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CHOLEGRAPHY

The new contrast medium Biligrafin

by

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The history of cholecystography is the history of the contrast media used for visualization of the gall-bladder and biliary passages. Since the pioneer work of GRAHAM and COLE in 1924 (10) every contrast medium used has contained iodine, combined with a hepatotropic vehicle. The chemical and pharmacologic properties of the iodine carrier determine the toxicity, the extent of the side-effects, the form of administration, and the timing of the examination, as well as the general value of the procedure.

In a historical review, four phases in the development of agents for roentgen examination of the gall-bladder and the biliary tract may be distinguished.

During the first phase (1924—1940), sodium tetraiodophenolphthalein was the best-known contrast medium. The commercial preparations had to be injected intravenously, and very often caused extremely unpleasant side-effects (nausea, vomiting, etc.).

The second phase began in 1940 when DOHRN and DIEDRICH (5) introduced β-(4-hydroxy-3, 5-diiodophenyl-)-α-phenylpropionic acid under the name of Biliselectan (Priodax in the U. S. A.) for peroral cholecystography. In numerous commercial preparations this compound is now known throughout the world. Its advantages and characteristics led to the rapid displacement of preparations containing the dangerous phenolphthalein group as iodine carrier, previously used.

The third phase (from 1952) was characterized by the introduction of three iodine atoms into the molecule of the contrast agent. The iodine content rose from about 52 % in Biliselectan to about 66 % in Telepaque, Teridax and Triodan (7—15, 18, 19). The intensity of contrast was thus enhanced in the radiograph, as a result of which non-opaque calculi were better outlined.

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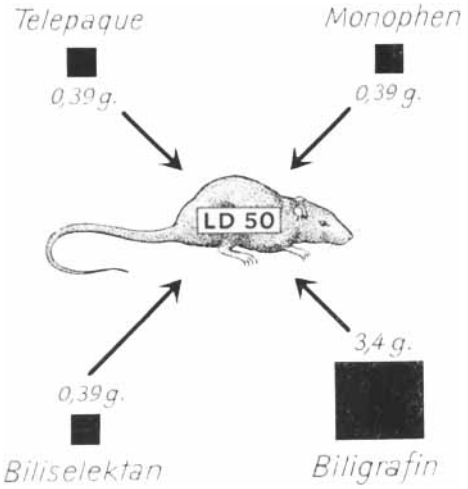


Fig. 1. Toxicity of various biliary contrast media on intravenous injection into animals (LD_{50} in the rat : g per kg body weight).

The fourth phase in the history has now (1953) been entered with the discovery by LANGECKER, HARWART and JUNKMANN (11) of adipic-di-(3-carboxy-2,4,6-triiodoanilide) as a hepatotropic substance. The neutral sodium salt of this substance is readily soluble in water, although on peroral administration it remains almost unabsorbed. One drop of a 40 % solution produces no irritation in the rabbit's eye. In a 20 % solution the substance is practically isotonic with physiologic saline, and is, therefore, admirably suitable for intravenous injection. Signs of local irritation, or fairly severe pain in the veins, do not appear. The toxicity on intravenous administration has been determined in extensive animal experiments (Fig. 1) and amounts to only 1/10th of that of Biliselectan and Telepaque solutions of the same strength.

As with the triiodo compounds, the 64.3 % iodine content of Biligrafin lies considerably above that of Biliselectan. The increase in the opacity with an increase in the thickness of the layer of the medium may be seen from Diagram 1.

