Current Practice

MEDICINE IN THE TROPICS

Hepatic Failure in the Tropics

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Patients with clinical features which readily suggest some degree of failure of liver-cell function, such as ascites, jaundice, fetor hepaticus, and endocrine or neurological changes are commonly met with in tropical medical practice. The patients themselves, and their relatives, recognize some of these symptoms and signs, as is shown by the descriptive terms which exist in various languages in Africa, such as "the fever that turns the eyes yellow" or "the disease which causes water to accumulate in the belly." Many parts of Africa have had or still have serious epidemics in which jaundice with or without fever is the major presenting symptom, and the fatal results which have followed the attacks in many cases have left the people in these communities in no doubt about the seriousness of the condition. In spite of this knowledge, however, these patients will try herbal preparations and local remedies first before they eventually turn up in hospital, often with well-established symptoms and easily recognizable physical signs.

Hepatic failure is seen in the tropics, as elsewhere, in the acute as well as the chronic forms. In its most dramatic form it occurs as a fulminant hepatitis with predominantly neurological signs, such as acute maniacal excitement, which may be mistaken for a psychiatric illness, as there may be very little time for any degree of jaundice to develop. The chronic forms are more insidious in onset with ascites, jaundice, fetor hepaticus, and other features of chronic hepatic insufficiency.

Environmental Factors

Both in tropical as well as in temperate climates acute viral hepatitis and cirrhosis of the liver represent the two commonest causes of acute hepatic failure, while the latter represents the commonest cause of chronic hepatic insufficiency. There are, however, significant differences as regards both aetiology and clinical course between cases seen in the tropics and those seen in temperate climates, differences which are associated, at least in some cases, with background differences in the social, physical, or biological environment.

Viral Hepatitis

The injection syringe is a popular instrument in many tropical countries because of previous successes achieved through it in mass injection campaigns against community diseases such as yaws, syphilis, and leprosy. As a result a widespread and very lucrative "injection practice," carried out largely by auxiliary medical personnel in rural areas, has developed in many tropical countries over a period of years, and it will

take some time to eliminate some of the worst aspects of this system of medical care. The "injections" are given to patients who demand and are willing to pay for them as a panacea for almost any symptom or illness. Knowledge of aseptic technique by those who give such injections is usually limited, and as clean water is not always easy to come by in many rural areas the setting is ideal for spreading the virus of serum hepatitis. This form of hepatitis is therefore probably more common in the tropics than might be thought at first sight.

The flooding of agricultural areas after periods of heavy rains may serve as a means of spreading hepatitis A virus in countries where heavy rainfall combines with poor sanitation and indiscriminate sewage disposal, as was the case in the Delhi epidemic of viral hepatitis in 1955.¹

Other viruses, such as that of yellow fever virus, may give rise to acute hepatitis in tropical areas. West Africa still constitutes an endemic area for yellow fever, and those who practise in such areas must be alert constantly for mild cases in which there may be fever and no detectable jaundice, as well as for fulminant cases which may present with predominantly neurological signs. Acute hepatic failure in late pregnancy and the puerperium is still an important cause of maternal death in pregnancy in many tropical countries. Viral hepatitis has been shown to be more severe in the pregnant than in the non-pregnant woman; and in the tropics, particularly in rural areas, pregnant women are often given a lot of unnecessary injections as part of routine antenatal care by poorly supervised auxiliary medical staff. In these cases the risk of developing viral hepatitis is greater than that which obtains in the rest of the population. Our experience at Ibadan shows that pregnant women who develop acute hepatitis during the second and third trimester of pregnancy run a greater risk of hepatic coma and death than those cases seen during the first trimester, and this emphasizes the need to take special care of pregnant women who develop acute hepatitis in pregnancy.

Hepatotoxic Agents

The story of the very careful and painstaking observations and experiments which uncovered the association between veno-occlusive disease and plants of the *Senecio* (ragwort) and *Crotalaria* (rattlebox) genera has been told before.² The practice of giving infusions and other medicinals prepared from plant sources to adults and children, either as medicine or as beverage, is still widespread in tropical countries, and there is always the possibility that some of these preparations may contain hepatotoxic factors. Hepatotoxic substances have been isolated from naturally occurring fungi and moulds. The best known of these is amanita toxin, from the mushroom, and *Amanita*

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phalloides causes cirrhosis in some of those who recover from the acute fatty infiltration and necrosis.³ Mushrooms are widely consumed as food in many parts of the tropics, and it would be as well to think of the possibility of toxic factors of plant origin in obscure cases of acute hepatic failure in tropical practice.

