

PRIMARY CARCINOMA OF THE GALLBLADDER*

AN ADDITIONAL REASON FOR EARLY REMOVAL OF THE CALCULOUS GALLBLADDER

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IN MANY WAYS it seems hardly worth while to offer a paper on such a surgically hopeless condition as carcinoma of the gallbladder. On the other hand, and paradoxically, that is the very reason we have the temerity to do so. Because it has such a bad prognosis once it has become established, is there anything that we can or should do to prevent its occurrence? We believe that the situation might definitely be helped in two ways. First, by stressing the fact that primary carcinoma of the gallbladder is much more common than most doctors, particularly the general practitioners, realize; and secondly, that, in a very large majority of instances, it develops as a relatively late sequela to a long-standing chronic cholecystitis and cholelithiasis. Any solution to the problem, then, would seem to lie in the realm of education; education of the doctor, from his medical school days on, in the many dangers of chronic gallbladder disease and gallstones even though *apparently* symptomless, of which the possibility of malignant degeneration is only one; and education of the public that there is only one treatment for gallbladder disease and gallstones, when their existence is proved, and that is operative removal, and the sooner the better. Most of you here hold teaching positions in some medical school. We would indeed be presumptuous to imply that we should teach you, but we do bespeak your aid in teaching others; we feel that all too frequently too little emphasis is given to the importance of operative treatment of the so-called "symptomless gallbladder" or "quiescent gallstone" until far-reaching systemic damage has been done, which is irreparable, then, by late operation. There has been a tremendous amount of discussion in recent years of the complicated operative technic for the treatment of carcinoma of the ampulla and head of the pancreas, but comparatively little has been said about the much less spectacular cholecystectomy to *prevent* the equally common primary carcinoma of the gallbladder, as well as a train of other concomitant and ultimately fatal systemic complications.

The senior author of this paper has had forcibly impressed on him the fact that carcinoma of the gallbladder is more common than is usually represented by having had among his personal cases in the ten years from 1932 to 1941, 11 patients with this affliction. It is one thing, statistically, to analyze this disease and another to observe the decline and sufferings of a fellow human being, realizing that perhaps this could have been prevented.

With this in mind we wish to reiterate the points made by numerous

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authors in recent years, that cholelithiasis is a potentially dangerous condition and that "silent stones" is a deceiving term. Among the medical profession in general there seems to be a curious reluctance regarding surgical therapy of cholelithiasis and chronic cholecystitis, until the patient himself precipitates the decision by an acute episode which does not subside under treatment with ice-caps, antispasmodics, and opiates. Every surgeon is familiar with the attitude of many a family physician or internist towards his wards as he watches them through subacute attacks of gallbladder trouble or allays the fears of the patient when gallstones are found roentgenologically or during some unrelated operative procedure. This is a most unfortunate circumstance for each such man will not observe many cases of malignancy in his own experience and thus will tend to discount his occasional patient who has a carcinoma of the gallbladder. It is the abdominal surgeon who sees most of these cases and it should be a moral obligation of his to know the facts and to urge early operation.

There are other excellent reasons that call for early operation, the most fundamental of which may be summed up in a statement of Lahey:¹ "It is definitely my conviction that if patients were submitted to cholecystectomy before they had been through repeated attacks of gallstone colic, not only would the end-results be infinitely better but mortality markedly lower.— Not only will early operation for gallstone be associated with a low mortality rate, but it will definitely preserve function and normal conditions in the biliary tract."

We stress also the occasional reference in the literature² to the eventual production of myocardial weakness by chronic gallbladder disease. This sequence has often been called to our attention by clinicians of wide experience. That this is no idle statement is illustrated by the fact that in the causes of hospital deaths in the 1940 series of biliary tract surgery at the Mayo Clinic, cardiovascular disease ranks first, having caused 32.1 per cent of the total mortality.³ This is a tangible factor which should affect one's decision in favor of early operation. Recent observations have also shown striking correlation between gallbladder disease and coronary artery disease,⁴ though it must be mentioned that this may be due to a basic underlying metabolic factor, as may be the case in myocardial disease.

There are other conditions which will not be elaborated upon, but which have been noted and recorded, from time to time, as resulting from calculus and infected gallbladders, such as functional gastro-intestinal symptoms, intestinal obstructions due to gallstones, arthritis, asthma, *etc.*, all with a more than presumptive cause and effect basis. Indeed, the silent gallstone is a very questionable entity.

