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Surgical Indications in Cholelithiasis:

Prophylactic Cholecystectomy Elucidated on the Basis of Long-term Follow up on 526 Nonoperated Cases *

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Introduction

THE MORTALITY of biliary-tract surgery has been continually reduced, and it is now below one per cent following simple cholecystectomy in representative American [4, 5, 12, 13, 16, 28, 44] and Scandinavian [6, 10, 23, 55] series. This has entailed a gradual extension of the indications for cholecystectomy. An increasing number of surgeons are advocating removal of *all* calculous gallbladders, regardless of the symptoms.[15, 19, 28, 47, 50, 52, 58, 60] It has been established that about 80 per cent of patients with typical symptoms of gallstones are satisfactorily relieved by cholecystectomy.[6, 27, 31, 55] It is just as widely known that the results are not equally good in patients with mild or uncharacteristic complaints.[9, 21, 31, 33, 57] In such cases, surgery is not undertaken to relieve the symptoms, but mainly for prophylactic reasons. In setting up the indication for surgery, it is essential, therefore, to know the prognosis in nonoperated cases, especially in cases with mild complaints. It is important also to know whether the risk of future severe symptoms differs in the different clinical types of the disease. This risk, and the spontaneous course of cholelithiasis, on the whole, has received too little attention in the surgical literature. The present study was undertaken in the effort to elucidate the spontaneous prognosis of the gallstone disease, by a follow up on nonoperated patients.

Evarts Graham,[32] in 1931, advanced the view that gallstones predispose to such a marked extent to gallbladder carcinoma that the stones are interpretable as a precancerous condition. Carcinoma of the gallbladder must still be considered an almost incurable disease,[2, 11, 19, 25, 26, 36, 45, 49, 52, 53, 60] a fact which has not been altered by modern, radical surgery.[29, 47] Many authorities share Graham's view,[13, 19, 24, 26, 29, 49, 58, 66] claiming that the risk of future gallbladder carcinoma alone indicates the removal of all calculous gallbladders, regardless of the severity of the symptoms.

As a rule, gallbladder carcinoma is found in one or two per cent of all biliary tract operations; [2, 3, 11, 26, 30, 34, 36, 37, 45, 47, 52, 53, 61] in the old age groups in a somewhat higher

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TABLE 1. *Present Series. 535 Cases of Nonoperated Cholelithiasis. Survey of Material*

	No.	Per Cent
Personal examination	299	56.1
Questionnaire	89	16.6
Died during follow-up period (but traced)	138	25.8
Not traced	9	1.5
Total followed up	526	98.5

percentage.[29, 59, 63] In large postmortem series, carcinoma of the gallbladder has been found in 0.5 per cent,[1, 3, 30, 34, 36-38, 46, 49, 61, 64] and 70 to 80 per cent of gallbladders, with primary carcinoma, contain stones.[1, 3, 11, 36, 46, 61] Autopsy studies have shown also that gallstones are present in 20 to 40 per cent of all patients over 60 years of age.[20, 38, 41, 43] On the basis of such statistics, Finney and Johnson[24] calculated that patients with gallstones ran a four to five per cent risk of developing carcinoma of the gallbladder. Others[53, 64] have found a considerably lower risk, basing their calculations upon clinical series. Of course, calculations of this nature carry a marked uncertainty, and moreover they are based on hospital series where cancer of the gallbladder is presumably more common than among the general population. It cannot be said that previous studies have adduced a proof, or even a likelihood, that the risk of gallbladder carcinoma in patients with cholelithiasis does outweight the slight risk of simple cholecystectomy.

TABLE 2. *Present Series. Diagnostic Criteria*

Nonvisualized gallbladder and clinical evidence	366 cases
Gallstone shadows in plain radiograms*	118 cases
Negative stone shadows in cholecystograms	42 cases
Total	526 cases

* In a few patients of this group, the gallstones were a chance finding in laparotomies performed for other reasons.

