Papers and Originals

Chronic Cholangitides: Aetiology, Diagnosis, and Treatment*

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Summary: A number of different chronic diseases affect the intrahepatic bile radicles or cholangioles. They include primary and secondary sclerosing cholangitis, primary biliary cirrhosis, chronic cholestatic drug jaundice, atresia, and carcinoma. Aetiological factors include infection, immunological changes, hormones, and congenital defects.

Patients with chronic cholestasis have decreased bile salts in the intestinal contents and suffer from a bile salt deficiency syndrome. Failure to absorb dietary fat is managed by a low-fat diet and by medium-chain triglycerides which are absorbed in the absence of intestinal bile salts. Fat-soluble vitamin deficiencies are prevented by *parenteral* vitamins A, D, and K₁. Calcium absorption is defective, and improvement may follow intramuscular vitamin D, medium-chain triglycerides, a low-fat diet, and oral calcium supplements.

In partial intestinal bile salt deficiency the anionic bile-salt-chelating resin cholestyramine controls pruritus though steatorrhoea increases. Pruritus associated with total lack of intestinal bile salts is managed by methyl-testosterone or norethandrolone, though the jaundice increases.

Introduction

In the last 10 years or so attention has been increasingly drawn to jaundice of intrahepatic origin which is due not to hepatocellular disease but to disturbance of the cholangioles or intrahepatic bile channels. This lecture is concerned with jaundice due to chronic disease of the cholangioles. Only chronic conditions are discussed. The condition must have persisted, usually with icterus, for at least six months. Particular attention is drawn to the aetiological factors concerned. These range widely and include infections, drugs, and disturbances of immunity (Fig. 1). The resulting clinical picture has many features in common despite the various aetiological factors. The basic treatment is similar whatever the cause, and in addition specific therapeutic measures must be considered.

Anatomy (Fig. 2).—For the purpose of this lecture the cholangiole has been defined as the portion of the intrahepatic biliary tree extending from the canaliculus to the main septal bile ducts. It therefore includes the ductule (or canal of Hering) leading from the canaliculus to the interlobular bile duct, which is the first duct to be accompanied by a branch of the portal vein and hepatic artery in the portal tract. The interlobular bile ducts form the septal bile ducts, which join together in ever-increasing size until the right and left main hepatic ducts emerge from the liver at the porta hepatis.

Functional Effects.—Lesions in the cholangiole result in the syndrome of intrahepatic cholestasis (Sherlock, 1966). The clinical picture is of obstructive jaundice with pruritus prominent. The serum shows an increase in all the usual constituents of bile, including conjugated bilirubin, trihydroxy bile acids, total cholesterol, and alkaline phosphatase. The general effects of intestinal bile salt deficiency include steatorrhoea. Faecal stercobilinogen is decreased.

Secondary Sclerosing Cholangitis (Chronic Intrahepatic Infective Cholangitis)

The aetiology of this type seems the easiest to comprehend. In the presence of prolonged extrahepatic obstruction, with infection in the dilated biliary tree, the intrahepatic bile ducts undergo progressive sclerosis. Light microscopy shows annular sclerosis of various sizes of intrahepatic ducts from major ones down to ductules. An inflammatory reaction, mainly polymorphonuclear, surrounds the ducts, infiltrates the wall, and is seen in the lumen. The sclerotic process continues slowly over the months and years. This sequence may account for the failure of an apparently successful reconstruction operation on large ducts to relieve a postoperative biliary stricture and to clear the cholestatic jaundice. It explains how a patient with choledocholithiasis of some years' standing fails to lose his icterus after removal of the stones. It also accounts for the difficulty in obtaining a successful percutaneous cholangiogram before operation in some patients with long-standing biliary stricture. The infection in the dilated ducts is largely Gram-negative and due to *Escherichia coli*, enterococci, and bacteroides. The sclerosis is presumably related to the direct effects of the infecting organism on the cholangiole and also to retention of toxic bile acids which infiltrate the duct wall and excite a periductular reaction.

"Primary" Sclerosing Cholangitis

In several instances the sclerosing cholangitis appears as a "primary" event. In the majority this condition complicates long-standing ulcerative colitis. Involvement of the biliary tract in patients with ulcerative colitis may be in the ductule, interlobular bile ducts (pericholangitis), main hepatic bile ducts (sclerosing cholangitis), and even the gall bladder (Thorpe *et al.*, 1967). It may be seen in an operative cholangiogram as typical irregular narrowing of the larger extrahepatic bile ducts and by beading of the intrahepatic bile ducts. Sclerosing cholangitis and pericholangitis may be part of a single disease process involving all or part of the biliary tract in patients with ulcerative colitis. The histological picture in both intrahepatic and extrahepatic ducts is quite non-specific, with chronic inflammation, lymphoid aggregates, fibrosis, and occasionally eosinophilia. Peribiliary fibrosis may be obvious. Polymorph infiltration is usual.

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The aetiology of the lesion is unknown. Portal venous bacteraemia has been reported more frequently in patients being operated on for ulcerative colitis than in other patients having abdominal operations (Brooke *et al.*, 1961). This is presumably due to absorption of intestinal organisms through the ulcerated colon into the portal venous system. This suggests a bacterial aetiology. However, the clinical picture does not resemble bacterial cholangitis. Wide-spectrum antibiotic therapy is ineffective. Surgical removal of the diseased colon does not seem to alter the progress of the biliary disease (Mistilis *et al.*, 1965). The hepatic histological picture is not that of a bacterial cholangitis.