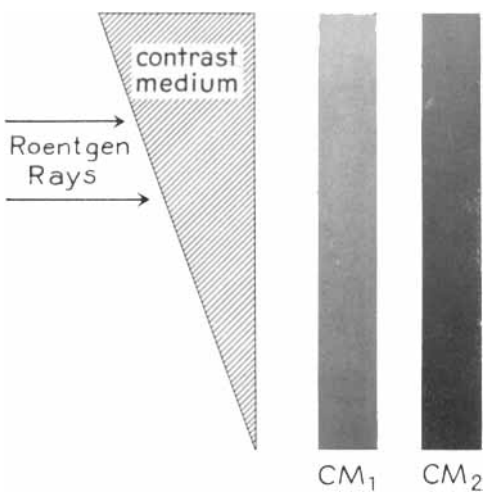
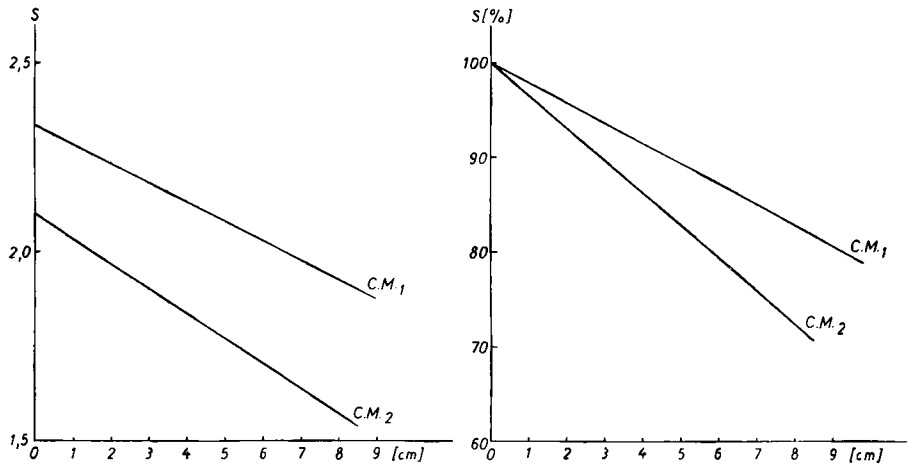


Diagram 1. Differences in blackening of film with layers, increasing wedge-fashion, of Biligrafin (CM 1) and Biliselectan (CM 2).

Uniform layers of 20 % solution of Biligrafin (CM 1) and Biliselectan (CM 2) increasing in thickness in wedge-fashion produce significantly different blackening of a roentgen film, as a result of the differences in absorption of the rays by the contrast agent (Diagram 1). Photometric evaluation of the films shows that not only is absorption greater as a result of the increased content of iodine, but the increase in contrast with increase in thickness of layer is even more marked (Diagram 2 a). If the photometrically determined values ($S = \log \frac{I_0}{I}$) for blackening of the film at the sites of greatest absorption are taken as 100 %, then the increased attenuation of the radiation by



a. b.

Diagram 2 a and b. Photometric evaluation of the differences in blackening in Diagram 1.

Biligrafin, even in thin layers, can be proved (Diagram 2 b). This is the factor determining the increase in contrast with surrounding soft parts and radiolucent calculi.

A critical survey of the second and third phases shows that the limits of clinical efficiency had been reached with the peroral contrast agents mentioned above. Inter alia, this opinion is supported by the results of studies with labelled Biliselectan (I^{131}) (13, 14).

The *peroral administration* of contrast agents appeared at first to represent a great advance in comparison with the intravenously injected and dangerous phenolphthalein preparations. It did not, however, permit any prediction of the extent or speed of absorption and it was quite common to encounter residues in the bowel; these are found less frequently with Biliselectan (although up to 25 %) (2) than, for example, with Telepaque (7, 8, 18, 20). It is true that these residues are an indication that the contrast medium has actually been ingested by the patient; on the other hand, they render the interpretation of the poorly-filled or non-functioning gall-bladder most difficult.

The excretion of contrast agents belonging to the second and third phases is very similar and takes place to a great extent through the kidneys. Only a small proportion is eliminated in the faeces (Fig. 2). Of the total quantity of Biliselectan administered, 60 % to 80 % may be demonstrated in the urine both of animals and human subjects up to 48 hours after administration; only 20 % to 40 % is recovered from the faeces. Diagram 3 gives data on the concentration of the contrast medium in the liver bile in animal experiments. These results correspond closely to those in human subjects. There is also an entero-hepatic circulation of the contrast agent, the extent of which is unknown in individual cases.

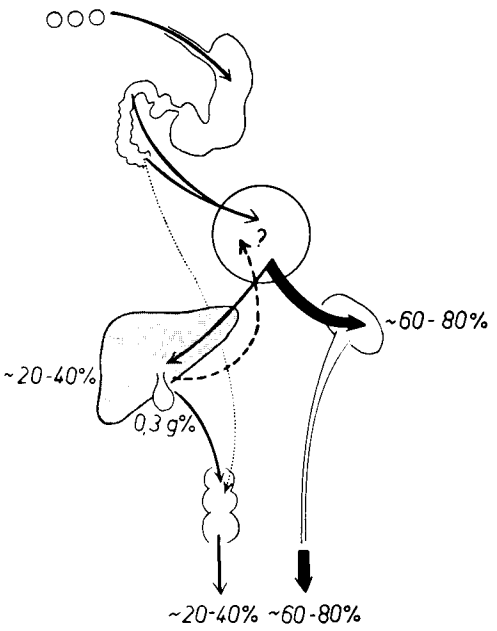


Fig. 2. Excretion mechanism of Biliselectan.

