CONCLUSION.

In conclusion we may urge two points, the recognition of which seems to us to be of paramount importance in the consideration of the treatment of malignant disease with lead at the present time.

First, no one in his senses would care to suggest that the possession of a knife and a few instruments is all that is required for the surgical cure of cancer of the stomach. Yet some seem to think that for lead therapy in this disease all that is required is that lead shall be pumped into the veins of the sufferer. We now realize that it was not the fault of radium that it was of so little clinical use twenty years ago.

Second, the scientifically minded inquirer will not demand that a new method of treatment for cancer operating on the worst and most advanced types of cases shall give far better initial statistical results than those obtainable with other long-established and standardized forms of treatment acting on early and selected cases; but, if it should do so, those capable of appraising evidential values will appreciate the vast possibilities that await full and proper development of the method tested.

I have to thank my colleagues Dr. Leslie Cunningham, Mr. J. B. Oldham, Dr. S. B. Herd, and Dr. M. Datnow, not only for the careful way in which they have conducted the laborious task of analysing the case records and tracing the fate of the patients, but also for co-operation in the clinical work, much of which has been conducted entirely on their own initiative and responsibility.

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CHOLECYSTOGRAPHY.

AN ANALYSIS OF 137 CASES SHOWING THE RELIABILITY OF
THE ORAL METHOD.

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(With Special Plate.)

I HAVE been stimulated to write this paper by the repeated inquiries of my colleagues and other members of the profession as to how much one may expect from the α -ray examination of the gall-bladder, and with special reference to what is termed the "Graham-Cole test." Up to a few years ago the radiographic examination of the gall-bladder had been most unsatisfactory, and results were so uncertain that little reliance could be placed upon them. No routine examination of the gall-bladder was carried out in hospitals, and one was rarely asked to attempt such an investigation in private practice. To the late Drs. Carman of Rochester and Robert Knox of London, Case, George, and others in America and on the Continent, is due the credit for valuable pioneer work done in connexion with the radiography of the gall-bladder by direct methods. The detection of gall-stones could be made with more certainty in those large hospitals or clinics which were heavily endowed with funds than in the smaller and less favoured institutions. Where it was possible to take a large number of films under varying conditions of tube penetration, exposure, etc., the chances of obtaining positive evidence of pathological conditions involving the gall-bladder were proportionately greater. But even in the most favourable circumstances the direct method of examination yielded only 37 per cent. of correct diagnoses. The normal gall-bladder casts no shadow in even the most technically perfect films. It was maintained, therefore, that if a shadow of the gall-bladder was shown upon a film it was an indication of pathology; that the walls were abnormally thickened, the contents of unusual density, or that multiple calculi

were present. This was probably true, and when positive shadows were obtained they were of definite diagnostic value. It was exceptional, however, to see such shadows in even the best films, and the absence of a shadow did not exclude disease, hence such a finding was of little value. The detection of gall-stones before the days of cholecystography depended upon the composition of the stones. If they contained sufficient calcium they produced well-defined shadows. Some were annular in form, depending upon the denser periphery of the stone, others cast a laminated shadow or concentric rings of dense and less dense material. Others, again, were more homogeneous and faceted. If the gall-bladder was filled with stones even of low density a faint, mottled shadow was sometimes shown. From time to time such radiographs were obtained, but were of rather rare occurrence, and were therefore looked upon more or less as curiosities.

In 1914 Cole called attention to the secondary manifestations of cholecystitis as revealed by the opaque meal, and these findings were further elaborated by George and others. Information so obtained, together with the direct visualization of stones, as already described, formed the basis for α -ray diagnosis of gall-bladder disease up to the year 1924. In February, 1924, Graham, Cole, and Copher¹ of St. Louis announced the success of their work in demonstrating the gall-bladder radiographically after the intravenous injection of tetrabromphenolphthalein. In a further communication² in 1925 these authors discuss the theory and application of this new method of examination:

"This procedure is based upon the theory that if any substance containing a metal or atoms of bromine, or iodine, can be introduced into the gall-bladder in sufficient concentration, then that organ would be made opaque to α rays. The substance must be one which can be given either by the alimentary canal or by injection. It would have to be a substance which would be excreted by the liver and carried to the gall-bladder in the bile. Moreover, the ability of the gall-bladder to concentrate its contained bile would indicate that a sufficient time must elapse before a shadow of maximal density would occur. Reasoning from these premisses, 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."

