duration of symptoms. The majority of the remaining patients gave histories which may be described as typical of chronic gallbladder disease, that is, of cholecystitis or cholelithiasis, extending over a period of years. Two patients had no symptoms ascribable to the biliary tract, both dying of cardiac disease. Their tumors were incidental findings at autopsy.

The symptoms which led the group of patients with short histories to seek medical attention may be reviewed in order of frequency of occurrence.

Jaundice, suddenly and rapidly established and persistent, occurred in 70 per cent of the cases. But it must be pointed out that it was also often late in its appearance, sometimes becoming apparent in the few days prior to admission. Ten per cent of the remaining patients had a history of jaundice at some time or other in the past.

A history of weight loss varying from 10 to 45 pounds was obtained in 70 per cent of the cases. It was almost always volunteered by the patient and described as occurring during a period of a few weeks to a few months.

Constant pain was a frequent complaint. It was recorded in 66 per cent of the cases and was most commonly localized in the right upper quadrant, less often in the epigastrium. It was described as ranging in severity from moderate to marked and only in its very early stages as being occasionally relieved by belching.

In 62 per cent of the cases there was recorded tenderness on palpation of the upper abdomen and in 23 patients, or 45 per cent, a mass was felt. The liver edge was frequently palpable as low as three to four finger-breadths below the costal margin. The moderately tender mass lay beneath the liver and could be made out by patient and physician alike. It varied slightly in size from patient to patient, averaging approximately 8.0 cm. in diameter.

Anorexia and vomiting were present in 40 per cent of the patients. These symptoms were, at first, intermittent; then they slowly became more regular in appearance and accounted, no doubt, for a large part of the rapid, severe, weight loss described above.

Ascites developed in 38 per cent of the patients.

The cachectic stage was marked by fever from infections, massive replacements of liver tissue by tumor, emaciation and hemorrhages. The bleeding resulted from invasion or ulceration of blood vessels by tumor or stones, or was due to disturbances in the blood clotting mechanism.

The histories of the majority of the patients who gave a long history of abdominal complaints differed from the above group in several respects. While

they gave a remote history, 5 to 20 years, of attacks of colic and jaundice suggestive of cholecystitis or cholelithiasis, they had, to judge from the patients' descriptions, a recent recurrence of pain, loss of weight, vomiting and jaundice, all of which were more constant, more severe, better localized, and less easily relieved, than they had been previously. Even those patients who were having symptoms rather regularly during the antecedent year or two complained of this rather explosive change in the character and severity of their symptoms.

Four patients described a period of one or two weeks of abdominal distress, then the abrupt appearance of anorexia and vomiting to be followed in a day or two by jaundice. At operation tumor tissue was found to be the cause of the common duct obstruction.

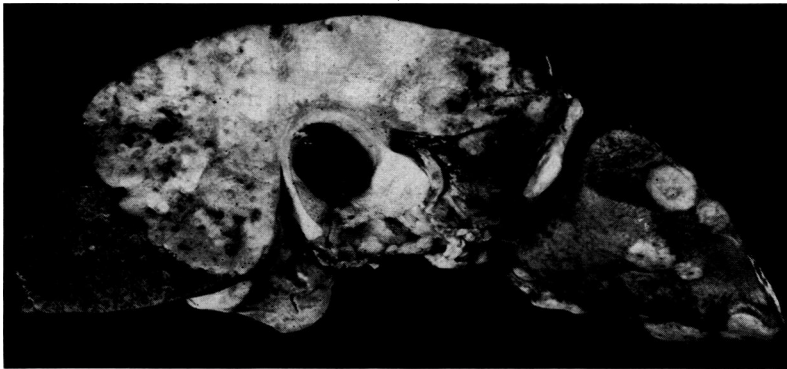


FIG. 1.—Carcinoma of the gallbladder with direct extension and metastatic spread to liver.

PATHOLOGIC FEATURES

One can conclude from observations made at the autopsy table that the primary growth tends to assume one of two forms, though gradations from one to the other may be found. These different forms were dependent, in part, upon the degree of cellularity of the tumor, the abundance of supporting stroma and the presence or absence of associated infections. In most instances the gallbladder was largely replaced by a solitary, hard, fibrous, shrunken, tumor mass. Occasionally, however, the primary growth was medullary instead of fibrous in character, and a very large, bulky, gallbladder distended either by tumor, mucoid material, or pus presented itself. Less commonly the organ was perforated and an abscess had formed, the walls of which were made up of parts of the stomach, pancreas, colon, duodenum or liver.