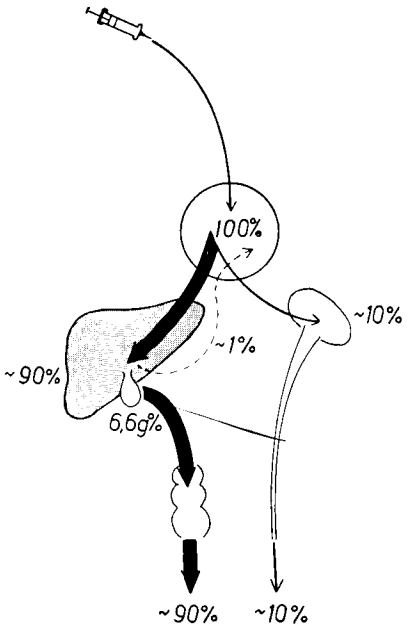


Fig. 3. Excretion mechanism of Biligrafin.

The concentration in the bile is so small that the large extrahepatic biliary passages are only occasionally visualized in special circumstances. It is never possible to show the intrahepatic ducts. Every radiologist is faced with this drawback when the question arises of a calculus overlooked in the biliary passages after cholecystectomy.

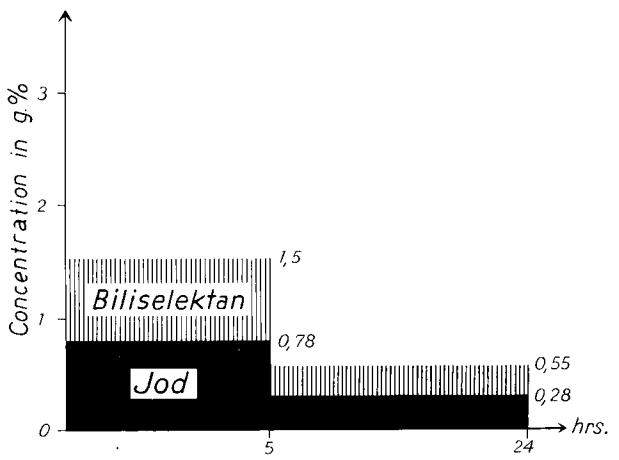


Diagram 3. Concentration of Biliselectan in the liver bile. Experiment in rabbits: dose 1 g per kg by mouth.

The mechanism of excretion of the triiodated contrast agents is essentially similar. Their introduction may therefore be designated only as a partial advance. The filled gall-bladder is probably better visualized in the radiograph. Our further assessment of the situation is, however, more cautious than that of WHITEHOUSE and MARTIN (20), who with other investigators (3, 6, 16), considered Telepaque to be

more reliable than Priodax as regards radiologic visualization of the gall-bladder. We found by careful re-testing that a negative cholecystogram with Biliselectan usually remains negative on repetition with another peroral contrast agent. We are also sceptical about the figures cited in the literature for positive cases, since the composition of the series decisively affects the proportion of successes. This is evident from other series in which a comparison is said to have shown a slight advantage in favour of Priodax as against Telepaque (12, 17).

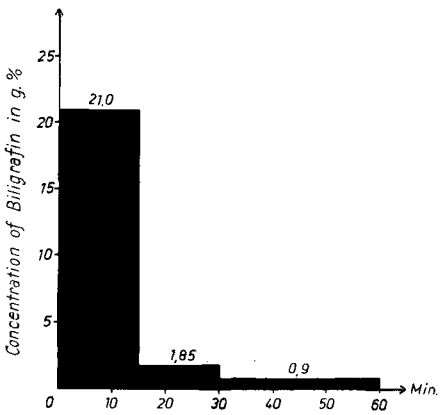


Diagram 4. Concentration of Biligrafin in the liver bile — hepatic duct — during the first hour after intravenous injection. Experiment in rabbits: dose 0.1 g per kg.

