1948

Etiology of cholecystitis

John H. Aga
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

ETIOLOGY OF CHOLECYSTITIS

BY

JOHN H. AGA

SENIOR THESIS

PRESENTED TO

THE COLLEGE OF MEDICINE

UNIVERSITY OF NEBRASKA

OMAHA

1948

The etiology of cholecystitis is a much debated subject; and in spite of extensive clinical observation and experimental investigation, there is no unanimity of opinion regarding causation or mechanism of production. The purpose of this paper is to present some of the more commonly accepted etiological factors producing cholecystitis.

Classification and pathologic description

Rolleston (1) gives the following classification of cholecystitis according to the various degrees of intensity of the inflammatory process.

1. Acute cholecystitis
   a. Catarrhal
   b. Suppurative
   c. Phlegmonous
   d. Gangrenous
2. Chronic cholecystitis

Catarrhal--An acute inflammation which stops short of suppuration. There may be no evident gross changes, but microspopic examination will show lymphocytic and leukocytic infiltration of the mucosa.

Suppurative--Inflammation of the walls of the gall-bladder gives rise to accumulation of pus in its cavity and may go on to ulceration and perforation. The mucous membrane is largely destroyed. The free surface shows

granulation tissue and is shaggy and red. Micro-
scopically, small-cell infiltration of the walls is
evident. The peritoneal surface is inflamed, dark
red or greenish-black. Fibrous adhesions may be pre-
sent.

Phlegmonous--This is a very acute infective form
and differs only in degree from the acute suppurative
form. It passes into the gangrenous form from which
it can hardly be separated. Grossly, the gall bladder
is purplish in color, edematous and inflamed. The
walls are swollen, friable and infiltrated with pus
and blood. The mucous membrane is swollen and may be
ulcerated, necrosed or separated in flakes from the
underlying tissue.

Gangrenous--This form is the result of phlegmonous
inflammation. The morbid anatomy is the same as in
phlegmonous with the addition of gangrene of the wall
of the gallbladder.

Chronic Cholecystitis may follow acute and is
often associated with gallstones. In other cases it is
chronic from the first. Grossly, the gall bladder is
usually distended with mucus. The walls are thick and
thrown into folds. Calculi may be present and adhesions
to other organs may be evident. Microspopic examina-
tion shows fibrosis and increased muscle tissue, between

which there may be edema and small-cell infiltration.

<u>Pathologic states</u>

Denton (2) believes the terms acute, subacute
and chronic cholecystitis are undesirable because they
carry the implication of infectious origin and cannot
be correlated with clinical conditions. Other factors
than bacterial infection are necessary for an explana-
tion of some of the commonly observed lesions of the
gallbladder. Pathologic states of the gallbladder
should be described in morphologic terms as edema,edema
and hemorrhage, hematoma, partial infarction, complete
infarction, edematous cicatrix, and cicatrix.

Feinblatt (3) also supports this morphologic
description. Intramural edema and venous distention
are produced by a large stone in the cystic duct which
closes off the veins and lymphatics before the artery.
If the stone is large enough intramural hemorrhage or
a condition analagous to infarction results. Organi-
zation of hemorrhage was observed to start soon and to
proceed rapidly at first. The most violent lesions
observed resulted in a condition which has many features
in common with hemorrhagic infarction. The gallbladder
was dark red to almost black and very friable. Intra-
mural edema and hematoma tend to be replaced by layers
of scar tissue of different ages. Extensive thickening

of the walls can result. Graham and Mackey (4) class-
ify the most frequently occurring chronic pathologic
conditions as: minimal lesion, chronic catarrhal
cholecystitis, chronic fibrous cholecystitis and
cholesterosis.

Judd and Phillips (5) found that in acute and
subacute cholecystitis, one of the outstanding features
from a microscopical standpoint was the presence of
edema of the wall of the gallbladder. The interstices
of the tissue were filled with fluid and the walls
infiltrated with leucocytes. In subacute cholecystitis,
there was a relative decrease of the proportion of
polymorphonuclear neutrophiles and replacement of them
by lymphocytes and plasma cells. Chronic cholecystitis
showed excess fibrous tissue in the walls of the gall-
bladder and unusual trabeculation macroscopically.

Etiologic Factors

Infection

According to Rehfuss (6), those believing infection
to be the leading factor in the etiology of cholecystitis
base their contention on the following:

1. The demonstration of infection at operation
   and isolation of certain bacterial strains
   from these cases.

2. Production of experimental cholecystitis
   by injection of certain of these strains.

3. Fullfillment of Koch's postulates in at
   least a limited number of cases in which
   the same organism produced identical
   pathology and was recovered from several
   generations of laboratory animals.