The former type of primary growth was stony-hard on section. The gallbladder which was firmly imbedded in the mass was thickened and contracted down over its contained stones. It was also generally firmly adherent to the adjacent liver due to extension of tumor into the liver bed (Fig. 1).

If the tumor was more cellular, as in the latter type, the gallbladder was relatively soft in consistency and distended. Its wall was very greatly thickened, rubbery soft to rubbery firm in consistency, and white in color. The presence of some sort of tumor was often suspected on gross examination. If infection had developed or portions of the growth had become necrotic, section would reveal a mass of tumor tissue with a central area of putrefaction or necrosis with all, or almost all, of the gallbladder wall totally destroyed. Its former position was marked by one or two stones lying in a small cavity. In a few instances the tumor had a gelatinous mucoid character. Fistulas between gallbladder and common duct or stomach or duodenum occurred in a few cases in both main types.

One patient who was admitted in a moribund condition died one hour later. Her family stated that she had been in apparent good health until three weeks before admission, when she began to complain of rather severe crampy abdominal pain. Twelve hours before admission she had experienced a massive hematemesis and collapsed. Autopsy revealed an extensive cancer of the gallbladder with a freshly formed fistula, apparently caused by the erosion of a stone, between the gallbladder and duodenum, with ulceration and perforation of a large blood vessel.

The carcinomatous growth was too extensive in a large majority of patients for one to decide the probable site of origin. In the few instances in which some sort of estimate was attempted, fundus or neck were thought to be the usual sources.

The various surgeons' descriptions of their findings at operation in the cases which did not come to autopsy bore a very close resemblance to the situations found in those that had postmortem examination. The exceptions occurred in a few patients in whom the primary growth was still at an early stage and resection was possible.

HISTOLOGIC TYPES

Carcinoma of the gallbladder, in general, occurs in four main histologic types. Representative examples of all were found in this series. The most frequent were the scirrhous and medullary types (Fig. 2). Typically, they were characterized by neoplastic acini occurring in groups or singly, scattered through a fibrous connective tissue stroma. The lining cells were cuboidal to columnar, with basally placed nuclei and relatively clear cytoplasm. Imperfectly formed alveoli were frequent. The neoplastic tissue usually had invaded all layers of the gallbladder and extended into neighboring structures. The tumors termed scirrhous were quite similar in appearance to those called medullary and differed only in possessing a more extensive growth of dense connective tissue with a slightly sparser distribution of neoplastic epithelium.

A less common form of cancer was the papillary adenocarcinoma (Fig. 3). Here, the mucosa of the gallbladder was thrown up into numerous branching papillary projections covered by frankly neoplastic epithelial cells. These

