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Biliary Secretory Failure in Man

The Problem of Cholestasis

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THE DIAGNOSIS of the type and cause of jaundice is usually an easy clinical exercise. The majority of patients will be suffering from hepatocellular jaundice due to acute viral hepatitis or cirrhosis or surgical cholestatic jaundice due to cholelithiasis or carcinoma of the pancreas or liver. Such conditions will be obvious to most junior physicians. There remains a proportion in which difficulty arises, and this is especially so when the distinction between medical and surgical jaundice is required. This paper describes a group of patients in whom surgical jaundice is simulated, although the origin lies within the liver. An anatomical classification of these various forms of intrahepatic cholestasis will be attempted.

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ANATOMY OF THE BILIARY SYSTEM *

Bilirubin is usually produced from the breakdown of effete erythrocytes within the reticuloendothelial system. A certain proportion has another origin (1), and may in part be formed by the liver itself (2). Once produced the bilirubin is transported through the microvillous wall of the hepatic sinusoid, through the liver cell to the microsomes where conjugation of bilirubin as a glucuronide takes place. The origin of cholestatic jaundice must be distal to this area in the cell, for the bilirubin circulating in the serum is of the conjugated variety. The conjugated bilirubin normally passes into the canaliculi, which consist of channels between the liver cells. Microvilli project into their lumen (3). The canaliculi form a network between the liver plates. The bile canaliculi empty into ductules sometimes called cholangioles or canals of Hering. These are largely found in the portal zones of the liver. The ductule passes into the interlobular duct,

* See Figure 1.

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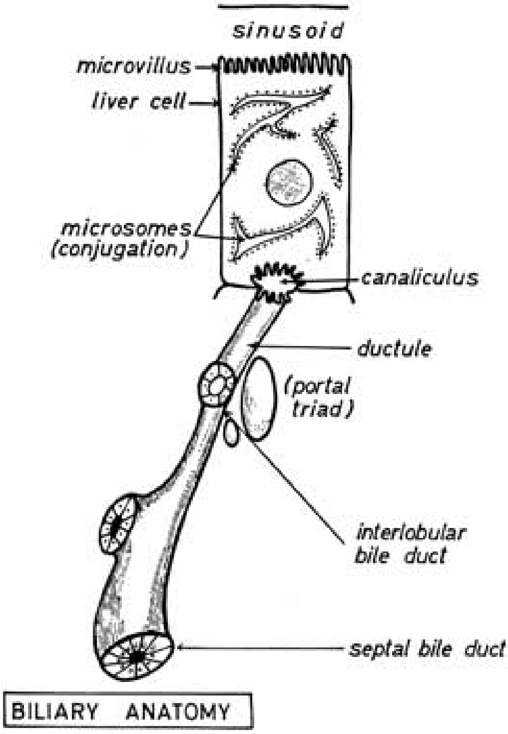

FIGURE 1. A schema of the anatomy of the intrahepatic biliary tree.

which is the first bile channel to be accompanied by a branch of the hepatic artery and portal vein. These are also found in the portal triad. These channels unite with one another to form septal bile ducts and so on until the large main hepatic ducts emerge from the right and left lobes of the liver at the porta hepatis.

Intrahepatic cholestasis could result from interference with bile flow anywhere along this path from the hepatocellular microsomes to the main bile duct. It might represent an actual stoppage of flow at a hepatocellular or canalicular level without mechanical obstruction. Wheeler (4) has suggested that one major mechanism of bile, water, and electrolyte excretion is located somewhere in the bile duct or ductular epithelium rather than in the bile canaliculi and that this might also be at fault. Once bile flow is interrupted at any point in its passage, secondary events will take place in the proximal part of the system and possibly in the more distal also. This makes delineation of the actual cause of the cholestasis difficult. The anatomical plan must be taken therefore as a "jumping-off" point for further studies in this field and as an attempt to summarize current evidence available on the problem of the intrahepatic cholestases.

Definition of Cholestasis

ANATOMICAL CHOLESTASIS

The liver shows constant changes irrespective of cause. Using light microscopy one can see bile accumulations in the liver, in the hepatic cells, Kupffer cells, and canaliculi. These can be identified by histochemistry as conjugated bilirubin (5). The bile pigment accumulation is usually maximal in centrizonal areas with the exception of primary biliary cirrhosis (see later) where it is periportal. The liver cells show a "feathery" degeneration of the cytoplasm. Cell regeneration and nodular hyperplasia are minimal. Electron microscopy (Figure 2) shows changes in the biliary canaliculi irrespective of the cause. These include dilatation and edema, blunting, distortion, and sparsity of the microvilli. The Golgi apparatus plays an important role in bile secretion, in concentrating, transporting, and excreting a part of the biliary substances (6). This apparatus adjoins the canaliculus, and in cholestasis it may show vacuolization. Pericanalicular vesicles appear that contain bile and that ultimately can be identified with the feathery degeneration of liver cells seen on light microscopy (7). Lysosomes become more numerous (8). Abnormal liver mitochondria have also been noted, consisting in the formation of intramitochondrial structures resembling myelin figures (9). Others have noted an elongation and irregular coiling of the cristae mitochondrales.

These anatomical changes are presumably due to the effect of retained bile (sometimes at increased pressure) on the

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liver cells. Alternatively they might be related to the production of an altered bile by the liver cell in the presence of obstruction (10).

CLINICAL CHOLESTASIS

Failure of bile to reach the duodenum is reflected as a clinical syndrome that has a constant pattern irrespective of the etiology. Various phenomena related to cause are added to this basic picture.

The patient develops jaundice slowly. Persistent fever and pain are absent. There may be initial pyrexia and pain, for instance in cholestatic viral hepatitis, but these go as the cholestatic picture makes its appearance. Pruritus is present. In general with intrahepatic cholestasis the interruption to bile flow is partial and the pruritus is relieved by cholestyramine, a bile acid-chelating resin (11). This, of course, offers no proof that the cause of the pruritus is in fact retention of bile salts but does suggest that these substances are in some way related.