The physiologic variation in the urinary excretion of Biliselectan labelled with I^{131} is wide, amounting to 28 % to 82 % of the dose in 48 hours (13). Concentrations in the urine and blood are also subject to great variation. Pathologic conditions or functional peculiarities cannot be differentiated. The cause of failure of the gall-bladder to fill with contrast agent in individual cases could not be elucidated in this manner.

The excretion of adipic-di-(3-carboxy-2,4,6-triiodoanilide) differs basically from that of other known contrast media (Fig. 3). It is characterized by the fact that about 90 % of the substance is excreted via the liver into the bile and the faeces, only about 10 % leaving the body in the urine. The relatively unimportant entero-hepatic circulation may be neglected. The almost selective hepato-tropic carrier is responsible for the hitherto unattainable concentration of the medium in the bile. In experiments in dogs, the level of this substance in the bile was about 30 to 100 times higher than the plasma level. Intravenous injection into rabbits also led to concentrations in the liver bile several times higher than with Biliselectan (Diagram 4). Cook et coll. (4) interpret this as a sign of active excretion of the substance through the liver cells. This totally different mechanism of elimination, which determines the superiority of this contrast agent, has been confirmed in investigations on patients.

Case 1. 48-year-old man. Operation for occlusion of the common bile duct by a calculus following cholecystectomy 2 years previously. After operative exposure of the common bile duct, the contrast medium (40 ml Biligrafin 20 %) was injected intravenously at the moment when the surgeon incised the duct to remove the calculus. By means of the insertion of a T-drain, bile was collected in individual portions beginning 5 minutes after the injection. Up to 40 minutes after the injection the branch of the tube leading

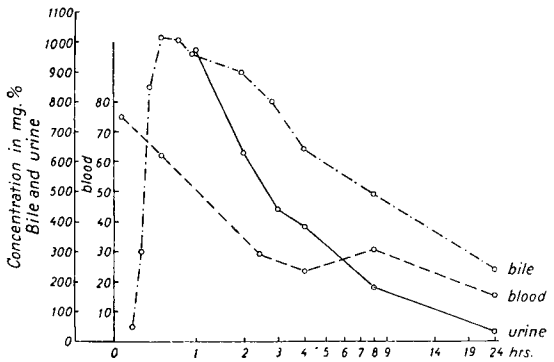


Diagram 5. Concentration of Biligrafin (Case 2). Following cholecystectomy: occluding stone at the papilla of Vater. See also Fig. 6 a and b.

to the duodenum was closed with a clamp, so as to ensure that all the bile secreted was collected for examination. The same effect was obtained by suction drainage after the termination of the operation. The picture was completed by urine analysis and determination of the bile level in the blood.

The concentration curves in Diagram 5 show the remarkably high content of contrast medium in the bile during the first two hours after injection, the figure then falling relatively rapidly. The total balance (Diagram 6) reveals the significant difference from earlier contrast agents. Within 24 hours of the injection, 59.8 % of the total dose was excreted in the bile. During the same period, only 19 % was found in the urine. If it be remembered that a small portion of the bile gets through to the duodenum in spite of the suction drainage — the stools were never bile-free — it is clear that at least 75 % to 80 % was excreted in the bile.

These astonishing values have been confirmed by studies with labelled Biligrafin. Of the dose, 70 % was found in the faeces within 48 hours of injection, and only 10 % to 13 % in the urine (1).

We have found studies in patients with biliary fistulae particularly valuable. If measurements on faeces and urine during Telepaque cholecystography have given similar end-values for excretion products, then, in our opinion, these should not be related to the mechanism of elimination until similar methods of measurement have disproved that the high Telepaque content of the faeces is to a large extent due to unabsorbed residues of the contrast agent.

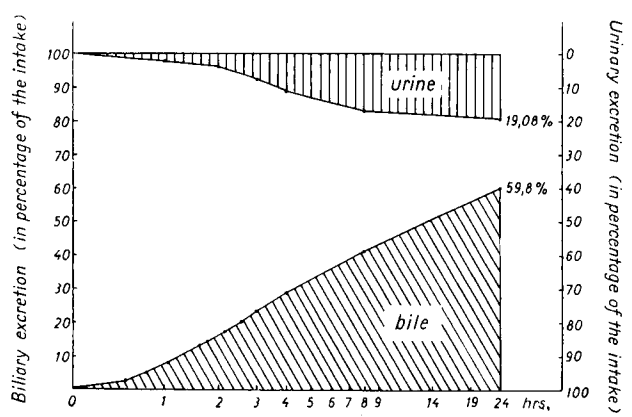


Diagram 6. Excretion after use of Biligrafin (Case 2). See also Diagram 5.