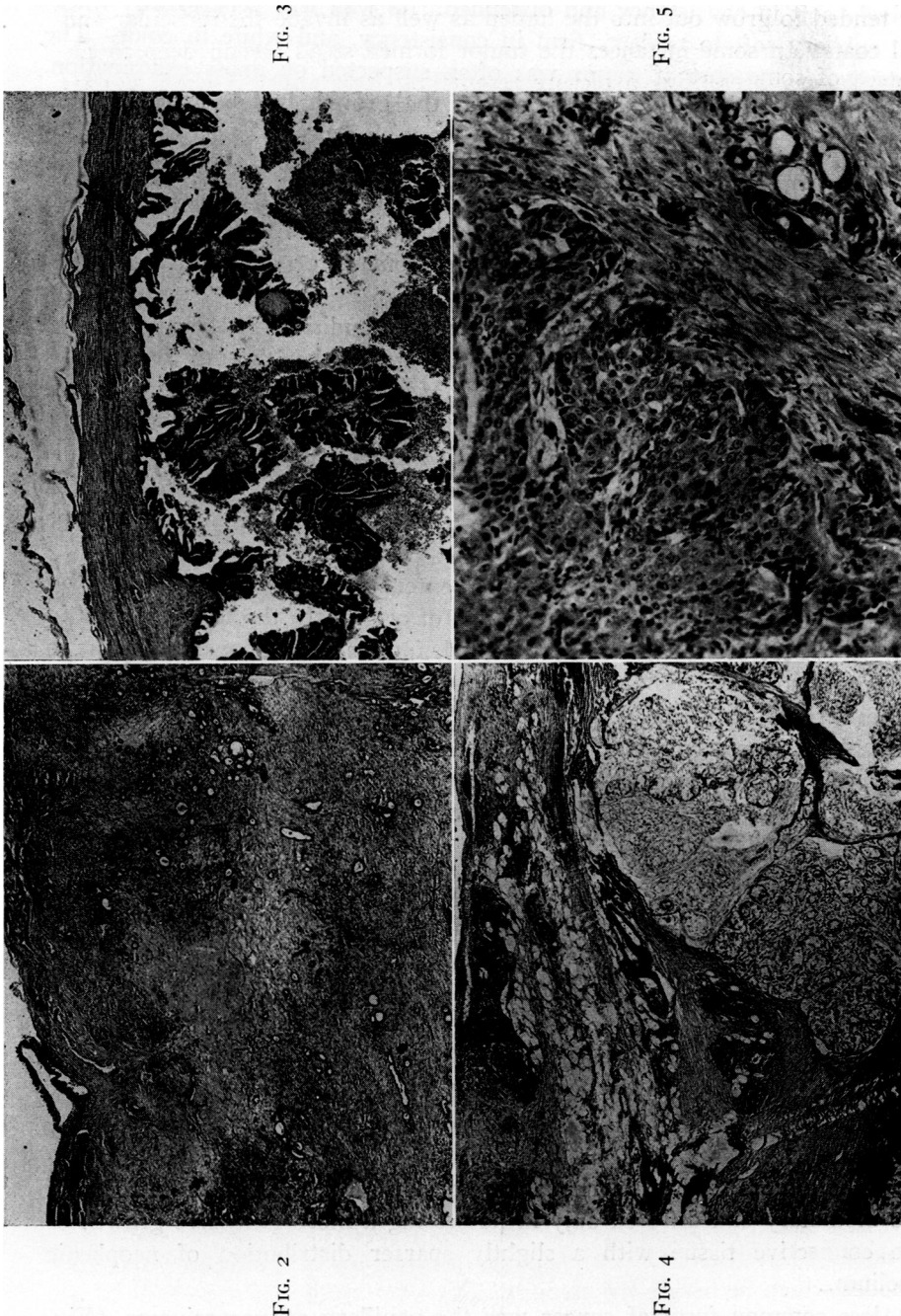


FIG. 2.—Photomicrograph of carcinoma of the gallbladder, scirrhous type. x 16.
FIG. 3.—Photomicrograph of carcinoma of the gallbladder, papillary type. x 24.
FIG. 4.—Photomicrograph of carcinoma of the gallbladder, mucoid type. x 16.
FIG. 5.—Photomicrograph of carcinoma of the gallbladder, squamous type. x 120.

were columnar to tall columnar with centrally to basally placed nuclei. The tumor tended to grow out into the lumen as well as invade the muscular and serosal coats. In some instances the tumor formed small alveoli deep to the muscular layers, presenting a picture resembling Rokitansky-Aschoff sinuses or cholecystitis glandularis cysticum. However, the malignant features of the individual cells and the histologic pattern in sections taken elsewhere from the organ revealed their true nature.

Sometimes parts of the tumor, or, in a few rare instances, the whole, secreted an abundant amount of mucoid material. In addition to the marked distention of the lumen with this material the cells themselves were often scattered as single acini or clusters of acini in a loose fibrous stroma, the intervening spaces being filled with mucus. A few cells retained the mucoid material within their borders, producing a vacuolated cytoplasm (Fig. 4).

In three cases the dominant histologic form was squamous cell carcinoma in which there were small areas of adenocarcinoma. Kerato-hyaline changes were frequent and at one or two points actual pearl formation was attempted. The supporting connective tissue was abundant.

Sections of gallbladder which were taken at a distance from the area of tumor showed evidence of chronic cholecystitis in every instance. Monocytes, plasma cells and lymphocytes were focally and diffusely distributed throughout all layers, along with an actual increase in the fibrous tissue stroma.

The frequency of occurrence of the different types of growth were as follows: 42 per cent scirrhus; 30 per cent medullary; 18 per cent papillary; 6 per cent squamous; and 4 per cent mucoid.

MODE OF SPREAD

The spread of carcinoma of the gallbladder is by direct extension into the neighboring tissues and by way of the lymphatics. Rarely does it extend by the way of blood channels or transperitoneally. The opportunities for local and distant spread by direct extension and via lymphatics are many, both because of the absence of a peritoneal covering separating the organ from the liver and of the luxuriant lymph plexuses draining the gallbladder.

In the cases being reviewed, local extension into the liver was a common method of dissemination. It occurred in 36 of the 50 cases, making it impossible to dissect the gallbladder free from its bed.

The gallbladder possesses two plexuses of lymph channels, one in the sub-epithelial layer and the other in the subserosal layer. These two plexuses communicate by way of numerous short anastomotic branches which perforate the muscular layers. The subserosal plexus in turn empties into several main vessels which follow the cystic artery to the neck of the organ and to the cystic node. From there, the lymphatics extend chiefly to the chain of mesenteric nodes which lie beside the common duct and portal vein up to the hilus of the liver. There also exists an intimate connection between the lymphatics of the liver and those of the subserosal layer of the gallbladder (Cooper,⁴ Poirer and Charpy,¹⁸ and Sudler²³).

