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RECENT ADVANCES IN LIVER DISEASE

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I. CIRRHOSIS

Cirrhosis implies fibrosis involving all parts of the liver, accompanied by nodular parenchymal regeneration. Necrosis of hepatic cells occurs at some stage.[1]

A. TYPES OF CIRRHOSIS

1. Portal and Post-necrotic Cirrhosis

These are the two common types of cirrhosis. Both terms are unsatisfactory, and intermediate forms occur. The name 'portal' is used when every lobule of the liver is involved, the connective tissue is in thick regular bands, and there are small regenerating nodules throughout the liver. This type is commonly associated with alcoholism. Post-necrotic cirrhosis denotes the presence of bands of fibrous tissue of varying thickness, nodules varying in size, and normal lobules within the larger nodules. The name Laennec's cirrhosis should be used to denote the terminal picture of either portal or post-necrotic cirrhosis.[2]

Aetiology

The role of viral hepatitis in the aetiology of cirrhosis remains controversial. Zieve *et al.*[3] examined 367 men who had had acute viral hepatitis 4 - 6 years earlier and showed that there was no greater incidence of liver disease amongst them than amongst normal controls. Cullinan *et al.*[4] followed up 91·6% of 1,293 cases of infectious hepatitis which occurred amongst British servicemen in the Middle East in World War II, and failed to find a single case of cirrhosis. Despite these reports, many accept the concept of post-hepatitic cirrhosis in civilian practice. This is based on a previous history of infective hepatitis in patients who have post-necrotic cirrhosis. Howard and Watson[5] obtained such a history in 17% of their patients. Sherlock[6] obtained it in 33% of her series of cirrhosis cases, and 50% of her patients had no detectable cause for their disease.

MacKay and his co-workers[7,8] discussed auto-immunization as the cause of some cases of cirrhosis. It seems possible that some substances in the liver cells might become antigenic, either because structural changes make them more accessible to the blood or as a result of damage by virus infection or malnutrition. It has been demonstrated that serum from patients with acute hepatitis may fix complement in the presence of human liver homogenate and this is presumed to be due to the presence of antibody-like substances in the serum. This reaction tends to become negative as the patient recovers from hepatitis. Most cases of chronic active hepatitis have a low titre when tested, and the highest titres have been obtained in 'lupoid hepatitis'.[8] Further research is in progress along these lines.

The nature of the association of alcoholism with portal cirrhosis is not clear, but it is estimated that 8% of alcoholics develop this complication.[9] Alcohol may cause an increase in the serum levels of glutamic oxalacetic transaminase and of glutamic pyruvic transaminase, indicating that liver damage, probably liver-cell necrosis, is sometimes caused by alcohol itself.[10] Only 18% of cirrhotics in England are alcoholics, but in New York the comparable figure is 54%, and it seems that in these patients malnutrition may be an important factor in the genesis of their cirrhosis. The relatively high intake of carbohydrate on the part of these patients has been incriminated in the past. It is well known that alcoholics suffer from protein malnutrition and it is possible that long-continued malnutrition may itself result in cirrhosis or may render the liver more susceptible to noxious agents.[11] The cirrhosis which occurs in the African, and is a precursor of liver carcinoma, may have the same aetiology. It is of great interest that long-term follow-up on children who have suffered from kwashiorkor has failed to reveal any evidence of hepatic fibrosis.

The work of Himsworth[12] highlighted the results of experimental dietary depletion in animals. Choline deficiency regularly produces diffuse fatty change in the liver of the rat, and this is followed by a diffuse fibrosis, which in turn results in an atrophic nodular cirrhosis.[13] To what extent these experimental results can be applied to human disease is unknown.

2. Cirrhosis from Other Causes

(*a*) *Hanot's Biliary Cirrhosis* (*Chronic Intrahepatic Obstructive Jaundice*)

This usually affects women between the ages of 35 and 70 and is rarely seen in males. The aetiology is unknown. Characteristically, the onset is insidious, with pruritus often preceding the jaundice by months or years. The jaundice is obstructive and is of varying degree. The patient feels well, has no abdominal pain or fever, is pigmented, may show skin xanthoma, and has a large, firm, smooth liver with an enlarged spleen and steatorrhoea.

