Historical Features of Cholecystography

The Carman Lecture[1]

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ALTHOUGH we may not be fully aware that each discovery in science is dependent upon another of equal importance, we realize this fact when we undertake a study of the development of any significant idea. Since this is true, we often wonder why the author of one discovery does not capitalize on it and proceed with the development of the other which appears to follow so obviously. It is amazing how seldom this progression is made by one man or group of men.

The concept of cholecystography was developed by Evarts Graham and was based upon two previous discoveries. One of these was the demonstration by Abel and Rowntree (1), in 1910 that phenoltetrachlorphthalein was excreted almost entirely in the bile. The other was the demonstration by Rous and McMaster (2), in 1921, that the normal gallbladder was able to concentrate bile eight to ten times by absorbing water (Fig. 1). Abel and Rowntree were searching for a cathartic which could be given by hypodermic injection, hoping also for one which had a prolonged action. They found that phenoltetrachlorphthalein when administered hypodermically, particularly in oil, was non-toxic and would produce a prolonged cathartic effect. They noted that about 90 per cent of this substance was excreted in the bile as the conjugated and free forms (both of which are colorless) and could be demonstrated without chemical analysis by adding a drop or two of alkali to bile collected a few hours after administration of the material. Phenolphthalein itself was found to be excreted primarily by the kidneys. It was found also that phenolsulfonphthalein was excreted partly by the liver but mostly by the kidneys. Rosenthal and White (3) utilized this data later (1925) to develop the Bromsulphalein test for hepatic function, which has survived during the decades and is now recognized as a valuable liver function test.

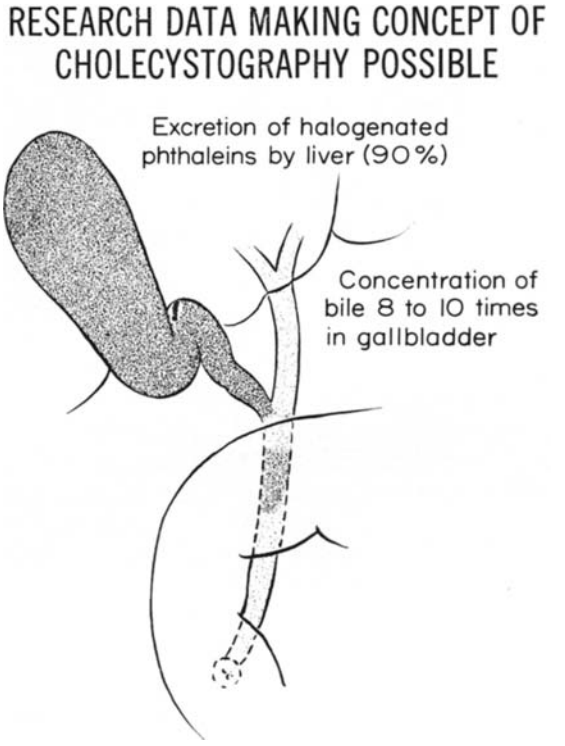

Fig. 1. The concept of cholecystography was dependent upon two experiments previously performed: (1) the discovery that 90 per cent of halogenated phenolphthaleins were excreted by the liver, and (2) the demonstration that the normal gallbladder could concentrate the bile eight to ten times.

At a meeting shortly after our discovery of cholecystography, Doctor Graham and I happened to see Doctor Rowntree. We expressed our appreciation for the valuable material he and his associate had presented and asked why they had not carried their experience further for the development of gallbladder visualization. He expressed chagrin and stated that he presumed it was

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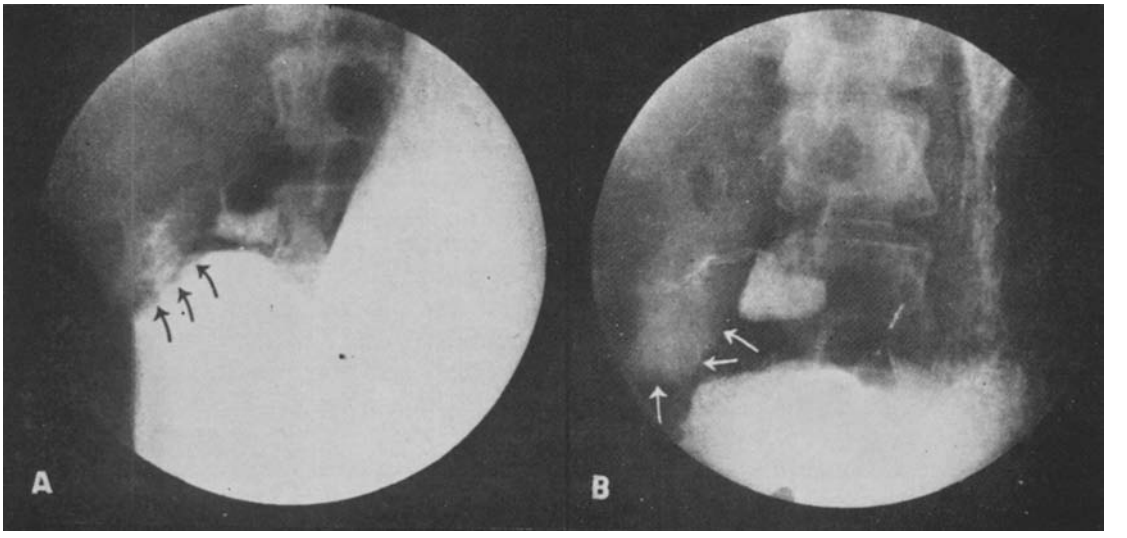


Fig. 2. A. Arrows indicate a supposed impression of the gallbladder on the antrum of the stomach. B. Cholecystogram is indicated by arrows. Normal gallbladder. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

another example of being "too close to the forest to see the trees."

RADIOLOGIC CRITERIA OF GALLBLADDER DISEASE BEFORE CHOLECYSTOGRAPHY

As an introduction to this discussion, it appears appropriate to call attention to the radiologic methods utilized in diagnosing gallbladder disease during the period preceding the development of cholecystography. As at present, opaque (calcium) stones were demonstrable on the plain film, but it was realized that such stones represented a minority of those existing and found at operation. The other mechanisms of diagnosing gallbladder disease were much less accurate. Some are referred to as the indirect method. Adhesions caused by pericholecystitis produced dislocation or immobilization of other organs, which could be demonstrated during the barium-meal examination. In this phase of diagnosis, Lewis Gregory Cole (4) was a pioneer and described deformities of the stomach, duodenum, and colon adjacent to the diseased gallbladder (Fig. 2). A little later A. W. George and R. D. Leonard (5) began emphasizing the production of a shadow (thickened wall) on the plain film by the pathological gallbladder. They maintained a working hypothesis that the normal organ is not visualized on a plain film.

These are only a few of the mechanisms utilized forty years ago by roentgenologists in diagnosing disease of the gallbladder. So common was such disease that discussion of the radiologic technics represented a paramount issue, and unfortunately involved a lot of controversy because the characteristics described as having diagnostic value were so uncertain. All of us realize that these indirect methods were subject to a high percentage of error, but by the arguments to which they gave rise they fostered the exchange of ideas. Some radiologists were so enthusiastic about these indirect methods that they were very loath to accept cholecystography as having any value.

I still have a vivid recollection of numerous occasions when, as a house officer, I would consult Dr. Sherwood Moore, Professor of Radiology in Washington University, concerning interpretation of films demonstrating possible gallbladder disease. Although the diagnosis in a few cases seemed obvious, the findings on the film appeared uncertain to me. Dr. Moore was an astute diagnostician and warned me of the questionable value of many of the indirect methods.

MY CONTACT WITH WALTER MILLS AND RUSSELL CARMAN

I suspect that the majority of radiologists in attendance upon this lecture are not old enough to have known Walter Mills and Russell Carman personally, although all of you know of their work. Walter Mills and Russell Carman were two of the important pioneers in the development of technics and criteria for diagnostic barium studies of the gastrointestinal tract. I, of course, knew Dr. Mills quite well because of my contacts with him in Barnes Hospital, St. Louis, when I was an intern and house officer. Dr. Mills was a serious-minded person who worked incessantly at his job. He was so busy he seldom stopped to talk to us, but I became deeply impressed with his very receptive mind and brilliance as a fluoroscopist. The sharpness of his eye was brought vividly to my attention one day in the viewing room.

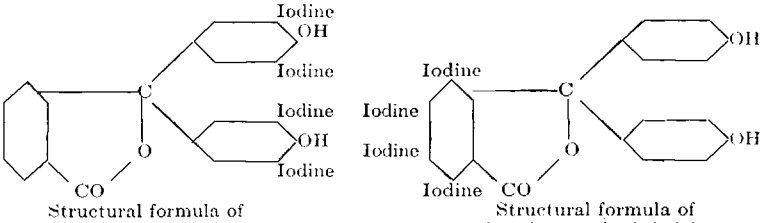
After we had obtained our first cholecystogram (in the dog), with negative results for several days thereafter, I went back to the Radiology Department, got the first positive film out again, and looked it over to be certain that we were not misled by some round bone or other object the dog might have swallowed accidentally. We did not make plain films of these animals before administration of the medium and foreign bodies therefore could not be ruled out satisfactorily. As I was standing near the view box studying the film to make sure the shadow was in fact that of a gallbladder, out of the corner of my eye, I saw Doctor Mills come through the door and walk through the viewing room toward an exit. He was wearing his dark glasses and peering staight ahead in his rush to get to the adjacent room. I heard him walking rapidly and then suddenly skid to a stop. "Young fellow," he said, "where did you get that film?" I replied that this was the film of an animal used by Dr. Graham and myself in some experiments attempting to visualize the gallbladder. I stated further that we had obtained this one positive shadow, but had been unable to reproduce it and that I was studying it to rule out a foreign body. To this his reply was: "Don't be silly, young man; this is a shadow of the gallbladder and it is so dense that application of the method to the human being is purely a matter of additional experimentation."

