MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

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SYNDROMES OF BILIARY TRACT DISEASE

PAIN PATTERNS IN BILIARY "COLIC"

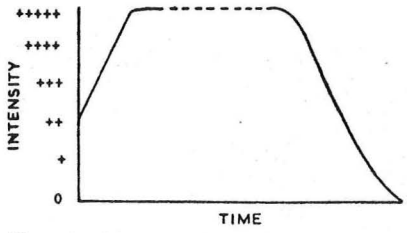


FIG. 1.—Biliary colic: 30 cases; renal colic: 17 cases.

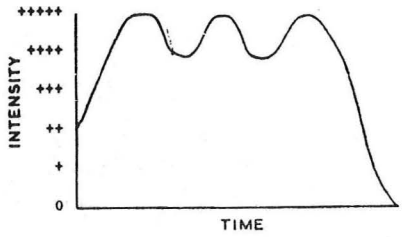


FIG. 2.—Fluctuant: biliary colic, 4 cases; renal colic, 21 cases.

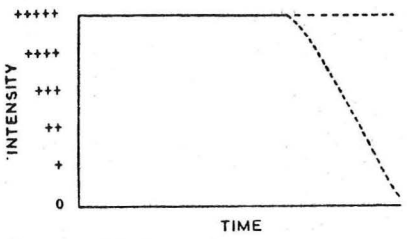


FIG. 3.—Maximum intensity at onset; sudden or gradual cessation. Biliary colic, 15 cases; renal colic, 12 cases.

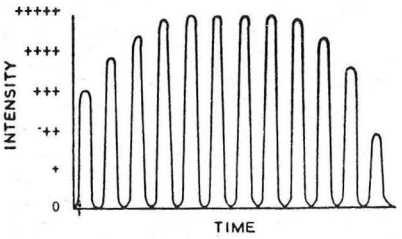


FIG. 4.—Intermittent pain—true "colic." One case of biliary colic; no case of renal colic.

Reproduced from Ref. 1

Onset of Pain:

Maximum severity present at onset	15/50
Intensity rose to maximal severity in 10-60 minutes	16/50
Pain reached maximum after several hours	19/50

Pain Relief Without Therapy: Gradual in most, abrupt in some

Frequency of Pain:

6: No previous attack
30: 1-5 previous attacks
14· Numerous previous attacks

Rarely two attacks in one day
Pain free interval: weeks, months or years

Duration of Pain:

15 minutes to 2 hours in 50%
Many hours to 2 days in 50%

Site of Main Pain:

Epigastrium - 34
Right hypochondrium - 10
Left hypochondrium, midline of back, below the left scapula, deep to sternum, the hypogastrium, and to the right of the umbilicus in one case each

Radiation:

None	11
Below right scapula	18
Right hypochondrium	12
Epigastrium	7
Dorso-lumbar region of back	6
Right shoulder tip	5

Associated Features:

Active and restless	45
Prefer to sit or lie still	5
Sweating	35
Vomiting	38
Persistent RUQ soreness after the attack	11
Felt quite well as soon as attack over	39

PAIN AFTER COMMON DUCT DISTENTION

Doran (2) distended the common bile duct by means of a Foley catheter. All studies were done on the 12th postoperative day, then the patients were completely conscious, cooperative and not on drugs which would decrease their sensitivity.

Patterns of Referred Pain in 56 Patients:

Only in abdomen	28
Confined to the back	9
Started in the abdomen, radiated to the back*	6
No pain could be produced	11

* Pain never radiated from the back to the abdomen

Location of Pain:

Out of 34 patients whose pain started in or was confined to the abdomen, it was in the midline in 24 and in the right hypochondrium in 10. The midline pain was mostly epigastric in location. One patient had umbilical pain and 5 had pain in the low substernal area.

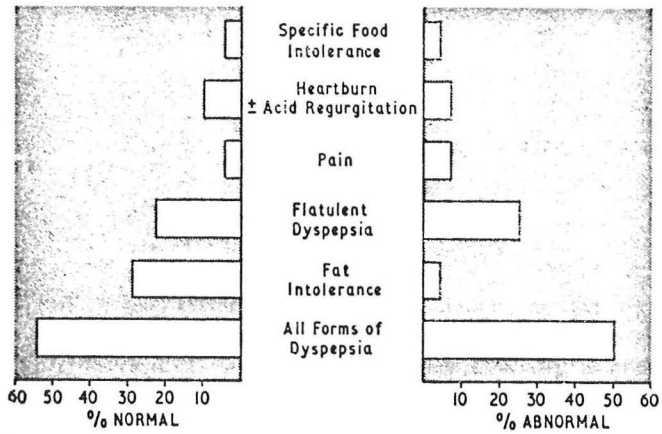
Out of 15 patients with pain in the back, it was midline, usually between the scapula in 11, but it was unilateral in 4. In one of the latter the pain was under the left scapula.