The presence of urobilin in the urine and stercobilin in the stool indicates that the obstructive jaundice is incomplete. The serum alkaline phosphatase is considerably raised, as are the cholesterol and total lipids and the $\alpha 2$ and β globulins. The prognosis is relatively good.

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(*b*) *Secondary Biliary Cirrhosis*

This occurs after long-standing obstruction of the extra- or intrahepatic bile-ducts; e.g. from calculus, traumatic stricture, congenital obliteration, or neoplasia.

(*c*) *Haemachromatosis*

In this disease there is an increase in total body iron, an increased serum-iron concentration and a raised saturation of the iron-binding capacity. It seems likely that haemachromatosis is due to an inborn error of metabolism resulting from an autosomal genetic defect of incomplete penetrance and/or variable expressivity which is transmitted as a Mendelian dominant.[14] About 20% of relatives of affected patients have elevated serum-iron levels and are therefore likely to develop the full picture of the disease in later life. It is probable that early treatment by repeated phlebotomies designed to bring the serum iron to normal levels, and keep it there, will prevent the development of the disease. The full syndrome is characterized by cirrhosis, diabetes, skin pigmentation, genital atrophy, loss of body hair, and cardiac involvement. Cardiac involvement occurs in 30% of cases and may lead to cardiac failure. Two further points should be made:

(i) There is still no proof that the deposition of iron directly causes the cirrhosis,

(ii) The rare occurrence in a young female is probably the occurrence of the disease in the homozygous form.

(*d*) *Hepatolenticular Degeneration* (*Kinnear-Wilson's Disease*)

This should be suspected if a patient with cirrhosis has signs of extrapyramidal disease, and an intention tremor in addition. A greyish-green corneal ring is present in 90% of cases. This rare disease often causes a low serum uric acid and a low serum phosphorus owing to urinary loss, and these are useful screening tests. The fundamental disturbance in copper metabolism is a deficiency in the synthesis of ceruloplasmin, the serum protein which normally binds and carries copper in the serum. The result of this is that the copper is loosely bound to serum albumin instead and is readily deposited in the liver, basal ganglia, and renal tubules. Treatment is with BAL or penicillamine, which is a copper-chelating agent. Some patients have improved on this treatment, but it must be continued for a long time. The response does not seem to be as good in severely affected young patients. There is a high incidence of consanguinity in the patients' parents. It is not yet certain that the increased liver copper itself is responsible for the cirrhosis.

(*e*) *Cardiac Cirrhosis*

This may occur incidently in cardiac failure of long duration.

(*f*) *Cirrhosis in Young Women*

In recent years reports from many parts of the world[15,16] have described a variety of cirrhosis with special features in young women. The patients are usually under the age of 35 years and the syndrome is rarely seen in males. They are mildly jaundiced and feel well but have periods of fever and polyarthritis. Acne is often present. Moon-shaped facies, abdominal striae and amenorrhoea are commonly noted. Ascites occurs terminally. The serum α globulin is high. Occasionally the Wassermann reaction is falsely positive and lupus erythematosus cells are found. For this reason the term 'lupoid hepatitis' has been used and some believe that the condition may be related to systemic lupus erythematosus.[7] It seems likely that it is not a variant of this systemic disease, but rather a non-specific reaction by the liver of the young woman. About half the patients have a previous history of acute hepatitis.[6] It is in the aetiology of this syndrome that the possible role of auto-immunization has received most attention in the field of liver disease. Cortisone treatment has its best results in patients who are more deeply jaundiced and have high serum α globulin; it sometimes results in clinical, biochemical and histological improvement. While it is not certain whether steroids should be used for long-term treatment, it seems wise to restrict their use to acute exacerbations of the hepatic process or other complications, e.g. polyarthritis, and to stop them as soon as possible. Even without treatment the prognosis is quite good.