The feces are pale due to interference with bile pigment (stercobilinogen) excretion. The bulky fatty nature is accounted for by the diminished excretion of bile salts. Secondary events include deficiency of fat soluble vitamins A, D, and K and defective absorption of calcium. Bone thinning is therefore a late feature.

BIOCHEMICAL CHOLESTASIS

All the constituents of the bile show an increased level in the serum. Conjugation of biliary substances is intact but excretion defective. This accounts for the rise in conjugated bilirubin, trihydroxy bile salts (12), and in the type of alkaline phosphatase believed to be normally excreted into the bile (13). When Bromsulphalein® (BSP) is administered this dye accumulates in the serum in a conjugated form. Serum cholesterol increases and, depending on the chronicity and completeness of the obstruction, deposits form in the skin as xanthomata. Low-density lipoproteins increase in the serum. Conjugated bilirubin appears in the urine. Urinary urobilinogen, which undergoes an enterohepatic circulation, is excreted in the urine in inverse proportion to the amount of bile reaching the duodenum. Likewise the fecal excretion of stercobilinogen is in proportion to the completeness of the cholestasis.

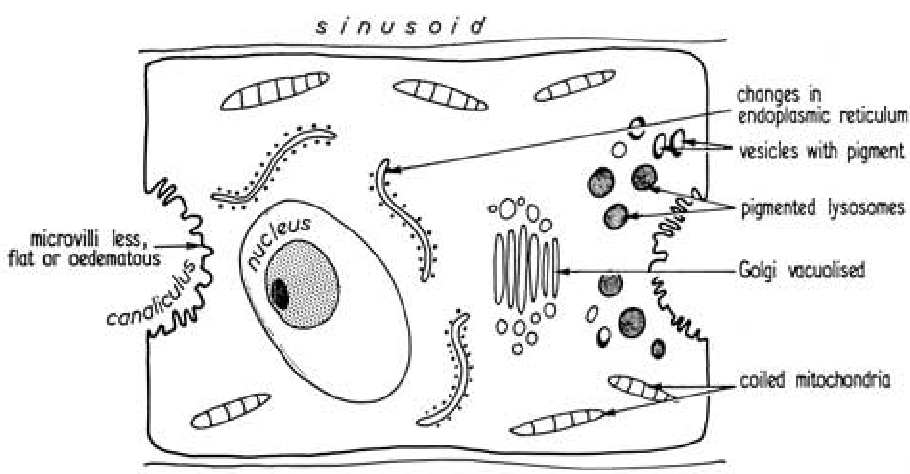

FIGURE 2. A diagram of the electron microscopical changes in the liver cell in the presence of cholestasis. (Based on the work of Ohkita, Iwasaki, Donomac, and Tatsumi (6), Popper and associates (7), Goldfischer, Arias, Essner, and Novikoff (8), Jézéquel (9), and Steiner, Carruthers, and Kalifat (10).)

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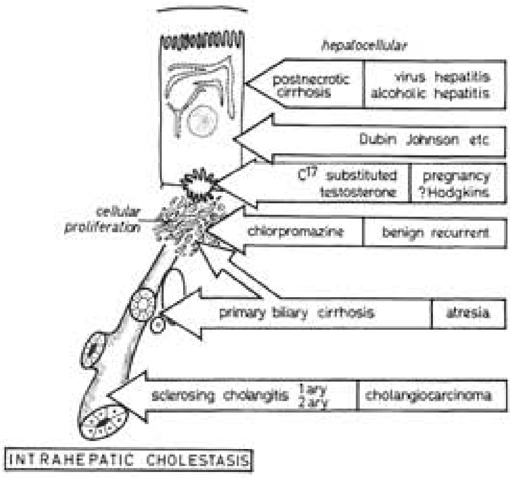

FIGURE 3. Classification of intrahepatic cholestasis according to possible major sites of involvement of the biliary tree.

CLASSIFICATION OF INTRAHEPATIC CHOLESTASIS *

CONJUGATED IDIOPATHIC HYPERBILIRUBINEMIA (DUBIN-JOHNSON AND ROTOR SYNDROMES)

The familial conjugated hyperbilirubinemias seem to differ from one another only in the presence of the dark melanin-like pigment in the liver cells in the Dubin-Johnson and its absence in the Rotor syndrome. This pigment is the origin of the term "black liver jaundice."

This intrahepatic cholestatic condition is considered first because it is the most incomplete of the group. Evidence of a generalized hepatocellular disorder is lacking. There is difficulty in excretion of bilirubin (conjugated with glucuronide) and BSP (conjugated with glutathione), indicating that the excretory problem is at a postmicrosomal level, for conjugation occurs in the microsomes. In addition, cholecystographic media and indocyanine green ("cardiogreen"), which is unconjugated but again excreted into the bile, are also retained (14). However, other features of cholestasis such as pruritus, steatorrhea, and increases in blood total cholesterol and alkaline phosphatase levels are lacking. The lesion in the Dubin-Johnson and Rotor syndromes therefore has to be placed somewhere between the microsomes and the canaliculus. The complexity of the subject, however, is intensified by the observation of Billing, Williams, and Richards (15) that patients with the Dubin-Johnson syndrome also show some difficulty in the hepatic handling of unconjugated bilirubin. This would certainly place the abnormality in the Dubin-Johnson syndrome well inside the liver cell.

* Figure 3.