Cirrhosis

Hepatic cirrhosis is world-wide in distribution, but its exact aetiology still remains in doubt. However, the important agents or mechanisms which have been considered in the pathogenesis of cirrhosis are hepatitis of various kinds, malnutrition, alcohol, infestations, plant fungi, and chemical hepatotoxins. It has been suggested that more than one factor may be operating to produce the established picture, and this seems more than likely to be the case in the tropical setting. Practically all the factors listed above are relevant to the aetiology of cirrhosis in the tropics. Protein malnutrition is still widespread in many tropical areas, and its role in the production of the kwashiorkor syndrome in children and of fatty liver in adults is now well accepted. Edozien⁴ showed that the mean plasma albumin among apparently healthy Nigerians is 3.35 g./100 ml. (49.5% of total plasma proteins) as against 4.05 g./100 ml. (58.5% of total plasma proteins) for Europeans resident in Nigeria. Similarly, Leonard and Shaper⁵ found the average plasma albumin among East Africans in Kampala to be 3.15 g./100 ml. The widespread consumption of locally brewed beer and of locally distilled gin from palm wine and other sources in certain parts of tropical Africa suggests that alcohol might be a more important factor in the production of cirrhosis in such areas than has been recognized in the past. The same consideration applies to the role of parasites in the pathogenesis of liver cirrhosis in the tropics. Many of these parasites migrate through the liver at some stage in their development in the human body, and they may cause serious damage to the structure and function of the organ directly or indirectly. Malaria has been incriminated in the aetiology of the so-called tropical hepatosplenomegaly syndrome. The role of the bilharzia fluke in the production of liver fibrosis in countries such as the United Arab Republic is well known. Gross liver fibrosis of the type so common in the countries bordering the Nile valley is very uncommon in parts of West Africa, where both *Schistosoma haematobium* and *S. mansoni* infections are common, and schistosomiasis is not an important cause of chronic liver disease in these areas. Finally, liver cirrhosis is seen in many countries in the tropics closely associated with primary liver-cell carcinoma.

Primary Liver-cell Carcinoma

Hepatic failure may arise from widespread malignant disease in the liver. In Nigeria primary liver carcinoma is the third commonest malignant disease in adults over the age of 15 years seen at the University College Hospital, Ibadan,⁶ the first two being lymphosarcoma and carcinoma of the cervix. A patient with primary liver cell carcinoma usually presents with abdominal swelling, a large nodular liver, jaundice, or ascites, which may be bloodstained. These patients usually progress downhill rapidly and are often dead within four months of the onset of symptoms. In some cases, however, the course of events may be so rapid that the clinical picture and the course is not unlike that of an acute or subacute hepatitis, and the patient may die in acute hepatocellular failure resulting from almost total replacement of liver cells by malignant tissue. In tropical Africa most of these cases are seen in young adults between the ages of 25 and 45 years, and below the age of 45 years males predominate over females in a ratio of approximately 6:1, while above that age the figure drops to about 2:1.⁷

Differential Diagnosis of Hepatic Failure

Acute Hepatic Failure

The diagnosis of acute hepatic failure rests mainly on the history and the physical signs, and a confident diagnosis can usually be made in spite of the limited diagnostic facilities which are usually associated with tropical medical practice. There are basically three steps in the clinical diagnosis of acute hepatic failure: (1) to differentiate the coma of acute hepatic failure from coma arising from other causes; (2) to decide whether the underlying liver disease is essentially an acute or chronic process; (3) to determine, as far as possible, what factors may be responsible for, or be associated with, the onset of coma.