4. The similarity of lesions produced in
   animals to those occurring in the human.

5. That such strains are frequently found
   in aberrant foci in individuals suffer-
   ing from biliary tract disease.

The common presence of streptococci in the wall
of the infected gallbladder and in the center of gall-
stones, often in pure culture, while absent from the
bile, and their affinity for the gallbladder in ani-
mals are strong evidence that streptococci are the
cause of the cholecystitis in man far more frequently
than believed. (7).

Judd, Nickel and Wellbrock (8) reported positive
cultures from bile alone in only 14% of cases of
chronic cholecystitic disease and observed that thin,
grainy, blood-tinged bile is more likely to yield a
growth of micro-organisms than the thick greenish-black
bile so commonly seen in association with stones. In
cases of chronic cholecystitis with stones a positive

culture was obtained from the stones in 31% of the cases and from the walls in 39% of the cases. In acute cholecystitis there was a higher incidence, 68% positive cultures, from all sources. Common organisms found were green-producing streptococci. Intravenous injection of the organisms into animals infected the bile of the gallbladder in about 75% of the cases. The colon bacillus was commonly found in association and was frequently cultured in patients who had empyema of the gallbladder.

Branch (9) studied 210 gallbladders surgically removed at Massachusetts General Hospital and obtained positive cultures from the wall in approximately 25% and 20% from bile alone. The colon bacillus was the most common organism found, varous types of staphylococci ranked second, and streptococci came third. Typhoid organism were rare. He observed that if the concentration of the bile salts in the gallbladder was 70%of normal, or more, there was no growth of organisms in the bile, and below this the bacterial growth showed inverse relation to the concentration of the bile salt. He concluded that primary infection of the contents of the gallbladder was not likely unless the bile was thinned by exudates or unless the concentration of bile salts was lowered.

Nickel and Judd (10) in a series of 300 surgically resected gallbladders found that 11% of the strawberry gallbladders and the majority of all chronic cholecystic cases were sterile unless complication factors were present. The majority of acute or subacute cholecystitis cases contain pathogenic bacteria which according to frequency are the green-producing streptococci, gram negative bacilli and staphylococci. Streptococci isolated from grossly diseased gallbladders are of etiologic importance since they tend to reproduce cholecystitis and cholelithiasis in experimental rabbits when injected intravenously.

Hutcheson and Magner (11) concluded that chronic cholecystitis of man is probably attributable, in most instances, to a streptococcal, intramural infection of the gallbladder, a conclusion which they confirmed by reproduction of cholecystitis on injection of organisms under the serous coat of the gallbladder of the rabbit.

Rehfuss (6) states that practically every form of cholecystitis seen in the human subject has been observed in the experimental cholecystitis induced by injection of bacteria. By alteration of technic and

more frequent innoculations over longer periods, he
has been able to increase the incidence of experiment-
al cholecystitis from 22% in the initial series to 68%
during the past 10 years of experimentation, and has
observed the effect of a single antigen, the non-hem-
olytic streptococcus, in nearly 700 animals. Any or
all of the layers of the gallbladder wall can be af-
fected in bacterial cholecystitis, the mucosa and
subserosa being most vulnerable and the muscularis
least so, as is true with human cholecystitis.
Cholecystitis may be an acute process but is more likely
to be due to mild repeated infection, acting slowly
upon different parts of the gallbladder. That such
changes may bring about or favor undue concentration
of certain elements of bile, or produce a pancreatic
reflux is not improbable, and it is possible that
bacterial sensitization may enact a role.

Fallis and McClure (12) obtained negative cul-
tures in nearly one-half of the gallbladders cultured
in their series. In the positive cultures, 25% were
B. coli, 11.5% staphylococci, and 11.5% streptococci.
Other orgamisms cultured were B. aerogenes, B. typhosus,
B. dysenterica, B. influenza, and yeast cells.
B. anthracis, B. pyocaneus, and B. perfringens have

also been reported in cases of Cholecystitis (13-14).

Lipshutz and Kaplan (15) reported 3 cases of colon bacillus septicemia associated with acute cholecystitis and in reviewing the literature found only 30 such cases reported. Graef and Sturtevant (16) reported a case of acute cholecystitis due to bacillus aerogenes-capsulatus along with 9 cases from the literature.

In a recent study, Lester (17) found that 20% of the acutely inflamed gallbladders were gangrenous. The gangrenous gallbladders had a higher incidence (59% compared to 28%) of positive bile cultures than non-gangrenous, but the proportion of B.coli organisms was approximately the same (69% versus 63%). Thus B. coli may be a secondary invader in the lumen of an inflamed gallbladder. Alvarez and collaborators (18) found living bacteria in the walls of 57% of the noncalculous gallbladders examined and in 82% of the calculous.