Such is the theory of cholecystography as briefly outlined by Graham, Cole, and Copher. As the object of this paper is to demonstrate by practical statistics the reliability of cholecystography by the oral method in particular, I do not wish to lengthen my communication unduly by recounting in detail the history of its development or the chemistry of the drugs used. No paper on this subject would, however, be complete without describing the Graham-Cole technique as first practised. In January, 1925, Graham used the tetraiodo-phenolphthalein sodium salt, and claimed superiority for this over the bromine salt in that it cast a denser shadow, a smaller dose was sufficient, and the toxicity was lessened in virtue of the reduced dose.

Technique of Intravenous Method.—In 30 c.cm. of freshly distilled water 3.5 grams of the salt are dissolved. The solution after filtration is sterilized in a boiling water bath for 15 minutes. It is given intravenously in two doses, half an hour apart, in the morning before breakfast, between 7.30 and 9 o'clock. Care should be taken not to allow extravasation outside the vein, as sloughing of tissue may occur. Certain orders are given to the patient and are essential:

1. Breakfast and lunch should be omitted.
2. Protein should be omitted from the evening meal.
3. Water is allowed *ad libitum*.
4. Stomach contents should be made alkaline by frequent doses of sodium bicarbonate.

The rationale of the latter procedure is explained in an article by Cole, who found experimentally on dogs that the flow of bile into the intestines through relaxation of the sphincter of Oddi is prevented by keeping the contents of the stomach alkaline. This probably tends to promote the concentration of bile in the gall-bladder. Films are taken at four, eight, twenty-four, and thirty-two hours after injection. A normal gall-bladder will begin to cast a shadow in four hours. This will be faint, but should reveal the

contour of the normally shaped organ. From sixteen to twenty-four hours the shadow becomes denser but the gall-bladder smaller in size. From that time onwards the shadow diminishes in density until the forty-eighth hour, when no dye should remain.

Interpretation.—If no shadow is obtained any of the following conditions may be present.

1. Serious disturbance of hepatic function resulting in insufficient secretion of the dye to cast a definite shadow. The gall-bladder may not be appreciably altered.
2. Obstructed ducts: (a) hepatic, (b) cystic, (c) common. In the case of the last the absence of shadow is said to be due to excessive diffusion of the dye in a large accumulation of bile.
3. A failure to concentrate bile as a result of inflammatory obliteration of the lymphatic vessels in the walls of the gall-bladder.
4. Multiple stones. If the gall-bladder is filled with stones the amount of dye which enters it may be insufficient to cast a shadow.

If the shadow is faint at the period when it should show a maximal density, or if the shadow is late in appearing, or persists for an abnormally long time, cholecystitis is said to be the cause. In my opinion, however, based upon my own experience, any of the conditions which have already been enumerated may be present, and I do not think it is possible to make a differential diagnosis. Stones which cannot be detected by ordinary radiography owing to their low density and extreme translucency may be by this method clearly demonstrated. I do not say that all can be visualized, but a proportion of them can be shown which would otherwise be missed.

The detection of stones depends upon: (1) their density in relation to the dye-stained bile; (2) the number of stones in the gall-bladder; (3) the situation of the stones—that is, whether in ducts or gall-bladder. If the stones are of very low density, and are not tightly packed, they will appear as discrete clear areas in the dye-filled gall-bladder. If in great numbers and the bladder is completely filled the entry of the dye will be prevented and no shadow will be seen. Stones showing as clear areas in the dye-filled gall-bladder are spoken of as “negative” shadows. If the stones possess calcium in their composition they may appear as discrete opacities in the gall-bladder, and are referred to as “positive” shadows. A proportion of stones will cast definite “ring” shadows with clear centres. If a stone is impacted in the cystic duct it may be visualized by the deposition of dye-stained bile upon it, while the absence of any gall-bladder shadow indicates the obstruction caused by the stone. Stones in hepatic and common ducts may be revealed in a similar way.

