effective, and in any case the fatal issue was undoubtedly hastened, and possibly caused in part, by the whooping-cough.

It was fortunate that the parents had been revaccinated about the same time as their children, since a source of human immune serum was then readily available. Parental immune serum proved to be of great value when given in large doses—e.g., 140 c.cm. The procedure can be followed without serious risk of serum reaction. It appears to us that in Case VII the dosage of parental immune serum was inadequate and, as in Case I, given too late to be effective. The rapidity of the illness seems to indicate that immune serum must be given early and in large quantity to be successful. Thus, when Case III was admitted, the patient did not appear to be ill enough to justify serum treatment, and in several hours he became comatose. We were convinced at the time that his life had been endangered by the delay of 24 hours in starting serum therapy.

The success of immune serum in the treatment of post-vaccinal encephalitis suggests that it is the virus of the vaccinia which is the causal agent. There is no method of ascertaining the virus content of lymph, and vaccinia may produce all degrees of severity of constitutional upset, and, as shown in our cases, the nervous complications may vary widely. Why should occasional cases develop serious involvement of the nervous system? Are they infections arising from the unsterile nature of calf lymph? Another possible explanation is that the susceptibility of the nervous system to the vaccinal virus may be increased by the presence of concurrent infection. In support of this theory it appears to us to be significant that most of our cases showed evidence of acute upper respiratory infection. Thus Case I had clinical whooping-cough and follicular tonsillitis; Cases II, III, and VI had acute pharyngitis; Case VII had "rales in chest"; and Case VIII had a history of laryngitis. The findings at least suggest that the hazard of encephalitis during vaccinia is much greater when there is concomitant infection in the upper respiratory tract.

Post-vaccinal encephalitis is extremely rare in infancy. Therefore, so long as the danger of smallpox exists, vaccination should be urged in infancy. With modern speed and facility in travel there is nothing to indicate that this danger is likely to disappear.

When primary vaccination of children becomes unavoidable—e.g., during an epidemic of smallpox—it would be a wise precaution to insist on vaccinating or revaccinating the parents at the same time. By so doing a source of safe immune serum would be made readily available if required, and this could be given in large doses—e.g., as a transfusion of plasma on the first indication of cerebral involvement.

Summary

In the Fife outbreak of smallpox in 1942, 8 cases of vaccinal encephalomyelitis occurred among a group of 52,772 recently vaccinated persons and 1 case among a group of 20,197 persons. The incidence in both groups is high, particularly in the first—1 in 6,600.

The case mortality was 44%.

In six of the cases symptoms were entirely of cerebral origin and in two they were of spinal origin—apparently an uncommon manifestation. In one the symptoms were predominantly meningeal.

Much benefit was obtained through the prompt use of parental immune serum in large doses.

It is suggested that there may be a liability to onset of encephalomyelitis in unvaccinated persons suffering from acute infections of the upper respiratory tract.

Vaccination is urged in infancy in view of the risk of involvement of the nervous system in later years.

If primary vaccination of children becomes unavoidable steps should be taken to secure a source of immune serum as a precaution.

Speaking at the twentieth meeting of the German Dermatological Society last year, Conti (*Dtsch. med. Wschr.*, 1942, 68, 1230) said that it was hoped in the future to have a uniform specialist service attached to the health offices. The obligation to obtain treatment must be enforced more strictly. Thus, in the case of syphilis, the accepted salvarsan treatment was obligatory, but a patient was not forced to accept some therapeutic measures, such as cystoscopy, catheterization, dilatation of the urethra, and lumbar puncture. The duty of secrecy still existed, and it was laid down that a patient who had not refused treatment must not be notified by name.

PHENIODOL: A NEW CONTRAST MEDIUM FOR CHOLECYSTOGRAPHY

BY

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The object of this communication is to introduce a new contrast medium for cholecystography which is claimed to be better than tetraiodophenolphthalein.