The cystic node and periportal lymph nodes were affected in over three-fourths of the cases. Small masses of tumor averaging 1 to 4 cm. in diameter were found deep in the liver substance in almost as many cases. The omentum and the peritoneal surfaces were studded with smaller masses of tumor in one-third of the patients.

The presence of lymphatic spread, but no local extension, was demonstrated at autopsy or operation in eight cases. During one other operation the surgeon became aware that he was dealing with a cancer and following resection of the gallbladder he made a careful search of the operative field, but no tumor was found elsewhere.

Pulmonary metastases were found in six cases, in one of which there was gross pulmonary embolism in the form of a mass of tumor tissue. Adrenal glands and pleurae in one case, and the lumbar vertebrae and angle of the jaw in another, were also sites of metastases. The presenting symptoms of the latter patient had been pain in the jaw and back, and weight loss.

Obstruction of the bile drainage occurred in one of three ways. Large tumor masses extending directly down from the neck of the gallbladder and compressing the cystic and hepatic ducts was one. Occlusion of the hepatic duct by enlarged periportal lymph nodes was another. Infrequently there was actual invasion and plugging of the common duct.

DISCUSSION

In the cases analyzed here a correct preoperative or antemortem diagnosis of carcinoma of the gallbladder was rarely made. The majority of other reviews of the subject describe a similar situation. In the present series of cases the marked prominence of colicky pain, or cachexia with obstructive jaundice, or a palpable mass with an enlarged liver, seemed to be the clinical features most often leading to an erroneous diagnosis of cholecystitis and cholelithiasis, or carcinoma of the head of the pancreas, or primary or metastatic carcinoma of the liver respectively. The actual occurrences of some of these diseases during the same 23-year period covered in this report were: carcinoma of the Ampulla of Vater four times; carcinoma of the bile ducts 28 times; carcinoma of the head of the pancreas 35 times; and primary carcinoma of the liver 16 times.

An attempt was made to determine whether any degree of correlation existed between the symptoms that led these patients first to seek medical attention, and the extent of the primary growth found at the time of operation. The following impressions were obtained. Firstly, those patients who complained of constant, severe pain almost always had tumors which were non-resectable. Secondly, marked weight loss was another, though somewhat less, constant feature, indicating local and distant invasion and metastases. And, thirdly, the presence of a palpable mass was not necessarily associated with a non-resectable lesion, for while the palpable mass often represented omentum, gallbladder, and colon or stomach all matted together, not uncommonly it proved to be merely an inflamed gallbladder distended with bile, pus

or tumor, the tumor being grossly restricted to the organ. Metastases to the regional lymph nodes might have been present, but resection of the gallbladder was technically feasible.

In the total series of 50 cases, 26 per cent of the patients were too ill to withstand an operation. Forty-eight per cent were operated upon but the tumor was found to be not resectable. Resection was possible in 14 per cent of the cases, but after careful search the surgeon found distant extension of the tumor in all but one case. In 8.0 per cent of the cases the operator was unaware that he was dealing with a cancerous gallbladder and made no search for regional lymphadenopathy or metastatic lesions. These 8.0 per cent were unfortunately also lost to follow-up. Two cases, or 4 per cent, of very early cancer of the gallbladder confined to the organ were incidental findings at autopsy in two patients, one of whom died of cardiac disease, the other of cancer of the urinary bladder.

The minimum mortality rate of 88 per cent in this series of cases approximates those described elsewhere in the literature. Of Smithies'²² 23 cases, 21 died immediately or within eight months after operation. Only two patients were alive at the end of four years. In Cooper's⁴ series of 48 cases there was a possible cure in only one case. Sainburg and Garlock¹⁹ considered the disease incurable, reporting a mortality of 98.5 per cent in less than three years after operation in 75 cases.

SUMMARY

Fifty cases of carcinoma of the gallbladder have been analyzed. The dismal prognosis described by other authors was found to hold for this group as well. Sixty-six per cent of these patients experienced the onset of their illness six months or less prior to hospital admission, and the majority of the remaining patients described a recent abrupt increase in the severity of long-standing symptoms. The mortality rate in the total series was at least 88 per cent, indicating that carcinoma of the gallbladder is still a virtually incurable disease. A brief comment has also been made on some of the current theories of the etiology of cancer of the gallbladder.

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