Ulcerative colitis has been included with the "autoimmune" diseases. The problem of possible immunological injury to cholangioles is discussed below. There is, however, little to

This condition, certainly in the early stages, is not a true cirrhosis, for nodular regeneration (a necessity for the diagnosis of cirrhosis) is not seen. It is more correctly termed "chronic non-suppurative destructive cholangitis" (Rubin *et al.*, 1965). The disease seems to begin in the septal and interlobular bile ducts, which are surrounded by a mononuclear reaction. The epithelium of the duct is distorted, duplicated, and necrotic. In the later stages portal zone fibrosis becomes marked, and ductules proliferate and finally disappear. The last stage is that of biliary cirrhosis.

The condition is associated with much immunological activity, but its relation to the destruction of the cholangioles remains in doubt. The mesenchyma adjoining the altered bile ducts contains basophilic P.A.S.-positive material (glycolipoprotein) (Paronetto *et al.*, 1964). Immunofluorescence

FIG. 1

BILIARY ANATOMY

FIG. 2

FIG. 1.—Aetiological factors concerned in disease of the cholangiole include infection, atresia, carcinoma, and immunological. FIG. 2.—Anatomy of the cholangiole. This extends from the canaliculus to the septal bile ducts, which join in branches of ever-increasing size until the right and left main bile ducts are formed.

support this concept when applied to the sclerosing cholangitis which is secondary to ulcerative colitis. All the usual serological tests which are said to indicate disturbed immunity are consistently negative.

Certain toxic secondary bile acids are formed from primary bile acids by bacterial action, usually in the colon. Lithocholic acid is one such toxic bile acid which is produced by bacterial 7- α -dehydroxylation of chenodeoxycholic acid. Lithocholic acid can cause cholestasis (Javitt, 1966). The reaction induced in the liver of experimental animals includes an inflammation with proliferation of hepatic ductules; gall stones may develop (Palmer and Hruban, 1966; Zaki *et al.*, 1967). Increased production of lithocholic acid may be associated with cirrhosis. Raised serum lithocholic acid levels in patients with liver disease have been reduced by feeding neomycin, a poorly absorbed wide-spectrum antibiotic (Carey *et al.*, 1966), which would reduce bacterial action in the intestine and so the formation of lithocholic acid from chenodeoxycholic acid. It seems possible, though not proved, that some of the cholestasis and biliary damage seen in patients with ulcerative colitis could be due to absorption of toxic bile salts of bacterial origin, particularly lithocholic acid, through the diseased colon (Carey, 1964).

Primary Biliary Cirrhosis

This disease is usually one of middle-aged women. It presents with pruritus followed by cholestatic jaundice of varying intensity. The duration of the disease is some three to seven years from diagnosis to death.

shows this to be gamma M (19 S) immunoglobulin. Serum immunoglobulin M (IgM) values are increased to a greater height and in a higher percentage of cases in primary biliary cirrhosis than in other forms of liver disease (Feizi, 1968). It has even been suggested that elevated IgM values may be used in the diagnosis of primary biliary cirrhosis (Hobbs, 1966). The diagnostic value, however, is in some doubt, as there is considerable overlap between the levels in primary biliary cirrhosis, surgical obstruction to major bile ducts, active chronic hepatitis, and cirrhosis of the alcoholic (Feizi, 1968).

These observations have raised the possibility that bile ducts may be destroyed as the result of an antigen-antibody reaction involving gamma M immunoglobulins. This hypothesis has not been proved.

Various non-specific serological reactions have been reported in patients with primary biliary cirrhosis. For instance, anti-nuclear factor may be present and latex tests for rheumatoid factor may be positive in a proportion of cases (Bouchier *et al.*, 1964). An antibody in the serum of patients with primary biliary cirrhosis has been described which reacts with bile ductules (Paronetto *et al.*, 1964). This is also found in cases of viral hepatitis (67%), secondary biliary cirrhosis (43%), extrahepatic biliary obstruction (32%), and cirrhosis of the alcoholic (22%).

The conventional complement fixation test detects antibodies to mitochondria and other cell constituents. Positive results have been reported with tissue extracts and serum from patients with primary biliary cirrhosis (Gajdusek, 1958; Deicher *et al.*, 1960; Asherson and Broberger, 1961; Gökçen, 1962; Walker *et al.*, 1965). A more refined immunofluorescent test, using

slices of rat kidney and serum from patients with primary biliary cirrhosis, has proved positive in 87% (Goudie *et al.*, 1966) and 98% of patients (Doniach *et al.*, 1966). More detailed studies have shown that the antibody in this test is pure, for it has been obtained from immunoglobulin G (IgG) prepared from serum of patients with primary biliary cirrhosis (Doniach *et al.*, 1966). The antigen is contained in the cristae of mitochondrial membranes (Berg *et al.*, 1967). Tissues having cells which are rich in mitochondria are therefore preferentially stained. This applies particularly to human kidney (used in this test), gastric parietal cells, and thyroid Askanazi cells. The reaction can therefore in no sense be regarded as an autoimmune one against bile ducts, and its possible significance in the aetiology of the disease is unknown. Its value lies in diagnosis.