It is conceivable that a proportion of stones may be of such a density that they occupy an intermediate position between the extremely translucent and the moderately opaque. Such stones may be present in a dye-filled gall-bladder without casting either negative or positive shadows, and these will therefore be missed by any method of examination. It is probable that they are not of frequent occurrence, but they are bound to cause disappointment in some cases, even when the most careful technique has been observed.

The interpretation of cholecystographic findings just given is equally applicable to the intravenous and oral methods of examination. Using the intravenous method, Graham, Cole, and Copher, in a series of 80 patients upon whom operations had been performed, found the x-ray diagnosis to be correct in 96.25 per cent. of the cases. Although the results were so good, there were certain objections to this particular method. In some patients toxic reactions occurred, varying from nausea or slight dizziness to a condition of temporary collapse with a rapid fall in blood pressure. By using the tetraiodo-phenolphthalein instead of the bromine salt these unpleasant reactions have been almost eliminated. Nevertheless, the possibility of such reactions and the fact that the intravenous method required a certain amount of surgical skill, as well as the usual aseptic precautions, to some extent acted as a deterrent to the general use of cholecystography. In collaboration with my colleagues in Mercer's and Richmond Hospitals a small number of cases were examined by the intravenous method during the year 1925, but the results were not very satisfactory, and were not proved to be

reliable by operation. I do not wish, however, on this account to condemn the method. First attempts are usually unsuccessful, and I have no doubt that our failures were due to faulty technique or defective drugs. In January, 1925, Whitaker and Milliken of Boston described their results in the oral administration of tetraiodo-phenolphthalein. This was followed from time to time by communications from other workers in America and elsewhere, testifying to the good results obtained by this method, and to-day it has become a routine procedure, and I think I am correct in saying that in this country, at all events, it has replaced the intravenous method.

It was some time before a satisfactory and stable drug could be produced. It acted as a severe gastric irritant, and for this reason it was necessary to enclose the drug in a pill, or capsule, which would pass through the stomach without dissolving. Chemists had many difficulties to overcome, but it is not my purpose to refer to them in this paper. Suffice it to say that many firms are now making keratin-coated capsules which are giving very satisfactory results. Each capsule contains 5 grains of the iodine salt, and the total quantity given varies from 35 to 50 grains, according to body weight. Even this method is not entirely free from unpleasant reactions, but at the worst these only take the form of nausea, with occasional vomiting and diarrhoea, and usually pass off in the course of a few hours. If this difficulty has not already been solved, I believe it will very soon be overcome by using a suspension of the tetraiodo-phenolphthalein in a finely divided condition, as described by Levyn and Aaron.⁴ Upon the addition of fruit juice a freshly precipitated acid is formed which is easily converted into a soluble salt by the alkaline duodenal contents. It is claimed that this method causes none of the unpleasant reactions associated with the taking of capsules.

The precise technique adopted varies with different workers, but I have found the procedure recommended by Stewart and Ryan⁵ to be very successful, and all my cases since January, 1926, have been examined according to this method.

Oral Technique.