The incidence of future benign complications in nonoperated gallstone patients is also insufficiently elucidated. Some early follow up series (prior to the cholecystographic era) suffer from diagnostic inaccuracy. Clagett[14] mentions that among 150 patients who refused operation, 27 per cent had to undergo surgery for a serious complication of their gallstone disease, within two years, but he does not give details of this series. The late prognosis of acute cholecystitis, treated without surgery, has been quite thoroughly studied in Scandinavian series,[39, 42, 54] which shows that about 40 per cent of the cases later develop severe symptoms and/or complications. The serious prognosis of unoperated common-duct stones has been investigated by Millbourn.[48] Follow up studies[7, 8, 22, 67] on patients with mild symptoms are few and the series small. Frequently, the diagnosis has not been confirmed radiologically. Comfort *et al.*[17] followed 112 patients with asymptomatic gallstones. Of them, 50 per cent developed symptoms, severe in 20 per cent.

It is clear that prophylactic cholecystectomy, i.e., removal of the gallbladder in patients with very mild or no symptoms, must prevent the development of future severe symptoms and complications in a certain percentage. The size of this percentage, however, is not known with sufficient accuracy. Furthermore, the spontaneous mortality of cholelitiasis has not been definitely elucidated.

Present Series. Follow up Results

The present series comprises 526 nonoperated patients followed up, five to 20 years after gallstones were diagnosed. The series comprises all patients with cholelithiasis, admitted to our department during the period 1936 to 1950, without having cholecystectomy. Now, we are operating upon more than 90 per cent of our gallstone cases, but during the years up to

1950 the operative rate was considerably lower.

The follow up is almost complete (Table 1). The aim was toward a personal examination of the patients, asking them leading questions. A higher percentage of these patients admitted having symptoms than the small group that had to be followed up merely by questionnaire. During the follow up period, 25 per cent had died (Table 1), and the cause of death is known in practically all cases. Fifty cases, however, since it was impossible to obtain sufficiently detailed data regarding the subsequent history, had to be left out of some of the analyses (Table 5, Fig. 1, 2, and 3).

A diagnosis of gallstones is never absolutely positive without operative (or postmortem) confirmation. The present series comprises only cases with x-ray signs of gallstones (positive or negative shadows of calculi) or cases with a suggestive or typical history of cholelithiasis plus nonvisualization of the gallbladder in the cholecystograms (Table 2). According to previous authors,[4, 44] and our own experience, this is nearly always tantamount to stones in the gallbladder. Thus, the diagnosis is based on accepted criteria.

Table 3 gives the age distribution which agrees with that found in other large series (e.g., Colcock and McManus[16]). There were 388 women and 138 men, a ratio of approximately three to one. The series is divided into four clinical groups, according to the condition at the time of diagnosis of the gallstones (Table 4). The results of the follow up are analyzed for each of the four groups separately (Fig. 1, 2, 3).

It applies to the series, as a whole (Table 5), that half the patients later developed severe symptoms and/or complications. Complications alone occurred in about one-third. Table 5 appears to show that the men have somewhat more favorable prospects than the women, and fewer men have undergone subsequent operation. The prognosis of the different clinical

TABLE 3. *Present Series. Age and Sex Distribution*

Age, years	139 Men		396 Women	
	No.	%	No.	%
10 to 20	0	0	4	1.1
21 to 30	5	3.6	37	9.4
31 to 40	15	10.8	57	14.5
41 to 50	28	20.0	65	16.4
51 to 60	38	27.3	99	25.0
61 to 70	37	26.6	87	22.0
71 to 80	16	11.6	46	11.8
81 to 90	0	0	1	0.3

groups may be seen from the figures. Irrespective of the original degree of severity, at least 50 per cent of the women and 30 per cent of the men develop severe symptoms and/or complications at a later date (Fig. 1). In this respect too, the prognosis is somewhat better among men (except in Group IV). The incidence of subsequent complications alone is apparent from Figure 2, which shows that even in the group with the mildest symptoms, at least one-quarter develop complications (acute cholecystitis, jaundice, pancreatitis). The duration of the symptoms, prior to diagnosis, proved to be of no significance to the future course. Classification of the series into three classes: those less than six months in duration; those between six and 24 months; and those over 24 months; revealed that each class showed the same follow up result as the entire series (Table 5). The significance of age to the future