Patients with primary biliary cirrhosis may show a granulomatous reaction usually related to the portal zones and to injured cholangioles (Rubin *et al.*, 1965; Goudie *et al.*, 1966). The reaction may not be confined to the liver, for in four patients we have found granulomata in hepatic hilar lymph nodes (two patients), omentum and lung (one patient), and mesenteric nodes (one patient). In three of these subjects granulomata were not present in the liver. The granulomata varied in size but usually included mononuclear and epithelioid cells and giant cells. They were identical with those found in other granulomatous diseases such as sarcoidosis. The Kveim test was performed in eight of the patients with hepatic granulomata and was in fact negative (Fox *et al.*, 1968). Such granulomata reflect an altered immunological state associated with delayed type (tuberculin type) hypersensitivity. They are not a feature of lesions said to be associated with organ-specific autoimmunity. The tuberculin skin test may also show impairment, and the lymphocytes lack response to tuberculin and phytohaemagglutinin in the *in vitro* transformation test. The significance of the changes in delayed-type hypersensitivity remains uncertain.

The great predilection of primary biliary cirrhosis for women, usually in the 30–60 age group, remains unexplained. The incidence of hormonal factors must be considered. Some oestrogens and progestins, both synthetic and natural, are known to have cholestatic properties. In normal pregnancy the last trimester is marked by changes in bilirubin metabolism indicative of a tendency to cholestasis. This is particularly so in those suffering from the rare cholestatic jaundice of the last trimester. These women may be genetically sensitive to the cholestatic action of sex hormones. They react abnormally to oral contraceptives (Kreek *et al.*, 1967). It would be tempting to regard primary biliary cirrhosis as a related condition. Certainly primary biliary cirrhosis may present in pregnancy. This, however, may be due to the steroids produced during pregnancy making manifest cholangitis already present. The administration of the sex hormones contained in oral contraceptives to patients with primary biliary cirrhosis causes an exacerbation of jaundice (Mulligan and Sherlock, 1968). However, patients with primary biliary cirrhosis who have had previous pregnancies have not suffered pruritus or jaundice in them, and it is difficult to relate the two conditions. The reason for the impact of primary biliary cirrhosis on middle-aged women remains unknown.

Chronic Cholangitis Due to Drugs

This is best illustrated by the hepatic reaction to the phenothiazines, an example being chlorpromazine. The cholestatic reaction to these drugs is usually acute and transient. The ductules are presumably the most involved, being surrounded by an inflammatory reaction in the portal zones of the liver. Hepatocellular damage is obvious but minimal. Rarely, the cholestatic picture continues for many months, and persistence for as long as three years has been reported (Read *et al.*, 1961). In these chronic cases hepatocellular damage has disappeared,

but the portal zones show expansion, with aggressive fibrosis and bile duct proliferation. In the more severe instances skin xanthomata are marked. The clinical picture may be identical with that of primary biliary cirrhosis. Recovery seems to be usual, and one patient in which jaundice lasted three years was well 12 years from the onset. One patient, after 13 months, developed portal hypertension (Myers *et al.*, 1957) and two others seemed to develop permanent biliary cirrhosis six and four years from the onset (Walker and Combes, 1966). There are immunological differences from primary biliary cirrhosis. Plasma cells are inconspicuous in the portal zones in chronic chlorpromazine jaundice. The mitochondrial antibody test is usually negative (Doniach *et al.*, 1966). IgM cannot be demonstrated in the liver (Levine *et al.*, 1966). The mechanism of the cholestasis is unknown.

Biliary Atresia

Atresia can be found in all sites from the ductules to the major bile ducts. In many instances a combination of lesions may be found (Smetana *et al.*, 1965). Absence of the intrahepatic ducts may or may not be combined with absence of the extrahepatic duct system. Where the ductules and interlobular ducts are involved a picture resembling primary biliary cirrhosis can be produced. Skin xanthomata may be obvious. Whether this condition represents an actual atresia of developmental (embryonic) origin (Stowens, 1963) or whether a disappearance of ducts secondary to an intrinsic defect in the liver causing bile stasis at a preductular level (Baker and Harris, 1964) remains uncertain. Virus infections, especially rubella and cytomegalovirus infection, in the first trimester of pregnancy and toxoplasmosis have been related, but it is difficult to be sure of the cause and effect. The liver secretes bile into the remaining proximal parts of the cholangiole even in the presence of atresia distally. Leakage of toxic bile acids from these ducts may account for some of the periductular sclerosis seen in patients with biliary atresia (Hollander and Schaffner, 1968).

Carcinoma of Intrahepatic Bile Ducts

The usual site of origin of carcinoma of the intrahepatic bile ducts is in the hilar region, the growth arising from right or left hepatic duct or from the common hepatic duct (Whelton *et al.*, 1968). It is often difficult to be sure of the exact origin. These tumours tend to be scirrhous, slow-growing, and difficult to diagnose. They are readily confused with primary biliary cirrhosis. Carcinoma arising from the cholangiole is unusual. It is usually confused with hepatoma, a tumour arising from the liver cells themselves. Cholangiocellular carcinoma seems to develop in the absence of cirrhosis. Chronic cholangitis may be an antecedent. Carcinoma has developed in the liver of a 3-year-old child with complete absence of the extrahepatic bile ducts and a biliary cirrhosis; the tumour was of hepatocellular type (Okuyama, 1965). Carcinoma of the hepatic ducts can complicate the primary sclerosing cholangitis associated with ulcerative colitis (Stauffer *et al.*, 1965; Rankin *et al.*, 1966).

Diagnosis

This involves the distinction of the chronic cholangitides from obstruction to main extrahepatic bile ducts (Sherlock, 1968) and also the diagnosis of the chronic cholangitides one from each other (Table I).

