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Cholecystography

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CHOLECYSTOGRAPHY

BY

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INTRODUCTION

In the preface of Graham and his associates' book, "Diseases of the Gall Bladder and Ducts", is the rather startling statement that between twenty and twenty-five per cent of all adults harbor gall stones and possibly an equal number suffer from cholecystitis without stones--or in other words, nearly one-half of the adult population is subject to disease of the biliary and hepatic systems. The clinical manifestations, however, do not correspond to this high incidence. Many are without symptoms and probably a greater number fall into the so-called functional gastrointestinal neuroses including "nervous indigestion" and "dyspepsia". Separation of the purely functional group whose chief complaint is indigestion from that group with early or late hepato-biliary disease is at best difficult and there is no degree of certainty as yet.

Prior to the advent of cholecystography, the roentgenologic evidence of cholecystic disease was very scant, and consisted chiefly in the visualization of opaque stones. Graham and Cole revolutionized the field of diagnosis in gall bladder disease with their monumental work on cholecystography in 1924. Since that time, cholecystography has been universally recognized as our most important agent in detecting gall bladder pathology. Cholecystography is relatively new and it involves an entirely new principle in roentgenology

since it is a test of functional capacity of a system.
Techniques are still not standardized and the matter of
interpretation is all important.

Therefore, since biliary disease is common, its differ-
ential diagnosis is difficult, and cholecystography offers our
single greatest aid in this matter, the author has constructed
this paper with the hope of gaining a better knowledge and under-
standing of this procedure. In addition to a discussion of the
subject as a whole, there is included in this paper a report of
a personal investigation of all cholecystographic studies made
in the University of Nebraska Hospital over an eleven-year per-
iod.

I DEFINITION

The discovery of a new method of roentgenological examination of the gall bladder was reported in 1924 by Graham and Cole (1). They demonstrated that when phenolphthalein, containing either iodine or bromine, was injected intravenously into animals or man, a sufficient concentration of the halogen was obtained in the gall bladder to cast a shadow on a film when exposed to the roentgen-ray. Graham and his associates applied the name "cholecystography" to the visualization of the gall bladder by this method, and the exposed roentgen-ray films were called "cholecystograms". (2)

II HISTORY AND DEVELOPMENT

The demonstration of the striking effectiveness of the roentgenological visualization of the alimentary canal by the opaque meal in the diagnosis of gastric and intestinal conditions, and of the kidney pelves after the intraureteral injections of opaque substances led naturally to the desire to find some method by which other structures could be made to reveal abnormalities. Because of the very great frequency of affections of the biliary tract it was particularly desirable to have a method which would permit the visualization of the gall bladder. The story of the development of cholecystography is so fascinating that it will be told in detail.

Evarts A. Graham (3) was a surgeon who was particularly interested in chemistry--so much so that he decided to give up his small surgical practice and spent the years of 1913 and 1914 at the University of Chicago in the study of chemistry. The time so devoted was fruitful to the extent that it enabled him to think somewhat in chemical terms and thus to take advantage of the possibilities of the application of some relatively simple chemistry to the problem of the improved diagnosis of gall bladder disease. On several occasions Walter Mills and he conversed about the desirability of visualizing the gall bladder in some manner comparable to the visualization of the stomach and other parts of the alimentary canal. No satisfactory method, however, suggested itself until suddenly one evening, in the

winter of 1922, the idea occurred to him that since Abel and
Rowntree (4) had demonstrated the fact that the chlorinated
phenolphthaleins were excreted almost entirely through the bile
it might be possible, by substituting for the chlorine atoms
other atoms which would be opaque to the x-ray, to obtain a
shadow of the gall bladder.

From the Eastman Kodak Company he obtained some of the
free acid of tetraiodophenolphthalein already prepared since
they had such a substance advertised in their list of indica-
tors. After receiving the material he turned it over to Warren
Cole, in July, 1923, and asked him to inject it into some ani-
mals to see if he could visualize their gall bladders with it.
Before injecting the material into dogs they converted it into
the sodium salt because the free acid was naturally less soluble
than the sodium salt. Six dogs were injected intravenously, and
x-ray photographs were made of the gall bladder regions in all
of them at frequent intervals after the injection. In five of
the dogs no shadow was obtained, but fortunately a faint shadow
was obtained in the sixth one. At first they were at a loss to
understand why they had obtained a faint shadow in one dog but
none at all in the other five animals. The idea then occurred
to them that the reason for the failure was probably due to the
fact that the animals were not fasting and that, therefore, the
injected substance was not staying in the gall bladder for a
long enough time to be concentrated and, therefore, to make a
shadow. Upon investigating the matter they found that by acci-

dent or through some mishap or other the animal keeper had
neglected to feed the one dog on the morning of the experiment
but he had fed all the others.

With the clue that the failure to cast a shadow was due
to the presence of food in the stomach and duodenum it was then
a relatively simple matter to determine that shadows could be
obtained in almost every instance during a fasting period. At
about this time Glover H. Copher was added to the group conduct-
ing the investigation. The matter of dosage and toxicity had to
be settled because several of the animals died. They turned
hopefully to the bromine homologue. After considerable experi-
menting with various dyes, the Mallinckrodt Chemical Works
supplied them with an exceptionally pure product of the sodium
salt of tetrabromphenolphthalein. With this dye they obtained
good shadows of the gall bladder with much less toxic effects,
in spite of the larger dose required.

Up to that time their only idea in visualizing the gall
bladder had been to introduce something into it which would
visualize any contained stones or deformities of the organ. A
colored woman in the Barnes Hospital who presented a very char-
acteristic clinical picture of gallstones seemed to present
satisfactory conditions for the first trial in the human. They
all had hopes that a sharp image of gallstones in the woman's
gall bladder would be demonstrated. An ordinary x-ray film
before the injection of the dye had failed to show any stones.

To their great disappointment and consternation the patient
showed no shadow at all of her gall bladder after injection,
in spite of a series of films which were made. Their disap-
pointment was made more intense by the fact that Graham
operated this patient and found a gall bladder which contained
many stones of different sizes. It seemed then, for the moment
as if their high hopes of improving the diagnosis of gall bladder
disease had been dashed to the ground. Soon, however, the idea
occurred to them that since they had been obtaining excellent
shadows in their experimental animals, which presumably had
normal gall bladders, the reason for their failure to produce
a shadow in the markedly diseased gall bladder might be be-
cause the diseased gall bladder could not properly concentrate
the material which was brought to it. They also took into
consideration the possibility that there might have been an
obstruction of the cystic duct which prevented the entrance
of the material into the organ, but in the case in which they
had had a failure Graham had found an abundance of bile in the
gall bladder at operation with no evidence of obstruction.
They were, therefore, forced to believe that a diseased wall
in itself might be sufficient to result in non-visualization
because of the failure of concentration.

This conclusion led them to the next step which was to
inject some patients who supposedly had normal gall bladders.
They obtained well visualized shadows. This result, while

gratifying, made it necessary to change their whole conception of the possible applicability of such a test to the patient. For instead of having a method which would with certainty reveal gallstones in the x-ray picture they found that they were, on the contrary, dealing with a method which was more of a functional test of the gall bladder and one which would show the gall bladder most plainly under normal conditions, and not at all in those conditions in which the organ was very badly diseased no matter whether stones were present or not.

The big disadvantage at first was that in patients in whom the best shadows were obtained sometimes severe reactions occurred. A search was then made for a better dye. In all they tried some forty-eight different substances, of which thirteen were shown to visualize the gall bladder. Most of these thirteen substances had disadvantages of one kind or another. Whitaker and Milliken (5), who were working independently of Graham and his associates, were fortunate enough to secure good samples of tetraiodophenolphthalein and they reported in January, 1925, a comparative study of the two dyes. They demonstrated that approximately one-half as much of sodium tetraiodophenolphthalein need be used as the bromine salt, and the smaller dose was less toxic. This was soon confirmed by Graham and Cole (6) (7). About a year later, Graham and his associates (8) reported on the use of the isomer of this sub-

stance, namely, sodium phenoltetraiodophthalein as the most suitable of the available dyes for intravenous injection. It is interesting to note that the first substance Graham and Cole used was tetraiodophenolphthalein which is still the dye of choice in cholecystography and it was only because of the toxic impurities in the initial product that it was ever abandoned. (2)

III PRINCIPLE

From the radiological standpoint the problem of visualizing the gall bladder differs in nearly every respect from that demanded for the development of any of the other artificial contrasts. It embodies an entirely new and original radiological principle, namely, the utilization of the specific functions of a system to engender a difference in density. Therefore, cholecystography is largely a test of physiological capacity in contradistinction to the almost wholly mechanistic nature of the opaque meal examination, pyelography, and the like.