Literature of the Phthaleins

Graham and Cole, in 1924, first succeeded in visualizing the gall-bladder by means of a radiopaque substance excreted through the liver. They were influenced by the pharmacological studies of Abel and Rowntree (1909–10), who showed that the phthaleins and some of their derivatives were mainly excreted in the bile. The first experiments were made with the free acid and sodium salt of tetraiodophenolphthalein, but unfortunately the preparations proved toxic and some of their animals died. Ultimately they achieved success with the calcium salt of tetrabromophenolphthalein. The drug was injected intravenously in doses of 5 to 5.5 g. in 40 c.cm. of distilled water, and films were taken 7, 8, 24, and 32 hours afterwards. A second report (Graham, Cole, and Copher, 1924) showed that the sodium salt was better.

The possibilities of the new test aroused the keenest interest. Within a year other American workers—notably Carmen and Counsellor (1924)—had confirmed its value. It was shown that the most common and most reliable sign of disease is failure of the gall-bladder to fill with the drug. However, many patients experienced severe toxic reactions after the injection, as the dose had too small a margin of safety.

Meanwhile, Graham and his associates (1925) had continued their researches. They reported that the toxic effects of tetraiodophenolphthalein were due to impurities, and could not advocate this compound for clinical use owing to the difficulties of obtaining pure preparations. Shortly afterwards Whitaker and Milliken (1925) showed that a pure preparation of tetraiodophenolphthalein had definite advantages. Though there was little difference in the comparative toxicity of the iodine and bromine compounds, the former was clinically superior because in a dose of only about half the size of that necessary with the latter it gave a denser and more sustained shadow. These findings were confirmed as preparations of tetraiodophenolphthalein became available.

At first tetraiodophenolphthalein was given intravenously, but some of the early workers were not entirely satisfied with this procedure and persisted with other methods. Stewart and Ryan (1925) stated that a considerable number of persons showed unpleasant reactions when it was given intravenously—"so much so, that in hospitals with which we are connected it was not deemed advisable to continue intravenous injections except when all other methods of diagnosis had failed." For routine purposes they preferred oral administration, and were supported by no less authorities than Carmen and Moore (1925). This view gradually gained support as the quality of the preparations improved, and nowadays oral administration is the method of choice.

With the oral method the majority of patients experience some unpleasant reactions. Some of them complain of its disagreeable taste, many have nausea, a few are sick, and many have diarrhoea. There seem to be differences in the severity of the reactions with various preparations in different localities. Menees and Robinson (1938) tried to find a better preparation. They examined calcium, lithium, potassium, and magnesium salts of tetraiodophenolphthalein, but for various reasons all were rejected except the magnesium salt. They found that a 5-g. dose of this salt gives a shadow of the same density as 3.5 g. of the sodium salt of tetraiodophenolphthalein. It was more palatable and was less apt to produce reactions. After use of the magnesium salt, 76% were symptom-free, whereas only 12% had no symptoms after the sodium salt. Though this report was favourable the manufacture of the magnesium salt was not taken up in this country.

Other Contrast Media

Attempts to produce other more suitable compounds have been recorded by Pribram (1927), who put forward iodized atophan as a contrast medium. It was sold in Germany under the name of biloptin. This substance gave good reliable contrast pictures; but though it was at first thought to be well tolerated, subsequent work showed that a large dose caused damage to the liver, and even with the necessary dose it was not unusual to find casts in the urine. Later, Pribram (1936) tested a derivative of quinoline containing iodine. This gave excellent pictures, rich in contrast, but on technical grounds it was not introduced commercially.

Dohrn and Diedrich (1940), working in the laboratory of Schering A.G., Berlin, tried to make a substance suitable for peroral administration which would be better tolerated than tetraiodophenolphthalein. They reported that they had tested a large number of synthetic compounds by estimating the iodine content of bile flowing from a biliary fistula in animals. One drug— β -(4-hydroxy-3:5-diiodophenyl)- α -phenyl-propionic acid—satisfied all required conditions.

The substance was given clinical trial by Kleiber (1940), who reported that it is an excellent, entirely harmless, well-tolerated peroral contrast medium which gives shadows superior to those obtainable by intravenous injection of tetraiodophenolphthalein. It is sold by Schering A.G. under the name biliselectan. Each dose of 3 g. of the active substance is put up in the form of sugar-coated granules.

