is supported by the observations of Topper and Stetten (1951), who fed D-galactose-1-C¹⁴ to rats and recovered glycogen from the liver which, on hydrolysis, yielded glucose having 90% of its isotope content in position 1. Thus inhibition or lack of any of the enzyme systems involved in reactions A or B would appear a possible lesion in these children. That disease may arise from such a lack of a specific enzyme system has been elegantly established by Cori and Cori (1952), who demonstrated lack of glucose-6-phosphatase activity in liver homogenates from certain cases of glycogen storage disease.

Alternatively the galactosaemia could arise as a result of hepatic damage, following immunization. The galactose-tolerance tests would offer no help in differentiating this secondary defect and the primary defect mentioned above. Bessis (1947) demonstrated profound histological changes in the liver in cases of fatal icterus gravis, but Gerrard (1952) could detect no significant residual hepatic damage in cases surviving Rh sensitization. Gorter (1951) reported galactosuria occurring in association with A-O blood group incompatibility, and in the mother of the present case an anti-A agglutinin was detected. However, Townsend *et al.* (1951), reviewing the relationship between galactosuria and Laennec's cirrhosis, concluded that the defect of galactose metabolism was primary and that the cirrhosis was secondary. This conclusion is supported by the normal liver-function tests in our case.

Bray *et al.* (1952) detected an excess aminoaciduria in two of their cases, but no observations were recorded on the blood amino-acid nitrogen. We were unable to detect this urinary abnormality on two separate occasions. Such an aminoaciduria might result either from liver damage or from renal tubular deficiency. It is noteworthy that the initial biochemical findings in our case resembled those of infantile renal acidosis. Latner and Burnard (1950) have ascribed this condition to failure of the proximal renal tubule to reabsorb bicarbonate ions.

It is conceivable that both these tubular lesions causing excess aminoaciduria and failure of bicarbonate resorption have arisen as toxic manifestations of the galactosaemia, but it must be admitted that we need to study many more such cases before any final conclusion can be reached, and that the association of the acidosis and galactosaemia may be fortuitous.

Summary

The clinical and pathological findings and response to treatment of a case of galactosaemia associated with hyperchloraemic renal acidosis and haemolytic disease of the newborn is described.

It is thought that galactosaemia arises as a congenital condition due to a specific lack of enzymes involved in the metabolism of galactose.

The possibility that the renal acidosis arose as a result of the toxic effect of galactose on the renal tubules is considered.

We are indebted to Dr. I. M. Anderson, whose case this was, and Professor N. F. MacLagan for their advice, help, and criticism in the preparation of this paper, and to Dr. K. Goldsmith for the haematological investigations.

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OPERATIVE CHOLANGIOGRAPHY

BY

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Surgeons are divided in their opinions concerning the value of radiology in the detection of stones in the common bile duct despite the unreliability of the usual surgical methods. Some have come to regard operative cholangiography as indispensable in the surgery of the biliary tract (Mallet-Guy *et al.*, 1947; Mirizzi, 1948; Hicken *et al.*, 1950; McNeill Love, 1952); others have criticized the investigation as being cumbersome, unnecessary (Maingot, 1952), and unsatisfactory because of a susceptibility to appreciable error in interpreting the films at the time of the operation (Waugh *et al.*, 1952).

The bile ducts can be visualized radiologically only after they have been filled by a direct injection of radio-opaque medium. Attempts have been made to do this before operation, but as yet there is no satisfactory standard method.*

Diagnostic Operative Cholangiogram.—The injection into the common bile duct is made after the abdomen is opened and just before the dissection on the biliary tract is begun. The film is developed at once; a stone will be visible as a filling defect.

Control Operative Cholangiogram.—When the common bile duct is opened it is customary after exploration to insert a tube into the duct for the purpose of external biliary drainage. Before the abdominal cavity is closed opaque medium can be injected down the tube into the duct and a further film taken. If an overlooked stone is disclosed the duct is re-explored.

Present Investigation

Operative cholangiography has been performed in a series of 50 patients subjected to operation on account of gall-stones. The investigation was conducted with a view to ascertaining the practicability or otherwise of operative cholangiography as a routine procedure; the value or otherwise of operative cholangiography in the diagnosis of stones in the common bile duct; the apparent advantages of control operative cholangiography over post-operative cholangiography; and the place of operative cholangiography in the recognition of disorders of the biliary tract coexisting with gall-stones.