B. MANAGEMENT OF PATIENTS WITH CIRRHOSIS

1. Cirrhosis without Complications

A good diet and total abstention from alcohol is important in the treatment of well-compensated cirrhosis. One should aim at about 2,500 calories a day with a protein content of 100 g. There is no evidence in favour of added choline or methionine, but vitamin supplements are usually given. If an associated anaemia is due to blood loss from varices, then it will respond to oral iron, but the anaemia of liver disease itself, which may have a latent haemolytic element, may not respond to iron, and blood transfusion is often necessary to maintain the haemoglobin at an adequate level. Sedatives should be avoided if possible. Pethidine should be preferred to morphine because of the liability of the latter to precipitate coma. Paraldehyde may precipitate coma too, and barbiturates should be used with great care. It is doubtful whether the course of the disease is changed by the use of cortisone or allied compounds.

2. Cirrhosis with Complications

(*a*) *Hepatic Pre-coma and Coma* (*Porto-systemic Encephalopathy*)

This is diagnosed when the patient develops all or some of the following symptoms and signs: Disturbed level of consciousness, particularly drowsiness by day and wakefulness at night; intellectual and personality changes; slurred speech; and a 'flapping' tremor of the hands best demonstrated when the arms are outstretched, the fingers separated, and the wrists hyperextended. The tremor may become more generalized and may result in ataxia; it is also seen in uraemia and respiratory failure associated with hypercapnia. Pyramidal signs may be elicited in the limbs, but plantar responses are often flexor. Foetor hepaticus is smelt in the breath and occurs not only in liver failure but also in any patient with extensive portal collateral circulation, e.g. after operative portocaval shunts, and is not in itself diagnostic when such collaterals are present. A high level of ammonium is often found in the blood and ammonium salts may precipitate coma. This led to the concept of the toxicity of ammonia and to the efforts to lower it in treatment.

Glutamic acid has been given because it combines with ammonia to form glutamine.[17] Arginine has been tried because it is said to 'stimulate' the Krebs cycle in the liver and so to encourage the detoxication of ammonia to urea.[18] It is true that both glutamic acid and arginine sometimes reduce blood-ammonia levels but neither is consistently successful in treatment.[19] It is unlikely that either will become

part of the routine treatment of hepatic coma. Artificial dialysis with the artificial kidney is probably only of use, if at all, in patients in whom the coma has been precipitated by a large gastro-intestinal bleed, and these patients have a better prognosis in any event.[6] Ion-exchange resins have also been used to lower the blood ammonia.[20] It seems likely that coma is due to a number of noxious agents[21] and that the elevated blood ammonia is only one of these. It is therefore not surprising that there is no good correlation between the blood-ammonia level and this syndrome. There is good evidence for the belief that some toxic substances may result from the breakdown of protein in the gut. These substances are then absorbed but not detoxified by the diseased liver, or are shunted past it by the collateral circulation, and so reach the systemic circulation and cause the syndrome.

This is the corner-stone of treatment—*protein restriction.* At the first sign of pre-coma the patient is given a protein-free diet; 20% glucose by the mouth usually provides adequate calories. Caval catheterization is avoided if possible, owing to the high incidence of infection associated with it. To prevent intestinal bacteria from breaking down protein, a broad-spectrum antibiotic is given by mouth, e.g. neomycin 1 g. 4-hourly for 1 week. It is of great importance to detect a *precipitating cause* and to treat it if possible; e.g. overdosage with morphine or barbiturates; the use of chlorothiazide, possibly through its hypokalaemic effect; haemorrhage from varices, operations, alcohol ingestion and infection; and the aspiration of ascites. Coma due to one of these precipitating factors carries a better prognosis. When there has been haemorrhage into the gastro-intestinal tract some authorities advocate washing the stomach free of blood to reduce the absorption of the products of digested blood.

Porto-systemic encephalopathy does not always present acutely, and in the more chronic cases treatment does not have to be so vigorous and a small amount of protein may be allowed in the diet. The limit of tolerance for each patient has to be determined. Patients treated with a high-protein diet who develop porto-systemic encephalopathy should be put on a protein-free diet until the signs of this complication have disappeared. Protein can then be reintroduced to the limit of tolerance. Broad-spectrum antibiotics are only used for acute exacerbations in these chronic patients, although in some it may be necessary to use them for long periods of time. Enemata and purges of magnesium sulphate are useful in keeping the bowel free from nitrogenous substances in the acute cases. There are conflicting reports on the use of cortisone and related compounds in the treatment of hepatic coma;[22,23] they are not usually of any value.