From a physiological standpoint then, the dye is administered either by mouth or intravenous injection. It is taken up by the blood stream, excreted in the bile by the liver, and diverted into the gall bladder by the action of the sphincter of the common duct, if the subject is fasting. Within the gall bladder, the bile and iodine become more concentrated, due to absorption of water by the wall of the viscus. The ability of the gall bladder to concentrate its contained bile, as shown by Rous and McMaster (9), indicates that a sufficient time must elapse before a shadow of maximal density occurs. It is during this period of about twenty-four hours that shadows may be procured on films by exposing the gall bladder to roentgen-rays. The iodine is removed from the normal gall bladder as it empties, and with it goes the opacity of the

organ to the roentgen-ray. By this means, the roentgenologist can study the size, shape and position, but more especially the filling, the concentrating function, and the emptying of the gall bladder. Reasoning from these premises, the conclusion would have to be drawn that the shadows of sharpest contrast would be obtained in normal individuals. Similarly, also no shadow would be expected to appear if the liver were unable to excrete the substance in sufficient amount, if the cystic duct were occluded, or if the function of the gall bladder were sufficiently impaired to prevent the concentration of the material. Intermediate degrees of changes from the normal conditions will result in the appearance of shadows which require expert interpretation. It is because of its sensitiveness to slight functional changes that cholecystography becomes of great value in the diagnosis of the cases of early and comparatively mild cholecystitis which are the most difficult to diagnose by any other method, either clinical or laboratory. Prior to the advent of cholecystography most cases could be accurately diagnosed only after they had gone to the stage of advanced pathology. By means of this test of function, its originators were anticipating another phase in preventive medicine by the possibility of early accurate diagnosis in gall bladder disease inasmuch as early operative treatment would prevent most of the ravages of long standing cholecystitis with its accompanying serious effects on the liver and pancreas. (2) (10)

IV ADMINISTRATION AND TECHNIQUE

A. Intravenous Method

There have been countless discussions devoted to the relative merits of the intravenous and oral methods. Graham and his associates (11) (6) (7) (8) (1) including Sherwood Moore (12) used the intravenous method from the first. Their conception was that cholecystography was a measure of functional capacity of the gall bladder and for that reason they held that for the sake of accuracy in making the test, the intravenous injection was the method of choice. As previously cited (8), they discovered that sodium phenoltetraidophthalein, the isomer of sodium tetraiodophenophthalein, gave more satisfactory results in the intravenous work. Intravenous administration made it certain that a full dose had been introduced into the circulation and excluded any question of absorption. In 1927, Graham (13) summarized the results of some fifteen different groups of workers as to accuracy in diagnosis. The percentage of correctness in three hundred eighty cases of all authors using intravenous method was ninety-five while the percentage of correctness in one hundred eighty-one cases of all authors by the oral method was eighty-nine--another point in favor of the intravenous route.

Zink (14), in 1926, reported the use of intravenous dye in five hundred thirteen cases and preferred this method to the oral except when contra-indicated by any one of the

following:

    1. Common duct obstruction

    2. Extensive hepatic destruction

    3. Hypertension

    4. Cardiac disease

    5. Hyperthyroidism

He used the oral method in one hundred thirty-one cases and
stated that cholecystograms made by that method were reliable
only in cases presenting

    1. Normal shadow

    2. Presence of stones

    3. Topographical defects (pericholecystitis)

Boardman (15) reached a similar conclusion in the study of
twenty-five cases examined by both oral and intravenous
methods. There was agreement in nine, or thirty-six per
cent, and disagreement in sixteen, or sixty-four per cent.
In every case of disagreement the intravenous method gave
evidence of a more normally functioning biliary system. He
emphasized the fact that after oral administration only the
evidence of a perfectly normally functioning tract was to
be accepted.

Verbrycke (16) was one of the ardent proponents of the
intravenous technique from the onset. Soon after Graham and
Cole's first report he began using the test and in 1927 re-
ported his preference for this method stating that toxic

reactions were the exception in his group of patients. He
concluded that in his estimation cholecystographic diagnosis
was probably twenty per cent more accurate than clinical
diagnosis and at least ten per cent more accurate than explor-
atory diagnosis.

Another of the early intravenous enthusiasts was Case
(17) (18) (19) (20), who found that method gave a maximum
amount of information in comparison with the oral, jejunal,
and rectal methods. He concluded that the absence of the
gall bladder shadow was worth at least ninety-five per cent
toward indicating operation, a normal Graham test should
deter the surgeon from operating except in the face of the
clearest clinical evidence of gall bladder disease, and
finally that impaired function by the intravenous method had
great significance and should be interpreted as disease while
such could not be said for oral administration.

Waters and Firor (21) summarized the advantages of
intravenous cholecystography quite adequately in 1930. First
they considered the complications---

1. Urticaria. This was the commonest and least
   serious--promptly controlled by five to ten
   minims of adrenalin hydrochloride given hy-
   podermically.
2. "Sore arm". This they considered a cellulitis
   due to the action of the dye in the subcutaneous

tissues and was the fault of the person who

made the injection. They recommended the

isomeric salt, phenoltetraiodophthalein be-

cause it was less irritating.

3. Endophlebitis obliterans. They considered the

commonly used term "venous thrombosis" as in-

correct and pointed out that in reality the

condition was not a thrombosis but an inflam-

ation of the intima resulting in obliteration

of the lumen of the vein. Digital pressure

upon the vein during or immediately following

the injection was conducive to intimal adher-

ence just as in the surgical treatment of

varicose veins by injection.

Only two conditions contraindicated the use of the intravenous

method, namely, cardiac decompensation and threatened uremia.

As regards diagnostic accuracy of the oral method in the

operative group of cases, they called attention to the fact

that this group usually presented outspoken clinical indica-

tions for surgical intervention. In two years' experience

with intravenous cholecystography, at least twenty-five per

cent of those cases who had previously been grouped as normal

by the oral method were, on the contrary, found pathological

by the intravenous method. Finally, they emphasized the fact

that the intravenous method insured a known amount of dye to

be used and the procedure could be easily and safely carried

out in office practice.

B. Oral Method.

The first report of oral administration for production
of cholecystograms was made by Menees and Robinson in February,
1925 (22). Their first work was done with sodium tetrabrom-
phenolphthalein. Various types of containers were tried
which would not dissolve in the stomach but would disintegrate
in the intestine. Salol and keratin coated capsules were used
but best results were obtained with formalin hardened gelatin
capsules. Bicarbonate of soda was given with the dye to pre-
vent precipitation by the hydrochloric acid of the stomach.
The chief disadvantage of the oral method in their work was
the nausea and vomiting and a certain number of patients
were not able to retain the dye. Slight looseness of the
bowels was observed in seven of thirty-seven cases. Thus,
they thought the amount of dye absorbed would not be con-
trolled.

Carman (23) noted catharsis after oral use of sodium
tetrabromphenolphthalein, usually after enteric coated pills
and less often following the use of plain gelatin capsules.
Palefski (24) noted the alimentary reaction with sodium tetra-
bromphenolphthalein and gave morphine and atropine to counteract
it. Whitaker, Milliken and Vogt (25), in forty-four instances
of oral administration of the sodium tetraiodophenolphthalein
noted vomiting five times, slight nausea seven times, and
mild diarrhea in five cases. Using oral administration of

sodium tetraiodophenolphthalein, Larimore (26), in 1926, tried
to associate the amount of free hydrochloric acid in the
stomach with the alimentary disturbances. All of his patients
sustaining reactions had an achlorhydria.

In 1925-26, Levyn and Aaron (27) compared the relative
value of different coatings of capsules in regard to their
dissolution in gastric and duodenal contents. Their results
showed that even though the plain capsules digested readily,
a large amount of a white acid form of tetraiodophenolphthalein
was formed. This acid radical was insoluble in the duodenal
contents. Therefore, they suggested the use of sodium bicar-
bonate to be given in combination capsules in order to do
away with the insoluble acid radicals that were formed. This
was accomplished by putting the dye in No. 3 plain capsules
which were inserted in No. 0, the outer containing the sodium
bicarbonate, and they proved superior to any other forms
used, offering the highest percentage of visualized gall
bladders. These men also experimented with strontium and
sodium bromide as suggested by Sabatini and Milani (28) of
Rome, who reported "remarkable results" in showing the gall
bladder after ten to twenty grams had been given by mouth
and fasting the patient over a long period of time. Though
Levyn and Aaron closely followed the recommended technique,
they were unable to obtain any vestige of a gall bladder
shadow in twelve normal individuals. Graham, Cole, Copher

and Moore (2) were unable to produce satisfactory shadows
of the gall bladder by using this method, although shadows
were obtained. The patients also objected strenuously to
the long fast and to the discomforts following such large
doses of bromides. McCoy and Graham, R. S. (29), likewise
did not find the method satisfactory.

In 1927, King and Martin (30) summarized their results
in four hundred seven cases at Johns Hopkins. Tetraiodophenol-
phthalein was used in gelatin capsules and they recorded very
satisfactory results but cautioned against normal functioning
reports and cited an error of twenty per cent in the non-filling
group.

Eusterman (31) summarized the cases at the Mayo Clinic
up to 1927 and concluded that the intravenous method was more
accurate, generally speaking, and in certain cases, especially
after the oral administration, the test should be repeated by
intravenous injection.

Stewart and Ryan (32) (33) were among the first and
probably the most diligent of the early advocates of oral
administration. Certainly they did much towards popularizing
the oral method.