Since RUQ pain was produced by bile duct distention in 10 patients, biliary pain located in this area is <u>not</u> necessarily due to local peritonitis.

BILIARY "DYSPEPSIA"

Chronic indigestion is considered by many to be frequently caused by gallbladder disease, especially gallstones. Fatty food intolerance, belching, flatulence, epigastric heaviness, upper abdominal pains of varying intensity and heartburn are some symptoms which frequently suggest the presence of gallstones. Rhind and Watson (3) defined gallstone dyspepsia as follows: "Epigastric discomfort after meals, a feeling of fullness so tight that clothing is loosened, eructation with temporary relief, and regurgitation of sour fluid into the mouth with heartburn."

Price (4) made a prospective study in women, first obtaining a careful history and then getting an x-ray of the gallbladder. 24 women had gallstones or nonvisualization of the gallbladder, and 118 had a normal oral cholecystogram. The results are summarized in the next figure:



Frequency of symptoms in subjects with normal and abnormal cholecystograms.

Note that 53% (63/118) of the women with normal oral cholecystograms had chronic dyspepsia.

Author's Conclusion: The association of dyspepsia and gallstones is purely fortuitous. Dyspeptic symptoms occurring day after day are rarely due to uncomplicated cholelithiasis.

These studies do not, of course, prove that the dyspepsia suffered by these women did not originate in the gallbladder--only that there is no association with gallstones. Most workers agree that these symptoms are <u>not</u> usually relieved by cholecystectomy (see references 4-6), but there are very little good data on this point. Rhind and Watson (3) reported that dyspepsia was often cured after cholecystectomy (19 out of 32 cases) but controls and observer bias may have influenced their judgment. Gunn and Keddie (6A) carefully studied 111 patients. 88% of these had epigastric discomfort or swelling, belching, heartburn or fatty food intolerance. In 69% of these, symptoms were improved after operation. Heartburn occurred in 43% of the patients, but was improved in only 31% by surgery.

These workers are aware of Price's study. They conclude: "Whilst accepting that dyspepsia is common amongst women and that some may have coincidental gallstones which do not cause symptoms (this would be Price's conclusion), this does not mean that patients who have dyspepsia as a result of biliary obstruction and inflammation will not have it relieved by cholecystectomy along with their pain."

Symptoms of Gallbladder Disease (Stones) According to Littler's Careful Survey (6):

Dyspepsia and fatty food intolerance are rare and usually not caused by gallbladder disease
Pain may not be excruciating; severe pain to particularly unpleasant aching pain in 50%
Pain often nocturnal (38%)
Attacks lasted 1/2 to 4 hours
Nausea and vomiting in 68%

Clinical Observations by Gunn and Keddie (6A):

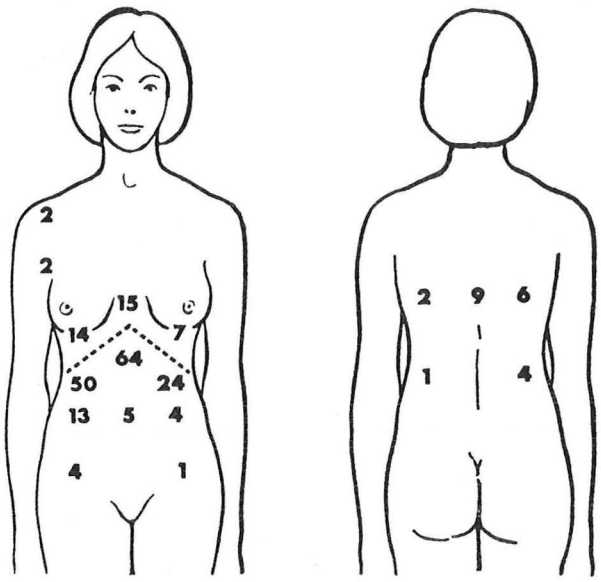


Fig. 1—Sites of most severe pain (%) in 107 patients with gallstones.