My only contact with Russell Carman was during a visit he paid us shortly after we published our first paper on cholecystography. I had, of course, heard much about him and felt highly complimented that he would come to St. Louis to talk to us about our work. He told us frankly that he wanted to institute the diagnostic procedure in the Mayo Clinic. We explained that we were making our solution of calcium tetrabromphenolphthalein in individual doses, that after its preparation it had to be sterilized, and furthermore it took an hour to give it. I estimated that it took three hours to prepare the solution and to complete the injection into the patient. He looked quite perturbed and said: "That's fine, young man, but how are we going to conduct these injections on 25 patients in one morning?" Although I had heard that the Mayo Clinic was a large institution, I did not realize it was that large, and Dr. Carman must have been amused at my obvious surprise and mild shock when I heard how many patients might be signed up for a gallbladder test on a single day. I told him that we were conducting some experiments with sodium tetraiodophenolphthalein, which was so soluble it could be prepared more rapidly. He seemed much relieved, but I added quickly that up to date the toxicity of the iodine compound was quite inconstant and undependable.

Dr. Carman made no further comment, but he obviously had made up his mind to try the procedure because a short time later he sent Dr. Virgil Counseller down to visit us and learn the technic. I recently had a very pleasant visit with Dr. Counseller (who now lives in Phoenix, Ariz.) over the phone. He told me that, after returning to the Mayo Clinic following his visit with us, he began injecting calcium tetrabromphenolphthalein solution, as we were

doing, and that he might inject as many as 15 to 16 patients per day. I do not know how Dr. Counseller arranged the intravenous injections with the required medical observations, but it speaks well for his organizing ability. Nor do I know whether he was trying to be kind to me when I asked him about reactions, but he stated that they were not troubled with serious reactions, although they had numerous minor ones.

naturally used a dose only slightly below the lethal level. On the contrary, when we began their use in human beings, we cut the dose to one-third the lethal dose of the bromine compound in animals and about one-fifth the lethal dose of the iodine compound. We did this to obtain a wide margin of safety, particularly since the inconstant toxicity suggested that some patients might be allergic to the drug. The fact that the toxicity for the various



Structural formula of tetraiodophenolphthalein.

Structural formula of phenoltetraiodophthalein.

Fig. 3. Structural formulae for the halogenated phthaleins. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

PHARMACOLOGY OF HALOGENATED PHTHALEINS

The halogenated phthaleins (Fig. 3) behave pharmacologically very much as does phenolphthalein itself. Tetrabromphenolphthalein has a molecular weight of 634 and contains about 50.5 per cent bromine by weight. Tetraiodophenolphthalein has a molecular weight of 822 and contains 61 per cent iodine. At the beginning of our experiments, we were aware of the fact that, because of the increased molecular weight, the iodine compound should yield better radiologic shadows than the bromine compound, but our preliminary investigations revealed a greater though inconstant toxicity of the iodine preparation. Later we learned that this toxicity was related to impurities. We also learned that the lethal dose of the various halogenated phthaleins is the same, namely, 0.2 to 0.3 gm. per kilogram of body weight; this was about one-fifth the dose required for clinical use with the iodine compound and about one-third the clinical dose for the bromine compound. When we gave these drugs to our animals, hoping to produce cholecystographic shadows, we halogenated compounds was about the same indicated rather clearly that the phenolphthalein radical and not the halogen was responsible for the toxic effect.

When we injected the solution rapidly into animals, a fall in blood pressure resulted. In animals lethal and sublethal doses injected intravenously often produced necrosis of the liver, but we did not encounter this effect in any human being from whom we obtained biopsy specimens. Vomiting was common in animals as well as in man. Diarrhea was observed after oral administration in both animals and human beings, but not after intravenous injections.

ANIMAL EXPERIMENTS

Before beginning work on our problem, we consulted the Mallinckrodt Chemical Works, inquiring if they would be interested in supplying several halogenated phthalein compounds to aid us in our efforts to visualize the gallbladder. They expressed a willingness to co-operate and assigned a chemist, Dr. N. Drake, to work with us in the manufacture and procurement of such compounds. It happened

TABLE I: OF 89 DRUGS TESTED EXPERIMENTALLY, THE 13 LISTED BELOW WOULD PRODUCE A SHADOW OF THE GALLBLADDER IN THE DOG OR RABBIT

I. HALOGENATED DERIVATIVES OF PHENOLPHTHALEIN COMPOUNDS
   1. Tetraiodophenolphthalein
   2. Tetrabromphenolphthalein
   3. Octabromphenolphthalein

II. HALOGENATED DERIVATIVES OF ISO-PHENOLPHTHALEIN
   1. Tetraiodo-iso-phenolphthalein

III. HALOGENATED DERIVATIVES OF PHTHALEIN COMPOUNDS
   1. Phenoltetrabromphthalein
   2. Phenoltetraiodophthalein
   3. Tetrabromphenoltetrachlorphthalein
   4. Tetrachlorphenoltetrabromphthalein

IV. SULPHONATED HALOGENATED DERIVATIVES OF PHENOLPHTHALEIN
   1. Phenoltetrabromsulphonphthalein (Bromsulphalein)

V. HALOGENATED DERIVATIVES OF RESORCINOLPHTHALEIN OR FLUORESCEIN
   1. Tetrabromfluorescein (eosin)
   2. Tetraiodofluorescein (erythrosin)
   3. Tetraiodotetrachlorfluorescein (rose bengal)
   4. Octaiodofluorescein

that the first compound we could obtain was phenoltetrachlorphthalein, which we injected into some dogs intravenously to obtain preliminary data on toxicity. We did not expect this compound to produce a shadow of the gallbladder, since the atomic weight of chlorine is 35.5 compared to 80 for bromine and 127 for iodine. Realizing that elements with high atomic weight would cast better x-ray shadows, we planned early in the experiments to obtain strontium and calcium salts of the bromine and iodine compounds. Practically all of the free acids of the halogenated phenolphthalein compounds are insoluble in water, but they become soluble when salts are formed by addition of alkalis.

Accordingly, week after week we tried the sodium salt, calcium salt, and strontium salt of tetrabromphenolphthalein and tetraiodophenolphthalein (see Table I). I made the solutions by the addition of sodium hydroxide, calcium hydroxide, and strontium hydroxide to the acid compounds. The injections were given to dogs and rabbits. The early samples of tetraiodophenolphthalein were more toxic than the bromine salt. For this reason, in our early experiments we devoted more of our attention to the bromine compound.

I injected at least 200 dogs and rabbits without obtaining a single shadow of the gallbladder. From physiologic knowledge already obtained, we deduced that six to eight hours would be required after intravenous injection of one of these halogenated solutions for it to reach sufficient concentration in the gallbladder to cast a shadow. Accordingly, even in our early experiments, we would inject the animals at 8:30 or 9:00 A.M. and take roentgenograms at 4:30 or 5:00 P.M. Not having any x-ray equipment in our surgery laboratory, we had to transport the animals across the street to the x-ray room in the hospital. This task fell to my lot, since our laboratory assistants left the building at 5:00 o'clock, although they did kill the animals for me before they left. I shall always be most grateful to Miss O'Brien, who was the chief technician in the hospital x-ray room at the time, because she was extremely co-operative in taking the roentgenograms for me. She did not hesitate to stay overtime to make sure that we had good films. Since the roentgenograms were the crucial part of the experiment, one can understand how appreciative I was of this congenial co-operation; without Miss O'Brien's willingness, the experiment would have been much more difficult and perhaps discouraging.

THE FIRST SHADOW AND THE ROLE OF SERENDIPITY

After injecting over 200 animals without success, we finally obtained a gallbladder shadow (Fig. 4) in one of our dogs (November 1923). The shadow was so dense that I became convinced it would be reproducible in the human being. Miss O'Brien developed the film and, when she saw it, called out to me from the darkroom, saying she had something to show me. After confirming the shadow, I called Dr. Graham, who as usual was working late. He immediately dropped his work and was at the hospital in a few minutes. We both stood there admiring the dripping film with a white shadow in the center as if we had found the traditional pot of gold at the end of the rainbow. After a few moments

of silence, he slapped me on the back and announced enthusiastically: "Well, Warren, we have a muskie on the line and, if the line doesn't break or the boat capsize, we should land him."

My logbook, in which I kept records of these animals, disappeared, as did the x-ray film of the dog showing the dense shadow. Accordingly, I do not have the exact date when this first shadow was obtained, but I am sure it was sometime in the middle of November 1923, perhaps November 15. Incidentally, the notebook and film disappeared about the same time that we had a visitor in town. After returning from a meeting a couple of years later, Dr. Graham told me that he had been told by a friend that the visitor had the first cholecystogram in his possession. When Dr. Graham was asked about the film, his jaw would set squarely, he would mumble some profane words, and would look into space. A short time later, he told us he had the film, although he would never tell us exactly where it had been and how he obtained its return to St. Louis. Incidentally, Glover Copher told me a short time ago that this early animal film and the first human cholecystogram were still part of an exhibit on cholecystography in the Mallinckrodt Institute of Radiology.