Technique

Three ureteric catheters (sizes 4 F., 5 F., and 6 F.) and a 20-ml. syringe with blunt needles fitting the corresponding catheters are needed. The medium used is a 35% solution of diodone ("pyelosil 35"). A 50% solution ("pyelosil 50") has been employed in the more obese without ill effect. Diodone contains 49.8% by weight of iodine. It is comparatively free from tissue irritation.

The middle segment of the rubber mattress on the operating table is replaced by a flat tunnel constructed of three-ply wood. The tunnel is long enough to take an x-ray plate 11 by 14 in. (28 by 35.5 cm.) and to allow for some readjustment to bring it to lie under the biliary tract, and high enough to accommodate the cassette and Lyscholt

*This paper was prepared just prior to experiments with intravenous cholangiography; results have been encouraging.

grid. Such a tunnel is not essential, but it facilitates the removal and replacement of the x-ray plate. The portable x-ray machine is wheeled to the left side of the table.

The operation proceeds in the usual way. The viscera are packed away, the fundus of the gall-bladder is held in artery forceps, and the cystic duct is defined and isolated. A length of fine silk is threaded around the cystic duct but not tied. A second ligature is tied around the

FIG. 1.—A normal cholangiogram with reflux up the pancreatic duct. Tributaries join within the liver to form the right and left hepatic ducts. The common hepatic duct and upper part of the common bile duct run medially, but then curve gently to the right to allow a more vertical course for the lower half of the common duct. Diodone has entered the duodenum.

cystic duct at its junction with the gall-bladder. A small cut is made in the cystic duct and a ureteric catheter of suitable diameter is inserted down into the lumen of the common bile duct for 4–5 cm.

The syringe containing 20 ml. of diodone is supplied with a needle that accurately fits the ureteric catheter, and 1–2 ml. is injected down the catheter to confirm that there will be no leakage of medium around it. All overlying instruments are removed; a pack is placed over the wound; the operating table is rotated 20 degrees to the right side; 10 ml. of diodone is injected as rapidly as possible, and at the conclusion of the injection the anaesthetist stops respiratory movements and the first film is taken (diagnostic operative cholangiogram).

Whilst the film is being developed the excision of the gall-bladder proceeds in a routine way, and often the surgeon has largely re-peritonized the gall-bladder fossa by the time the film is ready. If the film is unsatisfactory a further one can be taken at this stage, because the ureteric catheter has been left *in situ*. If the film is satisfactory and no stones are present, the ureteric catheter is removed and ligation of the cystic duct completed.

If the film shows or suggests the presence of a stone the common duct is explored. After this has been completed a tube is sutured snugly into the duct. An x-ray plate is reinserted and a second cholangiogram performed (control operative cholangiogram). The abdominal wound is not closed until this film has been developed, because if it should reveal a stone that has eluded the surgeon a further exploration is required.

Normal Operative Cholangiogram

The intrahepatic radicles are displayed, and, as tributaries join within the liver, the right and left hepatic ducts finally emerge, joining to form the common hepatic duct (Fig. 1). The common hepatic duct and the upper part of the common bile duct run medially, then curve gently to the right to allow the lower common bile duct to take a

more vertical course, parallel to the spine, to end at the level of the second lumbar vertebra. The lower end of the common duct tapers abruptly into the intramural portion, which can often be followed into the duodenum. There may be reflux up the pancreatic duct for 3–4 cm. Some medium should be visible in the duodenum.

Abnormal Cholangiogram Due to Biliary Calculi

Calculi usually appear as filling defects in the common bile duct shadow and particularly at its lower end (Fig. 2). The duct above is often dilated. In some cases no dye enters the duodenum, presumably because the stone is within the intramural part. In some films rounded shadows of lesser density suggest the presence of stones in the intra-hepatic radicles.

Results

Technical Aspects.—There were no deaths in this series of 50 cases, and the only complication which could be attributed to operative cholangiography was an acute dilatation of the stomach. There were five unsatisfactory films; in one case the diaphragm moved at the moment of the exposure, in another a pair of forceps concealed the outline of the lower end of the common bile duct, whilst in a third the film was incorrectly centred. In two other cases the lower end of the common bile duct was obscured by excessive dye in the duodenum.