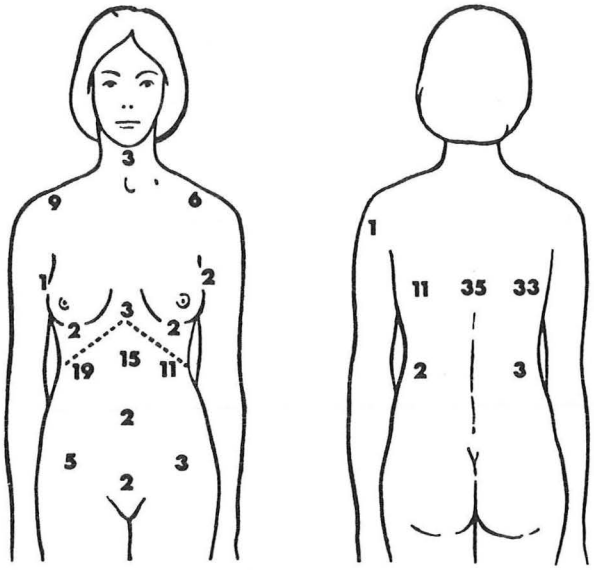


Fig. 2—Sites of pain radiation (%) in 107 patients with gallstones.

Findings in 111 patients with gallstones generally agree with those reported in reference 1. The pain was often very severe for 2-3 hours, the mean total duration of the pain was 16.0 hours. In 59% the pain was aggravated by food. In 15% there was some pain relief by alkalis. The pain was associated with vomiting in 80%, and in 44% vomiting gave some relief.

The dyspepsia experienced by these workers and its relief in 69% following cholecystectomy has already been mentioned (page 4).

One-half of those seen during an acute attack had guarding in the RUQ or epigastrium, some with rebound. Murphy's sign was positive in 27% and in 14% there was a suspicion of a mass or fullness in the RUQ.

ORAL CHOLECYSTOGRAPHY

Technical causes of nonvisualization of the gallbladder:

1. Failure to ingest dye
2. Vomiting or diarrhea
3. Gastric outlet obstruction or esophageal stricture
4. Malabsorption
5. Abnormal location of the gallbladder
6. Liver disease,* including incipient hepatitis
7. Dubin-Johnson syndrome
8. Fat-free diet prior to the examination (7)
9. Breast feeding (?) (8)
10. Previous cholecystectomy

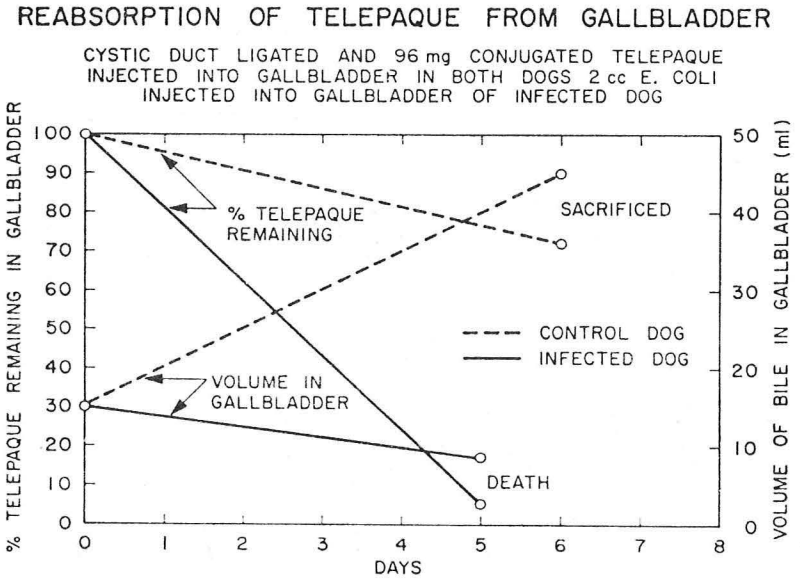
* Satisfactory visualization usually occurs up to a bilirubin of 2. Visualization is poor or unlikely above a bilirubin of 3 and almost never occurs when the bilirubin is over 4 (14).

Mechanism of Visualization of a Normal Gallbladder (9,10):

Telepaque is a moderately lipid soluble substance but it is poorly soluble in water. It is absorbed by passive diffusion across the gut mucosa, and within 2 hours of ingestion peak blood levels are reached. The blood level remains elevated for longer than 14 hours. Once in the blood Telepaque is bound to albumin and transported to the liver. In the liver it (like bilirubin) is conjugated with glucuronide, a process which is dependent on glucuronyl transferase. In this way Telepaque is converted from a non-polar lipid soluble substance to a polar, water soluble compound. In this form it is not absorbable across the normal gallbladder mucosa.