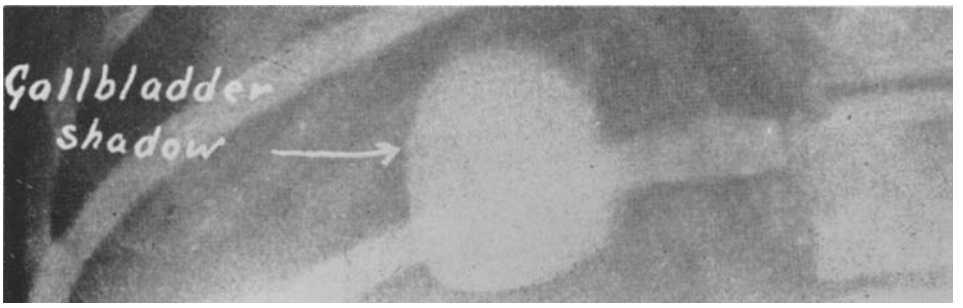
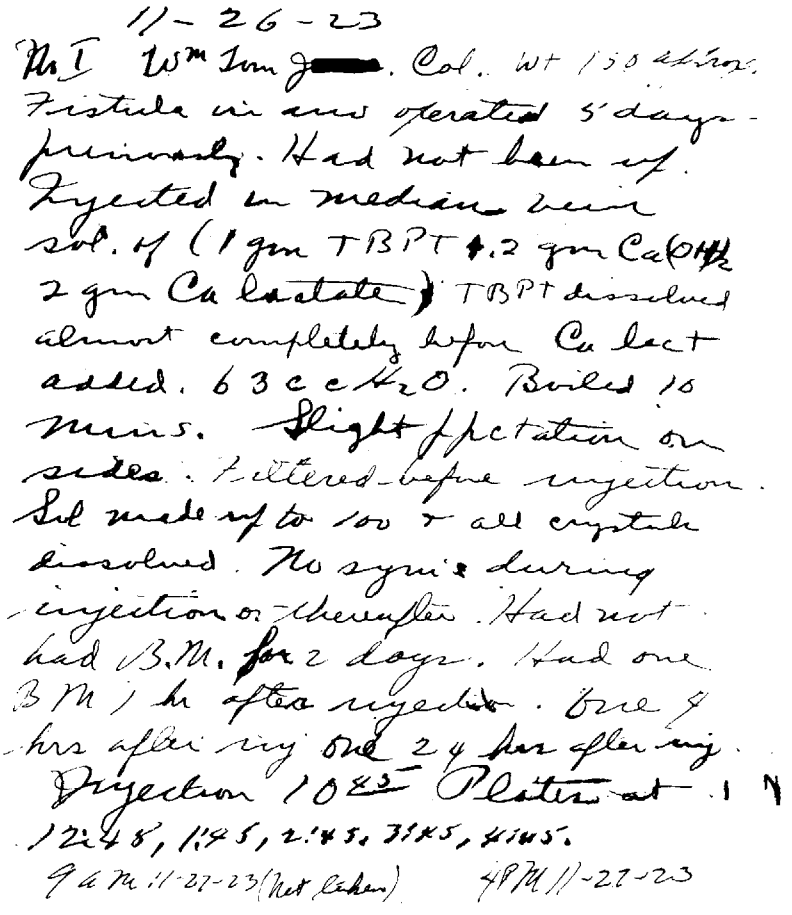


Fig. 4. The first successful cholecystogram in a dog. The animal, weighing 5.25 kg., was given 1.5 gm. of tetrabromphenolphthalein with 0.3 gm. of calcium hydroxide. (Reproduced by permission from Graham and Cole: J.A.M.A. **82**: 613, 1924.)

This first visualization in the dog was obtained with calcium tetrabromphenolphthalein. We repeated the experiments on several animals during the next several days but did not obtain a single shadow. I went over the protocol of the animal that gave the positive shadow, trying to find a clue as to why it was positive and none of the others were, but I was not able to detect any difference in my technic. Needless to say, this was very discouraging, and in desperation I asked Bill, the animal caretaker, if the particular dog which gave the positive shadow had been treated in any way differently than the others. Bill thought for a minute and with some hesitation replied that he could not recall any differences in the treatment of the animals. I thought I had detected a slightly guilty expression on his face and, with the hope of breaking down any reticence, told him that this animal produced the results we were working for. With this statement his expression of apprehension changed completely, and after a few moments he remarked meekly, "Well, Dr. Cole, there *was* something different. I forgot to feed that dog the morning you injected him." He said this with great hesitation, presumably expecting a reprimand. I was so elated with this statement that I lunged at him, apparently like a wild animal, slapped him on the back and grasped his hand at the same time. He retreated backward, apparently thinking I was going to throttle him. However, I seemed so joyous over the occasion that he quickly lost his fear and became himself again.

I was aware of the report made by Boyden (6) at the annual meeting of the American Society of Zoologists that feed-



11-26-23
No 1 Wm Jon J[redacted]. Col. Wt 150 abt.
Fistula in ano operated 5 days
previously. Had not been inj.
Injected in median vein
sol. of (1 gm TBPT 4.2 gm $Ca(OH)_2$
2 gm Ca lactate) TBPT dissolved
almost completely before Ca lact
added. 63 cc H_2O. Boiled 10
mins. Slight ppt'tation on
sides. Filtered before injection.
Sol made up to 100 + all crystals
dissolved. No sym's during
injection or thereafter. Had not
had B.M. for 2 days. Had one
B M / hr after injection. One 4
hrs after inj one 24 hrs after inj.
Injection 10:45 Plates at 1 P
12:45, 1:45, 2:45, 3:45, 4:45.
9 A M 11-27-23 (Not taken) 4 P M 11-27-23

Fig. 5. Photograph of page 1 of my log book. We were using proper caution, as indicated by the fact that I gave this patient, the first one, only 1 gm. of tetrabromphenolphthalein. No reaction was sustained. (Reproduced by permission from Am. J. Surg., February 1960.)

ing (especially fat) was an important item in the filling and emptying of the gallbladder in animals, although he had not clarified the exact role it played in gallbladder function. Nevertheless, I felt confident that we had now found the key to the means of obtaining shadows and knew why our original experiments had been unsuccessful. Accordingly, I injected more animals after a short starvation period and obtained positive shadows in a high percentage. After demonstrating that the visualization could be duplicated at will, we moved rapidly to developing a technic which could be utilized in human beings.

We continued our experimentation with numerous drugs, most of which were halogenated phenolphthalein of some type or other. Altogether we tested 89 drugs, 13 of which (see Table I) would produce shadows of the gallbladder in animals. All except three or four, however, had serious drawbacks, such as severe toxicity, instability, and high cost.

APPLICATION OF THE METHOD TO THE HUMAN BEING

Needless to say, we were gravely concerned about the toxicity of these halogenated compounds when we began their use in the human being. As stated previously, the compound was brought into solution only after the addition of an alkali; believing that the calcium or strontium salt would produce a better

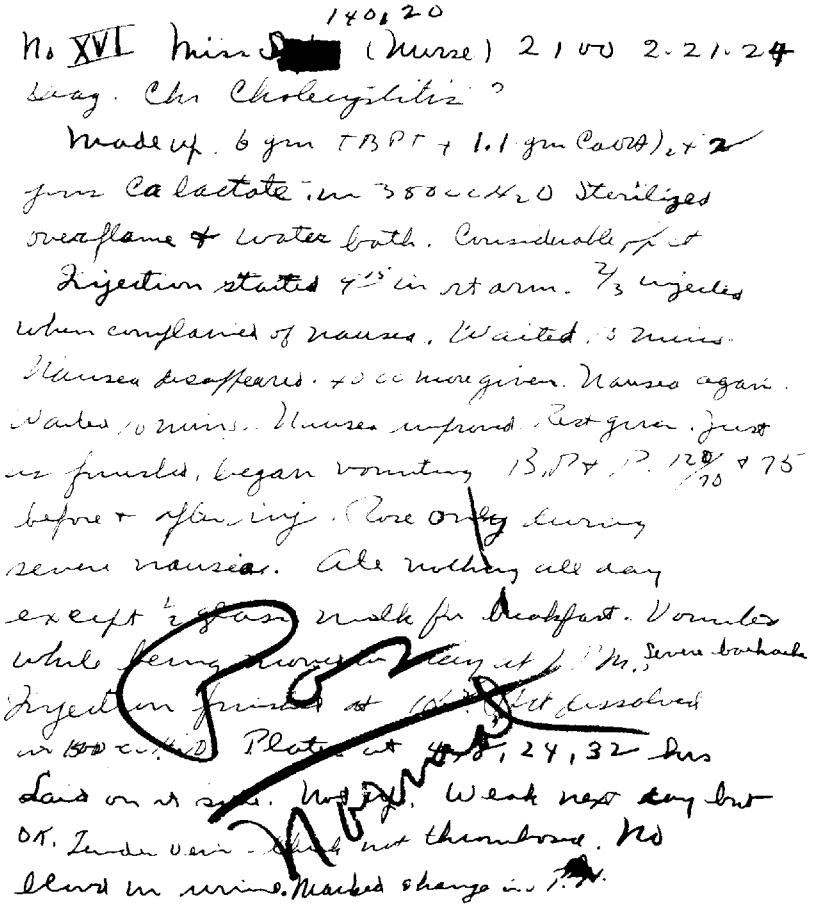


Fig. 6. Photograph of my notes on the first patient upon whom a definite cholecystographic shadow was obtained (see Fig. 7). She experienced severe nausea, back pain, and mild vomiting, and was extremely miserable. She was a nurse, and therefore I felt particularly apprehensive about her welfare. After about twenty-four hours, however, her symptoms disappeared, although she told me she had no appetite for days. (Reproduced by permission from Am. J. Surg., February 1960.)

shadow, we concentrated on these two elements as positive ions. Later we realized that the amount of calcium was so small compared to the halogen that there would be very little advantage of the strontium salt over the sodium. Moreover, the sodium salt was more physiologic.

By trial and error I learned that, for each gram of tetrabromphenolphthalein, 0.2 gm. of calcium hydroxide had to be added to 50 to 60 c.c. of distilled water to obtain solution of the compound. Even with this amount of alkali, it was necessary to grind the mixture with a mortar and pestle.