TABLE 4. *Present Series. Groups According to Clinical State at Initial Admission*

		Men (138 Cases), %	Women (388 Cases), %
I	Asymptomatic or only slight symptoms	18	18
II	Frequent and/or severe attacks of pain	36	39
III	Acute cholecystitis	24	23
IV	Jaundice and/or pancreatitis	22	20

TABLE 5. *Present Series.* Follow up, Men and Women Compared*

	Men (119 Cases), %	Women (359 Cases), %
Asymptomatic or only slight symptoms	53	36
Frequent and/or severe attacks of pain	18	32
Complications	29	32
Operations for gallstones	19	27

* 19 men and 29 women were left out, since in these cases the subsequent course was insufficiently known.

morbidity of gallstone patients may be seen in Figure 3. It is evident that the morbidity is highest among young patients, regardless of their original clinical condition. There are no marked differences in the frequency of complications in the four age groups, however. It is a different matter altogether that the mortality increases considerably with advancing age. It might be argued that the longer follow up period for the younger patients might have influenced the findings of a higher morbidity. This was not so, however, as is apparent from the fact that 90 per cent of the patients who developed symptoms later did so within the first five years of the follow up period. All patients were followed for a minimum of five years.

In approximately 100 cases, the gallstones were chance findings in x-rays of the abdomen. Upon further questioning, only 34 had not had any symptoms that might be ascribed to gallstones. In this group of silent stones, about one-third subsequently developed severe or frequent attacks of pain and one-fifth developed complications. Twenty per cent had been cholecystectomized, i.e., about the same proportion as in the series as a whole. The previously asymptomatic stones also induced symptoms, in the majority of cases, within the first five years, if they did give rise to symptoms. In a few cases, symptoms appeared many years after.

Fourteen patients died of gallstone disease, the mortality increasing with advanc-

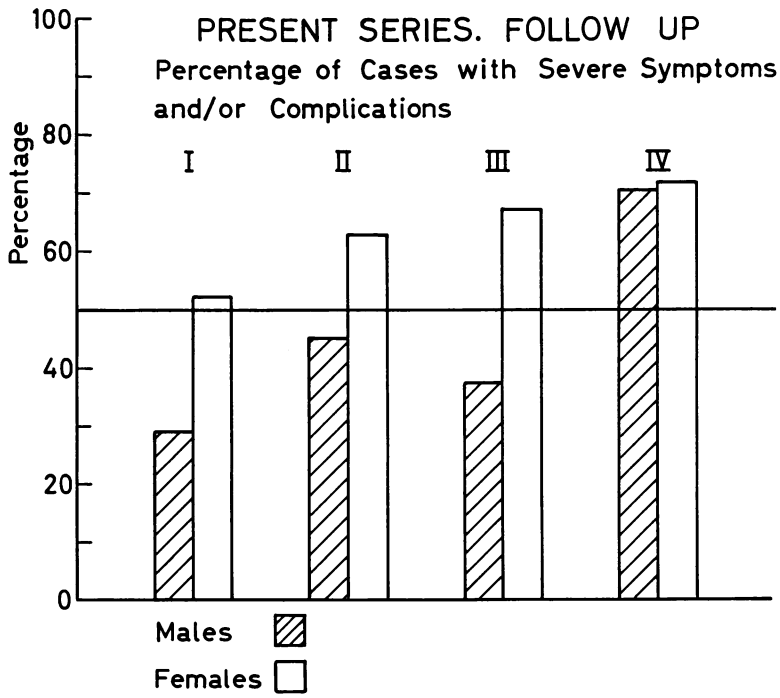

FIG. 1. Percentages of subsequent severe and/or frequent attacks of pain and/or complications; 119 men and 359 women. Groups I, II, III, and IV refer to the subdivision in Table 4.