Nonvisualization of the Gallbladder:

Telepaque is rapidly absorbed from an inflamed gallbladder, but not from the normal gallbladder (9).



Reproduced from Ref. 9

There are two reasons why Telepaque might be absorbed from an abnormal gallbladder. First, if the mucosa is ulcerated or atrophied, the normal barrier to diffusion is destroyed, and conjugated Telepaque is absorbed. Second, deconjugation of Telepaque-glucuronide by hydrolyzing enzymes in bile. These might be of bacterial or cellular origin.

In contrast to Telepaque, Cholografin, which is used for intravenous cholangiography, is water soluble, poorly absorbed from the GI tract, and is not conjugated prior to biliary excretion.

If a gallbladder fails to visualize with Telepaque, but shows normal visualization by intravenous cholangiography (Cholografin), it is likely that gallbladder absorption of Telepaque is the cause of non-visualization after the oral study. In this instance, a diseased gallbladder might be present even though it appeared normal on the intravenous study. If the gallbladder fails

to visualize with either the oral or IV study, this would suggest cystic duct obstruction, especially if the common duct is visualized on the IVC. However, it is possible that gallbladder absorption of Cholografin might be responsible for failure to visualize the gallbladder on an IV study.

The consecutive dose phenomenon: This is the phenomenon in which a second dose of Telepaque results in excellent visualization of apparently normal gallbladder when the first study shows nonvisualization or poor visualization. The frequency of this is shown by the results of Berk (11):

	Initial Nonvisualization	*Initial Faint Visualization*
No improvement	75%	20%
Moderate improvement	10%	30%
Marked improvement	15%	50%

Berk restudied 38 patients with the consecutive dose phenomenon 1-4 years later and showed that 33 (86%) had initial good opacification. Two of these had gallstones which had not been present earlier. A second dose of Telepaque in the other 5 patients again resulted in the consecutive dose phenomenon. Hence the phenomenon is not reproducible in the majority of cases.

The cause of poor visualization one day and good visualization the next is not known. Technical problems with the first study including stasis of the gallbladder are probably responsible in some instances. At present, it seems best to conclude that such patients probably have normal gallbladders.

The Fate of the Nonvisualized Gallbladder:

If the gallbladder does not visualize after a single oral study, Berk's data indicate that in 75% of patients it will remain nonvisualized on a repeat study.

Achkar et al. (12) did intravenous cholangiograms on 11 patients with nonvisualization of the gallbladder after one or two oral studies. Their results were as follows:

Stones seen in the gallbladder	3
Normal common bile duct but no gallbladder visualization*	4
Faint visualization of the gallbladder	2
Normal appearing gallbladder	2

* This is highly suggestive of cystic duct obstruction by stone, edema, tumor or stricture, or previous cholecystectomy

Visualization of the biliary tract after IV Cholografin depends upon liver function. If the serum bilirubin is 1 or less, visualization occurs in 92.5%

of injections. If the level is 4, visualization occurs in only 9.3% of injections (13). In some patients who visualize poorly with the routine test, slow infusion of twice the usual dose of Cholografin may result in visualization (20).

Conclusions:

Most workers agree that initial nonvisualization or faint visualization should be repeated on the following day. The second dose should be the same as the first, not a double dose. A large dose throws an additional unnecessary burden on the excretory mechanism without enhancing gallbladder or bile duct visualization (14). Care should be taken to avoid the technical causes of nonvisualization.

If an IVC is done for nonvisualization after an oral study, only 12% of the results will be considered normal according to Wise (13), who studied 201 patients. However, Wise studied patients by IVC after only one oral study had failed to visualize. If he studied patients by IVC only after two oral studies failed to visualize, the percentage of "normal" gallbladders by IVC might be even less.

If a patient fails to visualize on two oral studies, but has a "normal" IVC, there is no proof that this patient actually has a normal gallbladder. He may have a damaged mucosa which preferentially absorbs the Telepaque or he may have hydrolyzing enzymes in his bile (presumably because of infection or inflammation) capable of deconjugating Telepaque-glucuronide.

The main value of IVC after nonvisualization on two oral studies would be that definite stones will be observed in some cases and the status of the common duct may be evaluated.

