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

of clinical resistance to chloramphenicol, aureomycin, and streptomycin had been established. Further supplies of oxytetracycline were not available at that time. The organism was regularly recovered from the stools.

The liver was first felt one week after admission; it increased steadily in size, the lower border reaching the umbilicus by December, 1951. The spleen was not felt until December, 1951. The enlargement was less rapid than that of the liver, and it did not reach the level of the iliac crest until November, 1952. Ascites appeared in December, 1951, and required repeated paracentesis. Dilatation of the superficial veins occurred gradually during the first six months of 1952 and oesophageal varices were demonstrated radiologically in August, 1952. Anaemia of hypochromic type developed gradually and transfusion was necessary at intervals of from three to six weeks during the period July, 1951, to February, 1953. Haematemesis, epistaxis, haematuria, and the presence of occult blood in the stools occurred repeatedly during the latter months of 1952. At the same time the child developed a thrombocytopenia and prothrombin activity fell to 10%, rising after the administration of "synkavit" to 30%. At no time was the child jaundiced. During the period March, 1951, to February, 1953, she did not grow, and her weight varied between 17 and 23 lb. (7.7 and 10.4 kg.).

In January, 1953, she was again given oxytetracycline. The dosage was at the rate of 100 mg. per kg. There was an immediate improvement. The temperature fell to normal, the appetite returned, and she became active and vivacious. The anaemia improved and the platelet count rose to normal.

After a month streptomycin was substituted for oxytetracycline. Clinical relapse occurred within a week. From February, 1953, onwards the child continued to take oxytetracycline and remained well. In June, 1953, her weight was 31½ lb. (14.3 kg.), height 33 in. (84 cm.). The liver and spleen were both enlarged 4 in. (10 cm.) below the costal margins and there was still some ascites.

Investigations.—The results of some laboratory investigations which may be relevant to the pathological changes in the liver are shown in the Table. The white-cell count

Laboratory Investigations

	December, 1951	July, 1952	January, 1953
Thymol:			
Turbidity	25 units	48 units	31 units
Flocculation ..	++++	++++	++++
Alkaline phosphatase (King-Armstrong) ..	19.2 units	30 units	41.5 units
Plasma proteins:			
Total	5.9 g. %	6.4 g. %	6.5 g. %
Albumin	3.3 g. %	3.2 g. %	3.4 g. %
Globulin	2.6 g. %	2.3 g. %	3.1 g. %
Blood cholesterol ..	176 mg./100 ml.	157 mg./100 ml.	106 mg./100 ml.
Van den Bergh ..	Negative	Negative	Negative
E.S.R. (1st hour) ..	48 mm.	74 mm.	45 mm.

varied between 6,900 and 20,000, but was usually low. There was always a shift to the left in the neutrophil series. The bone marrow was normal in December, 1951, and in August, 1952. In January, 1953, there was moderate hypoplasia of the red-cell series, a slight myeloid reaction, and some increase in the number of megakaryocytes. The urine throughout the illness has shown varying amounts of albumin and an occasional granular and hyaline cast. Red cells were present during the periods when bleeding was occurring. The blood urea remained within normal limits. The faeces always contained *Salm. typhi-murium* except for a short period during the treatment with oxytetracycline, when a profuse growth of *Proteus vulgaris* masked all other organisms.

In April, 1951, the serum agglutinated a suspension of non-specific salmonellae at a dilution of 1:640. In August, 1952, the agglutination of *Salm. typhi-murium* by the patient's serum was: "O" +, 1:20; —, 1:40. "H" +, 1:4,000; —, 1:4,500.

Liver Biopsies.—The first operation for biopsy was carried out under general anaesthesia on January 23, 1952. Sections showed a polymorphonuclear inflammatory reaction in the portal tracts, and much fibrous tissue. There was an apparent increase in the number of bile capillaries. Mitoses were not seen, however, and it is probable that the appearance was due to crowding together of the bile ducts as the result of the loss of intervening liver tissue. The material in the bile ducts consisted of masses of Gram-negative bacilli (Figs. 1 and 2). The second biopsy was carried out on July 23, 1952.

FIG. 1.—Liver biopsy on January 23, 1952, showing fibrous tissue and polymorphonuclear cells surrounding bile ducts packed with bacteria. (H. and E. $\times 750$.)

FIG. 2.—Liver biopsy on January 23, 1952. Masses of Gram-negative bacilli in the bile ducts. (Gram. $\times 1,440$.)

an attempt to measure the portal venous pressure was unsuccessful because of the enormous size of the liver and spleen. The sections from the liver showed an increase in both the degree of inflammatory reaction and the extent of the cirrhosis. Organisms were again seen in the bile ducts, but were fewer than at the previous biopsy. Culture of a piece of liver gave a pure growth of *Salm. typhi-murium*.

Discussion

The pathological findings in this case are unlike the lesions described in typhoid fever, which consist typically of foci of necrosis in the lobules as the result of sinusoids being blocked by macrophages.