STATISTICAL SURVEY

Admittedly, surgical statistics regarding the occurrence of carcinoma of the gallbladder are misleading. Autopsy findings are more reliable, generally speaking. Mohardt,⁵ in a recent collective review, and Kirshbaum and

Kozoll⁶ have presented large series showing that the general incidence of gallbladder carcinoma is from one-quarter to three-quarters of 1 per cent of all autopsies, or about 5 per cent of the total of all cancer disclosed at autopsy. Eight to 10 per cent of all cancer occurring in the female is primary in the gallbladder, as compared to the male incidence of 1 to 4 per cent. This discrepancy is not so striking, however, when one recalls that the occurrence of gallstones in women over 50 is about 14 per cent, but only 6 per cent in men, maintaining approximately the same sex ratio.

Primary cancer of the gallbladder is very rare in the young, there being only a few cases reported in the literature under 30 years, the youngest 22 years of age. The majority are between 60 and 70 years of age.

About 75 to 80 per cent of all carcinomatous gallbladders are found at autopsy to have coexisting cholelithiasis. Surgical pathologic reports may well show less than this, for, as we have found, inoperable malignancies cannot be satisfactorily explored for stones at the operating table. It may also be noted that in carcinoma of the biliary tract, exclusive of the gallbladder, about one-third of the cases are associated with stones.

This brings us to the fact that, statistically, we are shown that between 4 and 5 per cent of all calculous gallbladders may eventually be associated with malignancy of that organ.

Now, what kind of mortality rate do we have in prophylactic removal of symptomless gallbladders? That is difficult to determine for mortality rates presented in the literature for cholecystectomy include mostly patients in whom symptoms have demanded operation. Graham⁷ gives a rate of 1.5 per cent; the Mayo Clinic, in the 1940 report,³ for cholecystectomy performed for a chronic cholecystitis with stones gives a 1.6 per cent of hospital deaths. Of this last group, 7 per cent were jaundiced. Thus, we see that on a purely statistical basis, regarding the possibility of malignancy as the only reason for advising cholecystectomy, we are entirely justified in our stand, by a mortality expectancy of 1.5 to 2 per cent as against a malignancy expectancy of 4 to 5 per cent.

TABLE I

PATIENT'S AGE AT TIME OF DIAGNOSIS	
40-49 years.....	1
50-59 years.....	3
60-69 years.....	6
70-79 years.....	7
80-89 years.....	1
Average age 67.4 years.	

Of the 18 cases which we are reporting in our series, two were males, 16 were females. As to age, one was in the 40's, three in the 50's, six in the 60's, seven in the 70's, and one in the 80's. The average age was approximately 67.4 years. The presence of stones was proved in 11 cases; in seven it was impossible to say, due to the extent of the growth. In 13 cases there was a history at least suggestive of gallstones for from one to over 20 years preceding the operation. In four other cases, giving sym-



toms of less than one year's duration, in every instance the complaint seemed based on already inoperable growth. In one case the history was so indefinite as to preclude any estimate of the duration of disease. In two cases there had been previous operations for the removal of stones, with drainage of the gallbladder, one, 20 years, and the other five years before the operation at which the malignancy was found. In each of these, the growth not only involved the gallbladder and adjacent liver, but also proceeded up the old drain tract into the abdominal wall. In both

TABLE II
DURATION OF SYMPTOMS SUGGESTIVE OF GALLBLADDER DISEASE

20 years or over.....	2
10-20 years.....	2
5-10 years.....	5
1-5 years.....	4
Less than 1 year.....	4
History too indefinite to determine..	1

TABLE III
SURVIVAL AFTER OPERATION DETERMINING DIAGNOSIS

Less than 1 month.....	6
1-3 months.....	3
4-6 months.....	4
7-12 months.....	2
13-18 months.....	2
Over 2 years (25 months).....	1
Less than 6 months—13.	Less than 1 year—15.