In our Department we are now able to survey nearly 1,000 Biligrafin cholegraphies. Since

a. b.

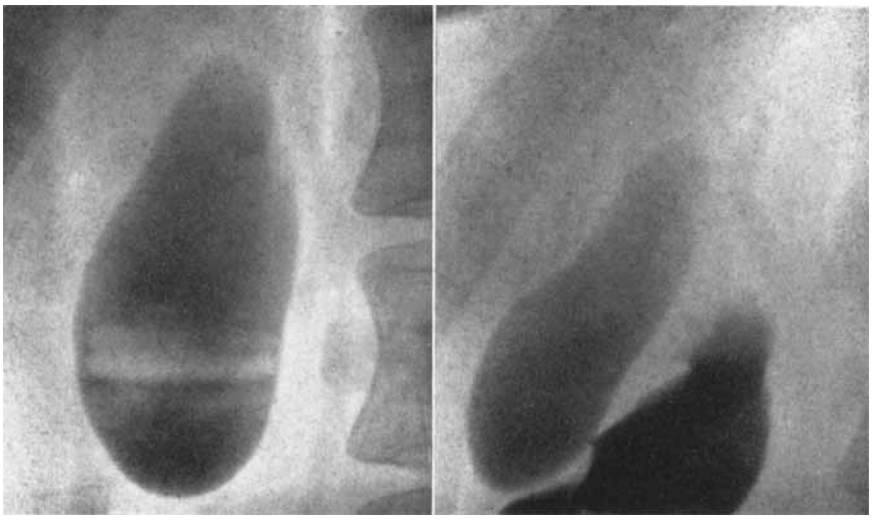
Fig. 4. Normal cholegraphy with Biligrafin. a. Radiograph 2 hours after injection of 20 ml Biligrafin. b. Radiograph 30 min. after egg-yolk meal. Visualization of large extrahepatic biliary passages.

we were the first to work with the substance, we feel justified in also referring to all the experience gathered elsewhere, even outside Germany.

A normal dose of Biligrafin (produced by Schering A. G. Berlin West) amounts to 20 ml of a colourless 20 % solution, or 4 g of the active agent. For the study of specific problems, especially the investigation of cholecystectomized patients, we have recently used 20 ml of a 40 % solution still under clinical trial. It was as well tolerated as the normal solution. We consider it preferable, especially as regards injection technique, to employ Biligrafin 40 % rather than to inject the double dose (40 ml = 2 ampoules) of Biligrafin 20 %, as recommended by many German authors (9).

The technique of examination does not differ essentially from that commonly employed.

In routine examinations, the optimum concentration of the contrast medium in the gall-bladder is reached about 2 hours after injection. In the great majority of cases, the large extrahepatic ducts are still recognizable at this time. After a suitable meal to ensure stimulation of the gall-bladder, for which we like to use two egg-yolks, an assessment of the functional state of the gall-bladder is possible (Fig. 4 a and b). It is, however, not uncommon to find layer formation of the contrast agent in the gall-bladder in films obtained with the patient erect. Narrow light stripes may simulate a row of small floating calculi. This appearance



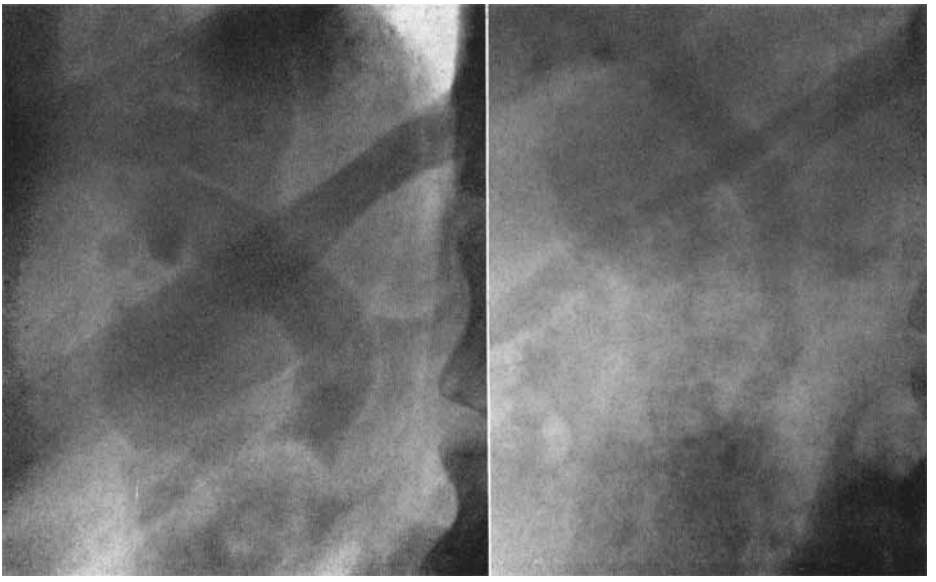
a. b.