Diagnostic Operative Cholangiography.—In 32 instances the cholangiogram was accepted as being within normal limits, and the common bile duct was not explored. In one of this “apparently normal” group biliary colic occurred on the second post-operative day; re-examination of the x-ray film revealed a small filling defect which had been overlooked in the operating theatre when the film was wet. In 12 cases stones were visualized as filling defects and were removed. In three no dye entered the duodenum, and from two of these stones were removed from the common bile duct. In three other patients the common bile duct was explored because it was thought that the wet

FIG. 2.—Operative cholangiogram to demonstrate a stone in the lower part of the common bile duct. Opaque medium has entered the duodenum. Note the normal narrow intramural portion of the common bile duct immediately below the stone.

films were abnormal, but no stones were found. In the whole series of 50 cases the duct was explored on 18 occasions, and stones were removed in 14.

Control Operative Cholangiography.—Control operative cholangiograms were performed on 10 of the 14 patients from whom stones were removed from the common bile duct; in one of these an overlooked stone was discovered and removed, and a second control operative cholangiogram showed normal ducts.

Detection of Other Conditions.—In one cholangiogram no medium entered the duodenum and no stone was found in the common bile duct on subsequent exploration; a

diagnosis of "hypertonic sphincter" would be permissible. Other than passing a fine sound into the duodenum no treatment was adopted, and the patient has since remained free of symptoms. No case in this series showed cholangiographic evidence of atonic sphincter. On two occasions on which there was considerable fibrosis around the junction of the cystic duct, common hepatic duct, and common bile duct an operative cholangiogram proved of assistance in displaying the anatomical arrangements of the ducts prior to their actual dissection. In this series of 50 cases a pancreatic reflux was observed in eight, but it appeared to be of no significance.

Discussion

Practicability of Routine Operative Cholangiography

This investigation has shown that the technical aspects of operative cholangiography need not be burdensome; the procedure prolongs the operating time, but has proved harmless to the patient—with the possible exception of one case of acute gastric dilatation. An early disappointment should not deter the surgeon from persevering. With attention to detail, satisfactory films can be obtained in a high proportion of cases with little inconvenience.

A ureteric catheter is better than a fine rubber catheter for conveying the dye—its rigidity facilitates negotiation of the valves of Heister (often a tedious procedure) and its centimetre ring graduation enables the surgeon to estimate at once the length of the catheter in the common bile duct. Needle puncture of the common bile duct is less reliable; if the gall-bladder has already been removed or if it proves impossible to gain entry through the cystic duct it may be necessary to use a needle, but even in these cases it is easier to push a ureteric catheter into the duct through a small puncture wound made by a needle; a catheter enables a second picture to be quickly taken if the first should prove unsatisfactory, and at the same time it allows the surgeon to keep his hands well away from x-radiations.

Respiratory movement must cease when the film is taken. For this reason controlled respiration anaesthesia is necessary, and, as the x-ray machine should be used in the absence of inflammatory gases, the anaesthetic of choice is nitrous oxide and oxygen, with endotracheal intubation and the use of a relaxant.

It is important to visualize clearly the terminal portion of the common bile duct. Interference by the lumbar vertebrae can be overcome by rotating the operating table. As the dye runs into the duodenum the folds of that viscus may overlap the terminal duct and conceal its true outline. This can be partly avoided by taking the first film immediately the injection is completed and before too much dye has entered the duodenum.

Place of Operative Cholangiography in the Diagnosis of Stones in the Common Bile Duct

The experience obtained in this series indicates that operative cholangiography can afford some assistance in diagnosing the presence of stones in the common bile duct, although it will probably only rarely disclose a stone the presence of which should not at least have been suspected by the surgeon. When the 14 positive cases of common bile duct stones were reviewed it was apparent that in 13 there were definite indications for opening the duct, but in the remaining case there was no clinical or operative evidence which favoured the presence of a stone.