An aperient should be given twenty-four hours before the ingestion of the capsules. On the morning following, a preliminary examination of the gall-bladder should be made. (This part of the Stewart technique I have usually omitted in order to save time, but when possible it is the ideal to be followed.) The usual lunch is allowed. At 6.30 p.m. the following meal is advised: thick soup, creamed chicken, bread-and-butter, and a glass of milk. The abundance of fat in this food will partially or completely empty the gall-bladder in from one to two hours. It is then in a receptive condition for the opaque bile. At 9.15 p.m. half a teaspoonful of sodium bicarbonate in half a glass of water is given. Commencing at 9.30 p.m., two kerosol capsules are given with half a glass of water every fifteen minutes until the complete number has been taken. The patients are instructed not to bite the capsules, but to swallow them whole. Two or three glasses of water may be taken gradually after the ingestion of the capsules. No aperient is allowed until the examination is completed, and no food is allowed until after the second radiographic examination has been made. The patients come for examination at 9.30 the following morning, and again at 1.30 or 2 p.m. Ordinary food is then allowed, and, if desired, another film may be taken an hour later. This I generally omit. A final observation is made at 9.30 the following morning—that is, thirty-six hours after ingestion of the capsules. Radiographs are taken with the patient lying prone on the Potter-Bucky diaphragm, and exposures should be short enough to allow the patient to hold the breath with ease. This is very essential, as the slightest respiratory movement may be sufficient to prevent the proper visualization of the gall-bladder, and if stones are present there will be little chance of demonstrating them. In normal cases the shadow should appear at the twelfth hour, should be smaller and slightly denser at the sixteenth hour, and should be gone in thirty-six hours, or only very faintly seen. The success of the method depends upon the most careful attention to details. For this reason I have printed instructions which are kept by the ward sisters in my hospitals. In my private practice, whenever possible, I like to interview the patients personally the day before examination, so that I can elicit their co-operation and explain the instructions. The points to stress are, “no food and no aperient until permission is given.” Failure to observe these instructions has in several cases produced a “no shadow” result, which could not therefore be accepted as reliable, and necessitated a complete repetition of

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

DESCRIPTION OF FIGURES.

FIG. 1.—Showing the outline of the normal gall-bladder, filled with the dye, at the lateral margin of the psoas muscle, beneath the shadow of the twelfth rib.

FIG. 2.—Shadow of dye-filled gall-bladder mottled by clear areas, signifying the outlines of stones in the opaque bile.

FIG. 3.—No dye has reached the gall-bladder; the outline of a stone can be clearly seen below the shadow of the transverse process of the third lumbar vertebra; this stone was in the common duct. A shadow is also to be seen above the upper border of the twelfth rib; it was cast by a stone recovered from the hepatic duct.

FIG. 4.—Multiple stones in the gall-bladder.

FIG. 5.—Same case as FIG. 4. Serial radiograms show a filling defect in the duodenal bulb, caused by pressure of the dye-filled gall-bladder, whose shadow is seen in the left upper angle of each film.

the whole procedure. Fallacious findings will usually be found to be due to faulty technique, or to failure on the part of the patient to follow the instructions. Fallacies due to defective drugs are now practically unknown, but to avoid such a possibility capsules should be bought only from reliable manufacturers. The patient may vomit immediately after taking the capsules; should this occur it is important to inquire whether any of the capsules have been ejected. If pyloric obstruction is present the capsules will dissolve in the stomach no matter how they are coated. The test is said to be contraindicated in elderly people with low arterial tension and myocarditis, and also in subjects of extensive arterio-sclerosis. While these precautions may be necessary for the intravenous test, the danger of severe reaction from the oral method is practically nil.

The following tables have been prepared to show on a percentage basis the confirmation of the x-ray findings by operation, and also an analysis of the surgical findings. The cases to which they refer were examined between January, 1926, and October, 1928. There were 47 males and 90 females. The ages were as follows:

Under 20 years	...	...	...	...	...	3
20-30 years	...	...	...	...	...	13
30-40 years	...	...	...	...	...	36
40-50 years	...	...	...	...	...	30
50-60 years	...	...	...	...	...	40
60-70 years	...	...	...	...	...	12
70-80 years	...	...	...	...	...	3

Total ... 137

TABLE I.

Description	No.	Operated.	Correct.	Per Cent.
Normally visualized ...	48	12	9	75
Faint shadow ...	19	10	10	100
Late appearance ...	11	5	5	100
No shadow ...	40	25	24	96
Stones ...	19	12	12	100
Total ...	137	64	60	93
Total cases reported pathological with or without stones	89	52	51	98

TABLE II.—Analysis of Surgical Findings in Cases Reported Pathological.