Fig. 5. Normal cholegraphy. a. Layer formation of contrast agent; patient erect 2 hours after injection of 20 ml Biligrafin. b. 30 min. after egg-yolk and barium meal. Good gall-bladder function. Disappearance of layer appearance.

depends on the difference in the specific gravity between the bile and the inflowing highly concentrated Biligrafin. In no circumstances should this layer formation be interpreted as a pathologic sign. It disappears on contraction of the gall-bladder, *e. g.* after a meal of egg-yolk which acts as a stimulator (Fig. 5 a and b), and is naturally never seen if radiographs are taken with the patient lying down.

For visualization of the biliary passages we recommend that radiographs be taken with the patient prone on the Bucky table. Corresponding to the rapid and highly concentrated excretion, the ribbon-like shadows of the larger biliary ducts may be differentiated as early as 10 minutes after the injection of 20 ml of Biligrafin 40 % or 40 ml of Biligrafin 20 %. The relationship of the biliary ducts to the vertebral column enables the positioning to be adjusted before taking the serial radiographs which should now follow at 10 minute intervals. It is usually best, and often indeed necessary, to turn the patient into the second oblique position. Optimum visualization, even of the intrahepatic ducts, is obtained between 40 and 90 minutes after injection. A definite opinion upon the function of biliary flow after cholecystectomy thus becomes a matter of routine.

Calculi occluding the common bile duct but not radio-opaque, the presence of which was previously never diagnosed, are now revealed by



a. b.

Fig. 6. Case 2. Cholegraphy. a. Radiograph 80 min. after injection of 20 ml Biligrafin 40 %. Visualization of an occluding stone at the papilla of Vater. Stasis in the biliary tract. b. Radiograph 40 min. after the injection of 20 ml Biligrafin 40 %. Three months after removal of occluding stone: return to normal of bile flow.

the appearance of dilated biliary passages with stasis and a sharp delimitation of the contrast shadow, convex cranially.

Case 2. 48-year-old woman. Cholecystectomy 2 years previously, since when repeated colic; several weeks in hospital for conservative treatment because calculi were not demonstrable. Cholegraphy with Biligrafin (Fig. 6 a) distinctly shows a stone the size of a plum-stone, occluding the papilla of Vater; this has led to an extraordinary degree of stasis as far as the liver. Operation confirmed the finding and the calculus was removed. Three months later the patient was completely free from symptoms. A control radiograph showed return to normal of the previously dilated biliary passages (Fig. 6 b).

Even when the biliary tract is not completely occluded, calculi giving rise to severe colic may be discovered.

Case 3. 32-year-old woman. Biliary symptoms since 1942. Peroral cholecystography in 1947 showed no signs of calculi. Gallstones were demonstrated in 1949; cholecystectomy performed in 1951. Symptom-free until June 1953, when increasing colic, nausea, but no jaundice. Examinations with Biliselectan and Telepaque gave no visualization of the biliary tract. Cholegraphy with 20 ml Biligrafin 40 % revealed multiple calculi in the common bile duct (Fig. 7).