(*b*) *Ascites*

Abdominal paracentesis should be performed as *infrequently* as possible. This is because the ascitic fluid is rich in protein, and repeated aspirations result in considerable protein loss in a patient who is unable to synthesize protein adequately. The keynote of treatment is restriction of salt and rest in bed. A patient with ascites usually excretes 5 - 10 mEq. of sodium in the urine daily. The loss from other sources such as sweating is usually about 22 mEq. so that any intake in excess of about 30 mEq. will be retained probably as a result of secondary hyperaldosteronism. Dietary sodium must not exceed 22 mEq. a day and this can be achieved by cooking without salt, eating salt-free bread and butter, and avoiding foods with a high salt content, e.g. pastries cooked with baking soda. Protein-rich foods contain salt. These patients require a high-protein diet, and so some meat and fish is essential, and the use of salt-poor protein supplements make the diet rich in protein while remaining poor in salt. Mersalyl and the chlorothiazide group of drugs are of great value. The action of mersalyl can be potentiated by the use of potassium chloride rather than ammonium chloride and, when the chlorothiazide group is used, potassium supplements are usually necessary and should be given on the days on which chlorothiazide is not being given. Chlorothiazide has been shown to precipitate coma in some patients and a careful watch should be kept for this complication.[24] Aldosterone antagonists (spirolactones) have been used with variable success in resistant cases.[25] Intravenous salt-poor human albumen and ion-exchange resins have not proved of much value. If there is no response to a fair trial of treatment the prognosis is poor.

(*c*) *Portal Hypertension*

Apart from ascites the important complication of portal hypertension is haemorrhage from oesophageal or gastric varices. Patients with cirrhosis, particularly alcoholics, may be bleeding from a peptic ulcer or from gastritis and not from their varices, and the differential diagnosis is sometimes difficult.[26] In doubtful cases, oesophagoscopy and gastroscopy may have to be resorted to, but the presence of large amounts of blood may make interpretation difficult, and it has been advised that the stomach should be washed out with iced water before endoscopy. Biochemically, the blood ammonia is raised in 87% of cirrhotics after haemorrhage into the gastro-intestinal tract, and the retention of bromsulphalein is abnormal in 93%. Bromsulphalein is retained to above 15% in 25% of non-cirrhotics, and the blood ammonia is normal in 95% of non-cirrhotics after haemorrhage. On the basis of these findings it has been suggested that in upper gastro-intestinal bleeding a blood ammonia of above 150 μg% and a bromosulphalein retention of above 15% are diagnostic of cirrhosis when taken together, while if both are normal there is no cirrhosis.[27] This might be useful in excluding cirrhosis, but even when the presence of cirrhosis is confirmed, an ulcer and not the varices may be responsible for the bleeding. Control of the haemorrhage by the Sengstaken tube suggests that the source is variceal. Emergency barium meal and splenic venography may be useful in selected cases.

The treatment of massive haemorrhage from oesophageal or gastric varices is blood transfusion to replace the blood lost. Sedation should be confined to small doses of barbiturates. Sherlock[6] advises that patients with cirrhosis (as opposed to those with varices on the basis of extrahepatic portal block) should be treated for incipient hepatic coma with glucose and neomycin. In this way neurological complications may be prevented. If bleeding continues, a Sengstaken tube should be passed and an attempt made to control the bleeding in this way. The use of this tube requires great care, and those using it should be fully conversant with the possible complications.[6] Results are variable. The tube often stops the bleeding only for it to recur when it is removed; reinsertion is then necessary. It is an unsatisfactory form of treatment, but the best available at present.