There is usually no difficulty in differentiating hepatic coma from coma due to such causes as meningitis, diabetes, or epilepsy. The possibility of hepatic coma should be considered in any patient who shows or has previously shown symptoms or signs of hepatic disease. Jaundice in hepatic coma is usually present and often deep and the patient may be febrile. Ascites may also be present if the illness has lasted longer than two to three weeks. In the jaundiced patient mental disturbances provide the earliest warning of a grave turn of events towards hepatic coma. Suggestive signs are personality changes, amnesia, confusion, and hallucinations. Other neurological signs are usually present, but they fluctuate; they often persist for days. The most characteristic of these is the "flapping tremor," but there may also be exaggerated deep reflexes and a positive Babinski's reflex. Though once considered to be a diagnostic sign, flapping tremor occurs in other conditions such as uraemia, heart failure, respiratory failure, and idiopathic steatorrhoea. Wernicke's encephalopathy is an acute vitamin B deficiency especially apt to occur with profound malnutrition and with alcoholism. In this condition strabismus and paralysis of oculomotor nerves with disorientation due to hyperaemia and haemorrhages in the midbrain are prominent. Other syndromes associated with alcoholism may be confused at times with acute hepatic failure, but the characteristic fluctuation of the clinical course of patients in hepatic coma is helpful in distinguishing this syndrome from primary toxic psychosis.⁸⁻¹⁰

Both the history and the clinical findings should help to distinguish acute conditions from chronic liver diseases such as cirrhosis, in which the onset of coma tends to be more insidious and the duration of associated clinical features such as ascites, jaundice, and endocrine or circulatory changes more prolonged.

Factors which may Precipitate Acute Hepatic Failure

It sometimes happens that patients admitted to hospital with liver disease in a state of consciousness subsequently develop hepatic coma. Any one of a number of events which are clearly avoidable may have been responsible. Such patients may have been given sedatives such as chlorpromazine, amytal sodium, or even morphia because of restlessness, acute maniacal excitement, or insomnia; the hospital diet may have contained more protein than the patient was accustomed to having, and this may have pushed him into coma; the patient's ascites may have pushed him into coma; the patient's ascites may have been tapped and a large quantity of fluid containing essential proteins and minerals may have been drained off rapidly. Brisk diuresis with diuretics such as chlorothiazide may induce hepatic failure in susceptible patients, possibly as a result of the iatrogenic hypokalaemia. Indeed, potassium depletion alone can elevate the blood ammonia level and intensify symptoms.

However, perhaps the most important factor which may precipitate acute hepatic failure in patients with chronic liver disease is gastrointestinal haemorrhage from gastric or oesophageal varices. This is a medical emergency requiring prompt

and skilled management. Other possible factors are acute infections such as pneumonia, acute alcoholism, and minor operations.

Chronic Hepatic Failure

Extensive damage to the liver may occur—for example, in cirrhosis—without any indication of such damage from either the history, the physical signs, or even the conventional liver function tests. The first evidence of chronic liver disease may be the detection of a shrunken, finely nodular liver as an incidental finding at laparotomy or even in the post-mortem room. More often, however, the clinical picture of chronic hepatic failure takes the form of some or all of the clinical features described above as indicating acute hepatic failure, with a more insidious onset and a slowly progressive course until death finally occurs. When jaundice is present, this may indicate failure of the liver cells to conjugate bilirubin with glucuronic acid, intrahepatic or extrahepatic bile duct obstruction, or increased destruction of erythrocytes. In any one patient the jaundice may be due to a combination of these factors, and examples of this are seen from time to time in patients with sickle cell disease in whom the basic abnormality is increased destruction of erythrocytes, but who in addition may develop obstruction from gallstones or cirrhosis with chronic liver failure from vascular obstruction brought about by impacted masses of sickled cells in the portal tracts or by Kupffer cells swollen with phagocytosed cells.¹¹ The picture of ascites as seen in tropical Africa, including the differential diagnosis of ascites and its relationship to chronic liver disease, has been fully dealt with in an earlier article in this series.¹² A number of endocrine changes are seen in these patients. Gynaecomastia is common in the tropics, both in adolescence as well as in middle-aged men, but this may be related to the widespread malnutrition which also exists in many tropical areas, and the precise relationship of this condition to chronic liver disease has not yet been established. Other changes which may be observed are palmar erythema, changes in the distribution of body hair, loss of libido, and infertility. Arterial spiders are very difficult to recognize in the African skin.