Andrews (19) in a study of 116 surgically excised gallbladders,55 of which were sectioned serially at intervals of 2 cm., found that there was a total lack of the proper correlation between the pathologic classification of these cases and the clinical and bacterial findings. The severely inflamed gallbladder

contains about the same flora as the normal or
quiescent one and is very often sterile. He con-
cluded that bacteria play but a minor role in the
production of primary injury of the gallbladder,
that the organisms found often are secondary invaders,
and that cholecystitis of purely infectious origin
probably is produced only with difficulty without
the additional factors of trauma and stasis. He
noted that the mere introduction of a sterile needle
into the gallbladder of a dog frequently would set up
as severe an infection as that which follows the
direct innoculation of bacteria.

Feinblatt (3) states that histopathologic study
of gallbladders removed at operation leads him to
believe that the role of infection in the causation
of cholecystitis has been greatly overestimated, while
the importance of metabolic and mechanical factors
has not received due consideration.

Aronsohn and Andrews (20) demonstrated that
most strains of bacteria even when injected in over-
whelming numbers do not cause cholecystitis, while
if trauma is added, these same strains do cause
cholecystitis.

Routes of Infection

The gallbladder itself conceivably can become infected in one of five ways (21).

1. Extension from an inflamed viscus.

2. Ascension through the common and cystic ducts.

3. Extension by way of the portal vein to the liver, infection being carried to the gallbladder by the hepatic lymphatic channels.

4. Conveyance through other, adjacent lymphatic structures and through the venous blood supply of the gallbladder itself,

5. By way of the hepatic artery.

Direct extension from an inflammatory process in an adjacent viscus is exceedingly rare in the production of cholecystic disease. Perforated duodenal ulcer and purulent collections in the subhepatic area may occasionally involve the gall-bladder and set up secondary inflammatory changes (21, 22).

The ascending (cholagenous) route is also a rare pathway of infection. The duodemun is usually sterile except in patients with achylia gastrica,

and the normal activity of the sphincter of Oddi
serves as a natural barrier (21,22). Introduction
of organisms into the gallbladder by means of a
retrograde catheter through an opening in the common
duct (non-traumatizing technic) has failed to pro-
duce any significant degree of cholecystitis in spite
of the use of a large number of virulent organisms (20).

Hurst (23) in his study of cholecystitis due to
the colon bacillus supports the possibility of ascend-
ing infection from the duodenum. Achlorhydria in-
creased the alkalinity of the contents of the small
intestine producing favorable culture for B. coli
which ascends from its normal habitat in the lower
ileum.

Graham and Peterman (24,25) in their observa-
tions support the theory of lymphatic origin of
cholecystitis. They found that in many cases, pro-
bably a majority, cholecystitis represented a direct
extension to the wall of the gallbladder from a
liver already inflamed. The hepatitis usually begins
and is most marked in the interlobular, or periportal,
tissue. It is apparently due to infection brought
to the liver by the portal vein and, more rarely per-
haps, by the hepatic artery. A pericholangitis then

occurs, and because of intimate anastomosis between
the lymphatics of the intrahepatic and extrahepatic
biliary system, a direct extension into the wall of
the gallbladder results.

Nichols (25) investigated the production of
gallbladder lesions in typhoid by descending infection
of the bile from the liver with the common duct fistula
method in the rabbit. In cholera and dysentery the
same mechanism is suggested with the additional factor
of a portal system septicemia. After the appearance
of micro-organisms in rabbit bile, their fate is ap-
parently largely determined by the antiseptic pro-
perties of the bile which are due largely to its
alkalinity.

Mentzer (27) in his series of cases of diseased
gallbladders found a high incidence of associated
disease in the appendix, stomach or duodenum. The
diseased gallbladders were accompanied by disease in
the appendix in 68% of the cases, and gastric or
duodenal ulcers were found in 29% of the cases. In-
flammatory changes in the liver were more frequent in
cases of inflammatory disease in the gallbladder
(stones) than in cases of non-inflammatory disease
(cholesterosis).

Moynihan (28) states that inflammation of the liver
is secondary to that of the gallbladder, and the
stream of lymphatics is directed from and not towards
the gallbladder. Colp and associates (29) perform-
ed biopsies of the liver in 40 cases of acute and
chronic cholecystitis without jaundice and in 9
cases with jaundice. Studies with finer histologic
technic revealed no changes in the liver cells in
biliary tract disease without jaundice. Focal liver
cell degeneration seen in cases with jaundice repre-
sents a reaction to bile stasis and is in no way re-
lated to the primary disease of the gallbladder.
The periportal infiltrations observed in biliary
tract disease are not specific for the disease, but
represent a reaction of the liver to extrahepatic
infection. Hepatitis is not an accompaniment of
cholecystitis as evidenced by the absence of in-
flammation and parenchymal changes in the liver.

Infection of the gallbladder by way of its other
venous and lymphatic connections would be consider-
ably less likely than lymphatic spread from the liver
but it cannot entirely be excluded (21). Cassity (30)
states that the immediate cause of cholecystitis is
infection with an organism of low virulence, such as
the bacillus typhosus or streptococcus viridans.