Attempts to lower portal venous pressure in an effort to prevent further haemorrhage must be preceded by portal

venography, which will demonstrate the extent of the collateral circulation and the patency of the portal vein. The latter is essential if a porto-systemic anastomosis is to be performed, which is the operation of choice. It should not be undertaken before the initial haemorrhage,[28] and is performed in an attempt to prevent repeated haemorrhage. Whether it is sufficiently successful in this will be shown by longer periods of follow-up than are at present available.[29] Porto-systemic encephalopathy may follow these artificial-shunt operations. This becomes more likely if there is any evidence of encephalopathy beforehand. Latent pre-operative porto-systemic encephalopathy can be detected by various tests, e.g. forced protein feeding and serial electroencephalographs, and if any tendency towards the development of this complication is detected, the operation is contra-indicated. As a general rule, older patients and patients with inadequate hepatic functions are unsuitable for porto-systemic shunts. The serum bilirubin, also, must be less than 1·5 mg.% and the serum albumin more than 3 g.%. Ascites is usually a contra-indication, although selected cases with ascites and with good hepatic functions have been operated upon, but the results are variable. Hepatic wedge pressure[30] is helpful in distinguishing between intra- and extrahepatic causes of portal hypertension. In cirrhosis it is raised while in obstruction of the portal vein it is normal. In both, the splenic pressure is raised. Recently portal hypertension has been described in the absence of cirrhosis, portal-vein obstruction, or any other detectable cause. It has also recently been confirmed that posterior pituitary extract reduces portal venous pressure in dogs with end-to-side porto-systemic shunts. As the portal venous pressure falls, so the oxygen saturation falls too, and it is possible that posterior pituitary extract may act by closing arteriovenous shunts in the stomach and bowel. Extensive vascular shunts are known to exist in cirrhosis in man and, when they occur in the pulmonary circulation, they may cause systemic anoxia and central cyanosis.

In the treatment of massive uncontrollable haemorrhage from varices, one of a series of operative methods may be attempted, such as resection of the oesophagus or stomach, carried out as an emergency procedure. These operations have a very limited success and emergency portocaval anastomosis is preferable, but not usually possible during the bleeding episode. Ligation of the hepatic artery is not indicated.

II. HEPATITIS

Acute viral hepatitis is the commonest form of liver disease seen in practice. It is usually mild and in some patients jaundice is absent, but this is rare. The differential diagnosis from serum hepatitis can only be made on the history, and patients who received transfusions or injections in the 6 months preceding the onset of jaundice may well have obtained their infection in this way. The diagnosis is usually easy and the patient makes an uneventful recovery. At the height of the illness the jaundice often becomes completely obstructive in type and urobilin disappears from the urine. Improvement is heralded by its return.

In some cases acute liver failure develops and ominous signs of this complication are a sudden considerable reduction in the size of the liver, widespread bleeding, and the appearance of 'foetor hepaticus'. The outcome is nearly always fatal. Also rarely, hepatitis may enter a subacute phase and the patient may die in liver failure after some months. Patients may recover from subacute hepatitis but may develop cirrhosis at a later stage. Those entering this subacute phase never recover completely from the acute illness, and if there is a relapse in a patient who has had good health for some months, either a fresh infection has occurred or the diagnosis is incorrect.

It is important to realize that even with complete recovery it is common for the flocculation tests to remain abnormal for many months and often for a year. This has no significance; the so-called 'post-hepatitis syndrome' is no more than post-infection debility and is far commoner than subacute hepatitis. The patient should be reassured after liver disease has been excluded.

Drugs may cause jaundice, which must be distinguished from infective hepatitis and may be haemolytic, hepatocellular or obstructive in type. Iproniazid (marsilid) is the most important drug amongst those which cause hepatocellular jaundice but it has also been ascribed to PAS, sulphonamides and various chlorinated hydrocarbons. The pathological picture is identical with that of infective hepatitis[31] and the clinical picture is very variable according to the extent of the liver-cell necrosis.[32] In severe cases there is deep jaundice and the patient may die in hepatic coma. Complete recovery occurs in milder cases. The results of corticosteroid therapy are still to be assessed.