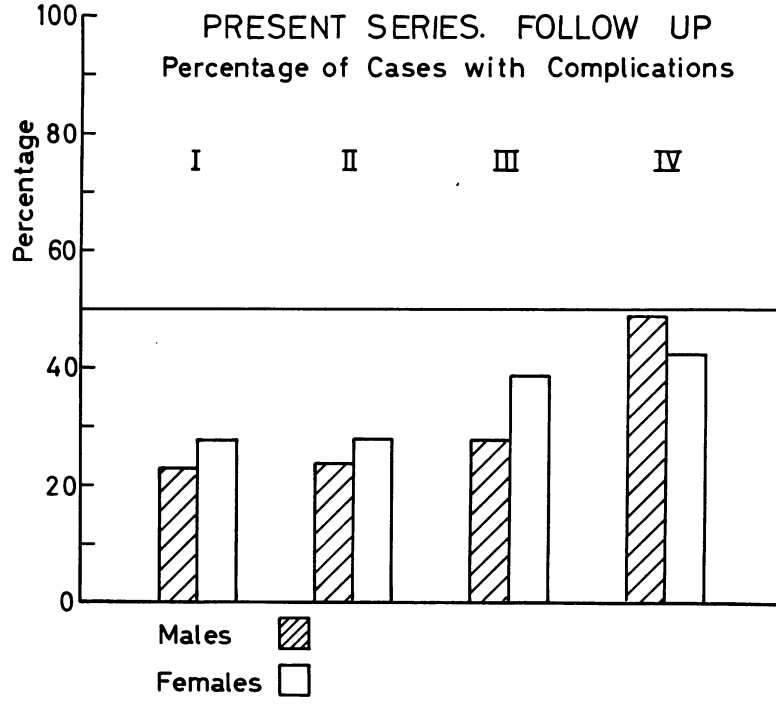

FIG. 2. Percentage of subsequent complications; 119 men and 359 women. Groups I, II, III and IV refer to the subdivision in Table 4.

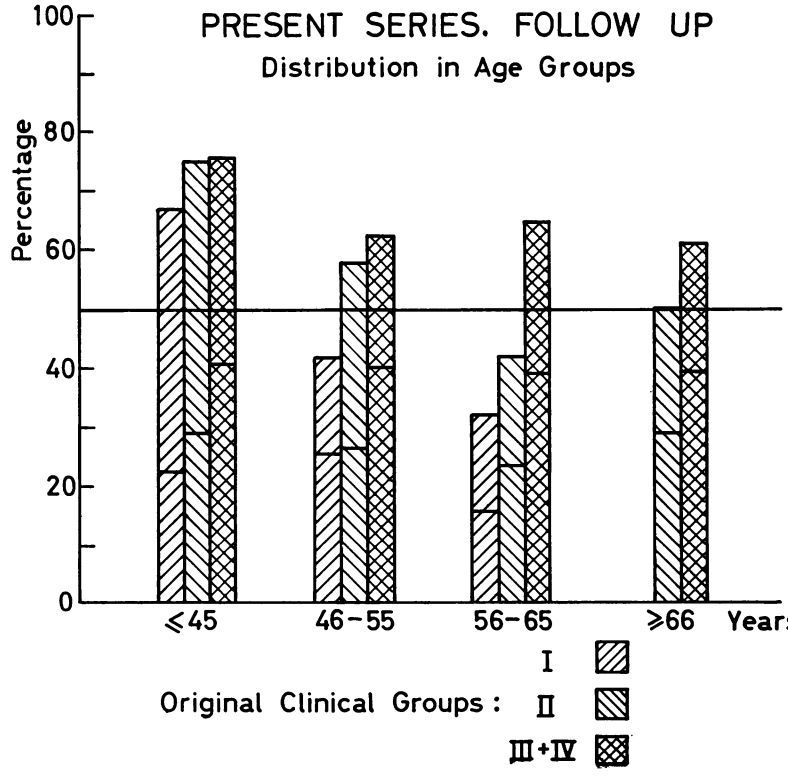

FIG. 3. Classification of entire series into age groups and clinical groups (Table 4). The transverse lines in the columns indicate the frequency of complications alone and the height of the columns the frequency of severe symptoms and/or complications. In the oldest age groups Group I is not shown (too few cases).