TABLE IV
PATHOLOGIC REPORT — TYPE OF GROWTH

Adenocarcinoma, primary in gallbladder.....	6
Squamous cell carcinoma.....	3
Carcinoma of gallbladder, primary, unspecified.....	7
Unsatisfactory biopsy.....	2

of these cases there had also been reformation of stones. Six cases survived the operation less than one month, three survived from one to three months, four from four to six months, two from seven to 12 months, two from 13 to 18 months, and one for 25 months. In three cases the gallbladder was removed. In one of these the presence of growth, in addition to stones, was suspected, but no evidence of extension beyond the limits of the gallbladder was demonstrable. This case survived 10.5 months. In the other two cases, very early carcinoma was found on microscopic examination, but was not suspected at the time of operation. One of these cases lived 16.5 months, the other 25 months, but *both died of a recurrence of the malignancy*. From this it would seem that our ability to cure already established primary carcinoma of the gallbladder by operative removal of that organ is very questionable. In a total of 1192 gallbladder operations during this ten-year period there were 18 pathologically proven cases of primary carcinoma of the gallbladder, or slightly over 1.5 per cent. This total included both calculous and noncalculous gallbladders. The percentage of cases showing primary carcinoma is considerably smaller than some other published series, but is still less than the mortality rate for this same series, which was 1.26 per cent exclusive of the carcinomas.

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TABLE V
COMPOSITE TABLE OF ALL CASES

Patient	Sex	Age	Stones	Operation	Duration after Operation	Duration of Symptoms before Operation
M. B.	F	78	+	Inop.*	Autopsy	Pain R. U. Q., back and shoulder for 4 years.
M. W.	M	74	?	Inop.	4 mos.	Jaundice for 6 weeks.
A. L.	F	61	?	Inop.	7 mos.	Nausea, gaseous distention, R. U. Q. discomfort for 5 years.
F. B.	F	67	+	Cholecystectomy	25 mos.	"Gallbladder trouble" dating to first acute attack 20 years before.
C. W.	F	87	+	Inop.	3 days	History too vague and indefinite to estimate.
J. D. L.	F	62	+	Cholecystectomy	16.5 mos.	Acute episodes for 9 years.
E. M.	F	57	?	Inop.	5.5 mos.	Attacks of gas and R. U. Q. discomfort about 15 years.
A. W.	M	73	+	Inop.	3 mos.	Gallbladder drained and stones removed 5 years previously, elsewhere.
W. F.	F	62	?	Inop.	9 mos.	Gas and pain in R. U. Q. for about 1 year.
E. T.	F	79	+	Inop.	2 mos.	Gallbladder drained and stones removed 20 years previously, elsewhere.
A. J.	F	56	+	Cholecystectomy	10.5 mos.	Gas, indigestion, R. U. Q. discomfort for about 6 years.
J. G.	F	76	+	Inop.	18 days	Attacks of R. U. Q. pain for over 2 years.
E. C.	F	74	?	Inop.	12 days (pulm. emb.)	Burning discomfort in "stomach" for "several years." Rapid progression, 8 mos.
A. K.	F	72	?	Inop.	2 mos.	Attacks R. U. Q. pain for 5 to 6 years.
R. A.	F	69	?	Inop.	20 days	Pain through upper abdomen for 5 mos.
D. C.	F	47	+	Inop.	26 days (pulm. emb.)	Loss of weight 1 year. Pain in back 3 mos.
E. B.	F	59	+	Inop.	4 mos.	Anorexia and loss of weight, 3 mos. Pain, 2 weeks.
E. K.	F	61	+	Inop.	15 mos.	Pain in upper abdomen, 3 to 4 mos.

* "Inop." means autopsy, or exploration with biopsy of growth.

DISCUSSION.—From our brief series several points can be emphasized. In nearly every case the symptoms presented were due to inoperable growth, with or without preëxisting symptoms of cholelithiasis. The only two cases of early carcinoma were operated upon for long-standing complaints due to the stones contained within the gallbladders, and the finding of malignancy was entirely accidental and unexpected. In spite of this, and removal of the gallbladder, both of these cases died—one in 17 months, the other in 25 months—of recurrence of the malignancy. Therefore, the result of surgery once malignancy is established is most discouraging and makes us reiterate the fact that the only hope that many of these deaths can be prevented is by early removal of simple calculous gallbladders. There are two cases included in our table which are of a group in which malignancy arose in gallbladders which had previously been drained and the stones removed. The new growth in this type of case often presents itself along the old drainage tract as it did in both of these instances. This brings up the point, that the mere removal of stones does not satisfy the moral obligation of the surgeon; removal of the gallbladder is necessary where possible.

Histopathologically, adenocarcinoma predominates; squamous cell carcinoma, usually anaplastic, is less common. Scirrhous growths are frequent; and the colloid type, with peritoneal extensions, are occasional.