Until Fantus (34) came along in 1927, the simplicity
of the oral method over the intravenous had been overbalanced
by two disadvantages, namely, greater tendency toward reaction
(especially nausea and vomiting) and lack of consistency in

absorption. He suggested giving the dye in a colloidal form
to prevent nausea and vomiting, thus giving better absorption.
Then Levyn and Aaron (35) found that the iodine dye could be
given in liquid form by dissolving the dose in a small amount
of distilled water and adding from 240 to 300 cc. of grape
juice. Kirklin (36) in 1929, reported the use of 4 gms. of
tetraiodophenolphthalein in simple fresh aqueous solution
with grape juice added. This was taken after the evening
meal which was fat free. In five hundred cases, nausea was
seldom seen and flocculi of unabsorbed dye were seldom noted
in the bowel.

Among the first men to combine the two methods of
administration in an attempt to obtain greater efficiency in
diagnosis were Sosman, Whitaker, and Edson (37). In 1925,
these men reported their results by both methods preferring
the intravenous method and suggested confirmation by this
method when the oral route provided faint or absent shadows.

Levene and Whitaker (38), in 1930, used the combined
method with two-thirds of the oral and two-thirds of the
intravenous doses and found that their patients were singu-
larly free from any of the reactions sometimes seen following
a full intravenous or a full oral dose. Such a method pro-
duced greater densities of the gall bladder shadows and
permitted greater accuracy without discomfort.

In 1932, Davidson, Biguria, and Rosenthal (39) reported

on their results using the combined method in some two hundred
sixty-five cases. All were ambulatory patients. Half doses
of each were used. In their opinion, such a method gave
accuracy comparable to that of the intravenous alone, produced
a higher incidence of filling and denser shadows than the oral
method, reactions were infrequent, it was time saving since no
repeat examinations were necessary, and they considered it the
most satisfactory means of studying ambulatory patients. How-
ever, Kirklin (36) (40) had a series of three hundred cases,
shown to be non-visualized by the oral method, which he re-
checked by the intravenous injection. By the latter method
he could demonstrate only a one per cent greater efficiency
and this convinced him that the oral method, if carefully
done, was as reliable as the intravenous.

Bockus (41) reported a small series of cases in 1931
indicating that the intravenous method was superior to the
oral if only one study was carried out.

C. Modifications.

Boyden (42) (43) was the first to demonstrate that foods such as egg yolk and cream were the most efficient in emptying the gall bladder in animals. Such meals were utilized clinically in 1926 by Whitaker (44) (37) to speed up the emptying time of the gall bladder in cholecystography in humans. This procedure was generally employed clinically until 1931 when Levyn (45) introduced a modified method of administering fats by substituting a mixture of egg yolk, lecithin, glycerine, and alcohol. The lecithin was considered the active stimulant. By this method examinations were less time consuming, only a small dose was necessary, gastric peristolsis was not retarded so that the stomach emptied promptly and barium meal examination could be done sooner, it eliminated the aversion of many patients to eggs and cream, and it provided a standardized method of administering a gall bladder stimulant in lieu of the many varieties of fat meals commonly used.

Whitaker and his associates (37) (46) conducted numerous physiological experiments upon the effects of various food substances on the emptying of the gall bladder and concluded that a carbohydrate meal could be given without any effect. In 1931 Whitaker and Ellsworth (47) (48) offered an improved "double oral" method of cholecystography which was based on this physiological principle. Two full doses of the iodine salt were given--one after the regular noon meal and one after a carbohydrate evening meal the day before the films were made. By

this procedure a large amount of dye could be given at suffi-
cient intervals to allow more time for better concentration
yet the patient had nourishment. Their results gave much
higher densities in the shadows produced.

Antonucci (49) shed new light on the relation of car-
bohydrates and cholecystography when he announced his "rapid"
method in 1932. He used two to three grams of dye dissolved
in 125 cc. of forty per cent glucose solution given slowly
by the intravenous method. This was followed by insulin.
Visualization of the gall bladder usually occurred within
one-half hour. It was his opinion that the dye necessitated
the presence of glucose in the liver to be absorbed and that
the dye first uses the glucose from the blood stream, deter-
mining an afflux of the glycogen from the tissues if this
becomes exhausted. The glycogen is then transformed into glu-
cose which is partly utilized by the dye and partly serves to
re-establish the normal glycemic level altered by the intro-
duction of the disturbing substance. However this may be,
it seems certain from the research performed so far that the
glucose plays a great part in the utilization of the dye.
Insulin is added so as to produce a more rapid and more com-
plete utilization of the glucose on the part of the liver but
its advantages have not been proved beyond doubt. Kestel (50)
mentions the report of Zappala who reported no errors in one
hundred of Antonucci's cases and he also reported that two

German workers, Biederman and Becher, obtained good shadows
in two or three hours when seventy-five grams of glucose
were given orally. However, Jung and Moore (51) failed to
observe shadows more rapidly, or to improve the quality of
the cholecystograms by the oral administration of glucose.
Basing his work on the theory that adding to the glucose re-
serve of the body may accelerate oral cholecystography,
Kestel (50) suggested the use of a carbohydrate meal instead
of a fat meal. In a small series of thirty cases which showed
relatively faint shadows, the patients were given the carbo-
hydrate meal--fourteen had denser and smaller shadows in two
hours, eight had same intensity but shadows were reduced in
size, five varied considerably, and three disappeared. His
results were not uniform but he suggested an advantage due
to increased density and smaller shadow which might allow
stones or other negative shadows to be discovered when over-
looked in the original cholecystogram.

In 1932, Sandstrom (52) introduced the so-called
fractionated oral administration. He called attention to
the fact that the phthaleins, once introduced into the system,
circulate for a rather long time in an enterohepatic cycle.
After being eliminated through the liver and its intermediary,
the bile, they are reabsorbed through the intestine, and so
on. By introducing orally during each phase of the cycle
additional small doses of the salt one may obtain a more com-

plete absorption. Frantionated method is entirely harmless
to patient and has no damaging action on the liver.

Intensified oral cholecystography was introduced in
1934, by Stewart and Illick (53) (54). This method was
suggested to them when they noted that the gall bladder shad-
ow became more intense when starvation was continued beyond
sixteen hours. The technique is based on three factors:

1. Increasing and fractionating the total dose of
   dye after the principle demonstrated by Sand-
   strom (52).

2. The free administration of sugar preceding and
   during the roentgen examination. This is based
   on the ample evidence that sugar splits up into
   glucose and other products and that the glucose
   acts as a whip for liver function including the
   faster and more complete absorption of the tetra-
   iodophenolphthalein as demonstrated by Antonuc-
   ci (49).

3. The use of the fast Potter-Bucky diaphragm and
   an exact exposure technique.

Intensified oral cholecystography requires additional work,
patience and rather more time than the usual procedure, but
the improved results amply compensate for these disadvantages.
It is of particular value in faint shadow cases where the
proper interpretation is difficult.

At the Cleveland Clinic in 1935, Collins and Root (55) began the use of pitressin in selected cases having confusing densities in the right side. Not uncommonly, more gas was noted in the intestinal tract after enemas than before. With the use of pitressin instead of enemata, they found results more effective by this simple procedure which required less time and was less troublesome to the patient.

D. Toxicity, Reactions, and Contraindications.

Since the introduction of tetraiodo phenolphthalein into medicine for cholecystography, attention has frequently been directed by various observers to the toxicity and the hepatic and renal lesions produced by this dye. Abel and Rowntree (4) who worked with the phthaleins as early as 1909, observed no toxic effects. Graham and Cole (1) noted toxic effects only when large doses were given intravenously. However, Ottenberg and Abramson (56) reported the production of extensive degeneration in the liver lobules after intravenous injection. Their doses were four to six times larger than the dose per kilogram of body weight necessary for cholecystography in man and they simply cautioned against the use of the dye in the presence of any liver damage. Rosenau's (57) experience was similar to that of these workers and he warned against the indiscriminate use of the dye.

Maddock and Whitaker (58) experimented in animals which had their common ducts ligated and found that the animals would tolerate seventy-five to eighty per cent of their estimated lethal dose. Graham and his associates (2) observed that many human beings with jaundice, due to common duct obstruction, had no increase in toxic symptoms following dye administration. On numerous occasions they removed small pieces of liver at operation in human subjects and never observed any evidence of hepatic damage. They also mention

Pribam, Grunenberg, and Straus, three German workers, who reported the administration of tetraiodo phenolphthalein in a case of subacute yellow atrophy of the liver without the production of any significant reaction. A good shadow of the gall bladder was obtained. Graham, Cole, Copher, and Moore considered cardiac decompensation, arteriosclerosis, and threatened uremia as the chief contraindications.