TABLE 6. *Present Series. Mortality (Age Groups)*

Age, years	Mortality	%
Under 46	0 of 150	0
46 to 55	1 of 123	0.8
56 to 65	4 of 128	3.1
Over 65	9 of 125	7.2
Total	14 of 526	2.7

ing age (Table 6). The total mortality of 2.7 per cent is a minimum figure. The spontaneous mortality of the disease is considerably higher. In a number of patients a fatal course was later prevented by surgery, but the exact number cannot be stated with certainty. Table 7 gives the causes of death in the above-mentioned 14 cases. All were confirmed by autopsy. Three of the five patients with acute cholecystitis died of subphrenic abscess and two of septicemia (both over 70 years of age). The patients with cholangitis died of hepatic abscesses, and the two patients with necrotizing pancreatitis had impacted stones in the ampulla of Vater. Carcinoma, originating from the gallbladder, was the cause of death in three patients, i.e., 0.6 per cent of the entire series. Three patients subsequently developed gallstone ileus; two of them were cured by operation, while the third patient, admitted in severe irreversible shock, died a few hours after admission. This list gives all the common causes of death in gallstone disease. The greater part of this mortality might have been prevented by operation at the time the presence of the gallstones was recognized.

TABLE 7. *Present Series. Causes of Death (14 Cases)*

	No.	Years After Initial Admission
Acute cholecystitis	5	1, 1, 9, 15, 16
Liver abscesses (cholangitis)	2	2, 9
Necrotizing pancreatitis	2	4, 10
Gallbladder carcinoma	3	2, 2, 3
Gallstone ileus	1	7
Postoperative death	1	3

Discussion

The present series does not represent cholelithiasis among the general population. No doubt, asymptomatic and mild cases are much more common outside of the hospitals (Mårtensson[43]). Therefore, the prognosis for mild as well as for severe cases was investigated. Irrespective of the symptoms, at least one-third subsequently develop severe symptoms and at least one-fifth develop complications. Only 34 had asymptomatic stones (6.3%). In other series too,[16, 40, 62] the number of asymptomatic stones is small. Schuberth,[56] of Stockholm, studying a similar number of asymptomatic cases, also found that about one-third developed severe complaints later. The investigations of Comfort *et al.*[17] point in the same direction: it is now evident that the prognosis of asymptomatic stones is not much better than that of other types of the disease.

Similar to this study, Ehnmark[22] found a mortality of 2.7 per cent among primarily nonoperated cases. In both series, the mortality of gallbladder cancer was about 0.5 per cent. A few of the cases that had subsequent cholecystectomy (about one-quarter) would otherwise have developed carcinoma of the gallbladder. There is a great likelihood that this would have been of the same frequency as in the nonoperated part of the series, so that a total of four or five out of 526 cases would have developed carcinoma of the gallbladder. It may be established, therefore, that the probability of developing malignancy of the gallbladder is a maximum of one per cent, in gallstone patients. In Jaguttis'[35] often-cited follow up, 5 per cent had carcinoma of the gallbladder. However, his series was very small, highly selected, and only 50 per cent were included in the follow up; therefore, his results are inaccurate and far too high.

Considering the indications for cholecystectomy, there is agreement among surgeons and internists that biliary colic and complications afford clear surgical indications. Good results may be expected in a large percentage. The results appear to be better, if operation is performed after a short duration of symptoms.[6] This is a stimulus to carry out the intervention (cholecystectomy) at as early a stage as possible.