In reading most reports concerning carcinoma of the gallbladder from

the surgical point of view, we have found a great deal of superfluous material, specifically in evaluation of the symptoms presented, and the laboratory findings. A simple understanding of the anatomy and pathology involved will be of most help to the clinician. Most new growths originate in either the neck or fundus of the organ. Extension is by local infiltration of the gallbladder wall, then into the liver and adjacent tissues and by lymphatics to the cystic nodes, then to the nodes about the common duct.

Distant metastases are rare, but may occur. The liver is usually already involved at operation.

Thus, we see that obstruction of any point of the biliary tract may occur or there may be only local extension or peritoneal implants. Due to obstruction of the cystic duct, either by stone or growth, empyema and hydrops may occur in conjunction with the malignancy.

With this simple basis of knowledge of the origin and manner of spread of carcinoma of the gallbladder in mind, it is easy to see why there is no syndrome that will make an early diagnosis possible. We have diagnosed this condition preoperatively and diagnosed patients dying without operation, but the diagnosis was based on symptoms arising as a rule from the extensive spread of the disease and other evidence of carcinomatosis. Early malignancies are found by accident, the symptoms indicating operation being due to the coexisting cholelithiasis. It is the occasional case of early carcinoma that makes us feel most futile in treatment as even here the outlook is bad because of the early spread.

CONCLUSIONS

1. Carcinoma of the gallbladder is more common than is generally supposed.
2. Cholelithiasis must be accepted as an etiologic factor because of its frequent association with malignancy.
3. Preoperative diagnosis of carcinoma of the gallbladder is difficult and treatment is rarely of value.
4. With present day surgical methods, prophylactic removal of symptomless calculous gallbladders is entirely justified in most individuals.
5. Valid reasons other than the possibility of malignancy are presented in support of an early cholecystectomy of calculous gallbladders.
6. A series of cases of carcinoma of the gallbladder seen in the years 1932-1941 at the Union Memorial Hospital is presented.

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DISCUSSION.—DR. J. SHELTON HORSLEY, Richmond, Va.: There have been many methods of attempts to reconstruct the common bile duct. One of the earliest was by Sullivan, who, in 1900, described an operation in which a rubber tube or catheter was fastened to the stump of the hepatic or the remaining end of the common duct, carried into the duodenum, and covered with neighboring tissue and omentum.

In 1918, I published a paper on reconstruction of the common bile duct in which the experimental work was carried out in dogs. A segment of vein was turned inside out and sutured into the defect made by resecting a portion of the common duct. The operation was technically successful but biologically a failure. After a few months the tissues of the vein, being unaccustomed to irritation by bile, contracted and formed a complete obstruction. It was then seen that it was necessary not only to have a primary mechanical union but to make a permanent channel; tissue accustomed to its environment must be used. The vein was accustomed to blood, not bile.

On August 13, 1921, I operated upon a patient, Mr. R. B. D., white, age 39, who had been operated upon elsewhere; the gallbladder had been removed at one operation and later the common duct was opened for stones. The patient had a recurrence; and I united the common duct, which was greatly dilated, to the duodenum. He was relieved for a while, but about two years later he had more discomfort and pain, and a roentgenogram, taken on May 27, 1924, showed that some of the barium meal entered the common duct and the hepatic ducts. (slide) Obviously, the common and hepatic ducts would be filled with the duodenal contents from the normal pressure there, and regurgitation into the biliary system occurred. On December 31, 1924, three years and four months after the operation I performed, he was operated upon elsewhere. Many adhesions and liver abscesses were found and the patient died five days after this operation. This would seem to show that any communication between the common duct and the duodenum, with its great peristaltic activity, and receiving gastric material under strong pressure from the stomach, would be unwise, as it almost certainly would be followed by cholangitis.

In October, 1943, Lt. Col Guy Horsley and I published a method of choledochenterostomy* in which a loop of jejunum about two or three feet from its origin was united to the common duct by a rubber band and an entero-enterostomy was made between the limbs of the loop by rubber bands to bypass the choledochenterostomy and so avoid the pressure that would force the intestinal contents into the biliary tracts. (slides) I have used this technic clinically, as mentioned in this paper, and have had successful cases since this paper was published.

* Cholecysto-enterostomy, Choledochenterostomy and Entero-enterostomy by Means of Rubber Bands: The Use of Rubber Bands in the Mikulicz Operation. *ANNALS OF SURGERY*, **118**, No. 4, 558, October, 1943.