A British worker, Carmen (59), in 1926, gave an excellent description of the reactions observed following the intravenous administration of sodium tetrabromphenolphthalein. More than one-half the patients experienced systemic reactions in varying degree. In most cases the symptoms were trivial, but in ten per cent the reaction was marked and in two per cent severe. The typical severe reaction began within five or ten minutes with a sense of uneasiness, followed by pain in the dorsal and lumbar region, flushing of the skin and a rise of from ten to fifty mm. in blood pressure, followed within three to five minutes by a sharp fall. After this, patients sometimes had intestinal cramps, nausea, vomiting or incontinence of the bowel and bladder. Systemic reactions occurred especially often in cases of obstruction of the common duct, in cardiovascular disease and in persons with extremely neurotic tendencies.

Huddy (60), in 1926, reported a death following the intravenous injection of a large dose of sodium tetraiodophen-

olphthalein.

In 1927, Friedenwald, Feldman, and Kearney (61) ex-
perimented rather extensively with dogs and concluded that
tetraiodo phenolphthalein administered orally for purposes
of cholecystography, even in massive doses, did not produce
degenerative nor necrotic changes in the liver or kidneys.

In 1928, Fitz (62) reported a reaction following
intravenous injection of the dye in a case of angina pectoris.
During and following the injection the clinical course was
characteristic of a cardiac infarct. An uneventful recovery
followed.

Dick and Wallace (63), in 1928, reported that the
common symptoms following dye injection were varying degrees
of upper abdominal pain, nausea, vomiting and diarrhea, often
attended by a rise in temperature. Three cases were described
in which they considered the dye accelerated the course of the
patients' illness and contributed to their fatal endings. One
case was one of common duct obstruction due to stones with
associated acute pancreatitis, the second was one of jaundice
with cholelithiasis, and the third case died from acute yellow
atrophy of the liver thirty hours following injection. They
carried out some experimental work in cats and concluded that
obstruction at the ampulla of Vater might produce an acute
pancreatitis following dye injection and considered it danger-
ous to give the dye in the presence of jaundice.

Adams (64), in 1929, reported that reactions ranged
from slight disagreeable sensations to severe shock and occas-
ional death. The common subjective phenomena were apprehension,
feeling of oppression, warmth and flushing, sensation of con-
striction in the chest, shortness of breath, vertigo, and
faintness. Objective symptoms were restlessness, flushing,
and dyspnea. Three types of severe reactions were described:

1. Those associated with vasomotor collapse and
   shock probably related to sensitization and
   anaphylactic shock.

2. Those dependent on preexisting cardiovascular
   disease.

3. Those occurring in the presence of liver damage
   or an acute process along the biliary tract.

Davis (65), in 1931, described flushing, nausea, vomit-
ing, palpitation, back pain, dizziness, sensation of warmth,
abdominal pain, headaches, weakness, chills, and fever. These
phenomena all belong to the collapse or shock-like group of
reactions. No fatalities occurred. He considered evidence
of myocardial damage and a systolic blood pressure above 180
as contraindications. In an attempt to lessen the reactions,
he gave a series of patients five minims of one to one thousand
adrenalin immediately before the dye injection, without any
beneficial result.

One of the most extensive studies of this nature was
that made by Palmer and Ferguson (66), in 1933. The following

table shows the frequency of the common reactions in two

thousand, one hundred thirty-five cases:

	Per Cent
No reaction	42.6
Flushing	42.4
Nausea	15.7
Vomiting	3.2
Pain in abdomen	17.3
Pain in back	13.9
Dizziness	3.8
Headache	4.4

Almost one-half of the patients had no reactions whatever.

The majority of the remainder had only slight transient dis-

turbances, and a few had moderately severe reactions. Three

serious reactions, including one death, were encountered.

They considered cardiovascular lesions such as decompensa-

tion, coronary sclerosis, or angina pectoris as absolute

contraindications to intravenous cholecystography.

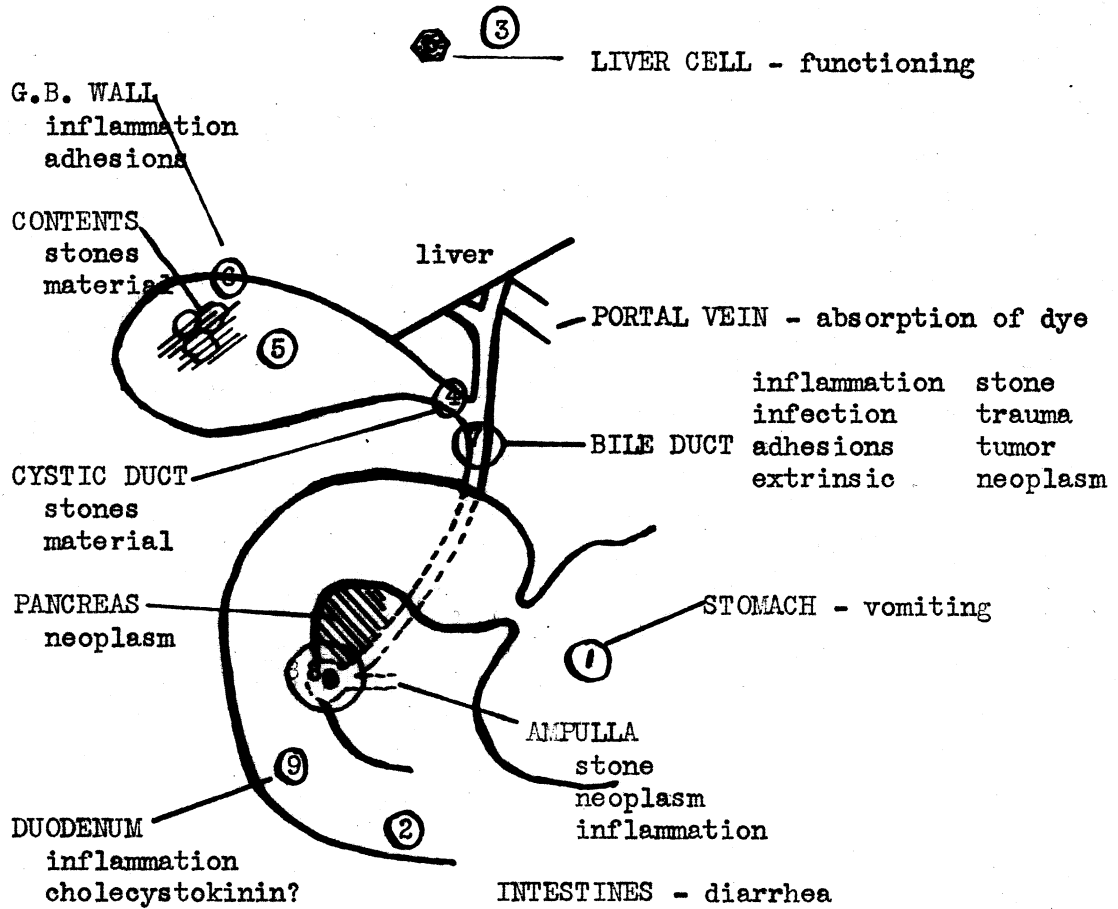pointed out the advantages of the lateral position in certain
cases. In 1936, Zaldin (43) emphasized the fact that the left
anterior oblique position was especially indicated in non-
visualized cases in which a mesial location of the gall bladder
was suspected. Again, in 1937, Feldman (69) stressed the pro-
bability of faulty roentgen technique as the principal cause
of error in non-visualization or in cases in which the gall
bladder was overshadowed by the hepatic flexure. He emphasized
the importance of obtaining views of gall bladder in different
positions and recommended the use of the left oblique or left
lateral position as a routine procedure in cholecystographic
study.

V CHOLECYSTOGRAPHIC INTERPRETATION

Before discussing the interpretation of cholecystograms,
it might be well to consider briefly the various possibilities
affecting the roentgengraphic study. The following diagram (70)
affords a concise but adequate illustration of the variables to
be considered.

LIVER CELL - functioning

G.B. WALL
 inflammation
 adhesions

CONTENTS
 stones
 material

liver

PORTAL VEIN - absorption of dye

inflammation	stone
infection	trauma
adhesions	tumor
extrinsic	neoplasm

BILE DUCT

CYSTIC DUCT
 stones
 material

PANCREAS
 neoplasm

STOMACH - vomiting

AMPULLA
 stone
 neoplasm
 inflammation

DUODENUM
 inflammation
 cholecystokinin?

INTESTINES - diarrhea

Note: The sequence of numbers in the above diagram represent
the course of the cholecystographic dye in the body.

A. Normal Response.

Preliminary films before the dye is given reveal no gall bladder shadow. After the tetraiodophenalphthalein the gall bladder outline becomes more intense from the twelfth to the sixteenth hour, is of normal size, shape, and position and contracts down markedly after a meal, and shows no gall stones. The gall bladder must fill with the dye, concentrate it, greatly contract after a meal, and completely empty. There must be no blurring or fuzziness of soft tissue or bony outlines from respiration or movement and bony detail in the lower ribs and vertebral bodies must be clear cut and distinct. (70)

B. Persistency of Shadow.

In some cases the gall bladder fails to respond to the stimulus of food and does not contract and empty as it should. This is usually fairly reliable evidence of a deficiency in the muscular tone of the gall bladder. One sees persistency of shadow as a part of a general condition of asthenia, and is often noted in cases showing marked six-hour gastric retention after barium. When the shadow disappears after food and again faintly appears thirty-six hours after administration of the dye, it usually indicates reabsorption (66), and the finding is disregarded as of no importance. (70) Hunt (71) mentioned this finding of inadequate emptying in cholesterosis. Recently, Feldman and Morrison (72) and Lipschutz (73) have

studied the matter of delayed emptying quite extensively.
The latter emphasizes this particular phase of cholecysto-
graphic study as being the most important sign in the diag-
nosis of biliary dyskinesia.