PRIMARILY HEPATOCELLULAR CONDITIONS

It has long been recognized that certain hepatocellular conditions, not usually associated with cholestasis, can occasionally produce such a picture out of all proportion to the degree of hepatocellular jaundice. This may even simulate surgical obstructive jaundice. This association was first recognized with acute viral hepatitis, and the term "cholangiolitis" hepatitis was coined (16). The lesion cannot be localized in the cholangioles (ductules), and the condition is better labeled hepatitis with cholestatic features. This probably represents an exaggeration of the cholestasis which marks the early stages of viral hepatitis. After some 3 weeks of jaundice, although the patient feels relatively well and appetite has returned, icterus remains deep with pruritus and all the other general effects of cholestasis. In particular serum alkaline phosphatase and cholesterol are high, and transaminases are very little increased. After a variable period of 18 up to 29 weeks cholestasis remits, and the patient makes a complete recovery (17). Hepatic histology shows bile stasis predominantly in canaliculi. Electron microscopy shows changes in the microvilli of the canaliculi. Histological changes do not differ from patients with hepatitis who do not show predominant cholestasis.

A similar sequence may develop in the acute hepatitis of the alcoholic (18–20). Liver biopsy in such patients shows severe

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fatty change and, in addition, necrosis and Mallory's hyaline change in the liver cells with polymorph infiltration. The mechanism of the cholestasis is uncertain. Light microscopy reveals swelling of the liver cells and compression of small bile canaliculi. Electron microscopy shows atrophy of canalicular microvilli (21). There is also an increase in size and number of pericanalicular vacuoles containing granular compounds presumably derived from bile and which probably reflect difficulity in biliary secretion.

In a series of 57 patients with postnecrotic (macronodular) cirrhosis, a high proportion was found to have cholestatic features such as pruritus, xanthomata, and high serum alkaline phosphatase and cholesterol values (Table 1) (22), and in 11 there was real difficulty in making a distinction from obstruction to main bile ducts. In every instance study of hepatic histology was diagnostic of macronodular cirrhosis, although, even with this aid, in some instances the distinction was not easy. The mechanism of the cholestasis is obscure.

In all these conditions the primary diseases are usually considered hepatocellular. They differ from other forms of cholestasis in that a profound diminution of serum bilirubin level can often be produced by corticosteroid treatment (corticosteroid "whitewash"). The mechanism of this action is uncertain. Fecal stercobilinogen excretion, at least in the early stages, does not increase, and the rate of destruction of mature erythrocytes (indicating bilirubin production) is unaltered (23). In this type of hepatocellular jaundice the corticosteroid effect seems to be on the liver cells. In these circumstances the metabolism of BSP can be considered to be analagous to that of bilirubin. Bromsulphalein metabolism is profoundly altered in patients with hepatocellular cholestatic jaundice (for instance viral hepatitis) by corticosteroid treatment. By use of the technique of Wheeler, Meltzer, and Bradley (24) the BSP storage capacity is remarkably improved by corticosteroids whereas the transport mechanism (indicating excretion into the bile) is unaltered (25). As corticosteroid therapy relieves the cholestasis in these patients it must do so at a hepatocellular level, and this provides indirect evidence that in this group the cholestasis is within the liver cell itself.

Canalicular and Pericanalicular Cholestasis

STEROID-INDUCED CHOLESTASIS

Cholestasis can follow the administration of certain steroid drugs, of which methyl testosterone was the first described (26). The condition is not a sensitivity one and seems at least in part to be dependent on the dose of the drug. The liver lesion is one of pure cholestasis. Alterations in the microvilli of the bile canaliculi have been seen on electron microscopy (27). Cellular reaction in the portal zones is absent, and ductules and ducts are unaffected. It seems reasonable to place the cholestasis in the liver cell, certainly at a postmicrosomal level and possibly in the region of the canaliculus. Corticosteroid drugs have no effect on the jaundice, stressing the difference from the preceding, hepatocellular, group. The jaundice is mild and rapidly reversible when the drug is stopped.

Many steroids are probably associated with this reaction and these include norethandrolone, norethynodrel, methandie-

TABLE 1. Cholestatic Features in 57 Patients with Cryptogenic Postnecrotic (Macronodular) Cirrhosis*

Feature	Number
Pruritus	14
Xanthomas	6
High serum alkaline phosphatase†	38
High serum cholesterol‡	23

* Datta, Sherlock, and Scheuer (22).
† More than 30 King-Armstrong units/100 ml.
‡ More than 250 mg/100 ml.

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none, mestranol, lynoestrol, and norethysterone. Most of these substances are ^{17}C-substituted compounds of testosterone, and although this configuration is not essential it is by far the most frequently associated chemical structure. All the substances responsible are pharmacologically active when given by mouth.

These observations are important in relation to jaundice developing in patients receiving pills to regulate the menstrual periods. Jaundice has now been reported in 20 young women receiving contraceptive pills in the usual dosage. The drugs concerned have been Conovid® or Enovid® (mestranol and norethynodrel), 4 patients (28–30); anovlar® (ethinyl estradiol and norethisterone), 12 patients (31–36); Lyndiol® (mestranol and lynestrol), 1 patient (37); Orthonovin® (mestranol and norethysterone), 2 patients (33, 38); and Volidam® (ethinyl estradiol and megestrol), 1 patient (39). These all contain ^{17}C-substituted testosterone derivatives.

These 20 patients reported to have developed jaundice represent a tiny fraction of the millions of women receiving "the pill." Individual susceptibility must be considered. It is of interest that 8 of the 20 had previously suffered from the cholestatic jaundice of pregnancy. This condition, developing in the last trimester, presents as a pure cholestasis, disappearing when the child is delivered but recurring with subsequent pregnancies (40–42). A decrease in the transport maximum can be shown in the last half of normal pregnancy (43). If alterations in BSP and bilirubin excretion reflect similar processes, then it is tempting to regard the cholestatic jaundice of pregnancy as an exaggerated response in a susceptible woman to some steroids normally produced in pregnancy. Natural estrogens, in large doses, do cause abnormalities in the handling of BSP (44). The steroid drugs contained in contraceptive pills are not normally produced in pregnancy. They do, however, cause a fall in BSP transport mechanism when given to normal nonpregnant women (45). Patients liable to the cholestatic jaundice of pregnancy might well react abnormally to these steroids, and this would explain the association of the two types of jaundice.