Patients with extrahepatic biliary obstruction have more complete and persistent cholestasis with acholic stools and very low faecal stercobilinogen excretion. Abdominal pain suggests large-duct block. Hepatomegaly is essential. The demonstration by radiology and otherwise of a local lesion such as a

primary carcinoma of stomach, colon, or pancreas or of gall stones adds weight to large-duct obstruction being the cause of the cholestasis. Needle biopsy of the liver may be helpful. If a pathologist experienced in interpreting these small specimens is available the picture of extrahepatic biliary obstruction

of the undesirable effects that follow deficiency of bile salts from the intestinal lumen.

TABLE I.—*Differential Diagnosis of the Chronic Cholangitides*

	Associations	M Test*	Other Tests
Secondary sclerosing cholangitis	Gall stones. Biliary stricture	Negative	Urinary indicans +
Primary sclerosing cholangitis	Ulcerative colitis	Negative	Operative cholangiography
Primary biliary cirrhosis	Middle-aged women	Positive	Wedge liver biopsy
Chronic chlorpromazine jaundice	Therapy with drug. Acute onset	Negative	—

* Mitochondrial immunofluorescent test.

can usually be distinguished from the chronic cholangitides. Important diagnostic points in the histological interpretation are ductular proliferation (the ductules having a wide lumen), oedema, and polymorphonuclears in the portal zones. Adjacent bile lakes may occasionally be noted. Misdiagnosis is often due to inexperience on the part of the interpreter of the biopsy. In difficult cases laparotomy, preceded by percutaneous cholangiography, may be necessary. Laparotomy should include wedge biopsy of the liver and direct operative cholangiography if the diagnosis remains in doubt.

The diagnosis of secondary sclerosing cholangitis is made on the long history of partial obstruction of the common bile duct, with intermittent fever, chills, and variable jaundice. The proliferation of bacteria in the biliary tree extends also to the duodenum and adjacent jejunum (Scott and Kahn, 1968). Duodenal juice is therefore infected. The bacterial increase in the upper intestines is reflected in an increased urinary indican excretion. The mitochondrial immunofluorescent test (M test) is negative.

Primary sclerosing cholangitis may be suspected if the patient gives a long history of ulcerative colitis. The jaundice fluctuates markedly. Hepatic histology may be difficult to interpret. The M test is negative.

Primary biliary cirrhosis is suggested by the insidious onset of pruritus and mild jaundice in a middle-aged woman. The M test is positive. Needle biopsy of the liver may be suggestive but not diagnostic. In case of diagnostic difficulty laparotomy must be done. Wedge biopsy of the liver shows the diagnostic destruction of interlobular and septal bile ducts. In the later stages the picture is that of a macronodular cirrhosis, and can be diagnosed only with difficulty from primary macronodular (post-necrotic) cirrhosis with cholestatic features (Datta *et al.*, 1963). The M test may be positive in both conditions. This raises the possibility that patients described as having primary macronodular cirrhosis with cholestasis may indeed be suffering from primary biliary cirrhosis in its later stages.

Chronic chlorpromazine jaundice is diagnosed by the acute development of jaundice within about six weeks of starting the phenothiazine drug. Serum phosphatase and cholesterol values rise sharply. Needle biopsy appearances in the liver may be difficult to interpret. The M test is negative. In long-standing cases laparotomy with cholangiography and wedge biopsy of the liver may be necessary to make a diagnosis.

The biliary atresias may be difficult to distinguish from neonatal hepatitis even if needle biopsy of the liver is available. In many instances laparotomy at about the fourth month is necessary. The operation should include cholangiography, both just before operation and at operation, and also wedge biopsy of the liver.

General Treatment

Treatment can be divided into the general treatment of prolonged cholestasis and more specific measures.

General treatment is particularly concerned with the control

Dietary Fat Digestion (Fig. 3)

Bile salts are necessary for the digestion of dietary fat. They emulsify dietary fat before its digestion by pancreatic lipase. At pH 6.5 they activate pancreatic lipase. It also seems likely that micelles are formed before fat absorption takes place and that bile salts are essential for this process. Bile salts may also favourably influence the resynthesis of triglycerides in the intestinal mucosa (Saunders and Dawson, 1967). If bile salts are deficient steatorrhoea results. Owing to practical difficulties, particularly in the accurate collection of the total volume of bile excreted, it is impossible to make quantitative correlations between the bile salts excreted and the faecal fat loss. However, if jaundice is taken as indicative of the degree of cholestasis, and so of failure of bile excretion, then there is an inverse correlation between serum bilirubin values and the percentage of dietary fat absorbed (Sherlock, 1959). Stools are frequent, loose, bulky, and offensive. Body weight is lost. Faecal fat loss in patients with primary biliary cirrhosis receiving about 70 g. of fat a day is of the order of 10 g. a day (Datta and Sherlock, 1966).

In chronic chlorpromazine jaundice the profound weight loss, in one patient of 42 lb. (19 kg.), has been attributed to steatorrhoea (Read *et al.*, 1961). This defect in fat digestion would

FIG. 3.—Failure of bile salts to reach the intestine, whether due to hepatocellular dysfunction or cholestasis, interferes with the digestion and absorption of fat.