In recent years several series of cases have been published which analyse the "post-cholecystectomy" syndrome, and it is clear that in most series a residual stone has played the leading part (Gray and Sharpe, 1944; Adams and Stranahan, 1947; Millbourn, 1950). Stones even when quite large often cannot be felt, and to detect these the surgeon must rely on less satisfactory indirect evidence such as a pre-operative history of jaundice, or the operative discovery of a dilated, thickened common bile duct, especially if it contains thick muddy bile, a gall-bladder filled with small stones, a widened cystic duct, and a thickened pancreatic

head. The significance attached to such indirect evidence varies widely, so accounting for the discrepancy in the frequency with which the duct is explored by individual surgeons.

If the surgeon explores the common bile duct in all cases in which there is some evidence of a common bile duct stone he will find that diagnostic operative cholangiography is of little value. Whilst small stones and even large ones might easily be overlooked by the most experienced surgeon, in the wet x-ray films of diagnostic operative cholangiography they may likewise pass unnoticed, for the most enthusiastic protagonist of operative cholangiography will not claim for it an accuracy of more than 95% (Mixer *et al.*, 1951).

Apparent Advantages of Control Operative over Post-operative Cholangiography

When the common bile duct is opened and drained it is common practice in the post-operative period to take an x-ray film of the biliary tract after injecting an opaque medium down the tube to test the patency of the duct. If such a post-operative cholangiogram discloses an overlooked stone in the common bile duct the surgeon is placed in a difficult position, because a second operation at this stage can be undertaken only with great reluctance.

In nearly one-third of the patients who died after removal of stones from the common bile duct stones still remained in the ducts at necropsy (Mayo, 1923). Hicken *et al.* (1950) and Mixer *et al.* (1951) claimed that cholangiograms performed a week after operation showed the average incidence of missed stones to be approximately 10%.

In the present series control operative cholangiograms were performed in 10 cases and an overlooked stone was found in one of them; it was a relatively simple matter to re-explore the duct at the time and remove the stone. Although interpretation of the films presents difficulties, in view of the impossibility of ensuring removal of all the stones after exploration of the common bile duct a control operative cholangiogram is useful and should certainly replace the post-operative cholangiogram with its restricted value.

Recognition of Disorders of the Biliary Tract Coexisting with Gallstones

Archibald (1919) suggested that spasm of the sphincter of Oddi might be responsible for acute pancreatitis, and Westphal (1923) published a classification of sphincter disorders based on a series of experiments performed on animals; functional disorders of the sphincter have since been held responsible for some of the poor results of cholecystectomy. Mirizzi (1948) and Mallet-Guy *et al.* (1947) have reported numerous instances in which operative cholangiography has demonstrated to their satisfaction sphincter spasm or sphincter atony of a degree sufficient to produce symptoms.

In the present series there was but one instance in which it appeared that the sphincter was in a state of spasm, although apparently this was of no consequence. Functional disorders of the biliary tract rarely call for operative treatment at the Royal Melbourne Hospital, where 97% of the gall-bladders removed contain gall-stones; even the remaining 3% can usually be explained on pathological grounds other than sphincter incoordination.

The diagnosis of ampullary stenosis should likewise be made with caution. Normally both the common bile duct and the pancreatic duct of Wirsung narrow abruptly where they meet just outside the duodenal wall (Hughes and Kernutt, in press); and they course together through the duodenal wall for a distance of up to 25 mm.: it is here that the cholangiogram often conveys a false impression of a long narrow stricture.

Operative cholangiograms direct special attention to the common bile duct, and for this reason lesions existing in conjunction with gall-stones might be demonstrated. In the present small series of cases this has not proved to be the case, probably because of the rarity with which such lesions occur.

Conclusions

As a diagnostic aid operative cholangiography has proved on the whole disappointing, and in view of the negligible added risk of exploring the common bile duct it is unlikely to be widely adopted. In obstructive jaundice and in cases in which the common bile duct required a second exploration, operative cholangiography can be recommended as an important step in elucidating the sometimes confusing pathology.

In view of the difficulty of ensuring complete removal of all the stones from the common bile duct in cases of choledocholithiasis, and because of the very limited practical value of post-operative cholangiography, a control operative cholangiogram performed at the conclusion of the operation but before suturing the abdominal wall is useful.

No operative cholangiogram in this series has demonstrated definite coexisting disturbance in the function of the sphincter of Oddi.