Genetic susceptibility may account for the geographic distribution of the reports of jaundice after "the pill." Although this method of population control is now almost worldwide, 14 of the 20 reports of jaundice come from Scandinavia and North Germany, only 4 from the United States and Canada, and 2 from Britain. Most of the large series of patients having cholestatic jaundice of pregnancy are of Scandinavian origin. Chile has a high proportion of patients with cholestatic jaundice of pregnancy, and in this country, too, appreciable numbers of patients are developing jaundice while receiving contraceptive pills (46). Before introducing this method of population control it would probably be wise to ascertain whether the cholestatic jaundice of pregnancy is common in the population exposed.

HODGKIN'S DISEASE

Jaundice is not uncommon in patients in the later stages of Hodgkin's disease. It usually has an obvious explanation such as excessive hemolysis, hepatic infiltration by abnormal tissue, or invasion of major bile ducts. Occasionally, however, the picture is of pure intrahepatic cholestasis (47–50). Hepatic histology shows accumulation of bile in canaliculi. There is no portal zone cellular reaction. The cholestasis does not seem to be related to chemotherapy. It is unaffected by corticosteroid treatment. The mechanism is most obscure. These patients have been included with the steroid group largely because they are certainly not hepatocellular and do not fit into the subsequent varieties where larger bile channels seem to be involved. No cause of the cholestasis has so far been identified.

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Ductular cholestasis

This group is characterised by a cellular reaction in the portal zones in addition to the common pattern of cholestasis. The cells surround ductules and interlobular bile ducts, and the primary site of cholestasis has been placed in this area.

Sensitivity-type drug cholestasis

The best example of this is the cholestatic jaundice that sometimes follows the administration of chlorpromazine and other promazine drugs (51). The reaction is unrelated to dose. It usually develops within the first 4 weeks of starting the treatment and affects only a very small number of patients receiving the drug. The reaction may include a rash, and tissue and blood eosinophilia. In contrast to the steroid type of drug cholestasis, the portal zones show mononuclear cells and eosinophils. In addition hepatocellular damage is greater than that seen in steroid cholestasis, and rarely the patient dies of liver failure.

Idiopathic recurrent cholestasis

In 1959 Summerskill and Walshe (52) described two patients with multiple episodes of cholestatic jaundice of unknown etiology. In every instance main bile duct obstruction was excluded by laparotomy and cholangiography. Permanent liver damage did not ensue, and recovery seemed to be complete after each attack. The first patient has now survived 22 episodes and 3 laparotomies (53). The onset is associated with itching, occasionally an influenza-like illness, and vomiting. Jaundice appears and persists for 3 to 4 months. The liver biopsy shows cholestasis and the portal zones expansion with mononuclear cells. Electron microscopy shows the usual canalicular changes of cholestasis and the presence of intracellular and extracellular vesicles (54).

This condition might be of genetic or environmental origin or indeed both. In favor of the genetic possibility is the early onset in some cases, before the age of 10 years in five of the ten reported patients. Kühn (55) has observed the condition in two brothers. Tygstrup (56) described two unrelated cases from an isolated community in the Faro Islands. Since then he has observed other patients, one of whom has a sister with long periods of pruritus and who has been jaundiced twice (57). She has never been examined while suffering an attack, and it is uncertain whether the condition is really benign recurrent cholestasis. If a genetically determined abnormality is concerned, then a recessive gene with poor penetrance is implied. On the other hand some of the patients have an allergic diathesis, rashes may be associated, and the condition may recur at definite times of the year. It therefore has been decided, perhaps erroneously, to include this group with the sensitivity type of intrahepatic cholestatic jaundice.

Ductules, Interlobular and Septal Bile Ducts

The group is characterized by the general features of cholestasis and with portal cellular infiltration. There is also evidence of involvement of interlobular and septal bile ducts.

Primary biliary cirrhosis (chronic intrahepatic obstructive jaundice)

This condition predominantly affects middle-aged women. Jaundice begins insidiously, usually preceded by pruritus, and continues to a variable extent. Death ensues, usually from liver failure or intercurrent infection, from 2 to 7 years from the onset (58, 59). Rubin, Schaffner, and Popper (60) have described the sequence of pathological changes in the liver. In its initial stage the process is characterised by a chronic nonsuppurative, granulomatous reaction surrounding and involving interlobular and septal bile ducts (Figure 4). At this early stage jaundice may be in

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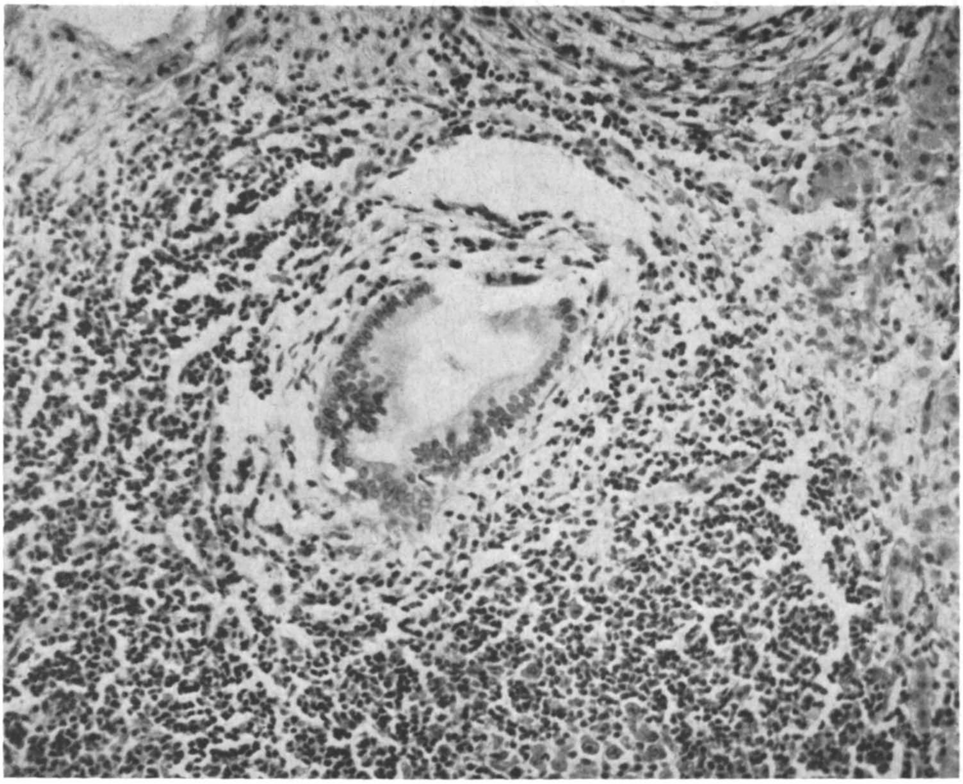