The Common Bile Duct:

These may be visualized on oral cholecystography after the fatty meal or with intravenous cholangiography. The cystic duct has a characteristic corkscrew appearance (spiral valve of Heister) with an average diameter of 2 to 3 mm. The caliber of the normal hepatic and common dile ducts is 0.5 to 0.6 cm. The intramural portion of the common bile duct is 1-2 mm in diameter. The ducts are equidistant from the anterior and posterior abdominal wall. A 10% magnification occurs in either an AP or PA projection. Contrary to previous belief, there is no dilatation of the bile ducts in response to cholecystectomy.

4-Day Telepaque Test:

Nonopaque stones may in some instances be rendered opaque by chronic exposure to Telepaque. The drug is incorporated into the rim of the stone, causing it to become radiopaque (15). This is probably the best test available for demonstrating bile duct stones in the jaundiced patient, where IVC usually fails.

One gram of Telepaque (2 tablets) is ingested t.i.d. for 4 days. A low fat diet is eaten during the study, hoping to avoid biliary colic. A high

fluid intake is encouraged in order to improve renal clearance of Telepaque. The x-ray is made on the morning of the fifth day with the patient fasting.

Significant renal disease and a bilirubin greater than 5 are contraindications. The test may cause diarrhea.

The test is apparently safe, no renal toxicity having been reported when Telepaque is the contrast medium (15). It will usually fail to work when the bilirubin is greater than 5, presumably due to reduced biliary excretion.

Ten of 13 patients with pathologically proven bile duct stones showed opacifying stones in their bile ducts. Intrahepatic duct stones may also be visualized. Only 12% of gallbladder stones are opacified by this method. In occasional cases it may visualize the gallbladder when routine oral cholecystography fails to do so.

The Accuracy of Cholecystography:

Oral cholecystography is generally considered to be an extremely accurate radiological method. The following table is from a paper by Baker and Hodgson (16):

Diagnosis, 1957	No. of Cases	Findings at Operation: Gallstones	Tumors	Chronic Cholecystitis: Slight Thickening	Chronic Cholecystitis: Moderate Thickening, Subacute	Chronic Cholecystitis: Marked Thickening, Acute	Miscellaneous	Normal	Diagnosis Confirmed at Operation (per cent)
Gallbladder									
Normally functioning	353	3	..	2	1	..	..	347	98.3
Poorly functioning	3	1	..	2	..	..	..	..	100.0
Nonfunctioning	229	188	6	3	2	4	21	5	97.8
Normally functioning with stones (474) / Poorly functioning with stones (37) / Nonfunctioning with stones (100)	611	599	6	1	..	..	..	5	98.0
Tumors	11	..	11	.	.	.	..	..	100.0
TOTALS	1207	791	23	8	3	4	21	357	..

Cases with positive cholecystographic data, 854; errors, 17 (98.0 per cent correct). Of 1,207 diagnoses, 1,184 (98.1 per cent) confirmed.

Cases with gallstones at operation, 791; positive cholecystographic data in 788 (99.6 per cent). Gallstones were visualized and reported in 599 (75.7 per cent) of the 791 cases.

Cases with disease of gallbladder at operation, 850; positive cholecystographic data in 844 (99.3 per cent).

Cases without disease of gallbladder at operation, 357; negative data in 347 (97.2 per cent).

Causes of Error in Various Categories:

Normal function: This diagnosis is probably erroneous more than any other. Some errors are unavoidable because certain diseased gallbladders without stones maintain their function sufficient to produce a normal shadow, or they may contain minute calculi undetectable by present methods. Poor quality films, gas and fecal shadows, and stones located high in the gallbladder near the cystic duct are other causes of error.

Data like those shown in the previous table suggest that less than 2% of patients with "normal" cholecystograms have gallstones (16,17,8).

However, as Farrar has emphasized (18), no truly valid figures can be derived for the following reasons: (a) the skill of radiologists differ, (b) if the clinician has confidence in the accuray of the report of normal gallbladder, an operation is not performed ("a convincing radiologist creates his own good statistics"). There is no doubt that gallstones are missed--how often is not known.

False-negative cholecystography has also recently been stressed by Kolodny et al. (19). Three patients with symptomatic biliary calculi and normal oral and IV cholangiograms were reported. The normal x-ray reports resulted in delayed therapy.

Poor or faint visualization or "poor function": This is clearly an unsatisfactory designation, but most of such gallbladders have pathologic abnormalities. With newer contrast materials, the frequency of this diagnosis has dropped markedly in recent years.

Nonfunction: Only 5 out of 229 (2%) of "nonfunctioning" gallbladders were found to be normal at surgery (although a few had relatively minor pathology). In the patients reported in the previous table, it is not clear that all of this group had two studies before a diagnosis of "nonfunction" was reached. If they did not all have two studies, perhaps even less than 2% would have been found to be normal at surgery.