Summary

Operative cholangiograms were carried out by us in a series of 50 patients. "Diagnostic operative cholangiogram" was the term applied to the film taken just before the dissection on the biliary tract was begun, while "control operative cholangiogram" referred to that taken after the duct had been explored but before closure of the abdomen.

The method employed involved the insertion of a ureteric catheter into the common bile duct. A solution of diodone ("pyelosil 35") was the medium used. Satisfactory films were obtained in 45 cases; in the remaining 5 a second film was necessary.

In 32 instances the cholangiogram appeared normal; in 12 cases stones were visualized as filling defects and removed. In three cases no dye entered the duodenum, and in two of these stones were removed from the common bile duct. In 13 of the 14 instances in which stones were found indications for opening the common bile duct were present. The operative cholangiogram appeared abnormal in three further cases but no stones were found on exploration.

Control operative cholangiograms were taken in 10 cases and in one an overlooked stone was discovered; the duct was thereupon re-explored and the stone removed.

In one case no dye entered the duodenum and no stone could be found responsible.

It is concluded that while diagnostic operative cholangiography has proved disappointing as a routine procedure it may assist in elucidating the pathology in obscure cases of obstructive jaundice and in patients with recurrent symptoms following cholecystectomy. Control operative cholangiography is much more useful than post-operative cholangiography.

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PATHOLOGICAL CHANGES IN THE LIVER IN SALM. TYPHI-MURIUM INFECTION

BY

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Damage to the liver in the course of illness resulting from infection by organisms of the *Salmonella* group is not usually so severe as to affect the clinical picture, and gross morbid changes are not described. Saphra (1950) collected 3,279 cases of salmonella infections. These included 174 deaths, 63 of them due to *Salm. typhi-murium*. No mention was made of any hepatic lesions. Guthrie and Montgomery (1939), in describing a series of cases of *Salm. enteritidis* infections, reported in their post-mortem findings only "the usual toxic changes" with cloudy swelling, fatty degeneration, and the absence of focal necrosis in the liver. Nasso (1947) reported two cases of infection by *Salm. cholerae-suis* which showed jaundice and enlargement of the liver and spleen. Giaccari and Idriss (1952), in a case of osteomyelitis due to *Salm. enteritidis*, noted jaundice during the illness. Their case also showed enlargement of the liver and spleen and there was anaemia requiring transfusion. Ashby and Wright (1905) quote a case in which cirrhosis occurred in a child who had suffered from clinical typhoid fever. Ascites, enlargement of the spleen, and anaemia began ten months after the acute illness. At necropsy a small hobnail liver was found. The bacteriology and morbid histology were not reported. In babies dying in an epidemic due to *Salm. oranienburg*, Epstein *et al.* (1951) demonstrated changes in the liver ranging from fatty degeneration to scattered foci of necrosis with oedema. Their illustrations show collections of myeloid cells in the portal spaces.

In the following case a clinical portal cirrhosis occurred in the course of an illness due to *Salm. typhi-murium*.

Case Report

A girl aged 1 year and 9 months was admitted to hospital on March 6, 1951. Two weeks before admission she developed bronchopneumonia. The signs in the chest cleared but the temperature did not fall. She lost weight rapidly and became severely ill.

On admission she was drowsy, dehydrated, and toxic; her temperature was 105.2° F. (40.7° C.). The abdomen was slightly distended and doughy. The liver and spleen were not felt. Her weight was 17 lb. 6 oz. (7.9 kg.) and her length 30 in. (76 cm.). The stools were profuse and fluid. The white-cell count was 9,300—28% neutrophils and 32% old metamyelocytes. Blood culture grew *Salm. typhi-murium*, and the same organism was recovered from the stool. The urine was physiological.

She was treated with chloramphenicol for 15 days. In three days the temperature was normal, the blood culture was sterile, and pathogenic organisms had disappeared from the stool. One week after stopping treatment the temperature rose again and the organism reappeared in the stools, but the blood culture remained sterile. This relapse was the first of a series each associated with a high temperature and illness. The relapses were treated with chloramphenicol, aureomycin, and streptomycin, alone and in pairs, and on one occasion with oxytetracycline. Courses of treatment were continued for periods of up to four weeks. Initially she responded well, but gradually it became difficult to control the pyrexia. After six months the temperature remained persistently raised in spite of treatment, and a state