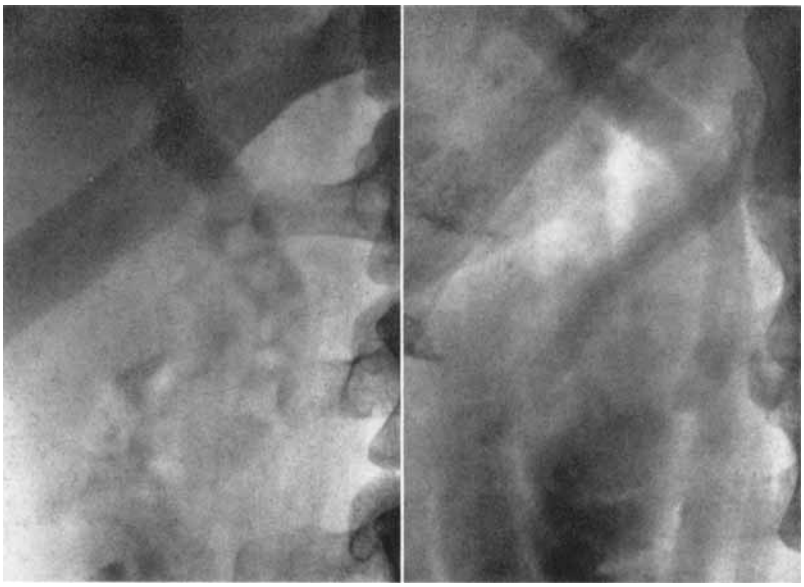


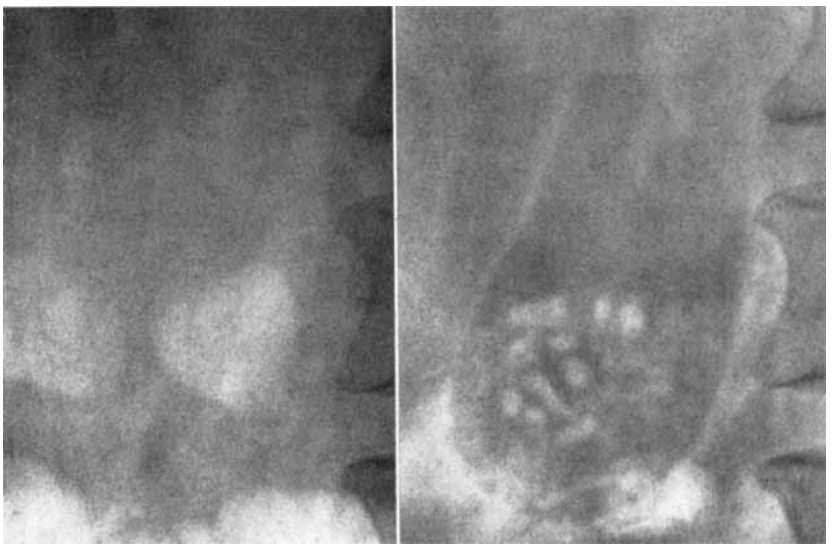
Fig. 7. Fig. 8.

Fig. 7. Case 3. Cholegraphy. Radiograph 20 min. after injection of 20 ml Biligrafin 40 %. Visualization of multiple calculi in the common bile duct.

Fig. 8. Cholegraphy. Radiograph 90 min. after injection of 20 ml Biligrafin 40 %. Visualization of dilated common bile duct. Probable occluding stone at papilla of Vater; gall-bladder not seen. (Occluding stone confirmed at operation. Gall-bladder and cystic duct filled with numerous calculi.) Delineation of duodenal loop with regular mucosal pattern.

Excretion of the contrast medium from the gall-bladder into the small intestine takes place in such high concentrations that shadows with adequate contrast are always observed in the duodenal loop in films obtained 30 to 90 minutes after the injection. The circular folds in the mucosa are usually very distinctly visualized. The form and size of the C-loop may be assessed (Fig. 8) and it should doubtless be possible to detect by this means deformities due to periduodenitic adhesions or displacements of the duodenum due to tumour.

Further investigation is necessary to determine whether Biligrafin may also be used as a means of estimating liver function. The fact that this is not possible with Biliselectan (13) does not permit the conclusion that no insight into the complicated processes of the hepato-biliary system may also be obtained with Biligrafin. Investigations are in progress with Biligrafin in which the iodine atoms have been tagged with I^{131}. These should bring further enlightenment. In experiments in rabbits, it has



a. b.

Fig. 9. a. Telepaque cholecystography: gall-bladder not visualized. b. Cholegraphy with Biligrafin 40 %: gall-bladder outlined and seen to be full of calculi.

been found that the figure of about 10 % for renal excretion rises considerably if there are disturbances in the hepato-biliary system. This might form the basis for a liver function test. It will, however, be necessary to relate results of serum protein electrophoresis to these studies, since 80 % of the contrast substance is bound to the plasma protein as transport medium. A non-filling of the gall-bladder is not necessarily due to a disturbance in the liver-bile system. The possibility of a pathologic composition or disturbance in the formation of the blood proteins must be taken into consideration in every case.