C. Faint Shadow.

This is probably one of the most difficult conditions
to evaluate properly. Standardized routine and experience
are all important factors, even then technical factors may
vary within wide limits, and two examinations on the same
case may result in somewhat different findings. Furst and
Gelber (74) consider that faint visualization could patholo-
gically be interpreted as:

1. The gall bladder was so thickened from old
   chronic inflammation that the density of the
   shadow of the dye-laden bile is decreased.

2. That the faint shadow resulted from some inter-
   ference with the normal function of concentration.
   This was especially true in acute exacerbations
   of chronic cholecystitis or in a passing edema-
   tous condition of the mucosa of the gall bladder.
   In the presence of an acute inflammation there
   is considerable edema, and that edema in the tis-
   sue decreases rather than increases absorption.

3. That the gall bladder is so packed with stones
   as to allow only a small amount of the opaque
   dye to enter.

Rehfuss (70) mentions the findings of German workers like Bronner, Schuller, Rosenthal, and Licht who believe that the inflamed membrane in acute cases absorbs the contrast bile in increased amounts and more rapidly than normal, so that by the time films are taken, the percentage of iodine in the opaque bile mixture is not sufficient to cast a shadow. There are many cases of old sclerotic gall bladders in which the function of concentration is defective, resulting in a faint shadow. There are probably many other individual causes for faint shadow but the important fact is, that regardless of whether the dye is given orally or intravenously, the finding of a faint shadow usually indicates pathology. It should always be carefully studied and correlated with the history and clinical picture with re-examination in certain cases. (70)

D. No Shadow or Nonvisualization.

What has been said for faint shadow cases applies in a measure to this group of cases. In this group, however, nearly all authors agree that gallstones are the most common cause of cystic duct obstruction. Constriction from adhesions accounts for some obstructive cases and extrinsic pressure from tumor or inflammatory masses may produce obstruction in certain cases. There are still a number of cases in which the explanation must be more or less theoretical. A number of possibilities have been offered.

1. The inflammatory process inhibits cell activity
   so completely that the dye is not concentrated
   (Chiray and Panel). (70)

2. The inflammatory process may cause breaking up
   of the bile-dye combination, and the toxic pro-
   ducts interfere with the chemical union of the
   dye and bile (Rohdenberg). (70)

3. It is possible that some disturbed physiological
   action between the gall bladder and the sphincter
   of Oddi may prevent opaque bile from entering
   the gall bladder but this has never been demon-
   strated (Naunyn). (70)

4. Kirklin (40) claims that a meal containing fats
   in the evening just before taking the oral dye
   test results in twenty-five per cent more cases
   of faint or not shadow than if a fat-free meal
   is allowed.

5. Lahey and Jordan (75) blame the colon and state
   that in forty-four per cent in a series of sixty-
   five cases, the gall bladder filled normally after
   five to ten days of bowel management, whereas,
   with the same intravenous technique it had pre-
   viously shown an absence of filling or inadequate
   filling.

6. Lyon and Swalm (76) point out that catarrhal ob-

struction of the cystic duct is a common occur-
rence and is frequently seen in grade I chole-
cystitis. The Graham test shows nonvisualization
thus giving surgical indication for a medical
condition.

7. Speaking of the limitations of cholecystography,
Eusterman (31) called attention to false positives
in asthenic or neurasthenic patients with gastric
subacidity and lowered basal metabolic rate and
also mentioned papilloma and duodenal ulcer as
causes.

8. Good and Kirklin (77) reviewed the histories of
seven hundred thirty-three cases at the Mayo
Clinic. Included in the group were peptic ulcer,
pernicious anemia, hyperthyroidism, myxedema, dia-
betes, obesity, pulmonary tuberculosis and chronic
appendicitis. All had oral cholecystography. One
hundred sixty-seven had gall bladder dysfunction.
The gall bladders of one hundred six of these one
hundred sixty-seven were examined at operation or
necropsy—one hundred four had gall bladder disease,
only two were normal. Error was only 1.9 per cent.
In fifty-seven of sixty-one not operated, the
clinical diagnosis corresponded with the cholecys-
tography. In the remaining four cases the clinician

did not feel that the evidence warranted a diag-
nosis of cholecystic disease. They concluded
that extra biliary conditions embraced in this
study had little or no influence on the function
of the gall bladder, as evidenced by cholecysto-
graphy.

9. Hunt (71) reviewed a series of two hundred ninety-
seven cases and reported that in ninety per cent
of nonvisualized cases, stones were found at
operation. He stated that excretion of the dye
is prevented in cases showing an icteric index
above twenty or with well marked clinical jaundice,
rendering administration of no value in such cases,
even though no untoward symptoms may occur. Furst
and Gelber (74) made similar observations as well
as many others. Visualization may be altered by
certain physiological variations, often being faint
during pregnancy due to stasis and added density,
and faint in diabetes due to rapid elimination
associated with the high blood sugar. Reflex
emptying, supposedly from vagal stimulation, often
occurs with carcinoma of the stomach and rarely
with duodenal ulcer.

E. Deformity of Shadow.

Throughout the last five years' experience in chole-
cystography there have been noted with increasing frequency

deformities of the gall bladder shadow of varying nature,
elongations, sacculations, folds, angulations, constrictions
and the like have been observed in gall bladders which gave
a normal response to the dye. For the most part they are in
the nature of anomalies and not very significant. However,
one must distinguish between deformities of this class and
those caused by pericholecystitic adhesions. In the latter,
there is usually a malposition, with or without evidence of
traction. The long axis of the gall bladder is commonly
directed inward, instead of downward or outward. The edges
of the shadow are apt to be roughened and irregular, especial-
ly in the presence of stones. With a typical normal response
to a meal the gall bladder contracts to about one-quarter of
its size when distended. Such a finding rules out any dense
adhesions from pericholecystitis, but a fadeaway emptying,
without any evidence of contraction, is strong supporting
evidence of adhesions involving the serous coat. (70)

F. Cholelithiasis.

There are two types of stones to be considered in re-
lation to cholecystography, the opaque and the non-opaque.
The former contain enough inorganic material, principally
calcium, that they can absorb sufficient roentgen-rays to
produce an image on radiography. They are sometimes called
"positive", "dense" or "calcium" stones. The non-opaque
stones, as the term implies, are permeable to the roentgen-
rays, and are composed almost wholly of organic material,

chiefly cholesterol. They are visualized radiographically only when situated in a medium of greater or less density than themselves. They are known as "negative" or "cholesterol" calculi. These are sometimes confused with gas bubbles in the colon or duodenum and small polypoid tumors. Careful cleansing the bowel or the use of pitressin (69) usually are sufficient to eliminate the former while a detailed study of the shadow following the fat meal will aid in the differentiation of the latter.(2)

VI DIAGNOSTIC EFFICIENCY AND EVALUATION

Statistics relative to the accuracy of cholecystography are generally based on operative findings. Because of this, the cholecystographic evidence alone is open to question. In most instances there is a positive clinical as well as positive cholecystographic evidence of biliary disease. However, Kirklin and Blake (78) summarized the cholecystographic evidence in patients not submitting to surgery but who did have a final clinical diagnosis of cholecystic disease. They found that the cholecystographic data coincided with the clinical diagnosis in approximately ninety per cent, which approaches the accuracy of cholecystography in cases proved by operation.

On the other hand, Jenkinson (79) cited a series of cholecystographic examinations done on ninety-two patients in whom all had symptoms thought to be due to gall bladder disease. Seventy or seventy-five per cent of these showed normal cholecystograms and only twenty-two pathologic responses were obtained radiographically. Eight, or forty per cent, of the patients with nonfunctioning gall bladders showed a normal response radiographically after medical management. Of the twenty pathological cases, five, or twenty-five per cent, showed a negative cholecystographic response on two or more occasions even after medical management. In his opinion, one negative cholecystographic response is not

an indication for immediate operative intervention even in the presence of gall bladder symptoms.

In 1934, Rose (80) summarized the data of twenty American authors who reported statistics concerning their series of cholecystographies, particularly those checked by surgery. These twenty authors reported a total of 39,280 cases, of which 5,983 came to operation. The largest number of cases is from the Mayo Clinic, in which 3,517 were operated on out of a total of 25,191. Kirklin divided the cases into four groups with respect to the reliability of the x-ray diagnosis:

1. Non-functioning gall bladder, with and without stones, 95 per cent.

2. Poorly functioning gall bladder, with and without stones, 94 per cent.

3. Normally functioning gall bladder, with stones, 100 per cent.

4. Normally functioning gall bladder, without stones, 81.5 per cent.

Averaging the first three figures of his conclusions, it is found that in 96 per cent of the cases the x-ray diagnosis of a pathologic gall bladder was confirmed by operation, an error of only 4 per cent, while the x-ray diagnosis of normal was found to be erroneous in 18.5 per cent.