Kleiber reported his findings after 55 cholecystographies. In 25 cases in which no gall-bladder shadow was found the examinations were controlled by means of intravenous tetraiodophenolphthalein, but a negative picture resulted in all. Of these 25 cases 24 were operated upon, and in each case a diagnosis of obstruction of the cystic duct was confirmed.

The British Preparation Pheniodol

Papers giving the chemical structure and some facts about the properties and clinical application of biliselectan reached this country in 1941, and Dr. W. Baker, working in the Dyson Perrin's Laboratory in Oxford, devised a method of preparing the substance, a certain quantity of which was available for preliminary experiments.

The free acid is a white crystalline powder which is insoluble in water. It is readily soluble in weak alkali, but in this form is extremely unpleasant to take. Prof. J. H. Burn of the University Department of Pharmacology reported that it was well tolerated by animals, with no signs of ill effects. In one experiment a bitch of 7 kg. weight received 3 g. of the drug by mouth. She was observed for 24 hours, during which time she displayed no symptoms. She was then killed and portions of the stomach, intestine, liver, and kidney were submitted for histological section. These tissues were all well preserved and showed no abnormality that could be detected by ordinary histological methods (Dr. A. H. T. Robb-Smith).

The first clinical trials were made with a small quantity of the preparation supplied by Dr. Baker. Three adults were each given a dose of 4.2 g. suspended in water or milk. They made no complaints other than a slight sensation of burning in the mouth, like the flavour of a radish. Films were taken in the usual manner at 10 o'clock on the morning after administration—i.e., 16 hours later. The drug seemed to have been completely absorbed in one case, as none was visible in the bowel, and only small amounts were unabsorbed in the other two. All three showed a dense shadow of the gall-bladder similar in appearance to that usually given with 4 g. of tetraiodophenolphthalein. Three other subjects were given doses of 5, 6, and 7.5 g. respectively. All three had diarrhoea and slight abdominal discomfort in the night. The shadows of the gall-bladder were no better than those given with 4.2 g.

As the results of these trials were satisfactory Dr. Baker sent in his report to the Medical Research Council, whose Therapeutic Trials Committee later asked me to undertake further

tests with preparations supplied by different firms. In the meantime it was decided that the drug should be known officially as pheniodol.

Pheniodol under Test

The preparations were submitted in powder form. With each dose of 4.2 g. instructions were sent to the wards that the powder was to be mixed and stirred into a glass of milk and to be taken instead of the usual preparation of tetraiodophenolphthalein on the evening before the examination. The results were most disappointing. Almost all the patients complained of an unpleasant taste and discomfort in the throat. Some had noticed that the preparation was lumpy and that the lumps tended to stick in the mouth and cause burning. Radiographs showed masses of unabsorbed drug in the bowel. It was clear that in the majority of cases the drug had not been properly mixed, but it seemed advisable to consider alternative methods of dispensing.

The symptoms can be easily explained. The drug is insoluble in water and soluble in weak alkali. In the soluble form it is very bitter to the taste, and when swallowed causes burning in the mouth and throat. When given as a suspension in milk or water there is a tendency for the powder to form lumps unless it is properly mixed. These small lumps tend to stick in the crevices of the mouth, pharynx, or oesophagus, where they are dissolved in the natural alkaline secretions. If the drug is carefully mixed into a paste and then stirred into milk there is seldom any complaint, very slight burning being readily relieved by a drink of water. If not given properly the patient may experience discomfort for hours, and is often sick.

In a second series of cases each dose was dispensed in 1 oz. of mucilage prepared by hand in the hospital dispensary. On the day before the examination the patient was given breakfast and lunch as usual, but no special fatty foods to empty the gall-bladder as some authorities advise. At 4 p.m. the patient had tea and toast or bread-and-jam without butter or margarine. He was encouraged to take sugar in his tea. The drug was given at 6 p.m. in a glass of milk. Films were taken 16 hours later.