FIGURE 4. Primary biliary cirrhosis. An interlobular bile duct shows degenerative changes and is surrounded by a granulomatous reaction. Operative liver biopsy. (Hematoxylin and eosin stain, × 120.)

part related to leakage of conjugated bilirubin from leaky ducts back into the blood stream. This seems to be followed by destruction of both ductules and interlobular ducts. The final picture is of septal cirrhosis. Electron microscopic studies support the concept that the disease is not primarily hepatocellular but that bile duct abnormalities constitute the main pathogenetic mechanism (61). Anatomically, therefore, there is good evidence to place the cause of the cholestasis, at least initially, outside the limiting plate of the lobule and in the ductule and interlobular and septal bile ducts.

This condition is associated with a diagnostic immunofluorescent test (62, 63) (Figure 5). The sera of 32 patients with primary biliary cirrhosis gave granular cytoplasmic staining in unfixed tissue sections using fluorescein conjugates of antihuman gamma globulin and anticomplement in the double layer immunofluorescent test. The staining reactions showed no organ or species specificity, and cells known to be rich in mitochondria were preferentially stained.

Possible confusion with the specific thyroid and gastric parietal cell antibodies can be avoided by using rat kidney as the substrate. This test was consistently negative in 21 patients with proved obstruction of main bile ducts and in 5 patients with cholestatic drug jaundice. In a patient with suspected primary biliary cirrhosis a positive result will prevent laparotomy to exclude main bile duct obstruction. The occasional positive in patients with active chronic hepatitis or cryptogenic cirrhosis is interesting, but

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neither of these conditions is an indication for surgical intervention.

INTRAHEPATIC BILIARY ATRESIA

Atresia can be found at all sites in the biliary tract from the ductules to the major bile ducts. In many instances a combination of lesions is found (64). Where the ductules and interlobular ducts are concerned, the clinical picture shows a striking resemblance to primary biliary cirrhosis. The prognosis is also much better than where the extrahepatic bile ducts are involved. It is about the same as for primary biliary cirrhosis from the time of diagnosis. Whether this condition represents an actual atresia of developmental (embryonic) origin (65) or whether it indicates disappearance of ducts secondary to an intrinsic defect in the liver causing bile stasis at a preductal level (66) remains uncertain.

Septal and Larger Intrahepatic Bile Ducts

SCLEROSING CHOLANGITIS

This is a chronic inflammatory and fibrosing lesion of the large intrahepatic

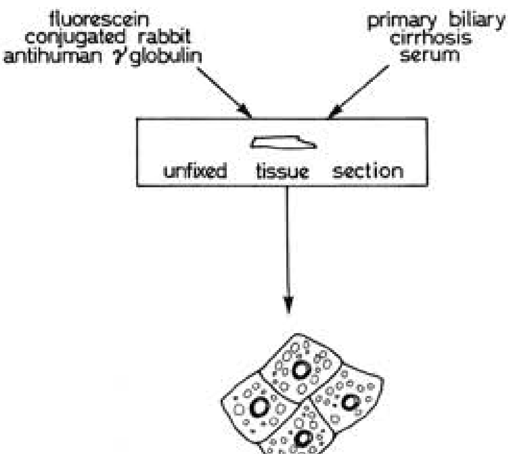

Figure 5. Immunofluorescent test in primary biliary cirrhosis (62, 63).

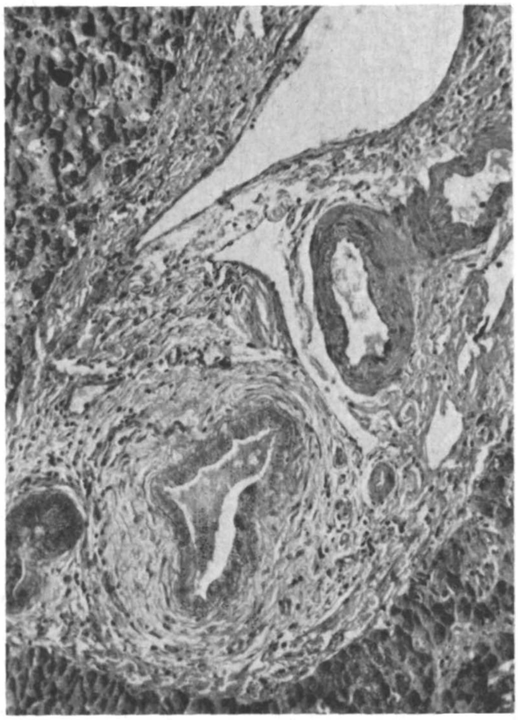

Figure 6. Secondary sclerosing cholangitis due to choledocholithiasis. Concentric fibrosis around a greatly thickened interlobular bile duct. The whole portal triad is fibrosed. Operative liver biopsy. (Periodic acid-Schiff stain, × 120.)

bile ducts. The condition is termed a cholangitis. Two varieties—primary and secondary—can be recognized.