The foci of infection is rarely, or perhaps never, primary to the liver or gallbladder. It is probably a lymph-borne infection, and the two most common foci from which infection arises are the Peyer's patches during or following typhoid fever and chronic appendicitis of long standing. Other foci, such as ulcers of the stomach, infected tonsils and teeth, and suppurating conditions about the rectum and colon, may also be the primary cause of this disease.

Hematogenous infection of the gallbladder has been reported by many investigators. Rosenow (7,31) presented the idea of selective affinity of bacteria to certain organs and tissue and tried to establish connection between foci of infection and gallbladder disease. He produced cholecystitis of experimental animals by injection of streptococci derived from teeth and tonsils. Wilkie (32), and Rehfuss and Nelson (6, 33) have added some experimental evidence to support this contention. Burton (34) noted that cholecystitis was not uncommon among patients who were suffering from subacute bacterial endocarditis. Wolfson and Rothenberg (35) believe that acute non-calculus cholecystitis is a distinct etiologic entity

produced by hematogenous infection rather than by obstruction of the cystic duct. Almost one third of the patients gave histories or showed signs of a focal infection which might have served as the primary source of the gallbladder infection.

Stasis of Bile

Mechanical Factors

Anomalies of the gallbladder and adjacent organs may be responsible for biliary stasis. Russell et al. (36) have described several abnormal conditions producing stasis. Congenital adhesions due to abnormal development and persistence of the cystic duodenal fold, or acquired adhesions due to inflammation of adjacent structures as duodenal ulcer or duodenitis may produce stasis. Any origin of the cystic artery that necessitates its crossing the cystic duct to reach the margin of the gallbladder can compress the cystic duct producing stasis of the bile. Tumors of the pancreas and extrahepatic bile ducts not uncommonly produce obstruction. Partial obstruction of the cystic duct due to a "foot valve" action of the valves of Heister results when an elongated cystic duct becomes convoluted to accommodate a shortened cystic artery. A congenital septum inter-

posed at some point in the cavity of the gallbladder, usually the fundus, can produce partial obstruction of the distal cavity. This is probably due to incomplete vacuolization of the cavity.

Kaikini (37) reports several cases of gallbladder disease resulting from uncommon etiologic factors. One case was due to an abnormal branch of the hepatic artery producing partial obstruction; one was the result of a congenital narrow lumen of the cystic and common ducts; and another as the result of ptosis of an elongated and atonic gallbladder with a long and narrow cystic duct. Seelig (38) observed that sharp kinking of the cystic duct at its emergence from the gallbladder opposes a barrier to the bile current and results in more or less stasis of the gallbladder contents. Stasis due to obstruction of the cystic or common duct is most commonly the result of impaction of a gallstone. Barrow and Massie (39) found stones in 92% of the patients in their series of 159 cases of acute cholecystitis associated with obstruction of the cystic duct.

Berk (40) states that approximately one in every ten patients with acute cholecystitis and one in every eight patients with chronic cholecystitis will have a common duct stone or stones.

Physiologic Factors

According to Ivy (41) the physiologic factors concerned in the production of stasis are:

1. Duodenal irritation or inflammation.

2. Reversed peristalsis in the duodenum.

3. Spasm of the sphincter of Oddi, due to nervous reflex disturbance or inflammation of the ampulla of Vater.

4. Motor inactivity of the gallbladder due to too little fat, fruit juices, or meat in the diet.

5. Abnormally small cystic duct requiring greater activity on the part of the gallbladder.

6. Possibility that sphincter may be located at the neck of the gallbladder.

Russell et al. (36) states that hypertonic dyssynergia disturbs the emptying mechanism of the gallbladder by increasing the resistence to the flow of bile through the sphincter of Oddi. The increased tone and hypertrophy at the sphincter of the Oddi may be associated with gastric hyperacidity and its associated duodenitis and papillitis, or the reflex spasm of the sphincter may be stimulated from some distant primary site as a diseased

appendix or the central nervous system. Hypotonic
dyssynergia with decreased contractility of the
gallbladder wall may also interferewith the empty-
ing mechanism. The gallbladder wall is thinned
out and atrophic. The clinical and experimental
investigations of Best and Hicken (42) indicate
that a hypertonicity or dyssynergia of the chole-
dochal sphincter may mechanically interfere with
the evacuation of the gallbladder and bile ducts,
thus producing a stasis of bile with a dilatation
of the biliary radicals.