The findings with three different preparations are summarized in the accompanying table. So far as could be ascertained all the preparations of different manufacture were similar.

	B.D.H.	Glaxo	Boots	Total
No. of tests	31	16	30	77
Unpleasant taste	16	6	21	43
Nausea	10	7	15	32
Vomiting	2	1	1	4
Diarrhoea:				
Slight	3	4	7	14
Moderate	—	3	2	5
Pain on micturition	5	2	2	9
Dense filling	24	12	23	59
Faint	3	1	—	4
No	4	3	7	14

Of those showing "No filling" the findings of a pathological lesion were verified at operation in ten cases, all being associated with stone. The others were not operated upon. Three of the cases showing a faint filling were associated with stone.

Analysis of Reactions

The patients' symptoms were analysed, with the following results:

Taste.—Many patients noticed a slight burning sensation in the mouth and throat. A few complained of a horrid taste and others disliked the mucilage. It was clear that the method of dispensing was still at fault.

Nausea and Vomiting.—Nausea was associated with persistent burning in the throat. Only four patients vomited, and of these two were subsequently found to have gastric or duodenal ulceration with gastric stasis, and another was in the habit of vomiting frequently. In one case there was no explanation other than the taking of the drug. All four patients had slight abdominal discomfort. The drug must be a mild gastric irritant, especially when there is delay in emptying the stomach, and for this reason it is suggested that the patient should always drink a glass of water after taking the drug, which will tend to wash it towards the bottom of the stomach and so hasten its elimination.

Diarrhoea.—About a quarter of the patients had diarrhoea. In many cases this was only slight, but in others it was sufficient to interfere with sleep. In most instances the diarrhoea was probably related to variations in individual susceptibility to the drug as an intestinal irritant. Bigger doses are more liable to produce

diarrhoea, without significant improvement in the contrast of the radiographic image.

Pain on Micturition.—A small number of patients complained of slight burning on passing urine on the morning after administration. Two had slight suprapubic discomfort, which suggested irritation of the bladder. None of these showed any sign of renal damage.

The manufacturers interested in pheniodol have since carried out further research into the dispensing of the drug. One firm (Glaxo Laboratories Ltd.) submitted samples of the drug in the form of sugar-coated granules. I carried out further tests, and found that the preparation was very satisfactory providing that the patient was asked not to chew or suck them. The granules readily dissolve in the intestinal juices.

Another firm (British Drug Houses Ltd.) has prepared the drug in the form of a fine powder which is readily suspended in water or milk. This preparation is also very satisfactory, though sometimes the patient mentions some slight burning in the mouth and throat; but this is readily relieved by a drink of water.

Comment

Since the introduction of cholecystography we have learnt a great deal about the behaviour of the gall-bladder in health and disease. Though numerous reports testify to its value many doctors still do not realize that reliable results can be obtained only by careful attention to technique and interpretation. Before giving any opaque material a preliminary radiograph should be taken, for failure to do so may result in faulty diagnosis. Unless definite gall-stones are revealed the examination should always be completed.*

The most reliable results are obtained by the intravenous method of administration, but this is seldom employed to-day on account of the liability of tetraiodophenolphthalein to cause unpleasant reactions, venous thrombosis, or sloughing of the tissues if any escapes from the vein. The oral method is simpler and the results are reliable in a large proportion of cases, but on account of the tendency of the sodium salt of tetraiodophenolphthalein to cause vomiting or diarrhoea the radiologist sometimes has difficulty in assessing whether enough of the drug has been absorbed. Rowden (1933) tried to avoid these difficulties by administering the drug in No. 3 gelatin capsules, which he himself filled so that the drug might be fresh. His procedure gives excellent results; but few people take the trouble to prepare the gelatin capsules, and most workers prefer to give the drug in fluid form. I hope that pheniodol will prove less troublesome and therefore more reliable, as I have tried to show in this paper.