GALLBLADDER DISEASE (?) WITHOUT STONES

In the United States today the only universally accepted cause for biliary tract pain is gallstones. "Biliary dyskinesia" is no longer an accepted disorder. A patient with undiagnosed abdominal pain suggestive of biliary tract disease, but with a normal cholangiogram, is generally considered to have psychosomatic disease. The question is, has the pendulum moved too far toward underdiagnosis of biliary tract disorders.

There are a number of marginal disease entities, and the question of physiologic disorders of the biliary tract needs to be reconsidered.

(1) *Mild cholecystitis*

There is no doubt that severe acute cholecystitis, even progressing to frank gangrene and perforation, can occur in the absence of gallstones. The etiology in individual cases may vary: cystic duct obstruction from fibrosis, kinks, etc., infarction, reflux of pancreatic fluid (?), or primary bacterial invasion (typhoid, for example) are possibilities. However, the frequency of definite acute and chronic cholecystitis without stones is rare (7 out of 541 cases in Munster and Brown's series [21]).

Most workers believe that when minimal evidence of mild chronic cholecystitis is the only pathologic finding, the patient's symptoms often are not relieved by the cholecystectomy (21-23).

(2) *The cystic duct syndrome*

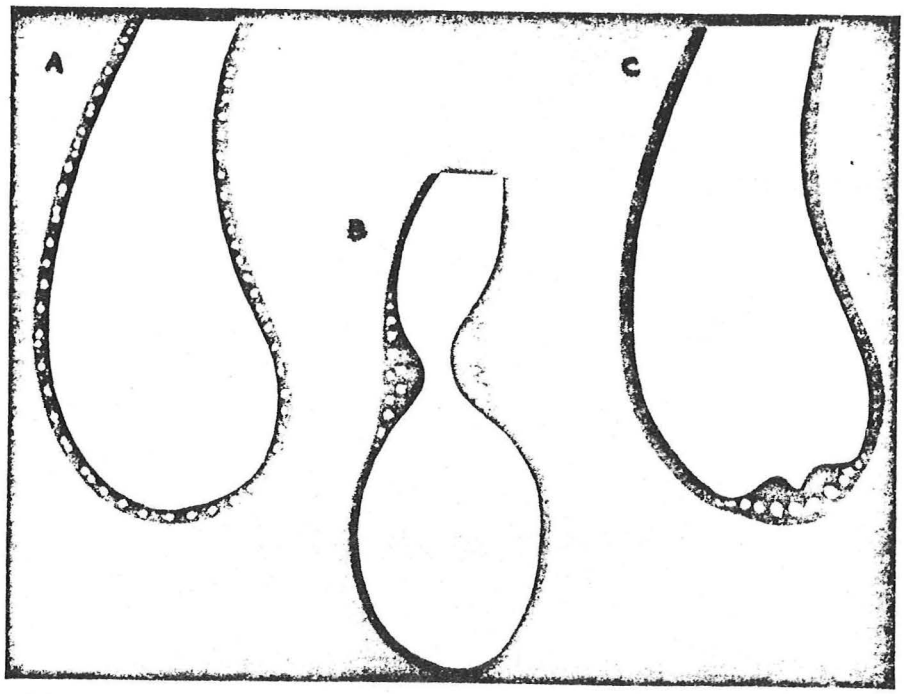
Cozzolino et al. reported 7 patients (all women) with postprandial abdominal pain in the RUQ "suggestive of biliary colic" (30). Their routine studies,

including cholangiograms, were normal. However, using cholecystokinin as a gallbladder stimulant, the authors claim to have demonstrated impaired gallbladder evacuation due to partial cystic duct obstruction in each case. Pain was reproduced by the CCK. Cholecystectomy was performed in all patients, followed by lasting relief (10 month to 3 year follow-up). They showed histologic data in one patient which convincingly suggests fibrotic stenosis at the proximal cystic duct. Five of the patients were said to have cystic duct obstruction due to adhesions and kinking.

(3) *Adenomya and Adenomyomatosis of the Gallbladder*

Adenomyomatosis refers to a hyperplasia of the gallbladder wall characterized by excessive proliferation of the surface epithelium and thickening of the muscle layer. When the process is well established, the mucosal folds are increased in number and height and project into or through the muscularis as tubules, crypts and saccules. These outpouchings are called intramural diverticula or Rokitansky-Aschoff sinuses. The hyperplasia of the muscularis may be so pronounced as to present the appearance of a myoma. Epithelial and muscular hyperplasia may involve the whole viscus or only part of it, and consequently three main forms may be recognized: generalized, segmental and localized. The name adenomyoma is a misnomer; it continues to be used in reference to a localized form of adenomyomatosis.