INTRAVENOUS USE OF CALCIUM TETRABROMPHENOLPHTHALEIN

Since we obtained the first shadow in the dog with calcium tetrabromphenolphthalein, we naturally decided to use this compound first in patients. We were very fearful of its toxicity, however, and began its use cautiously, as indicated by the reproduction (Fig. 5) of the page in my work book describing the injection in the first patient. We gave this first patient only 1 gm. of tetrabromphenolphthalein. We did not expect a shadow with this small dose, and we gradually increased the amount to 5 or 5.5 gm. Actually, we increased the dose 1 gm. per patient until

the fifth patient received 5 gm. The patient receiving 5 gm. displayed no reaction beyond a brief feeling of warmth over the entire body. Nor did the sixth patient, receiving 6 gm., sustain any reaction of greater intensity. By this time, however we apparently had used up our share of good luck, and serious reactions occured in several patients receiving 6 gm. We appreciated that this dose was too large and reduced it to 5 or 5.5 gm. Roentgenograms on the ninth patient did show a very faint shadow but we did not obtain a really good shadow until the sixteenth injection. Most of these patients had symptoms of gallbladder disease, and it is very likely that none of the modern compounds would have produced a shadow.

The sixteenth patient was a nurse who had pain in the right upper quadrant, with a questionable diagnosis of gallbladder disease. In this instance I mixed 6 gm. of tetrabromphenolphthalein with 1.5 gm. of calcium hydroxide and 2 gm. of calcium lactate and, after grinding the chemicals together, added distilled water up to 350 c.c. (Fig. 6). The injection was done on Feb. 21, 1924. Knowing that rapid injection in animals tended to increase reaction and even cause a drop in blood pressure, I started very slowly, particularly since the patient was one of our nurses at Barnes Hospital. My hopes of completing the injection uneventfully were blasted, although the reaction was not as serious as in some of the other cases. As indicated in the account in my logbook (Fig. 6), when about two-thirds of the material had been introduced, the patient began complaining of nausea. After a wait of ten minutes, the nausea disappeared and injection was resumed, but after introduction of about 40 c.c. the nausea returned. This was repeated a few times, an hour or two being utilized for completion of the injection. Just after it was finished the patient began vomiting, although her blood pressure and pulse remained stable. She remained nauseated for a couple of days and I felt very guilty at being responsible for her extreme discomfort. It is fortunate that we obtained a good visualization of her gallbladder because she was so miserable that I would certainly have lost a lot of my enthusiasm for continuing with the injections which to date had not yielded any good shadows of the gallbladder.

As I remember, the symptoms, which consisted of pain in the right side of the abdomen, particularly the upper quadrant, later were proved to be of renal origin, although the patient had very few urinary symptoms at the time. At least we were able to tell her that her gallbladder was normal and thus probably saved her a needless cholecystectomy, which might have been advised erroneously because the urinary findings were not as clear-cut as they should have been.

This shadow, which was a very dense one (Fig. 7) gave us renewed enthusiasm, since we were now convinced that the theory of producing a shadow of a normal gallbladder in the human being was valid. We had no idea as to how often the medium would get into the gallbladder containing stones, and just what the contrast of the stones with the opaque medium would look like.

ROLE OF GASTRIC CONTENT ON TONUS OF THE SPHINCTER OF ODDI

The importance of an empty stomach for the production of a positive gallbladder shadow was so striking that I decided it was essential to have more data on this point if we were to obtain optimum shadows. Accordingly, I planned a series of experiments on dogs, for observing the effects of various foods and chemicals in the duodenum and stomach on the tonus of the sphincter of Oddi (7). By inserting a cannula in the proximal end of the common duct of a dog and attaching it to a bottle containing saline colored with methylene blue, I was able to determine the pressure required to force fluid through the sphincter of Oddi. An incision 2 inches long was made in the duodenum over the ampulla of Vater, and the pylorus as well as the cardia was occluded with a ligature. I then removed the gastric contents through a small incision into which

was fitted a T-tube through which the stomach could be irrigated.

Various solutions and food mixtures were placed in the stomach, and the pressure reading required to break through the sphincter of Oddi was recorded. With an empty stomach the pressure necessary varied between 40 and 100 mm. of water. Irrigation of the stomach with physiologic saline required 10 to 30 mm. of pressure. When 75 to 150 c.c. of 0.5 per cent of sodium hydroxide were put into the stomach, the amount of pressure necessary to force fluid through the sphincter of Oddi rose to a point between 100 and 125 mm. When the sodium hydroxide was replaced with 0.5 per cent hydrochloric acid, the requirement dropped 75 to 100 mm. It was apparent that maintaining an alkaline medium in the stomach would cause a contraction of the sphincter of Oddi, thus allowing a better flow of bile into the gallbladder, where concentration could then take place most effectively. Actually these experiments were so conclusive that we adopted the principle of giving 2.5 gm. of sodium bicarbonate every three hours while the patient was awake during the first twenty-four to forty-eight hours following administration of the medium.

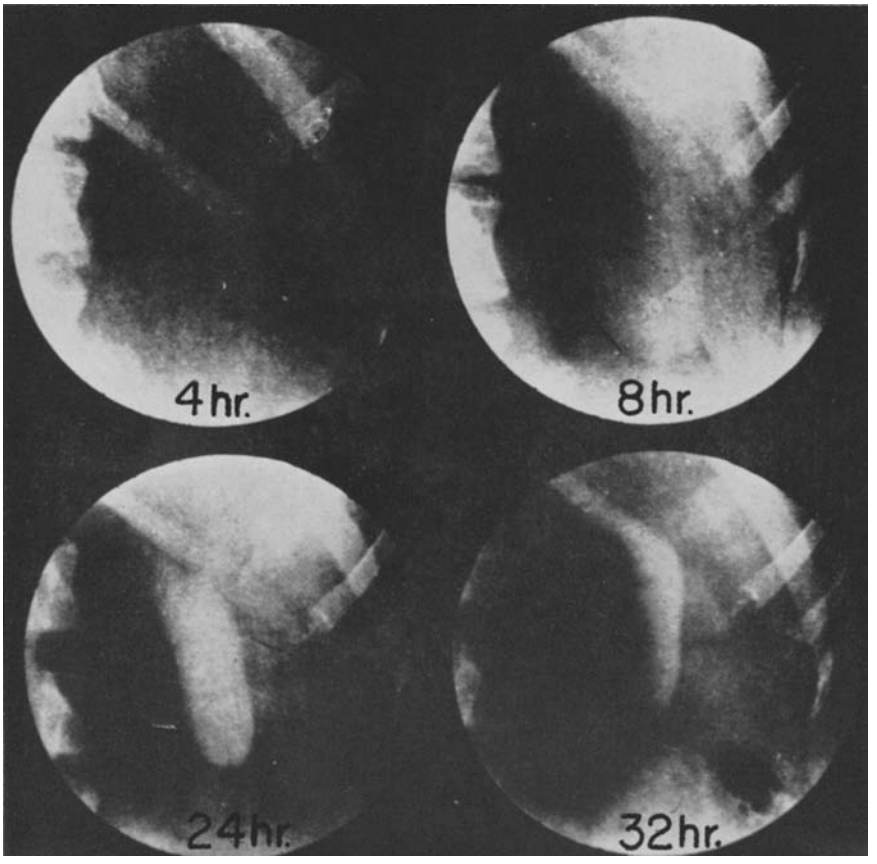


Fig. 7. The first successful cholecystogram in the human being, obtained Feb. 21, 1924. The patient received 5.5 gm. of tetrabromphenolphthalein. Films were taken at four, eight, twenty-four, and thirty-two hours. No shadow is seen on the four-hour film; on the eight-hour film the shadow is large and faint. A dense shadow is observed at twenty-four hours. The persistence of the shadow is attributed to the prolonged starvation period. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

STANDARDIZATION OF TECHNIC AND USE OF VARIOUS COMPOUNDS

After modifying our procedure slightly

for the first 20 or 30 cases, we were able to arrive at some conclusions concerning a standard technic. These were described in our first report (1924) on visualization of the gallbladder (8) and seemed so pertinent and so peculiar to us now that I am quoting from that report.

"Six grams of tetrabromphenolphthalein are mixed with 1.2 gm. of calcium hydroxide, ground in a mortar with a few cubic centimeters of water, and dissolved in from 325 to 350 c.c. of distilled water. Addition of calcium lactate was found to produce a more stable solution and slightly increase its solubility. Therefore, a solution of 2 gm. of calcium lactate in a few cubic centimeters of water is added. The solution has been sterilized by heating it to the boiling point over a flame, and maintaining the temperature between 95 and 100° C. for fifteen minutes. Occasionally, a small amount of the calcium salt precipitates on the bottom of the receptacle. This dissolves readily on the addition of a small amount of water or saline solution after the clear solution is decanted off. The solution is filtered and given intravenously by the gravity method, similar to an arsphenamine injection. The solution is introduced slowly. Usually from twenty-five to thirty minutes is consumed in the injection, so that symptoms, if present, can be detected early. Roentgenograms of the gallbladder region are taken at intervals of several hours, beginning three hours after the injection."

Orders, as listed in our second report (9), were as follows:

"1. Omit breakfast.
"2. Omit lunch (a glass of milk may be given if hunger is too pressing).
"3. Take 40 gr. (2.6 gm.) of sodium bicarbonate every three hours for forty-eight hours, day and night, while awake.
"4. Lie on the right side of the abdomen or be up.
"5. Take water, if desired, by mouth.
"6. Omit protein from the evening meal on the day of injection."

"X-ray films are then taken at four, eight, twenty-four, and thirty-two hour periods (no special technic)."