Normal Cholecystography.—A dense well-filled gall-bladder shadow which is normal in size and shape and of uniform opacity and which contracts after a fatty meal to a much smaller size is almost always normal. Very occasionally gall-stones may be obscured by the density of the shadow and are revealed only by a film taken with the patient standing erect or by serial films of the emptying of the gall-bladder. More frequently, mistakes are made because the observer does not appreciate that the gall-bladder is seldom completely filled with the opaque medium, and so fails to realize that it is possible to report normal findings when a stone may be held in the ampulla of the gall-bladder or in Hartmann's pouch. Likewise it is generally assumed that stones in the cystic duct always cause no filling, whereas there may be several stones in the duct without impairment of filling, concentration, or emptying.

Faint Filling.—Even when technical standards are fully satisfied I doubt whether the opinion given by Graham and his associates (1925) can be upheld. They state that "the sensitiveness of cholecystography in revealing abnormalities of the gall-bladder is one of its most striking assets in the diagnosis of slight degrees of chronic cholecystitis"; or, in other words, slight degrees of chronic cholecystitis cause impairment of the ability of the gall-bladder to concentrate the drug. I believe that this view is incorrect, for I have seen two cases of chronic cholecystitis with gross inflammatory thickening of the walls of the gall-bladder which had shown no impairment of concentration of the drug. With the oral method, too many factors influence the absorption of the drug for us to state whether variations in its concentration in the gall-bladder are of functional significance, so that a faint filling should be

classified as normal unless it is shown to be constant at repeated examinations.

No Filling.—The most reliable sign of disease is no filling of the gall-bladder. In most cases this signifies either that the cystic duct is blocked by stone or mucus or that the gall-bladder is grossly diseased or full of stones. To be sure that there is no mistake the radiologist should check all factors influencing the absorption and elimination of the drug and should make certain that the films are properly centred and exposed. The test should never be conducted when the patient is jaundiced or when there are other clinical signs of hepatic insufficiency, for the medium is likely to induce further hepatic injury and the gall-bladder rarely fills. In less severe cases of liver disorder a satisfactory shadow is given if the gall-bladder is normal. There may be no filling if the patient is unable to absorb fats or if he has been on a fat-free diet for a long time.

In every case cholecystography should be followed by a barium meal to show whether the stomach empties naturally and to exclude any organic disorder which may affect the significance of the findings.

Conclusions and Summary

Pheniodol is a reliable peroral cholecystographic medium. Suitable preparations in doses of 3 to 6 g. give a shadow of the gall-bladder similar in density and filling to the best obtained with 4 g. of tetraiodophenolphthalein. It is less objectionable to take, and seldom causes vomiting. Diarrhoea occurs in some cases, but not more often than with tetraiodophenolphthalein.

An account is given of the interpretation of oral cholecystography in the light of present-day knowledge.

I wish to thank the Medical Research Council for allowing me to carry out this investigation. I am indebted to Prof. L. J. Witts for his help with the clinical work and to Mr. F. H. Robinson of Glaxo Laboratories for his invaluable criticisms. Messrs. Glaxo Laboratories, the British Drug Houses, and Boots of Nottingham supplied me with the different preparations of pheniodol. I very gratefully acknowledge the help of Dr. J. F. Brailsford, who first taught me the principles of cholecystography.

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A CASE OF CONVERSION HYSTERIA

BY

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We seldom see a case summary that shows in outline the actual course of a short and successful psycho-analytical treatment: a lot is said about psychotherapy in general, but very little about its methods and techniques. Here is such a case. I hope the technique explains itself. The actual conversion symptoms are unusual.

A. B., an insurance clerk aged 30, complained of increasing difficulty in drinking. He could drink water in the morning, though not easily. Later in the day fluid always "went the wrong way," and in consequence he dared not try to swallow. His trouble started four or five years previously, when he thoughtlessly bolted some iced lemonade at a dance and choked himself so severely that he was in a panic and waiters had to rush to his assistance. Fourteen days later, and after describing this incident to some friends, he was for the first time unable to swallow readily. The disability then got steadily worse. His medical student fiancée had recently expressed the opinion that he was suffering from a spasm of the throat and from an inferiority complex.

A. B. was a very tall, gracious, and immaculate young man with a fresh fair complexion, rather anxious blue eyes, and a very