Primary Sclerosing Cholangitis: This is a rare condition with only some 26 reported cases (67, 68). The submucous inflammation and fibrosis involves mainly extrahepatic bile ducts. Liver biopsy shows, however, in contrast to the findings associated with main bile duct obstruction, inflammatory change and fibrosis in the portal tracts but without reduplication of ductules and interlobular ducts. This suggests that the intrahepatic biliary system is incapable of dilatation and is involved in this sclerosing process. Operative cholangiography also shows an undilated biliary tree. This condition is part of a general systemic disease. All four patients personally observed also suffered from ulcerative colitis. Other associated conditions

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include retroperitoneal fibrosis (69) pancreatitis, and bilateral exophthalmos (68).

Secondary Sclerosing Cholangitis: Patients with chronic extrahepatic biliary obstruction, usually due to choledocholithiasis or to biliary stricture, suffer many attacks of acute ascending bacterial cholangitis. This inflammation may spread into the small intrahepatic bile ducts, which show periductal sclerosis (Figure 6). In such patients release of the extrahepatic biliary block fails to relieve the intrahepatic obstruction. Cholestatic jaundice persists in spite of the patent main bile duct. There is presumably a mechanical, ductal intrahepatic cholestasis.

Cholangiocarcinoma: Carcinoma of the liver can arise in the intralobular bile ducts and ductules where the differentiation from tumor arising from the liver cells can be exceedingly difficult. This condition must be included in any survey of intrahepatic cholestasis.

Discussion

The syndrome of intrahepatic cholestasis has a common anatomical, clinical, and biochemical pattern. Imposed on these are effects related to the cause. The diagnosis can be exceedingly difficult, and to facilitate this an attempt has been made at an anatomical classification (Figure 3). This scheme is based as far as possible on what is known of the anatomical changes both by light and electron microscopy. To some extent, however, it must be regarded as hypothetical. This is likely to remain so until more is known concerning the mechanisms by which bile is secreted and the changes produced by disease. It is also apparent that once cholestasis is present secondary events involve other parts of the biliary tree, and these may obscure the original mechanism. This paper is intended as a base line for others to solve the riddle of cholestasis.

Summary

Cholestasis (failure to secrete bile into the intestines) has multiple causes. The basic pattern—anatomical, clinical, and biochemical—is constant. A broad etiological classification can be made into extrahepatic (surgical) obstruction and cholestasis of intrahepatic origin; this paper concerns the latter group. Intrahepatic cholestasis may be due to hepatocellular, canalicular, ductular and interlobular, and septal bile duct lesions. The various causes are described and related to the anatomy of the biliary tree and hepatic histological appearances.

Summario in Interlingua

Cholestasis intrahepatic es non-secretion hepatic de bile. Le syndrome ha un commun base hepatic histologic, clinic, e biochimic, e imponite super isto es le characteristicas del varie conditiones causative.

Le syndrome occurre a omne nivellos in le cellula hepatic e le intrahepatic systema de duction biliari. Illo se manifesta in varie typos. Le gruppo genetic include le typo Dubin-Johnson de hyperbilirubinemia conjugate.

Pharmacos tal como northandrolona e testosterona methylic causa un typo canalicular de cholestasis. Le relation inter isto e le uso de pharmacos anticonceptional es commentate. Le jalnessa idiopathic del tertie trimestre de pregnantia pare esser de un simile typo. Quando patientes predisponite a disveloppar iste condition prende pillulas anticonceptional, le disveloppamento de jalnessa pote esser expectate con un alte grado de probabiltate. Altere pharmacos causa cholestasis como parte de un reaction de sensibilitate. Le promazinas pertine a ille gruppo de drogas. Idiopathic cholestasis recurrente es possibilemente de un typo similar.

Morbos predominantemente hepatocellular, tal como hepatitis a virus, cirrhosis postnecrotic, e hepatitis alcoholic, pote passar per un phase prolongate de cholestasis e assi causar grande difficultates diagnostic per un obstruction de major ductos biliari.

Le cholestasis pote esser manifeste al nivello del ductos o del ductulos. Primari cirrhosis biliari es le melior exemplo de isto. Altere conditiones al mesme nivello include cholangiitis sclerotisante primari o secundari a un obstruction de grande ductos biliari e certes del congenite atresias biliari.