FIG. 4.—Failure of bile salts to reach the intestine results in failure to absorb fat-soluble vitamins and calcium.

ideally be corrected by feeding adequate amounts of bile salts by mouth. Unfortunately, preparations of bile salts found in human bile are not yet available commercially. Bile salts that are obtained are from animals such as the ox and contain large amounts of unconjugated bile acids which are irritant to the bowel. They may be unpleasant to take and can provoke violent diarrhoea. Enteric-coated capsules tend to pass through into the faeces. As definitive measures are impossible a low neutral fat diet (about 30 g. a day) is given. Additional fat may be supplied in the form of medium-chain triglycerides. These triglycerides are of chain length C8 (caprylic or octanoic acid) or C10 (capric or decanoic acid) and are prepared from coconut oil. They are easily hydrolysed in the absence of pancreatic lipase and are digested and absorbed quite well in the absence of bile salts. They are principally absorbed via the portal vein. They are absorbed in patients with cirrhosis and steatorrhoea at the same rate as in normal subjects (Linscheer *et al.*, 1966). They have been shown of value in patients with steatorrhoea due to biliary obstruction (Iber *et al.*, 1963; Burke and Danks, 1966). A commercial preparation (Portagen) is prepared as a beverage and also supplies protein and carbohydrate. Four glasses are taken a day and provide 44 g. of medium-chain triglyceride, 38 g. of protein, and 960 calories.

Fat-soluble Vitamins and Calcium (Fig. 4)

Lipid-soluble substances such as cholesterol, vitamins D and K, and carotene (vitamin A) are almost completely dependent on the action of bile to facilitate their absorption. In the presence of steatorrhoea, calcium forms insoluble soaps and is not assimilated. Deficiencies of vitamins A, D, and K and of calcium might therefore be expected if intestinal bile salts are deficient.

Vitamin A deficiency rarely reaches clinical significance. Failure of dark adaptation occasionally develops in patients with primary biliary cirrhosis who have suffered from cholestasis for many years and who have never been given parenteral vitamin A supplements. Vitamin A should therefore be given intramuscularly in a dose of 100,000 international units every four weeks. Unfortunately it is difficult to obtain an intramuscular preparation of vitamin A.

Vitamin K deficiency is readily corrected by Vitamin K₁ injections—10 mg. every day for seven days and then 10 mg. every four weeks intramuscularly.

The problem of vitamin D and calcium deficiency is a difficult one. Bone disease has been noted in patients suffering from prolonged biliary obstruction and biliary cirrhosis (Atkinson *et al.*, 1956), but it is not clear whether the thinning is due to osteoporosis or osteomalacia. Among the 25 patients studied seven had osteomalacia, three seemed to be suffering from only osteoporosis, and two from both conditions. Osteoporosis and osteomalacia must be distinguished, as the aetiology and treatment are completely different. Osteomalacia is characterized biochemically by a low serum Ca × P product, by a raised serum alkaline phosphatase value, and histologically by wide osteoid seams. Osteoporosis, on the other hand, is a disease of unknown aetiology. There is no evident biochemical disorder, and histologically the bone trabeculae are thinned. In practice, osteoporosis and osteomalacia often coexist, particularly in patients with malabsorption. Though differential diagnosis depends ultimately on the bone histology, even this can be confusing (Morgan *et al.*, 1965).

Bile salts are essential for the absorption of vitamin D. In addition the bile salt deficiency could allow insoluble calcium soaps of unabsorbed fatty acids to form in the small lumen, and so making dietary calcium unavailable for absorption (Kehayoglou *et al.*, 1968b). Finally, the bile salts may directly stimulate calcium absorption (Webling and Holdsworth, 1965). In fact, in chronic cholestasis the retention of isotopic (³⁷Ca)

calcium given as soluble CaCl₂ in water (Kehayoglou *et al.*, 1968a) does correlate inversely with the serum bilirubin level (and presumably the amount of bile salt excreted into the bowel) and to a lesser extent with the degree of steatorrhoea. Unpublished observations show that vitamin D also improves absorption of isotopic calcium chloride given in milk. Intramuscular vitamin D therapy did restore a subnormal calcium-47 retention of this water-soluble CaCl₂. Intramuscular vitamin D therapy should be given to all patients with chronic cholestatic jaundice. The dose is uncertain: 100,000 international units intramuscularly every four weeks has been tested and shown to be effective, but this may be an excessive amount.

At the Royal Free Hospital this routine has been in use since 1959, and the very gross bone disease described by Atkinson *et al.* (1956) in patients with chronic cholestasis has not been seen. However, even after vitamin D therapy two patients have developed crush fractures of the vertebrae and one patient had multiple fractures of the metacarpals after minimal trauma. This apparent progression of bone thinning despite therapy was also noted by Atkinson *et al.* (1956). Continued high losses of endogenous faecal calcium (Rose, 1967) and failure to absorb food calcium may have been responsible. Calcium supplements are therefore also required. These are given in the form of oral calcium (Sandoz) six tablets daily (equivalent to 32 g. of calcium gluconate). Unfortunately, calcium absorption is unpredictable. Parenteral calcium supplements would be more valuable, but these have marked side-effects and are not available for use. Medium-chain triglycerides may also be of value in stimulating calcium absorption (Kehayoglou *et al.*, 1968b). In rats with ligation of the common bile duct—that is, with the intestinal bile salt deficiency syndrome—olive oil depressed calcium absorption (Kehayoglou *et al.*, 1968b). This emphasizes the importance of keeping dietary triglycerides low, supplementing with medium-chain triglycerides, and giving oral calcium supplements in milk between meals.

The problem of bone thinning associated with intestinal bile salt deficiency is particularly prominent in children with biliary atresia. If such babies are not given intramuscular vitamin D supplements they may develop severe osteomalacia (biliary rickets).