Author	No.of Cases	Method	CHOLECYSTOGRAPHY Normal	Path.	Surg	SURGICAL CHECK Normal Correct Per cent	Path. Correct Per cent
Carman	178	ivi			39		87.0
Zink	663	both			131		94.2
Stewart-Ryan	100	oral	40	60	23		95.0
Whitaker	60	ivi			28		93.0
King-Martin	407	oral			62	55	88.0
Chandler-Newell	662	both			50		
Aspray	493	both	186	312	80	93.7	100.0
Stewart-Illick	600	oral	273	327	69		97.1
Oakman	305	oral	143	162	37		97.3
Lord	100	both	19	81	100	52.6	86.4
Lockwood-Skinner	1500	oral	890	610	192		96.4
Watkins-Mills	625	oral	305	320	100	68.2	97.0
Case	2000	ivi			277	83.4	90.0
Robins-Goldberg	1014	oral	502	512	182		87.0
Kirklin	25191	both			3517	81.5	96.0
Moore	3044	both	1477	1567	416		98.7
Hawley	500	both	236	242	146		91.0
Beilin-Carlson	750	oral			150	100	98.3
Fleming	233	both			233		88.2
Littig-Lisk	800	ivi	403	397	151		
Rose	1616	both	911	801	295	64.7	96.7

The above table is taken from Rose (80). From this data, he concluded that the x-ray diagnosis of a pathologic gall bladder is dependable up to about 98 per cent. On the other hand, the diagnosis of a normal gall bladder by the x-ray is correct in an average of only 76 per cent of cases, although there is one report of 100 per cent. It is in this "x-ray normal" group that the co-operation between the clinician or surgeon and the roentgenologist is most important. The accuracy of the intravenous method over the oral method is only slightly better and so small that there is no appreciable difference.

Since Rose made his summary in 1934, numerous reports have appeared in the literature. The following table has been prepared from the recent literature of representative authors:

AUTHOR	YEAR	PLACE	NO. OF CASES	CHOLECYSTOGRAPHY			
				Normal	Impaired	Non-vis	Stone
				(Accuracy in percentage)			
Palmer and Ferguson (81) (intravenous)	'35	Univ. of Chicago	102	---	58.3	90.0	---
Hunt (71) (oral)	'36	Univ. of Nebraska	297	60.0	97.6	99.0	99.0
Bloom (82) (oral)	'36	Michigan	---	70-80	50-75	95	100
Allen (83) (oral)	'37	Delaware	31	---	---	96.7	---
Collins (84) (oral)	'37	Cleveland Clinic	150	0.0	100	96.3	97
Hardman (85) (oral)	'37	Dublin	185	72.4	83.7	91.5	95.8
Univ. of Nebraska (oral)	'38	-----	398	39.0	85.6	98.0	95.5

By way of summary, it may be said that above figures correspond rather well with those previously cited -- the average for the entire group is 91 per cent. Visualization of stones by cholecystographic methods seems to give the highest diagnostic efficiency with the no shadow group not far behind. The margin of greatest error seems to be with the group of cases showing normal cholecystograms. This is interesting inasmuch as the early writers all seemed to stress the high number of errors in the no shadow group of cases. This fact would seem to substantiate the improved methods of cholecystography.

With regard to evaluation of cholecystographic findings
Collins and Root (84) summarized one hundred fifty cases hav-
ing cholecystectomies in which the cholecystograms were accurate
in 93 per cent. They concluded:

1. A gall bladder normally visualized by cholecysto-
    graphy may be pathologic, even though in most
    instances it denotes a normal gall bladder. Con-
    vincing clinical evidence is necessary in order to
    justify surgery on the grounds of biliary disease
    if the cholecystographic findings are normal.

2. On the other hand, gall bladders which are full
    of the calcium-type stones commonly function
    normally with the dye test. In the absence of
    stones, the routine use of multiple doses of dye
    should logically increase the error in diagnosis
    so far as normally functioning gall bladders by
    cholecystography alone are concerned. There must
    be many patients who have symptoms due to chronic
    cholecystitis without stones who have normal chol-
    ecystograms. The patient should not be told that
    his gall bladder is normal on the basis of chole-
    cystographic findings alone.

3. Nonvisualization of the gall bladder without eve-
    dence of opaque calculi usually indicates a non-
    functioning gall bladder containing calculi of the

cholesterin type, often blocking the cystic duct.
But consideration should be given to the possi-
bility of other causes and re-examination done in
certain cases.

The author of this paper has made a statistical study
of 836 cases of biliary disease in the University of Nebraska
Hospital from July, 1925 through July, 1937. In this group,
there were 408 cases having cholecystographic studies who
were submitted to surgery. A tabulation of the cholecysto-
graphic findings correlated with the pathological findings
will be found on the following page. It might be well to
keep in mind that all cases over this eleven-year period are
included in the summary. This means that the cholecystogra-
phic methods used in these cases have not been well standard-
ized inasmuch as the technique used has advanced in relation
to the improved methods in cholecystography. However, the
oral method has been used in the majority of cases and the
usual routine consisted of:

1. Two doses of dye on successive days following
the evening meal.

2. Butter, cream, and greasy foods were forbidden.

3. Rectal enema on third morning.

4. Eight cc. paregoric following second dose.

5. Re-examination in cases not showing dense shadow
or calculi. $\frac{1}{2}$ glass 20 per cent cream given di-
rectly following recognition of a dense shadow.

Correlation of cholestography with pathology found in 408 cases:

CHOLECYSTOGRAPHIC FINDINGS	NO.	PATHOLOGICAL FINDINGS	NO.	PER CENT OF ERROR
1. Normal response	18	Negative gallbladder	7	61.0
		Cholecystitis with stone	1	
		Cholecystitis no stone	8	
		Cholesterosis no stone	2	
2. Non-visualized with no evidence of stone	153	Cholecystitis with stone	110	4.0
		Cholecystitis no stone	25	
		Cholesterosis with stone	3	
		Acute Cholecystitis, stone	3	
		Carcinoma of Gallbladder	5	
		Carcinoma of Pancreas	1	
		Negative gallbladder	6	
3. Non-visualized with opaque stone seen	28	Cholecystitis with stone	26	7.0
		Cholecystitis no stone	1	
		Carcinoma of Gallbladder (no stone)	1	
4. Stone with impaired concentration	80	Cholecystitis with stone	70	8.8
		Cholecystitis no stone	2	
		Cholesterosis with stone	3	
		Cholesterosis no stone	1	
		Negative gallbladder	4	
5. Stone with normal concentration	4	Cholecystitis with stone	4	0.0
6. Impaired concentration with normal emptying	125	Cholecystitis with stone	35	14.4
		Cholecystitis no stone	48	
		Cholesterosis with stone	4	
		Cholesterosis no stone	20	
		Carcinoma of Pancreas	1	
		Negative gallbladder	17	

Summary:
    (1) 82 per cent of the non-visualized group contained stones.
    (2) 40 per cent of calculi were visualized by cholecystography.
    (3) 8 per cent error in cholecystographic diagnosis of stones.
    (4) 11 per cent gross error in cholecystographic diagnosis.
        (a) 61 per cent with normal response were pathologic (11 of 18)
        (b) 7 per cent histologically normal gave dysfunction (27 of 381)
    (5) 87.5 per cent non-visualization in biliary tract carcinomas (7 of 8).

Discussion:

In the non-visualized group of cases there were 149 of 181, or 82 per cent, which had stones discovered at operation. This figure compares favorably with the 78 per cent reported by Collins (84) in a series of 100 cases. It is interesting to note that seven of eight, or 87.5 per cent, of biliary tract malignancies failed to produce a gall bladder shadow. On the other hand, there were six in this group giving no shadow and that were found to be negative in the pathologist's report. Checking this group, there were associated extra biliary conditions in all--two with diagnosis of neuresthenia, two with peptic ulcer, one toxic thyroid, and one with nephrolithiasis. The latter four were all diagnosed at operation. Thus, nonvisualization does not necessarily indicate a pathologic gall bladder and this diagnosis should not be made unless there is a suggestive history, and all other causes for the symptoms have been excluded by a complete examination.

Forty per cent of calculi, or in 103 of 265, were visualized by cholecystography. The error of 8 per cent in cholecystographic diagnosis of stones may be attributed for the most to confusing densities on the right side due to gas in the intestine in spite of the enemata that were given.

There was 11 per cent gross error in cholecystographic diagnosis. On the negative side were eleven cases having normal cholecystographic findings in which there was found micro-

scopical evidence of pathology. It will be noted that four of the cases showing normal concentration revealed the presence of stones which was confirmed at operation and the pathologist reported chronic cholecystitis. Of the eleven under consideration, one was found to contain stones so it is possible that pathologic gall bladders containing stones, function with the cholecystographic dye. Collins (86) considers this a common occurrence. It should be remembered that this represents only eleven of 408 cases so that relatively speaking, this percentage of error is more apparent than real.