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References

1. Yamamoto, T., Skanderberg, J., Zipursky, A., Israels, L. G.: The early appearing bilirubin: evidence for two components. *J. Clin. Invest.* 44: 31, 1965.
2. Robinson, S. H., Owen, C. A., Jr., Flock, E. V., Schmid, R.: Bilirubin formation in the liver from nonhemoglobin sources. Experiments with isolated perfused rat liver. *Blood* 26: 823, 1965.
3. Elias, H.: Embryology, histology and anatomy of the biliary system, in *The Biliary System*, edited by Taylor, W. Blackwell, Oxford, 1965.
4. Wheeler, H. O.: The function of the biliary tract, in *Progress in Liver Diseases*, edited by Popper, H., Schaffner, F. Grune & Stratton, New York and London, 1965.
5. Raia, S.: Histochemical demonstration of conjugated and unconjugated bilirubin using a modified diazo-reagent. *Nature (London)* 205: 304, 1965.
6. Ohkita, H., Iwasaki, R., Donomae, T., Tatsumi, S.: Electron microscopic studies of bile canaliculi. *Kanzo* 3:9, 1961.
7. Popper, H., Schaffner, F., Rubin, E., Barka, T., Paronetto, F.: Mechanisms of intrahepatic cholestasis in drug-induced hepatic injury. *Ann. N. Y. Acad. Sci.* 104: 988, 1963.
8. Goldfischer, S., Arias, I. M., Essner, E. Novikoff, A. B.: Cytochemical and electron microscopic studies of rat liver with reduced capacity to transport conjugated bilirubin. *J. Exp. Med.* 115: 467, 1962.
9. Jézéquel, A. M.: Dégénérescence myélinique des mitochondries de foie humain dans un épithélioma du choledoque et un ictère viral. *J. Ultrastruct. Res.* 3: 210, 1959.
10. Steiner, J. W., Carruthers, J. S., Kalifat, S. R.: Disturbances of hydration of cells of rat liver in extrahepatic cholestasis. *Virchow, Arch. Path. Anat.* 336: 99, 1962.
11. Datta, D. V., Sherlock, S. Cholestyramine for long term relief of the pruritus complicating intrahepatic cholestasis. *Gastroenterology* 50: 323, 1966.
12. Osborn, E. C., Wootton, I. D. P., Silva, L. C. da, Sherlock, S.: Serum-bile-acid levels in liver disease. *Lancet* 2: 1049, 1959.
13. Chiandussi, L., Greene, S. F., Sherlock, S.: Serum alkaline phosphatase in hepato-biliary and bone diseases. *Clin. Sci.* 22: 425, 1962.
14. Caesar, J., Shaldon, S., Chiandussi, L., Guevara, L., Sherlock, S.: The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin. Sci.* 21: 43, 1961.
15. Billing, B. H., Williams, R., Richards, T. G.: Defects in hepatic transport of bilirubin in congenital hyperbilirubinaemia: an analysis of plasma bilirubin disappearance curves. *Clin. Sci.* 27: 245, 1964.
16. Watson, C. J., Hoffbauer, F. W.: The problem of prolonged hepatitis with particular reference to cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver. *Ann. Intern. Med.* 25: 195, 1946.
17. Shaldon, S., Sherlock, S.: Virus hepatitis with features of prolonged bile retention. *Brit. Med. J.* 2: 734, 1957.
18. Phillips, G. B., Davidson, C. S.: Acute hepatic insufficiency of the chronic alcoholic: clinical and pathological study. *Arch. Intern. Med. (Chicago)* 94: 585, 1954
19. Ballard, H., Bernstein, M., Farrar, J. T.: Fatty liver presenting as obstructive jaundice. *Amer. J. Med.* 30: 196, 1961.
20. Beckett, A. G., Livingstone, A. V., Hill, K. R.: Acute alcoholic hepatitis. *Brit. Med. J.* 2: 1113, 1961.
21. Schaffner, F., Loebel, A., Weiner, H. A., Barka, T.: Hepatocellular cytoplasmic change in acute alcoholic hepatitis. *JAMA* 183: 343, 1963.
22. Datta, D. V., Sherlock, S., Scheuer, P. J.: Postnecrotic cirrhosis with features of cholestasis. *Gut* 4: 223, 1963.
23. Williams, R., Billing, B. H.: Action of steroid therapy in jaundice. *Lancet* 2: 392, 1961.
24. Wheeler, H. O., Meltzer, J. I., Bradley, S. E.: Biliary transport and hepatic storage of sulfobromophthalein sodium in the unanesthetized dog, in normal man and in patients with hepatic disease. *J. Clin. Invest.* 39: 1131, 1960.
25. Cook, G. C., Velasco, M., Sherlock, S.: Effect of corticosteroids on bromsulphalein metabolism in liver disease. In preparation, 1966.
26. Werner, S. C., Hanger, F. M., Kritzler, R. A.: Jaundice during methyl testosterone therapy. *Amer. J. Med.* 8: 325, 1950.
27. Schaffner, F., Popper, H., Perez, V.: Changes in bile canaliculi produced by norethandrolone: electron microscopic study of human and rat liver. *J. Lab. Clin. Med.* 56: 623, 1960.
28. Adlercreutz, H.: Steroid induced icterus. *Nord. Med.* 72: 1004, 1964.
29. Elliott, A. J., Hendry, J.: Cholestatic jaundice complicating pregnancy; recurrence after norethynodrel with ethinylestradiol (Enovid). *Canad. Med. Ass. J.* 92: 344, 1965.
30. Boake, W. C., Schade, S. S., Morrissey, J. F., Schaffner, F.: Intrahepatic cholestatic jaundice of pregnancy followed by Enovid-induced cholestatic jaundice; report of a case. *Ann. Intern. Med.* 63: 302, 1965.
31. Fawcett, J. W. Pederson, D. L.: Oral contraceptives and liver damage. *Brit. Med. J.* 2: 755, 1964.
32. Ikonen, E.: Jaundice in late pregnancy. *Acta. Obstet. Gynec. Scand.* 43 (suppl. 5): 1, 1964.
33. Larsson-Cohn, U., Stenram, U.: Jaundice during treatment with oral contraceptive agents; report of two cases. *JAMA* 193: 422, 1965.
34. Barnes, G. F.: Jaundice in a patient taking more than one compound tablet. *Brit. Med. J.* 1: 108, 1965.