The radiographic pattern of adenomyomatotis may be found in references 24 and 26. A diagrammatic illustration of some of the x-ray changes are shown in the next figure:



Diagrams of types of adenomyomatosis: *A*, generalized type; *B*, segmental type; *C*, localized type (fundic adenomyoma).

Adenomyomatosis is more common in women than in men (3:1) and the incidence increases with age, especially after age 32 (24). There is general agreement that the risks of malignant degeneration is very low, though one case has been reported (31).

The clinical significance and management of this condition continue to provoke controversy. Because of the frequency with which some degree of adenomyomatosis may be found in prospective necropsy surveys, as high as 7% in some series (31), it is clear that in most instances the lesion does not produce symptoms. Therefore, in the absence of gallstones, many find it difficult to accept that symptoms may arise from adenomyomatosis, especially since gallbladder function as gauged by cholangiogram is usually normal.

However, Bevan (31) has recently reported 6 patients with acalculous adenomyomatosis of the gallbladder and biliary type pain that had been present from 2 to 20 years. All except 1 had x-rays suggestive of adenomyomatosis. The other had a nonfunctioning gallbladder. All 6 of the patients received relief of their pain after cholecystectomy. None of the gallbladders had stones or inflammatory changes. The author believes that acalculous adenomyomatosis can produce pain, probably because of excessive neuromuscular activity of the hyperplastic gallbladder. This mechanism of pain has been proposed by others, also (24).

One problem is that the "disease" is much more common pathologically than radiographically. For instance, 50% of patients submitted to surgery because of gallstones have associated but unsuspected R.A. sinuses microscopically and 12% have localized adenomyomatosis (27). These results are shown in the table on page 14. A negative x-ray does not, therefore, rule out adenomyomatosis, which if present might be the cause of pain.

(4) *Cholesterolosis (Strawberry Gallbladder)*

This is characterized by abnormal deposits of cholesterol esters in fat-laden macrophages situated in the lamina propria of the gallbladder. The lesion may be diffuse or localized (27). Diffuse involvement is generally associated with good function of the gallbladder, and since it presents no diagnostic radiologic features, it is infrequently diagnosed by cholecystography. The localized form consists of single or multiple polypoid lesions which may be sessile or pedunculated, and on x-ray these appear as fixed filling defects. The gallbladders characteristically visualized well on oral cholecystography. When gallstones are not present, the gallbladder often has soft walls and on microscopic examination there is no evidence of inflammation. A fine-to-coarse yellowish speckled marking, often diffuse but at times circumscribed, appears on the level of the mucous membrane folds. This gives a strawberry appearance. However, inflammation, cholesterol concretions and polyps may also occur.

Histologically, the cholesterol is in the form of esters (partly in crystal form) in the foam-like cells of the submucous connective tissue.

Gallstones are said to be present in about 70% of cases and this has been used as evidence that the stones form secondary to the cholesterolosis (28). The cause of the deposits is unknown, although many have attributed the disease to excess cholesterol absorption across the gallbladder mucosa.

Strawberry gallbladders are frequently found in stone-free gallbladders removed because the patient complained of unbearable pain (28).

The following data are taken from the paper by Salmenkivi (32):

269 Cases Cholesterosis Without Stones

Diffuse	83%
Polyps	8%
Both	9%
Symptoms > 2 years	73%
>10 years	20%
Abdominal pain	96%
Abdominal tenderness	66%
Complete relief by surgery	69%
Partial relief by surgery	19%
No relief by surgery	12%

Autopsy Incidence of Cholesterosis Without Stones in Different Series

# Cases	% Cholesterosis
100	11
633	35
612	32
1000	34
2492	5
3446	7
550	15
1319	11

Other Possible Causes of Biliary Pain (24-28): Neuromatosis, Elastosis, Dilated Luschka Ducts:

These are even less well characterized pathophysiologically than cholesterosis and adenomyomatosis.