It is known that liver damage can be caused by aureomycin and oxytetracycline, but probably only when these drugs are given parenterally as well as orally (Lepper *et al.*, 1951). The clinical picture in such cases includes jaundice, and the morphological change consists of severe vacuolation and disintegration of cytoplasm, particularly near the

central vein of the lobule. These findings were absent in my patient and neither of the incriminated drugs had been given by injection.

Cirrhosis can occur as the result of impaired intestinal absorption in chronic disease in the bowel. Dyson (1950) reported three cases of long-standing ulcerative colitis in which a fine portal cirrhosis was found. There was also a necrosis of liver cells in the central areas of the lobule. In the case reported here there was no evidence of impaired absorption from the bowel, and the liver damage was essentially peripheral.

Cameron *et al.* (1940) produced morbid changes in the livers of rats by the intraperitoneal injection of a toxic fraction derived from *Salm. typhi-murium*. The changes included congestion of the portal vein and a peripheral necrosis of the hepatic lobule.

The observation of the organisms in the intrahepatic bile ducts is important, and suggests that the gall-bladder, which has been regarded as the main reservoir of infection in carriers of salmonellae, may play only a secondary part.

The partial suppression of the organism by treatment altered the normal course of the illness in this case. This child would probably have died if antibiotics had not been given. She was allowed to live long enough for the salmonellae surviving in her bile ducts to cause an inflammatory reaction, with destruction of liver tissue and the development of cirrhosis.

Bacteriology

The antigenic structure of the organism obtained from the liver was O=IV, V, XII; H=i—1, 2, 3.

In vitro the organism cultured from the stools was consistently resistant to penicillin but sensitive to 2.5 µg. of streptomycin and to 25 µg. of chloramphenicol per ml. Sensitivity to 1:1,000 sulphathiazole was reported once in November, 1952, but on all other occasions the organism was resistant. The sensitivity to aureomycin was not constant. It varied from complete resistance to 25 µg. to moderate sensitivity to 10 µg. There was resistance to 10 µg. of oxytetracycline in November, 1952, weak sensitivity in January, 1953, and sensitivity in March, 1953. These *in vitro* assessments of the sensitivity bore no relation to the clinical results obtained. Chloramphenicol, aureomycin, and streptomycin were clinically useless after the first six months of the illness. Oxytetracycline produced a spectacular clinical improvement at a time when the organism was showing only weak sensitivity. A similar discrepancy between the effect of antibiotics *in vivo* as compared with the sensitivity of the organisms *in vitro* was noted by Epstein *et al.* (1951) in infections due to *Salm. oranienburg*. The discrepancy may be related to the varying extent to which the antibiotics are excreted in the bile. Welch (1950) showed that, following test doses, chloramphenicol appeared in the bile of rabbits in a higher concentration than aureomycin or oxytetracycline, while in human beings the concentration of oxytetracycline in the faeces was higher than that of either of the other two. In this case the effects of antibiotics on the bacteria in the bile ducts would be reduced as the result of the isolation of the organism from the blood stream by fibrosis and the absence of a flow of bile through the ducts following the destruction of liver tissue.

Summary

A case is described in which cirrhosis developed in a child suffering from a chronic *Salm. typhi-murium* infection.

The cirrhosis was confirmed by liver biopsies.

The living organism was demonstrated in the intrahepatic bile ducts 16 months after the onset of the illness.

The sensitivity of the organism to antibiotics *in vitro* was inconstant and did not correspond with the clinical effects of the drugs.

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ADDENDUM.—Since this report was prepared for publication the child has died. Treatment with oxytetracycline was continued for a year. The child remained well and grew. The evidence of portal hypertension became less. Repeated culture of the stools failed to show salmonellae. Three months after stopping the drug there was a sudden relapse and she died. At necropsy the changes in the liver were essentially the same as those found during life, but there was acute inflammation of Peyer's patches. *Salm. typhi-murium* was grown from the stools, from the gall-bladder, and from the liver.

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PRIMIDONE IN THE TREATMENT OF EPILEPSY

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Handley and Stewart (1952) first reported the use of primidone ("mysoline"; 5-ethyl-5-phenyl-hexahydro-pyrimidine-4:6-dione) in the treatment of epilepsy, and since then a number of papers have appeared indicating the effectiveness of the drug in controlling epileptic manifestations of various types (Butter, 1953; Whitty, 1953; Smith and Forster, 1953). Many of the cases in these surveys—including that of Whitty (1953) and of Greenstein and Sapirstein (1953)—were given primidone in addition to other drugs. Nathan (1954), however, reports satisfactory results in 43% of 21 cases of symptomatic epilepsy treated with primidone alone. The present report deals with 44 cases of epilepsy of various types in which previous medication was completely replaced by primidone.

The 44 patients (19 male, 25 female) varied in age from 13 to 52, and were representative of the types seen in a neurological out-patient department. Handley and Stewart's patients were in an institution and so were possibly more refractory cases than the average epileptic not requiring institutional care. An adverse selective factor also operated in our series, since all the patients had failed to respond satisfactorily to other forms of treatment. The period of survey was 3–14 months, the majority of the patients having been followed for six months at least. The tabulated results deal with only 42 patients, as two were unable to continue their treatment for more than a few days. These 42 comprised the following clinical types: 3 post-