On the positive side only 7 per cent, or 27 of 381, having impaired cholecystographic response, were found to be histologically negative. The associated pathology found in this group included pericholecystic adhesions in three, one peptic ulcer, one ptosis of colon, one fatty degeneration of liver, and one with a gastric neoplasm. In addition, it may be said that there is no universal agreement among pathologists as to what constitutes a pathological gall bladder. Inasmuch as there was an incidence of 7.2 per cent, 47 of 570 operated cases, of histologically negative gall bladders in this series under consideration, it can be safely said that the pathologists were rather critical in their reports. Even so, this margin of error is so small that it nearly nullifies the error on the negative side.

The diagnosis of cholesterosis by cholecystographic

methods is uncertain at best. Two gave normal response, three with associated stones were non-visualized, and the majority showed impaired concentration or faint shadow. In many instances, it was observed that although there was fairly good concentration of the dye there was delayed emptying in this group of cases.

VII CHOLECYSTOGRAPHY AND PROGNOSIS

In the literature to date, there has appeared only one
article relative to prognosis in cholecystography. This was
written by Graham and Mackey (87). They summarized the clin-
ical results in 114 cases of stoneless gall bladder subjected
to cholecystography as follows:

CHOLECYSTOGRAPHY			CLINICAL RESULT			Per cent
	Total	Well	Improved	Unimproved	Death	Relieved
Normal	10	5	1	4	0	60
Deformed shadow	8	4	2	2	0	75
Faint shadow	75	22	22	28	3	59
No shadow	21	6	7	5	3	62
Total	114	37	32	39	6	60

The ten patients who were operated on, in spite of a nor-
mal cholecystographic response, had their operations because
it was felt that the symptoms warranted the operation in spite
of the negative roentgen examination. And of the six patients
considering themselves either well or improved after operation,
Graham is of the opinion that probably the removal of the gall
bladder had little or nothing to do with the relief of the
symptoms. Routinely, he removed the appendix and is of the
opinion that possibly the removal of appendix was responsible
for the relief of the symptoms.

The gall bladder appearing normal on cholecystographic
examination rarely shows any marked pathological change in
their opinion. The fact that only 62 per cent of non-visualized
cases were relieved of symptoms caused astonishment, but they

suggested the possibility of extra biliary conditions as causes

in the unimproved cases. They concluded that in the absence

of severe pain, the beneficial results to be obtained by

cholecystectomy in cases of a stoneless gall bladder are like-

ly to be unsatisfactory in 40 per cent and to subject patients

with beginning cholecystic disease is not always the best

judgment.

A comparable study was made in the University of Nebraska

series compiled by the author. There were 229 patients having

Graham-Cole studies subjected to operation in whom follow-up

records were obtainable. Patients having cholelithiasis were

also considered. The results are summarized briefly in the

following table:

CHOLECYSTOGRAPHY			CLINICAL RESULT			Per cent
	Total	Well	Improved	Unimproved	Death	Relieved
Normal	11	8	2	1	0	91
Faint shadow	56	33	9	9	5	76
No shadow	77	51	16	3	7	87
Stones	85	61	16	3	5	92
Total	229	153	43	16	17	85

The fact that 91 per cent of the cases showing normal

responses to the Graham test considered themselves well or im-

proved needs further explanation. There were only eleven cases

in all and only two of the eleven had histologically negative

gall bladders. Six had mild cholecystitis, two had cholestero-

sis, and one had cholecystitis with cholelithiasis. Statistics

indicate that in a stone case one may expect 90 per cent re-

lieved. Routine appendectomies were done and as Graham and
Mackey (87) pointed out, the removal of the appendices could
very likely account for the improvement following cholecystec-
tomy. The single unimproved case was one of cholesterosis
while the two showing only partial relief from symptoms had
minimal pathology. It would seem that the ordeal of surgery
might account for a certain amount of improvement in functional
cases. It must be remembered that this series covers a period
of ten years and it is entirely probable that some of the
early cholecystograms were not so reliable.

The faint shadow group gave the poorest clinical re-
sults which compares favorably with Graham's figure. Since
we have already demonstrated that 82 per cent of non-visualized
gall bladders contain stones it is to be expected that the
results in this group would be close to the result in the stone
cases. The small difference could easily be accounted for by
the extra biliary conditions which sometimes produce non-
visualization. It is only reasonable to assume that stones
indicate advanced pathology and we should expect a more favor-
able prognosis in this group of cases. However, due to the
unusually high figure in all groups it can only be concluded
that as a prognostic instrument cholecystography is somewhat
unreliable--the figures speak more for the benefits of chole-
cystectomy in biliary disease.

VIII CONCLUSIONS

1. Cholecystography is essentially a test of functional
    capacity.

2. The modified oral methods are comparable to the intra-
    venous methods in efficiency and are safer and simpler.

3. Success of the methods depends upon the most careful
    attention to detail in preparation and radiographic
    technique.

4. Cholecystography in the presence of cardiovascular disease,
    extensive liver damage, and threatened uremia is contra-
    indicated.

5. Composite statistics indicate a diagnostic efficiency in
    90 per cent or more of cases whether the gall bladder is
    normal or pathological.

6. The fact that there may be error in 10 per cent of cases
    is good reason for not considering the Graham-Cole as an
    independent diagnostic instrument but should be considered
    together with the history and clinical picture.

7. Prognosis by cholecystography is not dependable.

BIBLIOGRAPHY

1. Graham, E. A. and Cole, W. H.   Roentgenologic examination
   of the gall bladder; preliminary report of a new method
   utilizing the intravenous injection of tetrabromphenol-
   phthalein, J.A.M.A. 82: 613, 1924.

2. Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S.
   Diseases of the gall bladder and ducts, Philadelphia,
   Lea and Febiger, 1928.

3. Graham, E. A.   The story of the development of chole-
   cystography, Tr. Am. Gastro-Ent. 33: 24, 1930.

4. Abel, J. J. and Rowntree, L. G.   On the pharmacological
   action of some of the phthaleins and their derivatives,
   J. Pharm and Exp. Ther. 1: 231, 1909.

5. Whitaker, L. R. and Milliken, G. A. A comparison of
   sodium tetrabromphenolphthalein with sodium tetraiodo-
   phenolphthalein in gall bladder radiography, Surg.,
   Gyn., and Obst. 40: 17, 1925.

6. Graham, E. A., Cole, W. H., and Copher, G. H. Chole-
   cystography: an experimental and clinical study, J.A.M.A.
   84: 14, 1925.

7. Ibid.   Cholecystography: the use of sodium tetraiodo-
   phenolphthalein, J.A.M.A. 84: 1175, 1925.

8. Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S.
   Cholecystography: the use of phenoltetraiodophthalein,
   J.A.M.A. 86: 1899, 1926.

9. Rous, P. and McMaster, P. D. Concentrating activity of
   the gall bladder, J. Exp. Med. 34: 47, 1921.

10. Graham, E. A., Cole, W. H., and Copher, G. H., Chole-
    cystography: its development and application, Am. J.
    Roen. and Rad. Ther. 14: 487, 1925.

11. Ibid.   Roentgenological visualization of the gall blad-
    der by the use of intravenous injections of sodium tet-
    rabromphenolphthalein, Rad. 4: 83, 1925.

12. Moore, Sherwood.   Cholecystography, after the method
    of Graham, Cole, and Copher, Rad. 13: 515, 1925.

13. Graham, E. A.   The present status of cholecystography,
    Surg., Gyn., and Obst. 44: 153, 1927.

14. Zink, O. C. A clinical study of cholecystitis with the aid of cholecystography. Rad. 6: 286, 1926.

15. Boardman, W. W. The relative value of cholecystography and the original Lyon test in establishing biliary tract function. Am. J. M. Sc. 174: 536, 1927.

16. Verbrycke, J. R., Jr. Cholecystographic gall bladder diagnosis. Tr. Am. Gastro-Ent. 29: 284, 1926.

17. Case, J. T. The relative value of cholecystography, Am. J. Roen. and Rad. Ther. 16: 238, 1926.

18. Ibid. Some clinical aspects of cholecystography. Tr. Am. Gastro-Ent. 29: 289, 1927.

19. Ibid. Some pseudo-vesicular shadows and other pitfalls in gall bladder roentgenology, Rad. 11: 1, 1928.

20. Ibid. Evalusation of cholecystography. J.A.M.A. 92: 291, 1929.

21. Waters, C. A. and Firor, W. B. Application of intravenous cholecystography in office practice. Am. J. Roen. and Rad. Ther. 25: 590, 1931.

22. Menees, T. O. and Robinson, H. O. Oral administration of sodium tetrabromphenolphthalein, preliminary report. Am. J. Roen. 13: 268, 1925.

23. Carman, R. D. Cholecystography in its application to diagnosis of gall bladder disease. Lancet, July 11, 1925.

24. Palefski, I. O. Visualization of gall bladder with sodium tetrabromphenolphthalein by oral or intraduodenal administration. Med. J. and Lec. 121: 474, 1925.

