CHOLECYSTOGRAPHY.

BY

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In the two years which have elapsed since Graham introduced the method of cholecystography a very large amount of evidence has accumulated as to its value and the discomfort or dangers which may attend its use as a routine method of clinical diagnosis. When any new method is on trial, particularly when it is one requiring the intravenous administration of a new chemical compound the manufacture of which is not fully standardized, there are apt to be a few instances of alarming disturbances which further experience proves to be readily avoidable.

In our earlier cases we used a dose which was larger than that recommended by Dr. Graham, but which in our hands gave rise to no alarming symptoms. The record of a fatal case, where this larger dose was used, has led to a certain apprehensiveness in regard to the use of the method which we greatly regret, and it is due to Dr. Graham to say that no case of serious complication has followed an injection of the drug as practised and recommended by him. Our own experience has been that the larger dose (5.5 grams) which we used in our first 50 cases, having based our practice on that of the Parisian hospital where we first saw the method employed, is unnecessary, and that sufficiently good shadows can be obtained with a smaller dose (3 to 4 grams). It cannot be too strongly emphasized that the solution (40 c.cm.) must be freshly prepared, and must be injected slowly and with care. In our last 60 cases there have been no severe reactions, and in the vast majority no noteworthy disturbance of any kind. Whilst in some clinics the oral method is that in general use and gives satisfaction, we have seen no reason to abandon the intravenous use of the drug, and believe it to be the more certain and accurate method.

As to the value of the test as an aid to diagnosis there can no longer be any doubt. The total absence of a shadow, in a case with the clinical symptoms of gall stones, is reassuring and convincing evidence of the necessity for operation. The presence of a perfectly normal gall-bladder shadow, in a doubtful case of dyspepsia, is strong, if by no means absolute, evidence that the gall bladder is not at fault. Perhaps the most beautiful piece of evidence is where, in the doubtful case, the gall bladder is outlined and in it is visible a negative shadow where a cholesterol stone has displaced the dye. The faint and poor shadow indicating defective concentration is almost pathognomonic of a cholecystitis with or without stones. Hardly less useful in diagnosis is the displaced or deformed gall-bladder shadow, in the case of a swelling in the right hypochondrium, indicating a growth or other swelling in an adjoining viscus. With increasing experience we find ever more numerous the helpful points of evidence furnished by this radiographic test.

Before analysing the clinical material at our disposal we give an exact description of the method now employed by us. In the evening, twenty-four hours before the injection is given, the patient takes a dose of liquorice powder. The following day a skiagram of the upper abdomen is taken. At 9 p.m. 3.5 grams of tetra-iodo-phenol-phthalein (British Drug Houses), freshly dissolved in 40 c.cm. of distilled water, is given slowly into the median basilic vein, great care being exercised that not a drop escapes into the subcutaneous tissues. At 9 o'clock the following morning a skiagram is taken. A small barium meal is then given, and as the barium is escaping into the duodenum another skiagram is taken to demonstrate the relation of the shadows of gall bladder and duodenum. At 1 p.m. a meal rich in fat is given, and at 3 p.m. a final radiogram is taken to show the emptying power of the gall bladder.

We have now examined 158 cases, and in 132 of these the data obtained have been controlled by subsequent operation.

Normal Gall-bladder Shadow.—In 58 cases the gall bladder presented what was judged to be a normal shadow. In 50 of these a normal gall bladder was disclosed at operations carried out for a variety of upper abdominal lesions. In one case several very minute calculi were present in a gall bladder of normal colour and texture. In one case a single cholesterol stone, the size of a pea, was removed from what appeared to be a healthy gall bladder. In 3 cases there was definite evidence of a mild chronic cholecystitis, confirmed by microscopic examination, and in one of these, where the gall bladder was removed, a small lipoid papilloma was present. In the remaining 3 cases there was a mild but undoubted catarrhal cholecystitis, and streptococci were grown on cultures made from a portion of the wall. It is thus seen that an apparently normal cholecystogram is not quite conclusive evidence that the early stages of disease in the gall bladder are not present.

Absent Gall-bladder Shadow.—In 50 cases no shadow could be detected in the radiogram. In 44 of these the gall bladder was grossly diseased. In many the cystic duct or neck was occluded by a calculus, in others the viscus was completely filled with stones, in yet others it was shrivelled and functionless. In 13 of these 44 cases there was obstruction of the common duct and the patient was jaundiced. In 6, although no dye entered the gall bladder, calculi were clearly visible in the film. In 6 cases, in spite of the absent shadow, a normal gall bladder was disclosed at operation. These cases were very difficult to explain, as in all the ordinary technique had been followed. Possibly a temporary kinking of the cystic duct was responsible for the failure of the dye to enter the bladder. Certainly in two of them normal cholecystograms were obtained some weeks later. Most of them occurred in our earlier cases, and we are inclined to attribute the fault more to some mismanagement than to any inherent weakness in the test.