Kaikini (37) considers biliary stasis as one
of the most common factors in causing damage to the
gallbladder. He believes that in the majority of
the cases this is due to dysfunction of the vagus
nerve or the incoordination between the vagus and
the sympathetic with disorganization of the duo-
denal reflex, resulting in obstruction to the flow
of bile from the gallbladder. The presence of acid
chyme in the duodenum not only causes relaxation of
the sphincter of Oddi but also stimulates evacua-
tion of the gallbladder. When acid is absent (due
to dysfunction of the vagus) and the gallbladder is
lacking in tone, the stimulus may be inadequate to

to produce evacuation which results in disease of the viscus. This is the hypotonic type of gall-bladder. In the hypertonic type, the stimulus may be due to duodenitis, appendicitis, spastic colon, pelvic diseases or pregnancy; and spasm of the sphincter of Oddi occurs followed by stasis of the bile. The stimulation of the vagus is not only caused by the above diseases but also by the habits of the patients, such as irregularity of meals.

Davidson (43) believes that stasis can result from motor inactivity of the gallbladder due to muscular atony or defective stimulation as a result of a diet deficient in fat and protein. Lack of exercise might also be included. In a comparative study of gallbladder disease in white and negro patients, Boland (44) suggests that physiological factors such as idleness, lack of exercise with excessive eating and drinking account for ten times greater incidence in white than colored.

Potter (45) manually examined the gallbladder in 390 cases during the course of Cesarean section and found 75% definitely distended and showing evidence of stasis. He concluded that disorders of cholesterol metabolism together with motor dysfunction

were the forerunners of biliary disease of pregnant
women. Biskind and Pevaroff (46) report that 78%
of the cases among women having cholecystitis
(1916 - 1938, Mt.Sinai Hospital) occurred during the
childbearing period.

Wannamaker (47) believes that gallbladder dis-
ease is closely correlated with dysfunctions of other
organs and probably represents a secondary manifesta-
tion of general systemic conditions.

Alterations of Bile

Aronsohn and Andrews (20) produced changes of
the gallbladder wall of dogs by injection of bile
salts which on gross and microscopic examination
closely resemble those found in human cholecystitis.
The difference in activity of the different fractions
of bile are mainly quantitative in nature. Desoxy-
cholic acid is the most effective fraction, causing
gangrene of the gallbladder and death of the animal
in many instances, while purified and hydrolized bile
salts are somewhat weaker. A quantitative study of
the toxic effect of bile salts was made by replacing
the gallbladder bile in dogs by bile concentrated
previous to the injection. Bile concentrated to
about half its volume proved to have a marked effect.

Intravenous injection of bile salts also caused a marked edema of the gallbladder wall. Changes in the hydrogen-ion concentration of bile rarely bring about a reaction in the gallbladder wall unless they are extreme. Such changes are not likely to arise in man. Chemical examination of 41 human post mortem biles and 13 biles obtained at operation showed that there was no definite correlation between the nitrogen content of bile and changes of the gallbladder wall.

Womack and Bricker (48) produced complete obstruction of the cystic duct in dogs and found no inflammation of the gallbladder wall if the imprisoned bile was replaced with a physiological solution of sodium chloride. By complete obstruction and leaving the bile, inflammation was produced. The severity and type of inflammation was in direct proportion to the content and concentration of bile.

Cole, Novak and Hughes (49) produced partial obstruction of the cystic duct in dogs by three different procedures: turning in a flap of gallbladder wall at the neck of the organ; infolding of the wall at the neck of the gallbladder with mattress sutures; and crushing the cystic duct. The

result in each case was a severe grade chronic
cholecystitis consisting of fibrosis and lympho-
cytic infiltration. If an anomaly is held re-
sponsible for the frequent occurrence of partial
obsturction it is a little difficult to explain
the low incidence of chronic cholecystitis in
children. The factor of time required for inflam-
matory changes to occur may offer a partial explan-
ation. The aging process and obesity may further
accentuate an anomalous mechanism which originally
was insufficient to obstruct the outflow of bile
from the gallbladder.

Reflux of Pancreatic Juice

Wolfer (50) showed that the introduction of
pancreatic juice into the gallbladder of the dog
invariably produced pathologic changes in the wall
of the gallbladder, varying from extensive necrosis
to simple inflammatory reaction. He also showed
that in the dog, when pancreatic juice is conveyed
into the terminal end of the common duct, it can
find its way into the gallbladder. By analogy, he
reasons that in the human, due to a continuous
pathway between the pancreas and bile ducts in a
variable percentage of cases, it is possible for

pancreatic juice to enter the gallbladder and pro-
duce pathologic changes.

Colp, Gerber and Doubilet (51) have reported
3 cases of acute cholecystitis associated with the
presence of pancreatic ferments in gallbladder bile.
They believe that if certain anatomic relationships
exists between the choledochus, duct of Wirsung
and the papilla of Vater, both ducts may be convert-
ed into a single continuous channel by obstruction of
the papilla. This might be caused either by a
calculous, or by edema of the duodenum and papilla,
or by spasm of the sphincter of Oddi. If pancreatic
juice refluxly enters the biliary system, no clinic-
ally recognized sequelae may result. On the other
hand, if the pancreatic ferments are present in
the gallbladder bile in sufficient concentration
and amounts to change its usual acid reaction to
alkaline, the bile salts may act destructively on
the gallbladder wall together with the activated
pancreatic ferments. As a result of the chemical
inflammation caused by these various factors, either
an acute cholecystitis or nonperforative biliary
peritonitis may result.