Pruritus (Fig. 5)

The relation of bile salts to the pathogenesis of pruritus in patients with cholestatic jaundice has always been conjectural. Certainly pruritus is relieved by procedures which withdraw bile salts from the body, such as external biliary fistula or the oral administration of resins which sequester bile salts. Oral administration of commercial preparations of bile salts exacerbates pruritus in those with a tendency to it. Serum bile acids

FIG. 5.—Failure of bile salts to reach the intestine results in retention of bile salts with subsequent pruritus and of cholesterol with subsequent tissue xanthomas. In partial bile salt deficiency these will be controlled by the bile salt chelating resin, cholestyramine.

are raised in patients with pruritus and cholestasis. Serum bile acid levels fall when pruritus is relieved by resins such as cholestyramine. However, all patients with raised serum bile acid levels do not have pruritus (Osborn *et al.*, 1959). Relief of pruritus by cholestyramine is not always associated with a fall in serum bile acid levels. These discrepancies are difficult to explain. Perhaps bile acids are not responsible for pruritus. Perhaps our methods of estimation of bile acids in biological fluids are still too inaccurate. Certainly this is so for normal blood. Bile acids have been found on the skin of patients with pruritic hepatobiliary disease (Schoenfield *et al.*, 1967). This places them close to the appropriate nerve endings but still does not necessarily implicate them in the aetiology of pruritus.

Pruritus in association with partial biliary obstruction is relieved by the administration of the strongly basic anion exchange-resin cholestyramine. The resin, which exchanges chloride for bile acids, results in increased faecal bile excretion. Bile acids are therefore withdrawn from the body. The drug is effective in a high proportion of patients with partial, but not total, biliary obstruction. In one series 23 out of 27 patients were totally or partially relieved (Datta and Sherlock, 1966). Failures are due to reluctance to take the rather unpleasant smelling and tasting powder and to the biliary obstruction being complete. The optimum dose is uncertain: 12 g. a day (three 4-g. packets) has been advocated, though 6–8 g. has also proved adequate. This lower dose certainly prevents pruritus and may have fewer metabolic complications.

Cholestyramine increases faecal fat excretion by about 5 g. a day in patients with partial cholestasis (Datta and Sherlock, 1966). This may be greater if doses of the resin larger than 6 g. a day are used. This increased steatorrhoea emphasizes the particular need to administer intramuscular fat-soluble vitamins A, D, and K and calcium to jaundiced patients having the treatment.

It has been possible to follow seven of the patients with primary biliary cirrhosis, reported previously, who have been successfully treated for pruritus with cholestyramine. All had taken the drug for at least four years and are continuing to receive 8–12 g. a day; relief of pruritus continues (Datta and Sherlock, 1968). Nutrition is preserved, body weight is maintained, and serum albumin levels exceed 3.5 g./100 ml. (Table II). Serum cholesterol levels were lower than at the

combination with the resin becomes less likely. Cholestyramine will be ineffective if the cholestasis is complete and no bile salts are reaching the intestine. Pruritus is then controlled by oral methyltestosterone 25 mg. daily in males or norethandrolone 30 mg. daily in females. Unfortunately this increases the jaundice, though that may be a small price to pay for relief of pruritus.

Specific Measures

Antibiotics may be useful in managing the sclerosing cholangitis associated with prolonged choledocholithiasis, stricture, or primary sclerosing cholangitis. Gram-negative infection is usual and the causative organisms may be recovered by blood culture taken when the patient is febrile. Tetracycline or rifamycin may be given as the attack begins. Continued use as prophylaxis is not recommended, as bacterial resistance soon emerges. Similarly, long-term use of an antibiotic in patients with the hepatobiliary complications of ulcerative colitis is ineffective (Mistilis *et al.*, 1965).

Antibiotic therapy will only be of temporary benefit, and, despite the intrahepatic sclerosis which may remain after operation, attempts should be made to deal surgically with any obstruction to extrahepatic bile ducts. In the case of primary sclerosing cholangitis a biopsy of any stricture of the common bile duct should be carried out to exclude carcinoma.

Needless to say, *immunosuppressant* therapy has been suggested for many of the conditions where there is evidence of disturbed immunology. In primary sclerosing cholangitis corticosteroid therapy has been used but is of doubtful value. In primary biliary cirrhosis the immunological disturbance is greater. Corticosteroids have been used, but, apart from occasional relief of pruritus, seem of little value and may be dangerous, as they aggravate bone-thinning. Azathioprine (Imuran) has been used in two patients (Fischer and Schmid, 1967). The first, in an early preicteric stage of the disease, seemed to benefit. The second showed some subjective improvement but without associated biochemical change. Good results could be expected only in early cases treated before the cholangiole had been irreversibly damaged. Primary biliary cirrhosis is a disease with spontaneous fluctuations. The place of *immunosuppressant* therapy could be established only by a controlled trial in a large number of patients. Because of the duration of the illness, about five years from onset of symptoms, the trial would necessarily be long-term and difficult to perform. On current evidence immunosuppressant therapy is not indicated. Corticosteroids are of no value in the treatment of chronic chlorpromazine jaundice.

The intrahepatic atresias cannot be relieved surgically. It is in this group that hepatic homotransplantation is being performed. Limiting factors are a supply of suitable cadaveric livers and tissue compatibility. Disturbances in blood coagulation are also encountered. The longest survival after transplantation to date is nine months in a child with a liver tumour (Starzl, personal communication).