Faint Gall-bladder Shadow.—In 10 cases the gall bladder was faintly visible, but there was obviously defective concentration of the dye. In 3 of these there were negative areas due to stones. In all of them a very definite chronic cholecystitis was found at operation and the gall bladder was removed. It is obvious that only after considerable experience with a particular technique and with a well established standard for comparison can conclusions be drawn from mere variations in the density of such shadows.

Shadow of Gall Bladder and Calculi.—In this group are included 11 cases; in 5 the gall bladder was clearly outlined and in addition there were positive shadows of calculi. In 6 cases negative areas in the shadow of the dye indicated the presence of cholesterol stones. Operation was carried out in all these cases, and the x-ray evidence was correct in each instance.

Displaced or Distorted Gall-bladder Shadow.—In this group there were 5 cases. In all the presence of a swelling below the right costal margin made the diagnosis of a distended gall bladder a possibility. In two cases the shadow of the gall bladder was visible below the swelling, which in one instance was a sarcoma, and in the other a hydatid of the liver. In two cases the gall-bladder shadow was present as a concave shadow lying over and above the swelling. In both instances this proved to be a growth of the hepatic flexure of the colon. In the fifth case the shadow lay in front of the swelling, which was later shown by pyelography to be a hydronephrosis.

Toxic Symptoms following Injection.

It may be stated at once that in no instance in our series of 158 cases have toxic symptoms, giving cause for alarm, been noted. In one case symptoms of collapse supervened during the injection, which was stopped before quite one-half of the usual dose had been given. The patient rapidly recovered with no untoward after-effects.

- In 93 cases there were no toxic symptoms.
- In 27 cases there was some nausea.
- In 33 cases there were nausea and vomiting.
- In 2 cases the patient complained of tingling in the limbs.
- In 1 case a rigor followed the injection.
- In 1 case nausea with headache was complained of.

There can be no doubt that with the reduction of the dose which we have made in our last 60 cases the toxic

symptoms have been markedly reduced and the radiographic results no less valuable, if not quite so striking. An injection of 4 grams for a stout subject and 3 grams for one of slender build, in each case dissolved in 40 to 60 c.cm. of distilled water, may be reckoned a perfectly safe dose. We have been unable to recognize any particular benefit from special preparation, or from the regular dosage with alkalis, which was followed scrupulously in our earlier cases. We have as yet had no opportunity to test the newer drug, phenol-tetra-iodo-phthalein, which, in Graham's clinic, is found to be less toxic than the tetra-iodo-phenol-phthalein.

Conclusions.

Cholecystography is a method of real clinical value in the diagnosis of diseases of the gall bladder. Not only does it show whether the gall bladder is functioning, but also how well or how ill it is functioning. It will frequently disclose the presence of gall stones which do not show in the ordinary radiogram. It may, by showing the relation of the gall bladder to an abdominal tumour, give strong presumptive evidence as to the site of the growth and the possibilities of surgical treatment.

Using pure sodium tetra-iodo-phenol-phthalein in a dose not exceeding 4 grams, freshly dissolved, and injected intravenously very slowly, no disturbing toxic symptoms need be feared. X-ray films made twelve hours after injection and six hours later, after a meal containing fat, should give reliable evidence as to the functional capacity of the gall bladder.

The method has its limitations, and an apparently normal cholecystogram does not exclude the possible presence of a small cholesterol stone or mild degrees of infective cholecystitis.

CHOLECYSTOGRAPHY.

THE RESULTS OF 125 CONSECUTIVE CASES EXAMINED
BY THE ORAL ADMINISTRATION OF THE SALT.

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THE existence of such divergent views as to the relative values of the intravenous and oral methods of cholecystography has led us to believe that our results will be of interest.

The difficulty of oral administration appears to be due to the fact that the compound is decomposed by the hydrochloric acid of the stomach, converting the soluble salt into the insoluble free acid, which acts as an irritant and may be vomited. Endeavours were made, therefore, to provide for its passage through the stomach and liberation in the small intestine, where it would be absorbed and carried by the portal system directly to the liver. Stewart¹ of New York reported recently that he had obtained successful cholecystograms by enclosing the dye in keratin-coated gelatin capsules and using x rays twelve hours later. Other observers, however, do not seem to have met with the same success, and presumably their difficulties have been due to the unreliability of the preparation used, and also to the unsuitable nature of the capsule and its coating. In many cases the drug appears to have been liberated in the stomach, and vomiting has ensued, or the coating has been so resistant to the digestive juices that the capsules have been passed on into the colon intact.