INTRAVENOUS USE OF SODIUM TETRABROMPHENOLPHTHALEIN

In this period when cholecystography was being developed, we were just becoming aware of toxic effects which were later ascribed to pyrogens. Severe reactions, including chills, fever, etc., were obtained occasionally after the administration of physiologic saline or 5 per cent glucose intravenously. With this possibility in mind, we decided that we should try the sodium salt of tetrabromphenolphthalein, since we knew that this compound was very soluble and could be injected in no more than 20 to 40 c.c. of fluid. It appeared that the large amount of fluid necessary to obtain a solution with the calcium salt might be responsible for the reactions, although we considered the possibility that the calcium salt itself might have a toxicity not possessed by some of the other salts, particularly sodium tetrabromphenolphthalein. Accordingly, we changed immediately to the sodium salt. For a time I made it myself, using sodium hydroxide to bring the tetrabromphenolphthalein into solution. By this time, the usefulness of the method was sufficiently established to convince the Mallinckrodt Chemical Works that they should prepare the sodium salt for commercial purposes. Upon request, they agreed to do this, partially putting me out of the pharmaceutical manufacturing business, though I still had to dissolve the agent and sterilize the solution. Actually, I believed that having them make the salt would possibly eliminate the reactions. I remember, however, that the reactions from solutions made from the salt prepared by them were just as common as they were from the sodium salt I made. I was anxious to be relieved of this extra task because I wanted to spend the time on a search for better chemicals and a wider application of the process, namely, visualization of the kidneys, spinal canal, and cerebral ventricles.

Knowing that we could give sodium tetrabromphenolphthalein slowly without any reaction during the first half of the injection, we decided to give the solution in two injections of 20 c.c. each, one half-hour apart. This reduced the reactions considerably and we maintained the principle of giving the medium in two doses even after we began the use of sodium tetraiodophenolphthalein and sodium phenoltetraiodophthalein. During injection of this concentrated material, the patient

would often display minor symptoms, which would be relieved if the injection was terminated for five or six minutes. This made it essential to devise a means of injecting the solution for a time and alternating with injection of physiologic saline to maintain patency of the vein. Accordingly, I devised a carrier (Fig. 8) for the two 20-c.c. syringes; in one we placed physiologic saline and in the other the medium. These syringes simplified the injections and minimized the danger of extravasation and the production of a slough, which would occur if more than 1 or 2 c.c. of the concentrated solution escaped outside the vein.

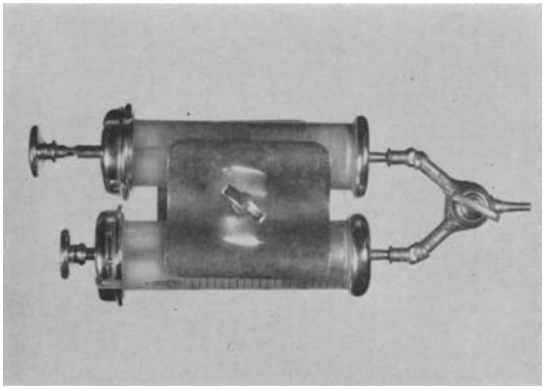


Fig. 8. Carrier for two syringes devised to allow alternate injections of physiologic saline solution and dye. This made it possible to stop the injection temporarily (and keep the needle open with saline) if a reaction was sustained. Often, early mild symptoms would disappear in a few minutes if the injection were stopped or the rate decreased. (Reproduced by permission from Am. J. Surg., February 1960.)

INTRAVENOUS USE OF SODIUM TETRAIODOPHENOLPHTHALEIN

Shortly after we started using sodium tetrabromphenolphthalein we began the use of sodium tetraiodophenolphthalein because the atomic weight of iodine is so much greater than that of bromine (127 *versus* 80). It was obvious that a substance with a higher atomic weight would be more impervious to the x-ray. As stated previously, we began the use of the tetraiodophenolphthalein compound before the bromine compound, but dropped it because of its greater toxicity. Unknown to us, Whitaker and Milliken (10) were also working on the comparative usefulness of sodium tetraiodophenolphthalein. Their article and ours (11) recommending the use of sodium tetraiodophenolphthalein appeared in print in January 1925.

ORAL ADMINISTRATION OF SODIUM TETRAIODOPHENOLPHTHALEIN

Since the intravenous administration of any diagnostic or therapeutic agent is more complicated than the oral, it was obvious that attempts should be made to administer cholecystographic media by mouth. In September 1925 we reported (12) our comparative experiences with intravenous and oral methods, noting that the shadows could be obtained with the oral method, although the accuracy seemed greater following intravenous injection (Fig. 9). A short time later, Menees and Robinson (13) reported fairly accurate interpretation of gallbladder shadows following the oral use of sodium tetraiodophenolphthalein. Both groups of investigators noted that 3.5 gm. was an adequate dose for adults. Obviously, the interval for taking films would be different than with the intravenous method, in view of the slower excretion following oral administration. Accordingly, with the oral method we took films fourteen, eighteen and twenty-four hours after administration of the medium.

Shortly after this, most clinicians adopted the oral route because administration by this method was more convenient. Also the reactions were less serious, even though they were more common (Table II). A big disadvantage of the oral method was that vomiting or diarrhea commonly developed. As a result of vomiting, the patient might not absorb enough of the medium to produce a shadow; accordingly, the test would have to be repeated or an intravenous examination be done. We did note that vomiting could be avoided by coating the capsule with some substance (*e.g.*, keratin) which was not absorbed in the stomach. This prevented the vomiting but did not eliminate diarrhea.

SIMULTANEOUS CHOLECYSTOGRAPHY AND LIVER FUNCTION

Early in our investigations we began experimenting in the laboratory with the phenoltetrahalogenphthalein compounds which are isomers of the tetrahalogenophenolphthaleins. Sodium tetraiodophenolphthalein is a blue powder which, when dissolved in water, produces a blue solution that does not stain the blood serum. Sodium phenoltetraiodophthalein is a purple powder producing a beautiful fluorescent color in solution that will stain a tube of blood serum to which a drop of sodium hydroxide (10 per cent) has been added. A few years previous to this work, Rowntree and associates (14) had published data indicating that phenoltetrachlorphthalein was useful in determination of liver function. Preliminary experiments with phenoltetraiodophthalein indicated that it would produce shadows as dense as the tetraiodophenol compound; in fact, no more than 2.5 gm. of sodium salt was necessary for a good shadow of a normal gallbladder.

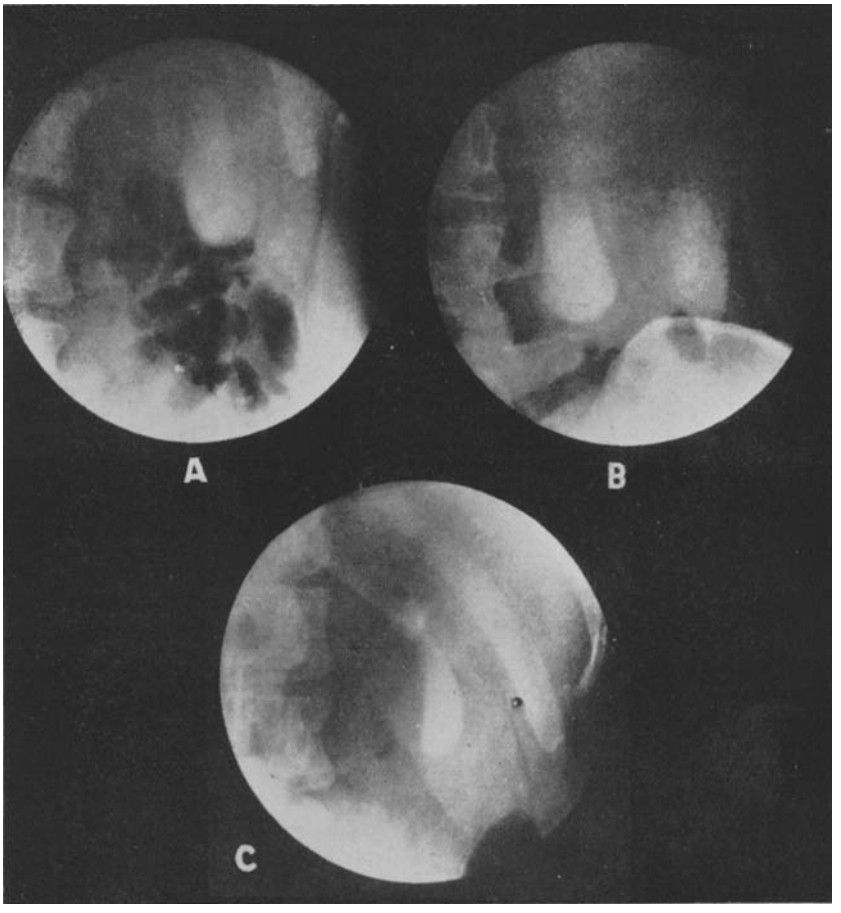


Fig. 9. Normal cholecystogram after oral administration of medium. A. Fifteen hours after ingestion. B. Nineteen hours. C. Twenty-three hours. (Reproduced with permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

The above data revealed that phenoltetraiodophthalein was effective as a diagnostic test, and that information could be obtained on liver function as well as gallbladder function (15). In this simultaneous technic we adopted a dose of 40 mg. per kilogram of body weight. Since a much smaller amount of medium was used in the other liver function tests, it occurred to us that this larger dose might detect