Stones ...	39
Chronic cholecystitis ...	8
Adhesions between gall-bladder and colon ...	1
Adhesions between gall-bladder and duodenum ...	2
Cirrhosis of liver and chronic cholecystitis ...	1
Normal gall-bladder ...	1
Total ...	52

TABLE III.—Faint Shadow—10 Cases. Surgical Findings.

Multiple stones in gall-bladder ...	5
Stones impacted in cystic duct ...	1
Adhesions between gall-bladder and colon ...	1
Adhesions between gall-bladder and duodenum ...	1
Reported pathological ...	2
Total ...	10

TABLE IV.—Late Appearance—5 Cases. Surgical Findings.

Adhesion between gall-bladder and duodenum ...	1
Multiple stones in gall-bladder ...	3
Cirrhosis of liver, small adherent gall-bladder ...	1
Total ...	5

TABLE V.—No Shadow—25 Cases. Surgical Findings.

Single large stone in gall-bladder ...	1
Multiple stones in gall-bladder ...	13
Multiple stones in gall-bladder and ducts ...	2
Single stone in common bile duct ...	1
Chronic cholecystitis ...	7
Normal gall-bladder ...	1
Total ...	25

Of the twelve gall-bladders normally visualized (Table I) upon which operations were performed it will be noted that the x-ray findings were incorrect in three cases. One had a malignant liver, and presumably the disease was not so advanced as to prevent the secretion of the bile-stained dye and the filling of the gall-bladder. The gall-

bladder itself was not directly involved. In the other two cases single stones were found in the gall-bladder. These were probably stones of intermediate density (to which type I have already referred), not translucent enough to cast a negative shadow and not sufficiently opaque to cast a positive shadow. Of the twenty-five "no shadow" cases which came to operation, in only one were the x-ray findings not verified. I cannot explain the cause of this failure. The patient was a hospital case, and may have taken food before the first radiograph. It is of interest also to note that in all those cases presenting faint shadows, or in which the shadow was late in appearing, which were submitted to operation, the x-ray findings were verified. This was contrary to what I had expected. In the past my reports upon these cases were made with very great caution, but the result of this study has considerably increased my confidence in the value of these signs. In all operated cases in which stones were visualized, stones were found, but in Table II it will be seen that of all cases reported pathological stones were found in 39, while in only 12 of these were stones demonstrated radiologically. That is to say, 69.3 per cent. of the stones did not cast definite shadows, either negative or positive, which could be recognized as stones.

Conclusions.

1. The oral method of carrying out the Graham-Cole test is reliable and is capable of giving a correct indication as to whether the gall-bladder is normal or pathological in 93 per cent. of cases.

2. Except in the case of visualized stones it is not possible by means of this test to give a precise diagnosis. Different surgical conditions will produce similar x-ray appearances, and therefore in the "no shadow, faint shadow, and late appearance cases" one is only justified in saying that the gall-bladder is pathological.

3. The success of the method depends upon the most careful attention to details in preparation and to correct radiographic technique.

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THE EFFECT OF OBSTRUCTED RESPIRATION ON HEART AND LUNGS:

ITS CLINICAL IMPORTANCE IN RADIOGRAPHY.

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(With Special Plate.)

DURING normal systole the heart changes its shape, size, and position, and pumps an average charge of 75 c.cm. of blood from each of the ventricles into the aorta and pulmonary artery. The discharge of blood into the pulmonary artery disturbs the size, shape, and position of the pulmonary vascular tree, and the pulmonary arteries are straightened in systole and relatively curved in diastole. Since the pulse wave in the pulmonary arteries is estimated to travel at three to six metres a second, it reaches the periphery of the lung in an interval of time which is probably not greater than one-sixtieth of a second. This indicates that the ideal radiogram of the chest requires an exposure of about one-hundredth to one-sixtieth of a second, so as to eliminate the effect of the propagation of the pulse wave along the arteries. The possibility of obtaining radiograms from such a brief exposure is entirely outside the range of most hospital x-ray equipments. In the majority of cases, with the existing apparatus, an exposure of less than half a second cannot be employed with any measure of success.