Management of Hepatic Failure

The management of a patient in acute hepatic failure in a well-equipped hospital in the tropics should follow the standard textbook lines. The facilities which are required, apart from skilled nursing care, include those for blood transfusion, medical staff who are experienced in the use and management of the Sengstaken oesophageal compression tube, laboratory facilities for the correction of electrolytic imbalance, the appropriate drugs for the treatment of infection, and surgical facilities for the definitive treatment of gastrointestinal bleeding. There are at least a few centres in most tropical countries in which the existence of such facilities can be taken for granted. Quite often, however, the doctor in the tropics is working single-handed or in an isolated station, and the lines of communication between the well-equipped hospital at the centre and the smaller peripheral unit where the patient may be lying are often poor and unreliable. The avoidance of factors which may precipitate coma and the early detection of warning signs of an impending coma are the two most important steps in dealing with the problems of hepatic failure anywhere: but in the context of the economics of medical care in the tropics it is relevant that these steps are cheaper, better, and more practical. Protein-rich diets should be avoided in patients with severe liver damage, and the appearance of even slight signs of impending coma is an indication for immediate reduction or even temporary cessation of protein intake. Low-protein diets for these patients should consist principally of carbohydrate, and should contain about 20 g. of protein daily.

Treatment of Established Acute Hepatic Failure

Treatment of Precipitant Factors.—The most serious and the most urgent of these is bleeding from oesophageal and gastric varices in a patient with cirrhosis of the liver and portal hypertension. The general measures needed are those that are usually adopted for haemorrhage—namely, regular observations on the pulse and blood pressure and estimation of the haemoglobin and haematocrit. If the bleeding has been severe and the patient is clinically shocked, the pulse rapid, and the blood pressure low, or if the haemoglobin is less than 8 g./100 ml., blood transfusion, if available, should be given preferably with fresh blood. Bleeding from oesophageal or gastric varices is likely to be a continuous ooze over many hours or even days, and when such patients arrive late in hospital they may be found to be already in a state of high output failure. Circulatory overload by transfusion should therefore be avoided in such cases by giving packed red cells very slowly. If blood is not available, or where it is impracticable to do so, pitressin should be given promptly. Kehne and his colleagues¹³ have shown that pitressin is effective in controlling haemorrhage from oesophageal varices by lowering portal pressure, and this has since been confirmed by other workers.¹⁴ The dose of pitressin is 20 units diluted in 100 ml. of 5% dextrose. It should be given intravenously over 10 minutes, and it is capable of lowering portal pressure for about one hour. This allows time for a clot to form over the bleeding point, and the haemorrhage from the varices usually stops.

Vitamin K should also be given, but little can be expected from it in true hepatic insufficiency. What more can be done if haemorrhage becomes persistent depends upon the facilities available; oesophageal compression, using the Sengstaken tube or surgical ligation of the varices, should be undertaken. All the surgical methods in use for the definitive treatment of gastrointestinal haemorrhage in these cases involve the diversion of portal venous blood from the danger area at the lower end of the oesophagus, and they are beyond the scope of the present article.

Elimination of Intestinal Flora.—Non-absorbable antibacterial agents when given by mouth inhibit the intestinal flora. Neomycin is given orally or through an intragastric tube, the adult dose being 2 g. six-hourly for about 5–10 days. Neomycin is an expensive drug, and it may not be readily available in many hospitals in the tropics. As a substitute, the intravenous infusion of a broad-spectrum antibiotic such as tetracycline 1 g. every six hours for about a week is quite useful. Although tetracycline is less effective in controlling the intestinal flora it takes care of systemic infection at the same time, as this is also an important factor in the production of hepatic coma.

Other General Measures.—These are designed to improve hepatocellular function, and to maintain a caloric, fluid, and electrolyte balance. A low-protein, high-carbohydrate diet is a necessity in impending hepatic coma. When the patient can swallow, glucose drinks, sweet fruit juice, rice, or even cereal should be given. In established coma, however, no protein should be allowed, and fluids and nutrients, including sugars (glucose, sucrose, laevulose) and water-soluble vitamins (thiamine, pyridoxine, ascorbic acid) should be given by gastric intubation. Additional liquid and caloric requirements can be met by slow intravenous administration of 2–3 litres 20%–40% dextrose solution a day depending on the requirements. This should be given through a caval drip, and the aim is to give at least 1,600 calories per day.