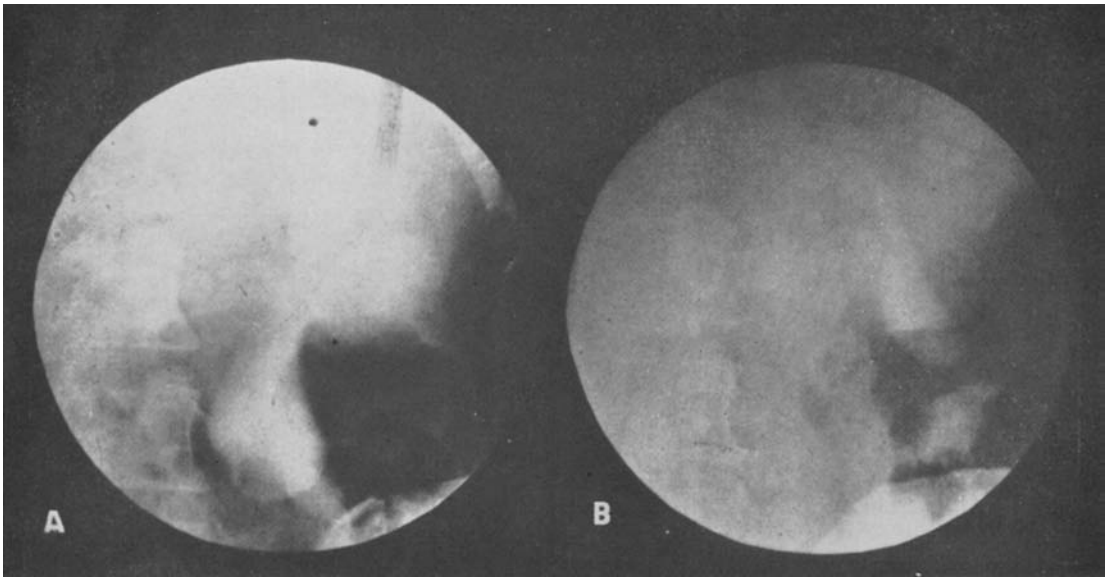


Fig. 10. Effect of fat meal. A. Normal cholecystographic shadows after intravenous injection of phenoltetraiodophthalein. B. The same gallbladder one hour after the patient had ingested 1/2 pint of cream and the yolks of three eggs. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

disturbances of liver function with more intensity than would the routine tests devised prior to our experiments. In 1925, when we were studying this problem, Rosenthal and White (3) reported on the successful use of Bromsulphalein for determination of hepatic function. They adopted the use of 2 mg. per kilo.

Before injecting the phenoltetraiodophthalein, we removed 7 or 8 c.c. of blood from the patient to be used as a control. Other samples of blood were taken thirty minutes and sixty minutes after injection of the dye. The serum was separated from the blood by centrifugation and a drop of 10 per cent sodium hydroxide put into each of the thirty and sixty minute samples. Utilizing a comparator box, as recommended by Rosenthal, we then determined the amount of dye remaining in the serum. We noted that a retention of 10 to 12 per cent in thirty minutes, and 5 per cent or less in sixty minutes, was normal. In our work with phenoltetraiodophthalein this test appeared to be quite accurate, and was very helpful in determining operability. For example, after data on 100 or more tests of liver function with phenoltetraiodophthalein, we learned that three of our patients having choledochostomy for stone and cholecystectomy had died. One patient was jaundiced and it is probable that the bilirubin in the serum intensified the discoloration of the serum by the medium. A second patient was also jaundiced and had a retention of 60 per cent in thirty minutes. Cholecystectomy was performed along with the removal of an intraligamentous cyst in the broad ligament, which should not have contributed significantly to the mortality. The third patient was not jaundiced, and yet had a retention of 90 per cent in thirty minutes. At operation, a duodenal ulcer was found to be present in addition to gallstones. A gastroenterostomy and cholecystectomy were performed.

During this period of observation, we had no other deaths following cholecystectomy. Since all three deaths occurred in patients with severe retention of dye following the test, we became very cautious about operating in the face of a high retention of phenoltetraiodophthalein. At that time we recognized that administration of glucose and blood as well as correction of malnutrition would be helpful in reducing

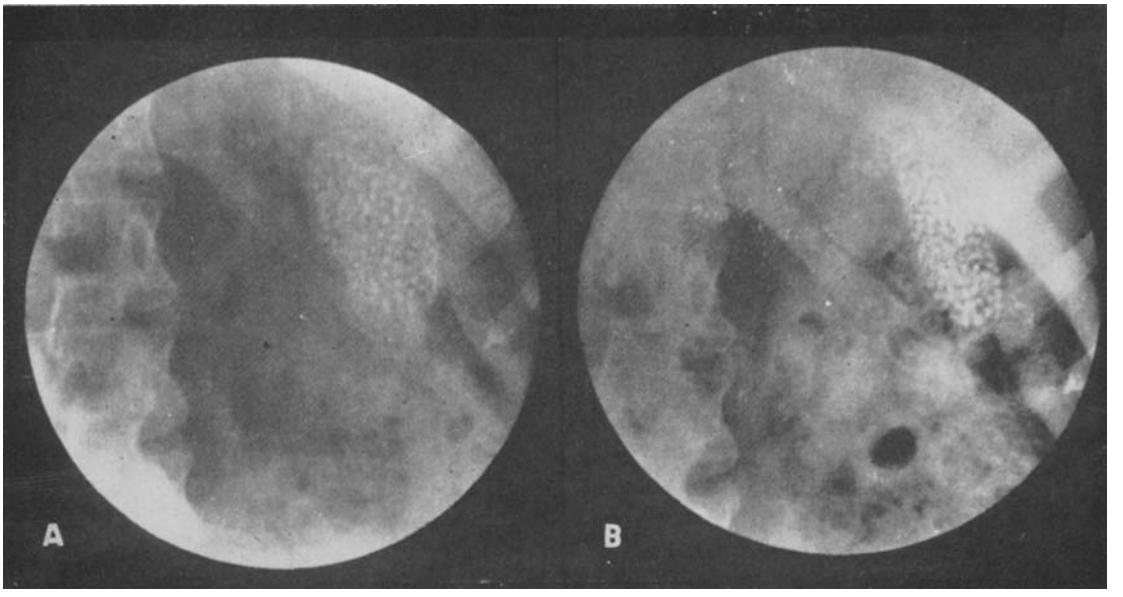


Fig. 11. Case of lithiasis, showing evidence of change of tonus in gallbladder. A. Phase of relaxation. B. Tonic phase. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

the liver retention. We concluded that, if a significant retention was present, either the operation should be cancelled or a minimal amount of surgery should be done at that time. Actually the average retention found in our patients with chronic cholecystitis without jaundice was 27 per cent in thirty minutes. During this period we had only one patient with virus hepatitis (then designated as catarrhal jaundice); this patient had a retention of 90 per cent in thirty minutes, confirming what is known today about the severe liver damage usually produced by this disease. The jaundice no doubt intensified the color of the dye in the serum, but there must have been some truth in the readings because the average retention in our patients with jaundice due to gallstones was only 55 per cent, and in patients with jaundice due to carcinoma of the pancreas and liver was only 25 per cent in thirty minutes.

We found that 85 per cent in thirty with gallbladder disease had a retention above normal. It was also noted that the retention was higher in those having symptoms of long duration. We had evidence, however, that an elevated retention in the absence of jaundice did not necessarily indicate that the liver would be unable to excrete enough dye for production of a shadow. On numerous occasions normal cholecystograms were obtained in patients with retention as high as 50 or 60 per cent thirty minutes after injection. However, we granted that severe liver damage might prevent sufficient excretion of dye for production of a gallbladder shadow even if the gallbladder was normal. We learned early that we were unable to obtain a shadow of the gallbladder in the presence of jaundice, regardless of its cause. Fried and Whitaker (16) confirmed our impression that considerable liver damage was necessary before it would prevent production of a shadow in a normal gallbladder; their experiments were done on dogs, with tetraiodophenolphthalein.

INTERPRETATION OF ROENTGEN SHADOWS

Very shortly after we obtained the first positive shadow of the gallbladder, we invited Dr. Sherwood Moore, head of the Department of Radiology at Washington University School of Medicine and Barnes Hospital, to collaborate with us, realizing that there would be many diagnostic prob-

lems in interpretation of the cholecystographic shadows. There was considerable controversy in the medical literature as to whether or not the gallbladder wall had sufficient muscle power to induce a peristaltic action. In fact, all normal gallbladder shadows observed for several hours usually decrease in size after a meal

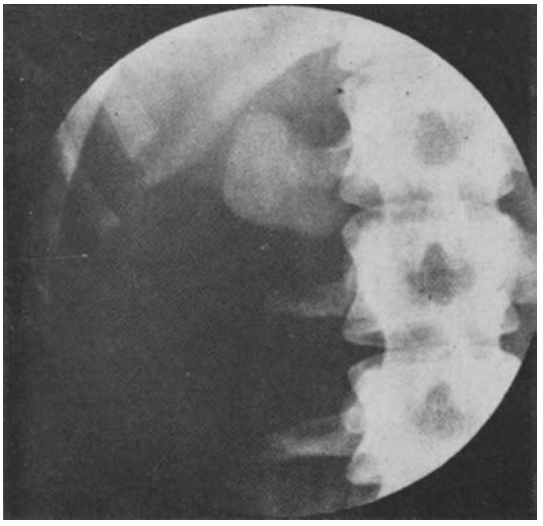


Fig. 12. At operation for chronic appendicitis the gallbladder was found free and pendulous. The condition observed in the cholecystogram was obviously due to the organ being folded up on itself and not to adhesions. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

containing fat (Fig. 10). This feature was, of course, not so much related to the question of disease as it was to the mechanism of emptying.

We continued numerous minor experiments, trying to demonstrate deformities which might be interpreted as muscle contraction, but we were never convinced that we saw a peristaltic wave in a gallbladder. It did appear, however, that the decrease in size was an expression of a gradual contraction of the muscle layer (Fig. 11).