TABLE II.—Cholestyramine for Pruritus in Primary Biliary Cirrhosis

Case No.	Duration (Years)		Daily Dose (g.)	Weight (kg.)		Serum/100 ml.				Fate
	Pruritus	Treatment		Before	After	Cholesterol (mg.)		Albumin (g.)		
						Before	After	Before	After	
6	7½	4½	8	—	—	603	503	—	—	Alive
7	5	3½	8	56	64	321	330	4.5	4.6	Alive
8	6½	5½	12	47	50	388	304	4.6	4.0	Alive
9	6	5½	8	60.5	61	650	430	4.0	4.0	Alive
11	9½	5½	8	62	56	767	225	3.8	3.5	Alive
15	4	7	12	—	—	—	—	—	—	Died liver failure
16	8	3½	8	—	—	340	295	3.5	4.2	Alive

outset of treatment. Such depression is difficult to attribute to the cholestyramine resin. Cholesterol levels fall spontaneously during the course of chronic cholestasis, particularly in the later stages when liver function deteriorates and the hepatic production of cholesterol falls.

Since cholestyramine is an anion exchange resin, it has a strong affinity for acidic molecules. It may also, to some extent, absorb neutral or, less likely, basic materials. In vitro cholestyramine may bind the acidic drugs acetylsalicylic acid, chlorothiazide, phenobarbitone, phenylbutazone, or tetracycline (Gallo *et al.*, 1965). These, and possibly other drugs, should be ingested one-half to one hour before cholestyramine so that

REFERENCES

- Asherson, G. L., and Broberger, O. (1961). *Brit. med. J.*, 1, 1429.
 Atkinson, M., Nordin, B. E. C., and Sherlock, S. (1956). *Quart. J. Med.*, 25, 299.
 Baker, D. H., and Harris, R. C. (1964). *Amer. J. Roentgenol.*, 91, 875.
 Berg, P. A., Doniach, D., and Rott, I. M. (1967). *J. exp. Med.*, 126, 277.
 Bouchier, I. A. D., Rhodes, K., and Sherlock, S. (1964). *Brit. med. J.*, 1, 592.
 Brooke, B. N., Dykes, P. W., and Walker, F. C. (1961). *Postgrad. med. J.*, 37, 245.
 Burke, V., and Danks, D. M. (1966). *Brit. med. J.*, 2, 1050.
 Carey, J. B., jun. (1964). *Gastroenterology*, 46, 490.
 Carey, J. B., jun., Wilson, I. D., Zaki, F. G., and Hanson, R. F. (1966). *Medicine (Baltimore)*, 45, 461.
 Datta, D. V., and Sherlock, S. (1966). *Gastroenterology*, 50, 323.
 Datta, D. V., and Sherlock, S. (1968). Unpublished observations.
 Datta, D. V., Sherlock, S., and Scheuer, P. J. (1963). *Gut*, 4, 223.
 Deicher, H. R. G., Holman, H. R., and Kunkel, H. G. (1960). *Arthr. and Rheum.*, 3, 1.