The need for adequate nursing care increases as coma deepens. In the precoma phase, retention of faeces (and accompanying toxins) should be avoided by the use of purgatives. Later enemas can be given. Retention of urine should be forestalled by the insertion of an indwelling catheter. The respiration should be watched carefully. Bronchial secretions

may impede ventilation and they may need to be aspirated. Oxygen administration is sometimes very helpful.

Electrolyte imbalance should be corrected. Low serum potassium levels should be corrected by oral administration of potassium (or fruit juices), while hyperkalaemia, on the other hand, suggests the need to increase the supply of glucose. Thiamine should always be given with abundant parenteral administration of sugar.

Corticosteroid Therapy.—In the absence of some specific therapy for the varieties of parenchymal liver disease which lead to hepatic failure, treatment with corticosteroids has been tried in almost all types of cases of hepatic failure. Corticosteroids are indicated in patients in coma resulting from acute hepatitis, particularly the fulminant variety. This is best given as hydrocortisone 100 mg. six-hourly in the intravenous fluid drip in adult patients in coma until they have regained consciousness; thereafter the dose is decreased progressively. When the patient is still conscious or in prehepatic coma oral prednisone 20 mg. daily in divided doses may be administered. In hepatic failure resulting from chronic liver disease many authorities agree that corticosteroids have not proved successful.^{3 8 10}

Prognosis

The prognosis in hepatic failure depends on the underlying disease; but it depends more on the state of liver function, and on whether there were any precipitating factors, than on the depth or the duration of the state of coma. The immediate prognosis in any one case must be guarded, for coma is essentially reversible, and the apparently moribund patients may suddenly rally round 12 hours later. In general, the earlier treatment is started the better the outcome. Coma following a haemorrhage usually carries a poor prognosis. Hepatic failure tends to be more severe in late pregnancy and at the puerperium. In cirrhosis the onset of coma in association with jaundice or other evidence of progressive deterioration of liver function carries a bad prognosis. In general in the tropics treatment is likely to be unavailing in the majority of patients with

established hepatic coma, and this underlines the need for strong prophylactic measures against the three commonest causative factors of hepatic failure in patients with hepatic disease—namely, haemorrhage, electrolyte imbalance, and infection.

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TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Urinary Antiseptics

Before the advent of sulphonamides several "antibacterial agents" were being given systemically to man for their effect (or alleged effect) in suppressing bacterial growth in the urine. Some—like methylene blue, which was the active ingredient of a celebrated commercial pill—produced an impressive colour change in the urine but little more, and have passed into history. Of the dyes, only phenazopyridine (Pyridium) remains, and even that is described principally as a urinary "analgesic." Hexamine and mandelic acid still have a limited place in therapy, and several new compounds which have come into widespread use have been labelled "urinary antiseptics" because they are active against the common urinary pathogenic bacteria and are excreted in the urine in high concentration, but they have little systemic antibacterial effect. The best known are nitrofurantoin and nalidixic acid.

Liberation of Formalin

Hexamine (hexamethylenetetramine, methenamine U.S.N.F.) is the most active of the compounds that were available in the pre-sulphonamide era. Its activity is due to the liberation of

formalin, which is inhibitory to all bacteria, but this occurs only in acid urine, and for any antibacterial effect to be obtained the pH of the urine must be reduced to 5.5 or less. Formalin will be liberated in the stomach unless the drug is given in enteric-coated tablets. Some patients on the drug complain of frequent and burning micturition, and prolonged administration or high dosage may lead to albuminuria, haematuria, and bladder changes.

Another compound which may be mentioned here since its action has been said to be due to the liberation of formalin is noxythiolin (Noxyflex). It is used only as a local application, but because of its wide antibacterial spectrum it may be useful for irrigating the bladder in otherwise intractable infections. Severe burning sensations may also occur with this compound, and in the commercial preparation for bladder irrigation a local anaesthetic is incorporated.

Urinary Acidification

Commercial preparations are still available in which hexamine is incorporated with acid sodium phosphate, but this commonly fails to produce the constant reduction in urinary pH which is required. Acidity of the urine is in itself inimical to the growth of many organisms, and some organic acids exert an inhibitory effect which is greater than can be accounted for simply by their effect on urinary pH. The success of the