Early in our experience, we appreciated the fact that the lack of a shadow implied a diseased gallbladder. Indeed, before we obtained the first positive film we anticipated that all the normal, or near normal, gallbladders would produce a shadow. One of the big problems with which we

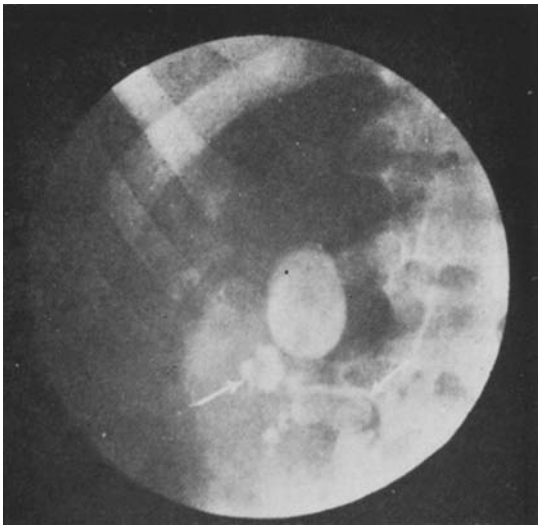


Fig. 13. Multiple right renal stones. Normal gallbladder. The left arrow indicates kidney calculi, thought to be gallstones; right arrow indicates a pelvic stone. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

were confronted, and which Doctor Moore studied in detail, was the interpretation of a faint shadow. Our impression then was similar to our impression now, namely, that it could represent a mild disease of the gallbladder wall. The filling defects of stones were of course self-explanatory and were expected before we actually encountered them.

A typical finding that gave us special difficulty and perhaps misled us most was the deformed shadow. I shall always remember our deep chagrin upon finding a normal gallbladder in a young female patient who had a badly deformed shadow (Fig. 12). We had thought that this represented pericholecystitis, but on operation for pain in the right upper quadrant and to the right of the umbilicus, we found an entirely normal gallbladder but a retrocecal appendix causing the symptoms. Having seen one concrete example of a gallbladder folded because of pressure during the taking of the roentgenogram, we were able to eliminate that cause of error in interpretation thereafter.

Early in our work we realized that demonstration of a normal gallbladder shadow could be of just as much diagnostic value as an abnormal film (*i.e.*, no shadow).

Figure 13 is a cholecystogram obtained in a patient who had asymptomatic kidney stones and was about to have a cholecystectomy (or celiotomy) because of opaque shadows thought to be gallstones. Figure 14 illustrates an equally important use for cholecystography, which pleased us very much; this patient had attacks of pain in the right upper quadrant which were typical for gallbladder disease. The cholecystogram, however, was normal; a careful history and investigation showed that the patient had an allergy to chocolate and had had three attacks shortly after eating chocolate candy. I did not realize that we had utilized change in position of the patient from prone to erect in order to accentuate the shadow of gallstones, but Figure 15, obtained from our gallbladder book, illustrates the point, which Dr. Moore had developed.

We presented papers on cholecystography at various medical meetings but immediately transferred to Dr. Moore the presentation of the subject before radiology meetings. For some strange reason, cholecystography was received with less enthusiasm by the radiologists than by our other friends. Perhaps it was because the criteria for diagnosing gallbladder disease by indirect methods and by the shadow of the thickened wall were just being advanced. It was very amusing to have Dr. Moore (17) describe to me, as he did a short time ago, some of the cool receptions he received at the radiological meetings.

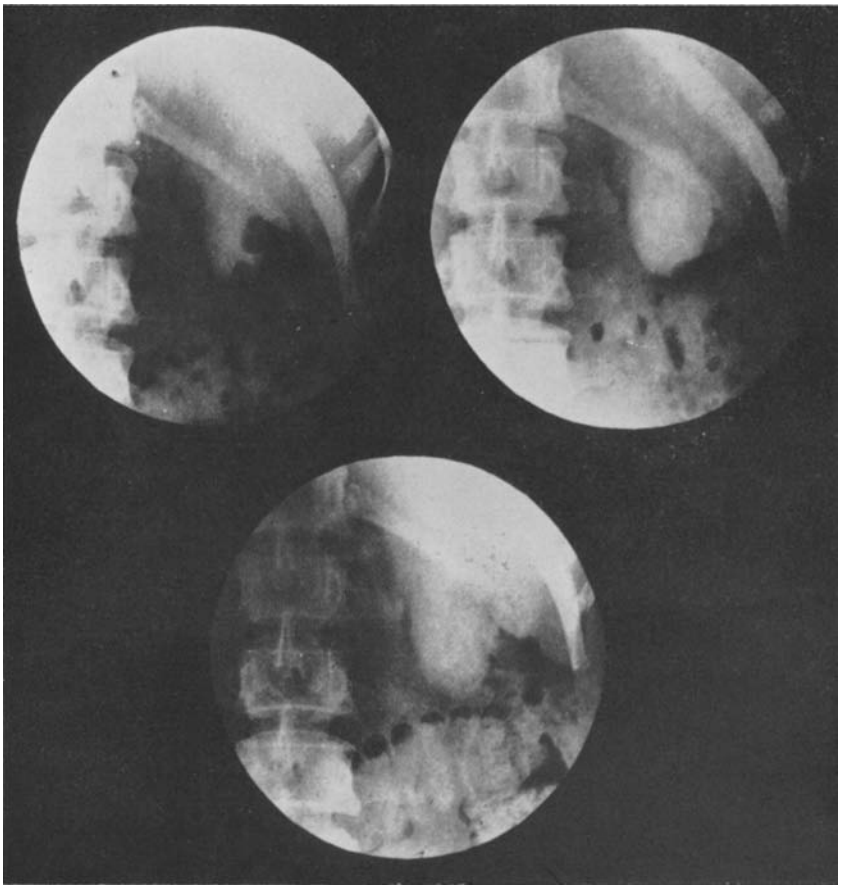


Fig. 14. Cholecystograms, which are normal, in a patient upon whom a clinical diagnosis of cholecystitis was made, but whose symptoms were found to be actually the result of an intestinal allergy to chocolate. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.)

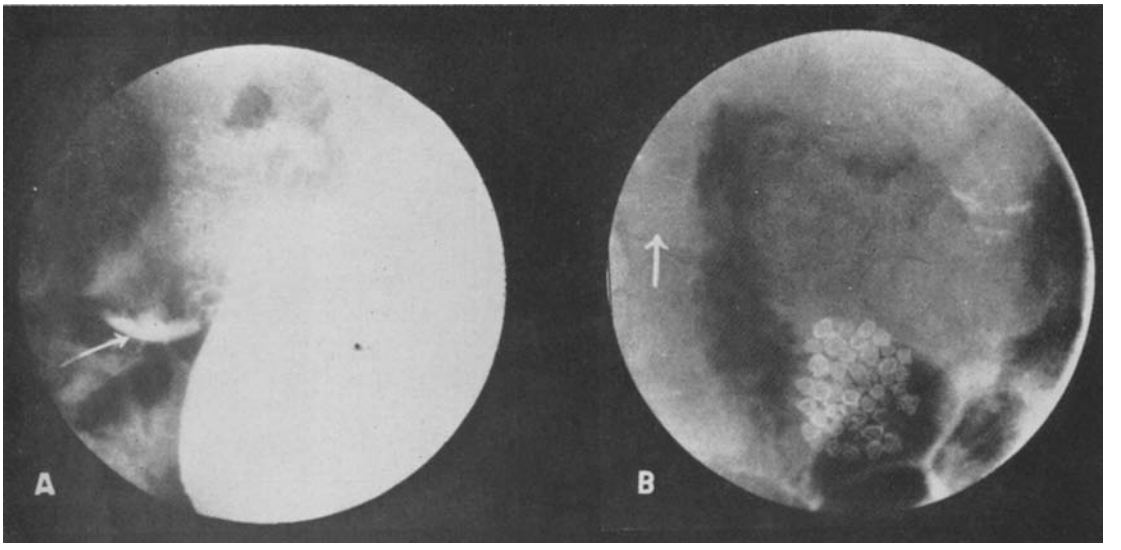


Fig. 15. Multiple gallstones. A. Patient erect. B. Patient prone. Arrow indicates a small stone, presumably in the common duct. Doctor Moore in these early years of cholecystography had noted the value of change in position for detection of gallstones. (Reproduced by permission from Graham, Cole, Copher, and Moore: Diseases of the Gall Bladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928).

At one meeting, he told me, a member of the audience arose in discussion to denounce cholecystography as being worthless, adding that anyone giving the medium by vein "should be put in jail." At another meeting, someone denounced the procedure in a paper entitled, "Gall and Gallbladder Diagnosis." That, said Dr. Moore, was the most venomous attack he had ever heard delivered in public against any method or procedure. I am not relating these incidents to indicate that the radiologists were giving our procedure inadequate attention, for some of my best friends have always been radiologists. I am merely bringing them up because such attitudes develop everywhere and are actually healthy, aiding in discrimination of worthy or worthless projects.

Among the many favors Dr. Moore extended me, I appreciated one particularly. He appointed Dr. Louis Aitken as an assistant in the department to give the injections, shortly after we began the use of sodium tetraiodophenolphthalein intravenously. This released to me a lot of time which I wanted to devote to further work in the laboratory, and I was very grateful to be relieved of the routine task. In a recent communication, Dr. Aitken(18) told me about some of his experiences with the drug. He encountered numerous minor reactions but, true enough, he seldom saw a serious one such as vascular collapse. He did recall one very strange reaction which for a time was difficult to explain. This patient was so apprehensive that he experienced hyperventilation followed by carpopedal spasm and fixation of the jaw. We thought this reaction was due to the medium, but could not recall anything similar to it. We were about to add this as another type of reaction to the long list already observed when Dr. Aitken discovered that the patient had been taking a large amount of alkali (citrocarbonate) to counteract ulcer symptoms, and had developed an alkalosis tetany.