Bisgard and Baker (52) carried out a series of
experiments on goats. They used these animals be-

cause the reaction of their gallbladder bile differs little from that of human; they normally develop gallstones and cholecystitis with a fair degree of frequency; and the anatomic arrangement of their duct system is adapted to purposes of study. They produced temporary and permanent obstruction both distal and proximal to the pancreatic duct. Temporary bile stasis alone with no pancreatic reflux produced no destructive action on the wall of the gallbladder unless infection supervened. Stasis plus the reflux of pancreatic secretions resulted in cholecystitis. Stasis played the essential and fundamental role but not the active one in production of cholecystitis and stones. The same factor inducing stasis caused reflux of pancreatic juice and in turn, distention of the gallbladder. Thus stasis either activated the pancreatic enzymes or by distending the wall of the gallbladder, rendered it vulnerable to the action of the enzymes and to infection. They concluded that neither stasis of bile nor reflux of pancreatic juice as a single factor was productive of cholecystitis, but when combined, cholecystitis resulted. Thus in man, temporary obstruction of the common duct, resulting

from spasm of the sphincter of Oddi or from reverse
peristalsis in the duodenum, in addition to stones
or other obstructing factors within the common duct
or at the ampulla, may produce cholecystitis.

Allergy

Aronsohn and Andrews (20) showed that it was
possible to produce an allergic condition in the
gallbladder experimentally. Intravenous injection
of egg albumen caused an edema in the gallbladder
wall of previously sensitized dogs, while no re-
action occurred in control animals.

Walzer et al. (53) experimentally demonstrated
that the gallbladder in the Rhesus monkey can be
the seat of an allergic reaction. The reaction was
characterized by edema, hyperemia and increased
mucus secretion. In none of the 7 experimental
animals studied was spasm of the gallbladder a
noticeable feature of the allergic reaction. Histo-
logic studies revealed a marked edematous reaction
with cellular infiltration including an increased
number of eosinophiles. This edematous reaction
was transitory. On the basis of these studies, the
conclusion is warranted that the gallbladder, in
allergic individuals, may be the seat of an allergic

reaction comparable to that observed in the monkey.

De Muro and Ficari (54) also studied allergic
cholecystitis experimentally. They sensitized 20
rabbits by four intravenous injections of 2-3 cc.
of sheep serum. The exciting dose was innoculated
into the cavity of the gallbladder. According to
the different experimental conditions, the animals
were divided into three groups. In the first group,
the cystic duct was ligated before the innoculation
of the exciting dose of serum; in the second group,
a small sterile ball of glass was introduced into
the cavity of the gallbladder; in the third group,
the exciting dose was simply innoculated into the
viscus. To follow the development of the allergic
reaction, the animals were killed at an interval
variable from one hour to seventy-two hours after
the exciting innoculation. An allergic reaction
was demonstrated in the gallbladder wall of the
animals. The pathologic changes were the same, al-
though slightly variable in intensity. The allergic
reaction observed can be divided into two phases:
degenerative-exudative and proliferative. In the
first phase, the degenerative phenomena of the
mucous membrane and muscle fibers were associated

with pathologic changes of the blood vessels,
edema and cellular infiltration, including a
great number of eosiniphiles, spread throughout
the layers of the gallbladder wall. In the se-
cond phase, the proliferative phenomena and the
histiocytic reaction occur. In the controls,
non-sensitized animals, the innoculation of sheep
serum into the gallbladder, the cystic duct having
been previously ligated, did not cause any patho-
logic changes.

Experimental X-ray Cholecystitis

Brams and Darnbacher (55) produced a definite
acute and chronic cholecystitis experimentally in
a series of dogs with dosages of X-rays that were
within the range of those used for therapeutic
purposes. The changes produced were destructive.
They consisted of hemorrhage, inflammatory edema,
round-cell infiltration, fibrous tissue hyper-
plasia, and in some instances, necrosis of the epi-
thelium, and resemble the type of cholecystitis
produced by chemical means. These investigators
believe that the gallbladder epithelium is compar-
atively more sensitive to roentgen-ray exposure
than the other organs in apposition to it.

Summary and Conclusions

The foregoing discussion has brought out evidence suggesting the possibility of several factors in the consideration of the etiology of cholecystitis. Infection, stasis and alteration of bile, reflux of pancreatic juice, and sensitization are the main theories proposed. Experimental investigation and clinical observation lend some support to all of these theories.