25. Whitaker, L. R., Milliken, G., and Vogt, E. C. Oral administration of sodium tetraiodophenolphthalein for cholecystography. Surg., Gyn., and Obst. 40: 847, 1925.

26. Larimore, J. W. Cholecystography: oral method of administration. Rad. 6: 156, 1926.

27. Levyn, L. and Aaron, A. H. Cholecystography by oral method. Rad. 6: 204, 1926.

28. Sabatini, G. and Milani, E. Radiologic visability of the gall bladder after administration of alkaline bromides by mouth. Inter. Med. Dig. 7: 259, 1925.

29. McCoy, C. C. and Graham, R. S.   Experience with chole-
cystography in cases coming to operation. J.A.M.A. 86:
1899, 1926.

30. King, J. H. and Martin, L.   Clinical evaluation of
cholecystography by oral administration. Tr. Am. Gastro-
Ent. 30: 203, 1927.

31. Eusterman, G. B.   Limitations of cholecystography. Tr.
Am. Gastro-Ent. 30: 203, 1927.

32. Stewart, W. H.   Some interesting observations on the
oral methods of cholecystography. Boston Med. and Surg.
J. 196: 509, 1927.

33. Stewart, W. H. and Ryan, E. J.   Some interesting ex-
periences with oral cholecystography. Tr. Am. Gastro-
Ent. 30: 210, 1927.

34. Fantus, F.   Peroral administration of colloidal contrast
media in cholecystography. J.A.M.A. 89: 162, 1927.

35. Levyn, L. and Aaron, A. H.   Cholecystography by oral
administration. Am. J. Roen. 18: 557, 1927.

36. Kirklin, B. R.   Cholecystography, a general appraisal.
Arch. Surg. 18: 2246, 1929.

37. Sosman, M. C., Whitaker, L. R., and Edson, P. J.   Clini-
cal and experimental cholecystography. Am. J. Roen. 14:
495, 1925.

38. Levene, G. and Whitaker, L. R.   New methods for clini-
cal study of the gall bladder. New Eng. M. J. 202: 203,
1930.

39. Davidson, P. B., Biguria, F. and Rosenthal, J.   Combined
oral and intravenous cholecystography. Am. J. Surg. 15:
525, 1932.

40. Kirklin, B. R.   Necessity for accurate technique in
oral cholecystography. Am. J. Roen. 25: 595, 1931.

41. Bockus, H. L., Shay, H., Willard, J. H. and Pessel, J. F.
Comparison of biliary drainage and cholecystography in
gall stone diagnosis. J.A.M.A. 96: 311, 1931.

42. Boyden, E. A.   The gall bladder in the cat. Anat. Rec.
24: 388, 1922.

43. Ibid. The effects of natural foods on the distension of the gall bladder. Anat. Rec. 30: 333, 1925.

44. Whitaker, L. R. The mechanism of the gall bladder. Am. J. Physiol. 78: 2, 1926.

45. Levyn, L. An effective gall bladder stimulant to supplant the fat meal. Am. J. Roen. 26: 409, 1931.

46. Krause, W. F. and Whitaker, L. R. Effects of different food substances upon emptying time of gall bladder. Am. J. Physiol. 87: 172, 1928.

47. Whitaker, L. R. and Ellsworth, S. W. Improved oral method for cholecystography. New Eng. M. J. 205: 1183, 1931.

48. Whitaker, L. R. "Double-Oral" cholecystography. Am. J. Roen. 35: 200, 1936.

49. Antonucci, C. La cholecystographe rapide, Presse med. 40: 983, 1932. Abstr.: Am. J. Roen 31: 415, 1934.

50. Kestel, J. L. A carbohydrate meal instead of a fat meal in cholecystography. Rad. 27: 672, 1936.

51. Jung, Tu-Shan and Moore, Sherwood. Am. J. Roen. 33: 194, 1935.

52. Sandstrom, C. De la cholecystographic par voie buccale et de sa valem, F. de Rad. et d'Electrol Ther. 16: 358, 1932.

53. Stewart, W. H. and Illick, H. E. Intensified oral cholecystography, preliminary report. Am. J. Dig. Dis. and Nutr. 1: 337, 1934.

54. Ibid. Advantages of oral cholecystography. Am. J. Roen. 33: 624, 1925.

55. Collins, E. N. and Root, J. C. The elimination of confusing gas shadows by pitressin. J.A.M.A. 107: 32, 1936.

56. Ottenberg, R. and Abramson, H. H. Production of liver necrosis by tetrachlorphenolphthalein and tetrabromphenolphthalein. J.A.M.A. 84: 800, 1925.

57. Rosenau, W. H. Dangers of the use of certain halogenated phthaleins as functional tests. J.A.M.A. 85: 2017, 1925.

58. Maddock, S. J. and Whitaker, L. R. Effects of sodium tetraiodophenolphthalein in complete biliary obstruction. Boston Med. and Surg. J. 194: 973, 1926.

59. Carmen, R. D. Cholecystography in its application to the diagnosis of cholecystic disease. Brit. J. Rad. 31: 163, 1926.

60. Huddy, G. P. B. Cholecystography. Brit. M. J. 2: 864, 1926.

61. Friedenwald, J., Feldman, M., and Kearney, F. Further experimental studies in cholecystography. J.A.M.A. 89: 195, 1927.

62. Fitz, R. A case of angina pectoris with cardiac infarct induced by intravenous injection of sodium tetraiodophenolphthalein. Tr. Assoc. Am. Phys. 43: 292, 1928.

63. Dick, B. M. and Wallace, V. G. A. Cholecystography, Toxic effect of dyes. Brit. J. Surg. 15: 360, 1938.

64. Adams, H. D. Toxic effects following the administration of sodium tetraiodophenolphthalein. S. Clin. N. A. 9: 1429, 1929.

65. Davis, W. E. Incidence of untoward symptoms following intravenous injection of sodium tetraiodophenolphthalein in cholecystography. New Eng. M. J. 205: 534, 1931.

66. Palmer, W. L. and Ferguson, A. N. Intravenous cholecystography, reactions and contraindications. Tr. Assoc. Am. Phys. 48: 385, 1933.

67. Barclay, A. E. The digestive tract. London, Cambridge Univ. Press, P.300, 1933.

68. Zaldin, Samuel. Value of left anterior oblique position in cholecystography. Rad. 26: 340, 1936.

69. Feldman, M. Importance of left oblique position. Rad. 29: 89, 1937.

70. Rehfuss, M. E. and Nelson, G. M. The medical treatment of gall bladder disease. Philadelphia, W. B. Saunders and Co. 1936.

71. Hunt, H. B. Evaluation of cholecystography in 297 cases. Nebr. M. J. 21: 372, 1936.

72. Feldman, M. and Morrison, S.   Newer interpretations of gall bladder function. Am. J. Dig. Dis. and Nutr. 3: 52, 1936.

73. Lipschutz, E. W.   Biliary dyskinesia. Rev. Gastroent. 5: 100, 1938.

74. Furst, N. J. and Gelber, L. J.   Comparative study of oral cholecystography. J. M. Soc. New J. 34: 315, 1937.

75. Lahey, F. H. and Jordan, S. M.   Management of biliary tract disease. Tr. Am. Gastro-Ent. 33: 57, 1930.

76. Lyon, B. B. V. and Swalm, W. A.   Obstruction of the cystic duct of a catarrhal variety. Tr. Am. Gastro-Ent. 31: 215, 1928.

77. Good, C. A. and Kirklin, B. R.   Influence of extra biliary disease on function of gall bladder: a cholecystographic study. Am. J. Roen. 37: 346, 1937.

78. Kirklin, B. R. and Blake, J. W.   Cholecystic disease, comparison of clinical with cholecystographic data concerning 500 patients not operated. J.A.M.A. 105: 1416, 1935.

79. Jenkinson, E. L.   Cholecystography. J.A.M.A. 107: 755, 1936.

80. Rose, C. B.   Some problems and results in cholecystography. Rad. 22: 197, 1934.

81. Palmer, W. S.   Gall bladder disease: remarks on symptoms, diagnosis and treatment. Internat. Clinics, 1: 111, 1935.

82. Bloom, A. R.   The development of the x-ray diagnosis of gall bladder disease. J. Mich. M. Soc. 35: 512, 1936.

83. Allen, B. M.   Results of gall bladder examination by varying x-ray technique. Del. St. M. J. 9: 43, 1937.

84. Collins, E. N. and Root, J. C.   Further observations on and evaluation of other procedures. Rad. 29: 216, 1937.

85. Hardman, T. G.   The efficiency of the Graham-Cole test. Brit. M. J. p. 733, Oct. 16, 1937.

86. Phillips, John.   Diagnosis and treatment of diseases of liver and biliary tract. New York, Oxford Univ. Press, 1936.

87. Graham, E. A. and Mackey, W. A.   A consideration of
     the stoneless gall bladder. J.A.M.A. 103: 1497, 1934.