To prevent spasm of veins during injection, Dr. Aitken began the procedure of injecting the solution through the rubber tubing of the intravenous set. This was a definite advance in so far as it eliminated almost completely the danger of extravasation, which would be serious if it were allowed to take place unnoticed. Extravasation, however, usually resulted in so much pain immediately after its development that we became aware of it shortly after it began.

TABLE II: REACTIONS TO VARIOUS CONTRAST MEDIA USED IN EARLY CHOLECYSTOGRAPHY*

Reaction	No. of Cases	Per Cent
TETRAIODOPHENOLPHTHALEIN (300 CASES)		
Intravenous method:		
No reaction	96	46.9
First-degree reaction	75	36.6
Second-degree reaction	34	16.5
TOTAL	205	...
Oral method:		
No reaction	31	33.3
First-degree reaction	17	18.3
Second-degree reaction	45	48.7
TOTAL	93	...
Rectal method (No reaction except difficulty in retaining the solution)	2	...
PHENOLTETRAIODOPHTHALEIN (FIRST 487 CASES)		
Intravenous method:		
No reaction	297	61.5
First-degree reaction	130	27.3
Second-degree reaction	54	11.2
TOTAL	481	...
Oral method:		
No reaction	3	50.0
First-degree reaction	2	33.3
Second-degree reaction	1	16.6
TOTAL	6	...
PHENOLTETRAIODOPHTHALEIN (200 SUBSEQUENT CASES)		
Intravenous method:		
No reaction	136	68.0
First-degree reaction	51	25.5
Second-degree reaction	13	6.5
TOTAL	200	...

* Modified from: Graham, E., Cole, W., Copher, G., and Moore, S.: Diseases of the Gallbladder and Bile Ducts. Philadelphia, Lea & Febiger, 1928.

REACTIONS TO ORAL AND INTRAVENOUS CHOLECYSTOGRAPHY

I need not remind the older members of this Society that the reactions to the halogenated phenolphthalein compounds used in cholecystography were frequent and sometimes alarming. These reactions were most common and perhaps most severe following the intravenous administration of calcium tetrabromphenolphthalein which was so insoluble it had to be dissolved in 300 to 350 c.c. of distilled water. Since the toxicity of the bromine and iodine compounds was found to be approximately the same, it appears that pyrogens in the water may have been responsible for some of the reactions. We discovered early in our experimental work that drug reactions were due to the phenolphthalein radical and not to the bromine or iodine. One of the remarkable things I have been unable to understand was the fact that, even though these reactions were frequent and severe in type, fatalities were practically non-existent. For example, among the 2,000 or 3,000 patients to whom we gave the drug only one death occurred, and this could probably not be classified as a drug fatality from the injection. The patient was a woman about sixty-eight years of age who had a fairly severe reaction consisting of nausea, vomiting, vertigo, and chills; but she had no significant change in pulse rate or blood pressure; she died of a vascular collapse during the night (about twenty hours after the injection). We were unable to obtain an autopsy but, since the death resembled a coronary occlusion so closely, that explanation would appear to be more likely than a reaction to the drug. Actually, we were able to find in the medical literature the records of only one death which definitely was attributable to injection of the cholecystographic medium. This patient received 5.5 gm. of tetraiodophenolphthalein which is a much larger dose of that drug than we had given.

Needless to say these reactions were very troublesome to us, and we tried numerous procedures to avoid them. In Table II are listed the reactions occurring in the first one thousand cases. In this compilation we have designated as first-degree reactions headache, vertigo, slight nausea, weakness, backache, and urticaria. Second-degree reactions consisted of severe nausea and vomiting, chill, circulatory depression, and severe abdominal cramps. If more than one symptom of the first-degree type were encountered, the reaction was classified as second-degree. With very few exceptions, the patient recovered rapidly from the reactions, and was reasonably comfortable three to five hours after termination of the injection. As noted in the table, the incidence of reactions was greater following the oral method than after the intravenous, but they were more severe after the latter. Fortunately, not over 5 to 8 per cent of the patients re-

ceiving the drug intravenously sustained a circulatory reaction with a significant drop in blood pressure.

Dr. James Case, a radiologist, began the use of cholecystography soon after we reported it. We obtained considerable gratification from his experiences, since he told us that in more than 1,600 injections for cholecystography only one patient gave him serious concern from the standpoint of reaction. He noted that, if a vascular depression was sustained, the use of adrenalin intramuscularly or in small doses intravenously would bring the blood pressure back to normal. After we encountered a fall in blood pressure in a few cases following injection, we began the use of a few minims intramuscularly just before the injection. I shall never forget one patient who had a rather sharp fall in blood pressure, for which we gave two or three minims of adrenalin intravenously; the pressure rose sharply to over 200, and she complained bitterly of severe headache. I am glad indeed that this patient was young since in an older person such a sharp rise in pressure might have produced a serious cerebral vascular complication. Following this experience we gave no more adrenalin intravenously. It is true that the incidence of reactions declined somewhat as time progressed, but they were never obliterated with the bromine and iodine compounds given either orally or intravenously.

The use of the double syringe (see Fig. 8) did reduce the incidence of reactions following intravenous injection, largely because we could slow down the injection of the drug without danger of clotting in the vein, by simply turning the stopcock and injecting physiologic saline to keep the vein open.

Looking back over some of our reprints, I find that we listed "threatened uremia" as a contraindication. It is difficult now to realize just why we considered this a contraindication, but I suppose we must have encountered a serious reaction in some patient who had a high non-protein nitrogen.

MODIFICATIONS OF TECHNIC

Within two or three years after introduction of cholecystography, dozens of modifications had been suggested. Most of them appear absurd now and some did so even then. I confess I am not very proud of the fact that we ourselves contributed some of those modifications, although we actually did not use them extensively. The introduction of the fat meal after a shadow had been obtained was more logical than most of the others, even though it was soon omitted. It was originally given to find out if the gallbladder was able to contract. Failure to obtain a decrease in the size of the shadow after administration of the fat meal would indicate that the gallbladder wall was diseased to such an extent that the muscular layer was not functioning. We learned later, however, that the ability to concentrate the dye or medium was more important than contractility, so important, in fact, that observation on contractility was unnecessary.

To minimize the reactions following oral administration, numerous workers including ourselves, had the capsule coated with various substances (*e.g.*, salol, phenyl salicylate, and keratin) to prevent it from being dissolved in the stomach so rapidly that it might produce nausea and vomiting. Unfortunately, these coated capsules frequently passed through the entire gastrointestinal tract intact. This obviously would jeopardize production of the shadow and might lead to an erroneous interpretation. Fortunately, these undissolved capsules could be seen on the x-ray film. When they were encountered, the test would have to be repeated, if no shadow or only a light shadow was obtained. To prevent this failure of dissolution of the capsules, Levyn and Aaron(19) recommended placing one inside another, with powdered sodium bicarbonate between. The theory behind this modification was that the sodium bicarbonate surrounding the capsule of medium would prevent the formation of the hard insoluble acid which would be produced by the acid

in the stomach, if the capsule dissolved there. We did not try this but did adopt for a time the suggestion of Larimore(20), working in our clinic, that powdered agar and sodium bicarbonate be put in the capsule with the medium. This truly prevented formation of non-soluble capsules, although addition of these two substances made it necessary for the patient to take more capsules to get the 4 or 5 gm. of tetraiodophenolphthalein necessary for good shadows. One author stated that if 3 or 4 gm. of sodium tetraiodophenolphthalein were mixed thoroughly in a small bowl of Cream of Wheat, no medium would be left unabsorbed and a smaller dose would be needed.

Fantus (21) reported that he was able to eliminate nausea and vomiting, and lack of absorption, by giving the medium in a colloidal form. He passed carbon dioxide through a solution of tetraiodophenolphthalein until it was discolored, or added carbonated water until a suspension was formed. The addition of dilute tragacanth mucilage was necessary to stabilize the suspension. This suspension was white in color and did not have the disagreeable taste of the regular powder. We tried this technic and confirmed Fantus' claims, but shortly abandoned it because it was a bit too complicated for routine use.

On several occasions we injected the medium rectally, but severe tenesmus and diarrhea resulted. For some unexplained reason, I also injected a dilute solution of sodium tetraiodophenolphthalein subcutaneously into rabbits, but to this day I do not understand why I wasted my time on such a procedure because a local irritating effect would certainly be produced by the drug. I suppose I became so disturbed with the reactions with oral and intravenous methods that I was grasping for straws, hoping to find a procedure which would eliminate them. Strangely enough, shadows of the gallbladder were reproduced in rabbits following this technic, but we never tried it in the human being.

Before introduction of the modern drugs which have eliminated reactions completely, or nearly so, numerous chemicals were suggested and reported as being effective in producing shadows. Sabatini and Milani (22) reported that oral administration of 10 to 20 gm. of sodium and strontium bromide would produce gallbladder shadows if the patient was fasted for a long time preceding injection of the drug. We tried this and somewhat to my surprise confirmed their claims, although the shadows were not dense enough to be reliable.

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SUMMARIO IN INTERLINGUA

Aspectos Historic de Cholecystographia

Isto es un relation historic del discoperta del cholecystographia e de su disveloppamento initial, presentate como le Conferentia Carman ante le Societate Radiologic de America del Nord.

Le prime successose visualisation del vesica biliari esseva obtenite in le can in novembre 1923 post le injection de tetrabromphenolphthaleina de calcium. Iste mesme medio esseva etiam usate in le prime studios in humanos. Le prime successose cholecystogramma in un subjecto human esseva obtenite le 21 de februario 1924. Post le relation de iste successos initial, le autor procede a describer su continue experimentos con varie medios e methodos de introduction, le standardisation del technica, le problemas del toxicitate del medio, e le reactiones evocate per le medio.