Infection has been supported by the isolation of organisms from surgically removed gallbladders, and the production of experimental cholecystitis by injection of certain of these strains. The lesions produced in animals are similar to those in the human, and these strains are frequently found in aberrant foci in individuals suffering from biliary tract disease.

Stasis and alteration of bile have received support because of the known changes which occur in the composition of bile and the experimental effect of altering the bile in the gallbladder.

An occasional case of cholecystitis may be explained by the reflux of pancreatic juice or sensitization. These factors have received some

support by experimental investigation, but they should not be considered as causative factors in the majority of cases of cholecystitis.

The general opinion seems to be that stasis of bile plays the fundimental role with infection as a secondary factor.

Bibliography

1. Rolleston, H. and McNee, J. W. : Diseases of the liver, gallbladder and bile ducts. Third edition. London, Macmillan & Co., 1929. pp. 658-687.

2. Denton, J. : The mode of origin of gallbladder lesions, Arch. Surg. 14: 1-13, 1927.

3. Feinblatt, H. M. : The infrequency of primary infection in gallbladder disease; study of 400 gallbladders removed at operation, New England J. Med. 199: 1073-1078, 1928.

4. Graham, E. A. and Mackey, W. A. : a consideration of the stoneless gallbladder, J.A.M.A. 103: 1497-1499, 1934.

5. Judd, E. S. and Phillips, J. R. : Acute Cholecystic disease, Ann. Surg. 98: 771-779, 1933.

6. Rehfuss, M. E. : Etiology of cholecystitis, Gastroenterology 7: 665-684, 1946.

7. Rosenow, E. C. : Bacteriology of cholecystitis and its production by injection of streptococci, J.A.M.A. 63: 1835-1836, 1914.

8. Judd, E. S. ; Nickel, A. C. and Wellbrock, W. L. A. : The association of the liver in diseases of the biliary tract, Surg., Gynec. and Obst. 54: 13-16, 1932.

9. Branch, C. F. : A bacteriological study of a group of diseased gallbladders, New England J. Med. 201: 308-312, 1929.

10. Nickel, A. C.,and Judd, E. S. : Cholecystitis: a bacteriologic study of 300 surgically resect-gallbladders, Surg., Gynec. and Obst. 50: 655-662, 1930.

11. Magner, W. and Hutcheson, J. M. : Cholecystitis: a bacteriological and experimental study, Canad. M.A.J. 27: 469-477, 1932.

12. Fallis, L. S. and McClure, R. D. : Acute cholecystitis; a review of 320 cases, Surg., Gynec. and Obst. 70: 1022-1028, 1940.

13. Sherrington, C. S. : Experiments on the escape of bacteria with the secretions, J. Path. and Bact. 1: 258-278, 1893.

14. Schmidt, E. A. : Emphysematous cholecystitis and pericholecystitis, Rad. 31: 423-427, 1938.

15. Lipshutz, B. and Kaplan, L. : Colon bacillus septicemia associated with acute cholecystitis, Surg. 10: 730-741, 1941.

16. Graef, I. and Sturtevant, M. : Cholecystitis due to bacillus aerogenes-capsulatus, Arch. Surg. 28: 771-781, 1934.

17. Lester, L. J. : Acute Cholecystitis, Surg. 21: 675-682, 1947.

18. Alvarez, W. C. I.; Meyer, K. F. ; Rusk, G. Y.; Taylor, F. B. and Eaton, J. : Present day problems in regard to gallbladder infection, J.A.M.A. 81: 974-980, 1923.

19. Andrews, E. : Pathologic changes of diseased gallbladders, Arch. Surg. 31: 767-793, 1931.

20. Aronsohn, H. G. and Andrews, E. : Experimental cholecystitis, Surg., Gynec. and Obst. 66: 748-768, 1938.

21. Walters, W. and Snell, A. M. : Diseases of the gallbladder and bile ducts. Philadelphia, W. B. Saunders Co., 1940. Chap. IV.

22. Bockus, H. L. : Gastro-Enterology. Vol.III. Philadelphia, W. B. Saunders Co., 1946. Chap. CI.

23. Hurst, A. F. : B. Coli cholecystitis, Guy's Hosp. Rep. 89: 470-481, 1939.

24. Peterman, M. G. ; Priest, W. S. and Graham, E. A. : The association of hepatitis with experimental cholecystitis and its bearing on the pathogenesis of cholecystitis in the human, Arch. Surg. 2: 92-115, 1921.

25. Graham, E. A. and Peterman, M. G. : Further
    observations on lymphatic origin of chole-
    cystitis, choledochitis and associated pan-
    creatitis, Arch. Surg. 4: 23-50, 1922.

26. Nichols, H. J. : Experimental observations
    on the pathogenesis of gallbladder infections
    in typhoid, cholera, and dysentary, J. Exp.
    Med. 24: 497-514, 1916.