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35. THULIN, K. E., NERMARK, J.: Seven cases of jaundice in women taking an oral contraceptive, Anovlar. *Brit. Med. J.* 1: 584, 1966.
36. OLDERHAUSEN, H. F. VON, EGGSTEIN, M., DOLD, U., KNORR, K.: Intrahepatic cholestasis with jaundice after taking contraceptive steroids. *German Med. Monthly* 11: 24, 1966.
37. CULBERG, G., LUNDSTRÖM, R., STENRAM, U.: Jaundice during treatment with an oral contraceptive, Lyndiol. *Brit. Med. J.* 1: 695, 1965.
38. HOLZBACH, R. T., SANDERS, J. H.: Recurrent intrahepatic cholestasis of pregnancy; observations on pathogenesis. *JAMA* 195: 542, 1965.
39. SOTANIEMI, E., KREUS, K. E., SCHEININ, F. M.: Oral contraceptives and liver damage. *Brit. Med. J.* 2: 1264, 1964.
40. THORLING, L.: Jaundice in pregnancy: a clinical study. *Acta. Med. Scand.* (suppl. 302), 1955.
41. SVANBORG, A., OHLSSON, S.: Recurrent jaundice of pregnancy: a clinical study of twenty-two cases. *Amer. J. Med.* 27: 40, 1959.
42. HAUSHEER, H. J., LAUER, D. J.: Recurrent jaundice of pregnancy. Report of a case. *New Eng. J. Med.* 267: 1300, 1962.
43. COMBES, B., SHIBATA, H., ADAMS, R., MITCHELL, B. D., TRAMELL, V.: Alterations in sulfobromophthalein sodium-removal mechanisms from blood during normal pregnancy. *J. Clin. Invest.* 42: 1431, 1963.
44. MUELLER, M. N., KAPPAS, A.: Estrogen pharmacology. 1. The influence of estradiol and estriot on hepatic disposal of sulfobromophthalein (BSP) in man. *J. Clin. Invest.* 43: 1905, 1964.
45. KLEINER, G. J., KRESCH, L., ARIAS, I. M.: Studies of hepatic excretory function. II. The effect of norethynodrel and mestranol on bromsulfalein sodium metabolism in women of childbearing age. *New Eng. J. Med.* 273: 420, 1965.
46. KATZ, R., VELASCO, M., REYES, H.: Jaundice during treatment with contraceptive pills. *Gastroenterology* 50: 853, 1966.
47. BROWN, B. L.: Primary intrahepatic cholestasis due to Hodgkin's disease with response to adrenocorticotropin. *Ohio Med. J.* 55: 1384, 1959.
48. BOURONCLE, B. A., OLD, J. W., JR., VAZQUES, A. G.: Pathogenesis of jaundice in Hodgkin's disease. *Arch. Intern. Med.* (*Chicago*) 110: 872, 1962.
49. JUNIPER, K., JR.: Prolonged severe obstructive jaundice in Hodgkin's disease. *Gastroenterology* 44: 199, 1963.
50. LEVITAN, R., DIAMOND, H. D., CRAVER, L. F.: Jaundice in Hodgkin's disease. *Amer. J. Med.* 30: 99, 1961.
51. SHERLOCK, S.: Hepatic reactions to therapeutic agents. *Ann. Rev. Pharmacol.* 5: 429, 1965.
52. SUMMERSKILL, W. H. J., WALSHE, J. M.: Benign recurrent intrahepatic "obstructive" jaundice. *Lancet* 2: 686, 1959.
53. WILLIAMS, R., CARTTER, M., SHERLOCK, S., SCHEUER, P. J., HILL, K. R.: Idiopathic recurrent cholestasis: a study of the functional and pathological lesions in four cases. *Quart. J. Med.* 33: 387, 1964.
54. SUMMERSKILL, W. H. J.: The syndrome of benign recurrent cholestasis. *Amer. J. Med.* 38: 298, 1965.
55. KÜHN, H. A.: Intrahepatic cholestasis in two brothers. *German Med. Monthly.* 8: 185, 1963.
56. TYGSTRUP, N.: Intermittent possibly familial intrahepatic cholestatic jaundice. *Lancet* 1: 1171, 1960.
57. TYGSTRUP, N.: Intermittent benign cholestasis. Personal communication, 1966.
58. AHRENS, E. H., JR., PAYNE, M. A., KUNKEL, H. G., EISENMENGER, W. J., BLONDHEIM, S. H.: Primary biliary cirrhosis. *Medicine* (*Balt.*) 29: 199, 1950.
59. SHERLOCK, S.: Primary biliary cirrhosis (chronic intrahepatic obstructive jaundice). *Gastroenterology* 37: 574, 1959.
60. RUBIN, E., SCHAFFNER, F., POPPER, H.: Primary biliary cirrhosis. Chronic non-suppurative obstructive cholangitis. *Amer. J. Path.* 56: 387, 1965.
61. KLION, F. M., SCHAFFNER, F.: Electron microscopic observations in primary biliary cirhosis. *Arch Path* (*Chicago*) 81: 152, 1966.
62. WALKER, J. G., DONIACH, D., ROITT, I., SHERLOCK, S.: Serological tests in the diagnosis of primary biliary cirrhosis.. *Lancet* 1: 827, 1965.
63. DONIACH, D., ROITT, I., WALKER, J. G., SHERLOCK, S.: Immunological tests in primary biliary cirrhosis. *Clin. Exp. Immun.* 1: 237, 1966.
64. SMETANA, H. F., EDLOW, J. B., GLUNZ, P. R.: Neonatal jaundice. A critical review of persistent obstructive jaundice in infancy. *Arch Path* (*Chicago*) 80: 553, 1965.
65. STOWENS, D.: Congenital biliary atresia. *Ann. N. Y. Acad. Sci.* 111: 337, 1963.
66. BAKER, D. H., HARRIS, R. C.: Congenital absence of the intrahepatic bile ducts. *Amer. J. Roentgen.* 91: 875, 1964.
67. SMITH, M. P., LOE, R. H.: Sclerosing cholangitis. Review of recent case reports and associated diseases and four new cases. *Amer. J. Surg.* 110: 239, 1965.
68. WENGER, J., GINGRICH, G. W., MEDELOFF, J.: Sclerosing cholangitis—a manifestation of systemic disease. *Arch. Intern. Med.* (*Chicago*) 116: 509, 1965.
69. BARTHOLOMEW, L. G., CAIN, J. C., WOOLNER, L. B., UTZ, D. C., FERRIS, D. O.: Sclerosing cholangitis: its possible association with Riedel's struma and fibrous retroperitonitis. Report of two cases. *New Eng. J. Med.* 269: 8, 1963.

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