Obstructive jaundice may be caused by chlorpromazine (largactil), methyl testosterone, norethandrolone (nilevar), thiouracil, and arsphenamine. While many patients receiving norethandrolone have excessive bromsulphalein retention,[33] only a small percentage develop jaundice. It is estimated that 1 - 2% of patients given chlorpromazine for 1 week develop jaundice. There is a latent period of 1 - 4 weeks followed by fever, anorexia, vomiting, abdominal pain, skin rash, and severe pruritus. Eosinophilia occurs in the early stages. Biochemically these patients characteristically show an obstructive jaundice with a high serum bilirubin, raised serum alkaline phosphatase (often higher than 30 King-Armstrong units, as it is also in mechanical obstruction, e.g. by stone), raised serum cholesterol, no bile in the stools, and no urobilin but a large amount of bile in the urine. The majority of patients recover completely in about 4 weeks. An occasional patient remains jaundiced for months and rarely a patient may succumb from this complication of chlorpromazine therapy. Pre-existing liver disease does not predispose to chlorpromazine jaundice.[6] The incidence of hepatic involvement is not related to the size of the dose or for the period for which it is taken.

The differential diagnosis between acute heptatitis with obstructive jaundice and mechanical obstructive jaundice may be very difficult. In differentiating between hepatitis and jaundice due to stone it must not be forgotten that older patients are no more exempt from developing hepatitis than younger people are from having stones. Severe abdominal pain suggests biliary colic but may also occur in hepatitis. Gall-stones in the common bile-duct may be painless. Rigors are characteristic of ascending cholangitis complicating mechanical obstruction but may occasionally occur in the early stages of hepatitis. An enlarged smooth liver commonly occurs in mechanical obstruction and even splenomegaly has been described. Nodules in the liver suggest intrahepatic obstruction by carcinoma, and a palpable gall-bladder indicates carcinoma of the ampulla of Vater or head of the pancreas. Carcinomatous masses may be felt in the pouch of Douglas. Straight X-ray of the abdomen may reveal gall-stones, 10% of which are radio-opaque. Previous biliary surgery suggests the possibility of traumatic stricture of the common bile-duct. It is clear that diagnosis may be difficult and the probabilities have to be weighed carefully in every case. If in doubt about the diagnosis the clinician is advised to observe the patient for 3 weeks before advising

laparotomy. During this period most patients with infective hepatitis will show improvement, underlying cirrhosis usually becomes apparent, and no irreversible damage will have been done to the liver. Liver biopsy is sometimes helpful but often inconclusive. ACTH (40 units twice a day for 4 days) or prednisone (40 - 60 mg. a day for 1 week) may be of diagnostic use.[6,37] A rapid fall in the serum bilirubin of over 70% of the previous level is strongly suggestive of hepatocellular jaundice and there is usually a lesser fall in obstructive jaundice due to gall-stones. If the clinician is still in doubt at the end of 3 weeks, then a laparotomy is performed and at operation not only must the common bile-duct be palpated and if necessary explored, but also an operative cholangiogram must be done, as must an operative liver biopsy. If operative cholangiograms are not done then small common-duct stones will pass undetected and the patient will have to be submitted to further operations needlessly.

Treatment of Hepatitis

It would seem wise to insist on bed rest in the treatment of patients with hepatitis who stay at home and are not admitted to hospital. It has been pointed out that the good results claimed for treatment with early ambulation were obtained in young servicemen during a mild epidemic.[34,35] Patients in hospital may be allowed up for a few hours each day if they have no symptoms. Strict bed rest is enforced if symptoms recur. Fuller activities are not allowed until the serum-bilirubin level reaches 1·5 mg.%. Patients should be allowed to choose their diet and should be encouraged to have one rich in protein as soon as possible. Antibiotics have no part to play in treatment. Corticosteroids induce a rapid remission clinically and biochemically but if treatment is stopped too early relapse occurs. As in the average case the prognosis is good and the illness short, these steroids should not be used as a routine. They may be used in patients with severe obstructive features and will result in a fall in the serum bilirubin but there is still no evidence that they shorten the duration of the illness. In the rare case of acute liver failure protein by mouth must be stopped and the regime for the treatment of hepatic coma instituted. Corticosteroids are given as a desperate measure.[36] The prognosis is very poor when this rare complication occurs.

Pruritus may present a problem in treatment. The mild pruritus due to hepatitis is best treated with calamine lotion or antihistaminic drugs. Methyl testosterone, norethandrolone or corticosteroids should be reserved for the pruritus of the more prolonged cases of severe obstructive jaundice.