In our early cases the results were similar. A British preparation of sodium tetraiodo-phenolphthalein, made into capsules by the manufacturers, was used. The capsules were not dissolved, as many as eight and even fourteen being seen in the large bowel next morning. We next obtained capsules of the iodine salt prepared in the United States. The results obtained were good but the cost ex-

sive. Finally, an American preparation of sodium tetraiodo-phenolphthalein made up into capsules by the dispenser of the hospital seemed to be the most suitable. Different coatings were tried, but the best results were obtained by the following method.

Preparation of the Capsules.

The drug used is the sodium tetraiodo-phenolphthalein obtained from Messrs. Kodak, Ltd.; 0.3 gram of the salt is placed in a gelatin capsule, which is then given three coats of a keratin solution, made (using Merck's keratin) according to the *British Pharmaceutical Codex* formula. The capsules are allowed to dry in the air after each coat without heating. They are now prepared by a Liverpool firm of wholesale druggists from the salt supplied by Messrs. Kodak.

It is important (1) that the salt be obtained as fresh as possible and carefully stored, and (2) that the capsules be made up freshly. If capsules are kept for more than seven days the coating is not dissolved readily in the small bowel.

Technique Employed.

Twenty-four hours before administering the drug the patient is given an aperient, preferably one ounce of castor oil. On the day preceding the examination the patient takes an ordinary diet containing fats. No food is allowed after 6 p.m. and no further aperient is given. Between 9 and 9.30 p.m. the capsules are swallowed whole with sips of water. (For an average patient fifteen capsules are taken—that is, 4.5 grams of the salt.)

At 9.30 the following morning the first radiogram is taken, using the Potter-Bucky diaphragm, the patient being in the prone position. The patient returns at 12.30 p.m., and the second radiogram is taken. If the gall bladder appears normal at both these examinations the patient is told to take a meal containing fat and to return between 3 and 4 p.m. for a third radiogram. Should the gall bladder be empty or nearly so the examination is concluded. If it has not emptied, the patient is asked to return the following day. But in those cases where there is no suggestion of a gall-bladder shadow on both the 9.30 a.m. and 12.30 p.m. radiograms the examination is carried no further and a "pathological gall bladder" is reported.

If the gall bladder is normal a definite shadow is visible on the radiogram taken twelve hours after administering the dye. At the end of fifteen hours the shadow is denser and usually smaller. The radiogram taken two or three hours after the meal containing fat shows either no gall-bladder shadow or one very much reduced in size. If the gall bladder is not markedly smaller the patient is examined the following day.

Using the method outlined above cholecystography is as satisfactory as with the intravenous method, and it has the advantage that the preliminaries are very much simpler. Though the shadow with the oral method appears a little later, it is equally dense and yields equally satisfactory evidence of the form and function of the gall bladder.

It is important to realize the theoretical considerations involved in the use of this test. It demands a liver capable of secreting the dye into the bile capillaries, a patent cystic duct to allow of its passage into the gall bladder, and, finally, a mucous membrane sufficiently healthy to concentrate it by the reabsorption of water. It follows, therefore, that the normal gall bladder yields the densest shadow. At the same time it is obvious that a variety of conditions—adhesions and tumours pressing on the cystic duct or gall bladder, infections of the mucous membrane interfering with its power of concentration, thick tenacious debris in its interior—in addition to stones either in the cystic duct or gall bladder itself, can cause all degrees of variation from the normal density to complete absence of shadow. In actual practice, however, as seen from Table I, a definite and unequivocal complete absence of shadow occurs in 77 per cent. of the cases reported as pathological. Probably the only contraindications to cholecystography by this method are (1) advanced disease of the liver—for example, cirrhosis, secondary carcinoma—and (2) pyloric stenosis. Both these conditions, however, should be discovered by other methods, and there is little likelihood of their being present to confuse the issue in the type of case in which this investigation is being carried out.

Toxic Effects.

In our own series of cases we have seen no severe reactions. In two instances there was a slight rise of temperature, but in neither did it reach 100° F. Eight patients complained of nausea lasting a few hours, but only one of them actually vomited. This patient stated that she had vomited "purple material," but subsequent radiograms demonstrated a normal gall bladder which was unusually well defined on the x-ray film. Two somewhat