- Doniach, D., Roitt, I. M., Walker, J. G., and Sherlock, S. (1966). *Clin. exp. Immunol.*, 1, 237.
- Feizi, T. (1968). *Gut*, 9, 193.
- Fischer, J. A., and Schmid, M. (1967). *Lancet*, 1, 421.
- Fox, R. A., Sherlock, S., Scheuer, P. J., Sharma, O., and James, D. G. (1968). In preparation.
- Gajdusek, D. C. (1958). *Arch. intern. Med.*, 101, 9.
- Gallo, D. G., Bailey, K. R., and Sheffner, A. L. (1965). *Proc. Soc. exp. Biol. (N.Y.)*, 120, 60.
- Gökçen, M. (1962). *J. Lab. clin. Med.*, 59, 533.
- Goudie, R. B., Macsween, R. N. M., and Goldberg, D. M. (1966). *J. clin. Path.*, 19, 527.
- Hobbs, J. R. (1966). *Proc. roy. Soc. Med.*, 59, 568.
- Hollander, M., and Schaffner, F. (1968). *Amer. J. Dis. Child.* In press.
- Iber, F. L., Hardoon, E., and Sangree, M. H. (1963). *Clin. Res.*, 11, 185.
- Javitt, N. B. (1966). *Gastroenterology*, 50, 394.
- Kehayoglou, A. K., Holdsworth, C. D., Agnew, J. E., Whelton, M. J., and Sherlock, S. (1968a). *Lancet*, 1, 715.
- Kehayoglou, A. K., Williams, H. S., Whimster, W. F., and Holdsworth, C. D. (1968b). *Gut*. In press.
- Kreek, M. J., Sleisenger, M. H., and Jeffries, G. H. (1967). *Amer. J. Med.*, 43, 795.
- Levine, R. A., Briggs, G. W., and Lowell, D. M. (1966). *Gastroenterology*, 50, 665.
- Linscheer, W. G., Patterson, J. F., Moore, E. W., Clermont, R. J., Robins, S. J., and Chalmers, T. C. (1966). *J. clin. Invest.*, 45, 1317.
- Mistilis, S. P., Skyring, A. P., and Goulston, S. J. M. (1965). *Aust. Ann. Med.*, 14, 286.
- Morgan, D. B., Paterson, C. R., Woods, C. G., Pulvertaft, C. N., and Fourman, P. (1965). *Lancet*, 2, 1085.
- Mulligan, R., and Sherlock, S. (1968). Unpublished.
- Myers, J. D., Olson, R. E., Lewis, J. H., and Moran, T. J. (1957). *Trans. Ass. Amer. Physns*, 70, 243.
- Okuyama, K. (1965). *J. Pediatr.*, 67, 89.
- Osborn, E. C., Wootton, I. D. P., da Silva, L. C., and Sherlock, S. (1959). *Lancet*, 2, 1049.
- Palmer, R. H., and Hruban, Z. (1966). *J. clin. Invest.*, 45, 1255.
- Paronetto, F., Schaffner, F., and Popper, H. (1964). *New Engl. J. Med.*, 271, 1123.
- Rankin, J. G., Skyring, A. P., and Goulston, S. J. M. (1966). *Gut*, 7, 433.
- Read, A. E., Harrison, C. V., and Sherlock, S. (1961). *Amer. J. Med.*, 31, 249.
- Rose, G. A. (1967). In *Scientific Basis of Medicine Annual Review*, p. 257. London.
- Rubin, E., Schaffner, F., and Popper, H. (1965). *Amer. J. Path.*, 46, 387.
- Saunders, D. R., and Dawson, A. M. (1967). In *Biochemical Problems of Lipids*, edited by A. C. Frazer. Amsterdam.
- Schoenfield, L. J., Sjövall, J., and Perman, E. (1967). *Nature (Lond.)*, 213, 93.
- Scott, A. J., and Khan, C. A. (1968). *Gut*, 9, 187.
- Sherlock, S. (1959). *Gastroenterology*, 37, 574.
- Sherlock, S. (1966). *Ann. intern. Med.*, 65, 397.
- Sherlock, S. (1968). *Diseases of the Liver and Biliary System*, 4th ed., p. 296. Oxford.
- Smetana, H. F., Edlow, J. B., and Glunz, P. R. (1965). *Arch. Path.*, 80, 553.
- Stauffer, M. H., Sauer, W. G., Dearing, W. H., and Baggenstoss, A. H. (1965). *J. Amer. med. Ass.*, 191, 829.
- Stowens, D. (1963). *Ann. N.Y. Acad. Sci.*, 111, 337.
- Thorpe, M. E. C., Scheuer, P. J., and Sherlock, S. (1967). *Gut*, 8, 435.
- Walker, C. O., and Combes, B. (1966). *Gastroenterology*, 51, 631.
- Walker, J. G., Doniach, D., Roitt, I. M., and Sherlock, S. (1965). *Lancet*, 1, 827.
- Webbing, D. D'A., and Holdsworth, E. S. (1965). *Biochem. J.*, 97, 408.
- Whelton, M. J., Petrelli, M., George, P., Young, W. B., and Sherlock, S. (1968). In preparation.
- Zaki, F. G., Carey, J. B., jun., Hoffbauer, F. W., and Nwokolo, C. (1967). *J. Lab. clin. Med.*, 69, 737.

Thermography in Occlusive Cerebrovascular Diseases

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Summary: Cooling of the skin over the medial supra-orbital region in 80% of patients who have an occlusion or severe stenosis of a carotid artery can be demonstrated by facial thermography. Minor stenotic lesions in the carotid arteries do not produce characteristic thermographic changes, while thermography is of no help in the diagnosis of vertebrobasilar arterial disease.

Thermographic changes suggestive of carotid arterial lesions are found occasionally in patients whose angiograms are normal, owing to variations in the size of the frontal sinuses, or factors such as fever or inflammatory lesions.

It is suggested that facial thermography is of value in the preliminary investigation of patients with occlusive cerebrovascular disease.

Introduction

Studies of cerebrovascular disease were, until fairly recently, concerned with the delineation of clinical syndromes caused by the occlusion of individual intracerebral arteries. Blockage of a carotid artery in the neck was reported by Cooper in 1836 and its clinical importance stressed by Hunt in 1914. Carotid arteriography (Moniz *et al.*, 1937) provided the means of accurate diagnosis of extracranial vascular disease, and directed

attention towards the clinical and pathological effects thereof. Hutchinson and Yates (1957) emphasized the association of disease of the carotid and vertebral arteries with cerebral lesions, and these same authors (Yates and Hutchinson, 1961) concluded that cerebral infarction was more often due to stenosis of extracranial than of intracranial arteries. Schwartz and Mitchell (1961) found that stenosis of vessels in the neck did not necessarily lead to cerebral infarction, but established a correlation between occlusion of these arteries and cerebral infarction.

The possibility of effective treatment provides a stimulus for the more precise diagnosis of extracranial lesions of the carotid and vertebral systems. Surgical treatment is helpful in some cases of atherosclerosis affecting the major vessels of the neck (De Bakey *et al.*, 1962), while Millikan *et al.* (1958) have recommended the use of anticoagulants in advancing occlusion of the carotid artery and in the treatment of transient cerebral ischaemic attacks.

Marshall (1967) stressed the inaccuracy of the clinical diagnosis of cerebrovascular lesions. He pointed out that about a quarter of a million strokes occur each year in the United Kingdom and advocated careful selection, from this vast number, of those patients who need neuroradiological investigation. Angiography is probably the most useful and accurate investigation, but usually only large radiological centres are equipped to carry out this technique, and even in the most experienced hands angiography may be hazardous in patients with atherosclerosis. Lumbar puncture and echo encephalography are useful preliminary investigations in patients suffering from strokes, but their main value lies in the exclusion of intracerebral haemorrhage and tumour. Ophthalmodynamo-

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