Side-effects, which used to be so much feared when intravenous cholecystography was practised with preparations of the phenolphthalein group, are practically non-existent with Biligrafin. They are decisively influenced by the injection technique. With any contrast agent containing iodine, trivial side-effects will be observed in about 5 % to 20 % of patients. They are not to be considered as indicating hypersensitivity to iodine but rather to the whole molecule of the contrast substance, and consist, as in urography, of mild nausea and, rarely, of vomiting. It should be recalled that Biligrafin lowers the blood pressure. The injection must therefore be given particularly slowly to hypotensive patients and those with a labile circulation. In general, 5 to 6 minutes is sufficient for the injection, which should be guided by the patient's condition. If the in-

jection is given more rapidly, unpleasant sensations varying from a feeling of heat to severe vomiting must be expected. On the other hand, we have never encountered noteworthy reactions in the gastro-intestinal tract or diarrhoea. Both these are relatively common when Biliselectan is employed. According to a communication from Schering A. G., Biligrafin has never caused a fatal outcome in about 40,000 examinations.

It is customary to assess the value of a contrast agent by the percentage of positive cases of visualization of the gall-bladder attained. We adopt a cautious attitude to this view, since such statistics, as already emphasized, depend essentially on the composition of the series. For this reason, we are not presenting a statistical evaluation of our examinations with Biligrafin. We have, however, on several occasions made the observation that in cases in which no visualization of the gall-bladder was possible with Biliselectan and Telepaque an examination with Biligrafin 40 % revealed gallstones, the presence of which was suspected on clinical grounds (Fig. 9 a and b). In our opinion, this and other observations offer more convincing proof of the superiority of the new contrast substance than statistical figures.

The purely technical advantages of intravenous cholegraphy over the peroral method are obvious. In studies on ambulant patients or in cases of medico-legal importance, intravenous injection of Biligrafin is the method of choice, since this does away with the uncertainty whether the patient has in fact taken the tablets or granules the previous evening. The shortening of the examination time from 15 hours with Biliselectan to 2 hours with Biligrafin increases the certainty of finding the optimum state of filling of the gall-bladder, and in itself should constitute an advantage.

We would stress that the introduction of Biligrafin, with its basically different chemical structure and completely new type of excretion mechanism, does not represent merely a further development of substances previously used in cholecystography but augurs an entirely new chapter in the radiologic diagnosis of diseases of the biliary tract.

SUMMARY

Cholecystography and the contrast agents employed are surveyed. The introduction of Biligrafin does not represent a simple development of the triiodated contrast agents but opens a new chapter in the radiologic diagnosis of diseases of the biliary tract. The time of examination is considerably shortened and side-effects are almost absent; the high concentration of the medium permits reliable visualization of the biliary tract even when cholecystectomy has been performed. The suggestion is made that Biligrafin may be found to be of value in the estimation of liver function.

ZUSAMMENFASSUNG

Historischer und kritischer Überblick über die Cholecystographie und ihre Kontrastmittel. Die Einführung des Biligrafin stellt keine einfache Weiterentwicklung der trijodierten Kontrastmittel dar, sondern leitet einen neuen Abschnitt in der röntgenologischen Diagnostik von Erkrankungen der Gallenblase und Gallenwege ein. Die Untersuchungsdauer wird erheblich abgekürzt und Nebenwirkungen fallen nahezu völlig weg; die hohe Konzentration des Mittels erlaubt eine einwandfreie Darstellung der Gallenwege auch bei cholecystektomierten Patienten. Es wird angedeutet, dass Biligrafin wahrscheinlich für die Beurteilung der Leberfunktion von Wert werden kann.

RÉSUMÉ

Les auteurs font une revue de la cholécystographie et des produits de contraste. L'introduction de la Biligrafin ne représente pas seulement un perfectionnement des produits de contraste tri-iodés mais elle ouvre un nouveau chapitre dans le diagnostic radiologique des affections des voies biliaires. La durée de l'examen est considérablement diminuée et les incidents sont presque absents; la forte concentration du produit de contraste permet une visualisation exacte des voies biliaires, même quand on a fait une cholécystectomie. Les auteurs suggèrent que la Biligrafin pourrait se montrer utile dans l'examen de la fonction hépatique.

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