III. SUPPLEMENTARY

TRANSAMINASES

The normal value for glutamic oxalacetic transaminase in the serum is 5 - 40 units; this value may be increased by 20 to 500 times in acute hepatitis.[37] The normal value for serum glutamic pyruvic transaminase is 7 - 23 units and this is also greatly increased in acute hepatitis. The clinical severity parallels the increase in the serum levels of these enzymes to a certain extent. Their greatest value lies in the early diagnosis of infective hepatitis and in detecting the development of subacute hepatitis or relapses. Patients with decompensated cirrhosis show higher serum levels than those with compensated disease.[38] Merrill *et al.*[39] have related the rise in the serum-enzyme level to the amount of cellular necrosis found on liver biopsy, and this has been confirmed by other workers.[40] It has also been shown that there is a corresponding decrease in the liver content of these enzymes. They have not proved of value in the differential diagnosis of obstructive jaundice, for serum levels may be increased to a certain extent even in posthepatic obstruction. This is due to the focal hepatic necrosis that commonly occurs in this condition. It is well known that serum values for these enzymes may also be increased after myocardial infarction and in muscular diseases. In summary, therefore, it may be said that these enzymes may be present in increased amounts in the serum when there is liver-cell necrosis.

BILE PIGMENTS

The advances in this field are due to the application of reverse-phase partition-chromatography.[41] By this means the bile pigments have been identified as consisting of haemobilirubin, pigment I, and pigment II. Haemobilirubin is unconjugated and is the pigment which reacts indirectly with the Van den Bergh reagent and is increased in the serum in haemolytic jaundice. In the normal liver haemobilirubin is converted to pigment I by conjugation with one glucuronide molecule; this in turn is converted into pigment II which is conjugated with 2 glucuronide molecules; 80% of bilirubin is excreted as a glucuronide conjugate and 10 - 15% as a conjugated sulphate. Some conjugation may take plase in extrahepatic sites, as has been demonstrated in the hepatectomized animal. In adult haemolytic disease, slight increases in the amount of pigment I and pigment II in the serum are thought to be due to associated hepatic dysfunction. In the normal premature infant, jaundice is probably related to a deficiency of at least 2 enzymes—glucuronyl transferase and uridine diphosphate glucuronic acid dehydrogenase, the enzymes necessary for the conjugation of haemobilirubin. In haemolytic disease of the newborn there is a great increase in circulating haemobilirubin, which is toxic to the cells and causes kernicterus. Pigments I and II are non-toxic. In mechanical obstructive jaundice, cirrhosis and hepatitis there is an increase in the serum levels of pigments I and II. In mechanical obstruction to the flow of bile the serum level of pigment II tends to be higher than that of pigment I, while in hepatitis and cirrhosis the reverse is the case. There is a considerable amount of overlapping and so this is of no value in distinguishing between these types of jaundice.

ESSENTIAL HYPERBILIRUBINAEMIA

1. *Gilbert's Disease*

The precise incidence of this disease is not known but it is probably far commoner than is generally thought. The patient usually has no symptoms but jaundice occurs from time to time. The serum bilirubin is usually less than 5 mg.% and is always of the unconjugated (indirect reacting) type. There is no bile in the urine. Liver biopsy is normal. The jaundice may be noted during an examination for an intercurrent illness, and hepatitis may be erroneously diagnosed. The persistence of the jaundice may lead to the diagnosis of subacute hepatitis and cirrhosis and unnecessary invalidism may result. The prognosis is excellent and no treatment is necessary.

2. *Dubin-Johnson Disease*

In this rare disease the patients often have symptoms. Bile is present in the urine and there is an increase of con-

jugated (direct reacting) pigment in the serum. The bromsulphalein test is abnormal. Oral cholecystography reveals a non-functioning gall-bladder, and on liver biopsy the liver is found to be coloured by a coarse brown pigment, though in rare cases there is no pigment.

3. *Crigler-Najjar Disease*

This is a very rare, severe form of Gilbert's disease characterized by kernicterus, mental defect, and death at an early age. It is inherited as a Mendelian dominant.

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