27. Mentzer, S. H. : A clinical and pathologic
    study of cholecystitis and cholelithiasis,
    Surg., Gynec. and Obst. 42: 782-793, 1926.

28. Moynihan, B. G. A. : The gallbladder and its
    infections, Brit. M. J. 1: 1-6, 1928.

29. Colp, R.; Doubilet, H. and Gerber, I. E. :
    The relation of cholecystitis to pathologic
    changes in the liver, Ann. Surg. 102: 202-
    217, 1935.

30. Cassity, G. H. : The etiology and treatment
    of chronic cholecystitis, Tri-State M. J.
    7: 1454 and 1458, 1935.

31. Rosenow, E. C. : The etiology of cholecystitis
    and gallstones and their production by the
    intravenous injection of bacteria, Collected
    Papers of the Mayo Clinic 8: 222-252, 1916.

32. Wilkie, A. L. : The bacteriology of chole-
    cystitis, Brit. J. Surg. 15: 450-465, 1927-
    1928.

33. Rehfuss, M.E. and Nelson, G. M. : Experimental
    Cholecystitis; final results of vaccine and
    filtrate therapy, Surg., Gynec. and Obst.
    81: 455-460, 1945.

34. Burton, J. A. G. : Cholelithiasis; a summary,
    Glasgow M. J. 121: 14-23, 1934.

35. Wolfson, W. L. and Rothenberg, R. E. : Acute
    non-calculous cholecystitis, J.A.M.A. 106:
    1978-1980, 1936.

36. Russell, T. H.; Carter, R.F. and Oppenheim, E. :
    Gallbladder disease: etiology, diagnosis and
    treatment, Bull. New York Acad. Med. 19: 77-124,
    1943.

37. Kaikini, V. M. : Uncommon etiologic factors in
    pathologic conditions of the gallbladder, Ind.
    M. Gaz. 80: 329-332, 1945.

38. Seelig, M. G. : Bile duct anomaly as a factor
    in the pathogenesis of cholecystitis, Surg.,
    Gynec. and Obst. 36: 331-335, 1923.

39. Barrow, W. and Massie, F. M. : Acute chole-
    cystitis, South. M.J. 35: 397-404, 1942.

40. Berk, J. E. : Choledocholithiasis, Am. J. Surg.
    55: 96-101, 1942.

41. Ivy, A. C. : Etiology and therapy of biliary
    tract disease from the viewpoint of applied
    physiology, Ohio State M. J. 32: 1185-1189,1936.

42. Best, R. R. and Hicken, N.F. : Biliary dys-
    synergia: physiological obstruction of the com-
    mon bile duct, Surg., Gynec. and Obst. 61:
    721-734, 1935.

43. Davidson, L. S. P. : The aetiology, prophy-
    laxis and treatment of cholecystitis and chole-
    lithiasis, Edin. M. J. 51: 184-200, 1944.

44. Boland, Jr., F. K. : Biliary diseases in the
    Negro, J. Med. Ass., Georgia, 26: 185-187,
    1937.

45. Potter, M.G. : Observations of the gallbladder
    and bile during pregnancy at term, J.A.M.A.
    106: 1070-1074, 1936.

46. Biskind, L. H. and Pevaroff, H. H. : Gall-
    bladder disease and pregnancy, Ohio State
    M. J. 38: 1013-1015, 1942.

47. Wannamaker, E. J. : Etiology and pathology of
    cholecystic disease, N. Carol. M. J. 2: 175-
    176, 1941.

48. Womack, N.A. and Bricker, E. M. : Pathogenesis
of cholecystitis, Arch. Surg. 44: 658-676, 1942.

49. Cole, W. H. ; Novak, M. W. and Hughes, E. O. :
Experimental production of chronic cholecystitis
by obstructive lesions of the cystic duct, Ann.
Surg. 114: 682-696, 1941.

50. Wolfer, J. A. : The role of the pancreatic juice
in the production of gallbladder disease, Surg.
Gynec. and Obst. 53: 433-447, 1931.

51. Colp, R. ; Gerber, I.E. and Doubilet, H. : Acute
cholecystitis associated with pancreatic reflux,
Ann. Surg. 103: 67-76, 1936.

52. Bisgard, J.D. and Baker, C. P. : Pathogenesis of
cholecystitis, cholelithiasis and acute pan-
creatitis, Ann. Surg. 112: 1006-1034, 1940.

53. Walzer, M.; Gray, I.; Harten, M. ; Livingstone,
S. and Grayzel, D. : The allergic reaction in
the gallbladder, Gastroenterology 1: 565-572,1943.

54. DeMuro, P. and Ficari, A. : Experimental studies
on allergic cholecystitis, Gastroenterology
6: 302-14, 1946.

55. Brams, J. and Darnbacher, L. : The effect of
X-rays on the gallbladder: experimental pro-
duction of an x-ray cholecystitis, Rad. 13:
103-108, 1929.