Surgeons are not agreed regarding the indications for prophylactic cholecystectomy, and in the opinion of most internists,[9, 51, 57, 65] operation should not be performed exclusively for prophylactic reasons. This disagreement is due to the differences in evaluating the morbidity and mortality in the spontaneous course. The morbidity in asymptomatic and mild cases has been elucidated. Relative to the mortality in mild cases, there were no deaths among 95 patients (of the present series) without symptoms, or with dyspepsia or rare, mild attacks of pain. However, 20 per cent had later undergone operation for their gallstones. A more detailed analysis of the operated cases revealed that, in four, the operation had been a life-saving procedure; three of these patients had perforating cholecystitis and one a common-duct stone, long-standing jaundice, and cholangitis. Although not directly life-saving, a number of the other operations were performed for severe complications. To the patients of this group, it would have been safer to have cholecystectomy at the time when their gallstone disease was first recognized.

In conclusion, it must be stated that prophylactic cholecystectomy prevents much future morbidity and presumably also lowers the future mortality. This presupposes, of course, that the patient is a reasonable surgical risk and that the operation and the pre- and postoperative management are of a good standard. It is true some patients will develop complaints owing to the removal of a functioning gallbladder, but this number is small compared with the number of patients who, nonoperated, would develop severe symptoms because of their stones.

Thus, the mere appraisal of the benign complications indicates cholecystectomy (possibly combined with other operations on the biliary tract), irrespective of the severity of the symptoms. The possibility of future carcinoma of the gallbladder strengthens this indication, but, *per se*, it does not indicate the removal of a calculous gallbladder. The risk of carcinoma of the gallbladder is no higher than the mortality of elective cholecystectomy, as shown in the present and previous studies,[18, 22] which have avoided the statistical error due to the accumulation of gallbladder carcinoma, in hospital series.

In a number of cases of gallbladder carcinoma, the biliary-tract symptoms are of quite short duration.[3, 26] The same applies to the benign complications of the disease, especially in elderly patients.[42] Prophylactic removal of calculous gallbladders, therefore, does not solve the problem regarding the mortality. A number of stones are not diagnosed until the complications set in. It is still as necessary as ever to try to improve the treatment of gallbladder carcinoma and of the benign complications of gallstones, particularly in elderly patients.

Summary and Conclusions

1. In cholelithiasis, biliary colic and complications are generally accepted indications for cholecystectomy (possibly combined with other suitable interventions on the biliary tract). On the other hand, there are differences of opinion regarding the indications for prophylactic cholecystectomy, i.e., removal of the calculous gallbladder to prevent future symptoms and complications. This disagreement is due to the differences in evaluating the spontaneous prognosis of cholelithiasis.

2. After reviewing the literature on the prognosis of cholelithiasis, here is presented an almost 100 per cent complete five to

20-year follow up on 526 primarily nonoperated cases. This study showed that, irrespective of the clinical severity, at least one-third to one-half of the patients subsequently develop severe symptoms and/or complications. Complications alone occur later in at least one-quarter (acute cholecystitis, common-duct stones). The prognosis of asymptomatic stones, according to previous publications and the present series (34 cases), is approximately like that in other cases.

3. The mortality of cholelithiasis proved to be at least 2.7 per cent. However, a number of deaths had been avoided by subsequent operation. There is a marked increase in the mortality with advancing age. Over the age of 60, there was a minimum mortality of 7.2 per cent.

Cancer of the gallbladder occurred, subsequently, in three cases. The risk of developing cancer of the gallbladder in the presence of cholelithiasis was found to be at the utmost one per cent.

4. Prophylactic removal of the gallbladder was found to be indicated in all gallstone patients, who are reasonably good surgical risks. This will prevent much future morbidity. With the present low mortality of elective cholecystectomy, primary operation is likely to carry a lower mortality than nonoperative treatment.

The risk of carcinoma of the gallbladder is no higher than the operative mortality in elective cholecystectomy. Thus, the risk of cancer, *per se,* does not indicate prophylactic cholecystectomy, but it intensifies the operative indication, since at present the only effective measure against gallbladder carcinoma is prevention.

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