Frequency of Adenomyomatosis, Cholesterolosis, etc., in Surgically Resected Gallbladders:

Lubera, et al. (27) carefully studied 100 gallbladders removed surgically, looking especially for cholesterosis, adenomyomatosis and related disorders. Their major findings are shown in the next two tables:

Pathology Findings in 100 Consecutive Cholecystectomy Specimens

Cholesterolosis	23	Neuromatosis	3
Diffuse	17	Superficial	2
Polypoid	3	Deep	1
Diffuse and polypoid	3	Elastosis	17
		Cholelithiasis (only)	32
Adenomyomatosis		Cholecystitis and cholelithiasis	58
Generalized	0	Miscellaneous	
Segmental	0	Inflammatory polyps	3
Localized	12	Adenomatous polyps	3
R-A sinuses (micro only)	50	Normal gallbladders	2

Relationships Between Various Pathologic Entities

	Cholesterolosis	Adenomyomatosis	Neuromatosis	Elastosis	Gallstones
Cholesterolosis (23)	-	4	2	3	17
Adenomyomatosis (12)	4	-	1	6	9
Neuromatosis (3)	2	1	-	1	3
Elastosis (17)	3	5	1	-	15

It should be noted that 2 of these 100 gallbladders were entirely normal, although lesions had been seen on cholecystography.

More than one pathologic abnormality was noted in many gallbladders. Gallstones were present in 90 of 100 cases.

Diffuse cholesterolosis was not diagnosed by x-ray in any of the 17 cases. Four out of 6 cases of the polypoid variety were correctly diagnosed by x-ray. Three of the 12 localized adenomyomas were correctly diagnosed by x-ray, and 4 of those missed were very small.

These data indicate the high frequency of cholesterolosis, adenomyomatosis, neuromatosis and elastosis in specimens removed surgically for treatment of what was apparently symptoms of gallstones. Unfortunately, the incidence of these entities in asymptomatic young subjects without stones or cholecystitis is not known.

Recent Clinical Studies in Patients with "Biliary Pain" in Absence of Gallstones:

1) Valberg et al. (29)

13 patients, all women, ages 21-47, with typical attacks of biliary pain according to references 1 and 2. No jaundice, fever or leucocytosis, and normal liver tests.

In all 13 patients injection of CCK (cholecystokinin) produced typical attacks of pain. None of 30 control subjects developed a similar attack.

In 12 the pain was so persistent and incapacitating that cholecystectomy was carried out. The gallbladder felt and looked normal. Histologically, the gallbladder was completely normal in 4, 4 had cholesterolosis, 3 had adenomyomatosis, and 1 showed mild chronic inflammation.

The patients were followed from 3 to 44 months. All obtained complete relief of biliary pain and vomiting.

In 2 of the patients, CCK was administered again following recovery from the operation. There was no reproduction of pain.

Authors' conclusion: Gallbladder was source of the pain, mechanism not known. They doubt the importance of the histologic findings, are more inclined to disturbed motor activity of the gallbladder.

2) Nathan, et al. studied a large group of patients with a history suggestive of gallbladder disease but normal oral cholecystograms. He also studied 50 normal controls. The interpretation of the results was not "blind".

Reproduction of pain by CCK and/or abnormal gallbladder contractions and spasms were used as indications of biliary tract disease. Apparently, no "abnormalities" were observed in the 50 normal control subjects. The results in the patients are summarized in the next two tables:

Review of Findings in 117 Patients Studied by Cholecystokinin Cholecystography

Patients with positive findings who underwent surgery	49
Proved positive by microscopy	47
Proved negative, 1 by microscopy and 1 by surgical inspection (False-positive; explored for other than biliary pathology)	2
Patients with negative findings who underwent surgery	5
Proved negative, 1 by microscopy and 1 by surgical inspection	2
Proved positive by microscopy (False-negative; explored despite negative CCK-GB)	3

Follow-Up 2 to 36 Months After Surgery in Patients With Positive Preoperative CCK-GB*

No. of patients in study	36
No. interviewed	35
No. enthusiastic about postoperative results	21
No. very happy with results	5
No. improved and glad for surgery but with some vague complaints	8
No. with poor results and patient unhappy about surgery	1

* Patients included in survey study are those who had cholecystectomy at time of surgery. Each patient was reached by telephone, and the results are based only on the patient responses.

In the gallbladders referred to as "positive by microscopy", this means that they had "chronic cholecystitis". In addition, adhesions about the gallbladder and ducts were frequent.

In interpreting the results of CCK cholecystography, Nathan et al. stress that to be significant, decreased or excessive emptying of the gallbladder must be accompanied by one of the following:

a) change in gallbladder shape
b) spasm of the gallbladder fundus, body or neck
c) dilatation of the common bile duct
d) reduplication of symptoms, particularly RUQ pain

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