Chapter 14

Liver Disease in India

By V. RAMALINGASWAMI, M.D., D.Sc. *and* N. C. NAYAK, M.D.

"To my mind, the supreme challenge of liver disease lies in the problem of cirrhosis. For forty years, I have studied its manifestations as a fully developed entity, followed its course from its origin to completion in human and experimental animals and sought, alas, in vain for its cause."

Sir Roy Cameron in *Harben Lectures* on "The Challenge of Liver Disease" (1963)

AN AURA OF MALNUTRITION surrounds even the very mention of the topic, liver disease in India. Visions of tropical infestations and infections are generated. Hepatotoxic substances derived from exotic tropical vegetation loom large in one's mind. But, unfortunately, to none of these can a definitive role be attributed in the genesis of human liver disease in India in the present state of our knowledge. In this chapter, we present at first some recent work on two enigmatic entities—idiopathic portal hypertension and Indian childhood cirrhosis—which have a special predilection to occur in India, especially the latter. Then follows a commentary on cirrhosis among adults and its relationship to malnutrition, viral hepatitis and hepatotoxins as viewed from local experiences.

IDIOPATHIC PORTAL HYPERTENSION

Portal hypertension of unexplained etiology had been described occasionally from several parts of the world. It was first clearly separated as a distinct disease entity in India in 1962 in the course of a study of the pattern of cirrhosis of the liver as seen at the hospital of the All-India Institute of Medical Sciences in Delhi.[27] It was characterized by an insidious onset and protracted course, splenomegaly and repeated, well tolerated attacks of hematemesis, relatively well preserved liver function and no cirrhosis or extrahepatic portal vein obstruction. A large series of similar cases was described subsequently from Calcutta under the titles "Non-cirrhotic portal fibrosis"[5,6] and "Idiopathic portal hypertension."[9] Such cases must have been included in earlier reports from various parts of India under the titles "Tropical Splenomegaly" or "Bengal Splenomegaly."[4] We believe that the condition is widespread throughout India. Hospital experience in Delhi and Calcutta indicates that nearly a third of all cases of portal hypertension belong to this category.[9,36] The patients are generally adults between 20 and 50 years of age; males are more often affected than females. Malnutrition and alcoholism are not significant in the history.

From the Department of Pathology, All-India Institute of Medical Sciences, New Delhi, India.

The chief presenting features are long-standing splenomegaly and repeated attacks of hematemesis. Melena is quite infrequent. Jaundice, ascites and signs of endocrine dysfunction are rare. Liver function is not greatly disturbed, the only consistent feature being increased BSP retention which generally lies between normal values and those characteristically seen in cirrhosis. Plasma volume is increased.[9] The hemodynamic pattern is variable but taking the group as a whole, there are interesting differences between its pattern and those in cirrhosis and in extrahepatic portal vein obstruction. The splenic pulp pressure is greatly elevated; the wedged hepatic vein pressure may be normal or elevated, although not to the same extent as in cirrhosis. The estimated hepatic blood flow is either normal or elevated and many cases show a gradient between the splenic and wedged hepatic vein pressure.[9,36]

Esophageal varices are readily demonstrable on barium swallow. Splenoportography shows a distinctive pattern. The extrahepatic portion is patent, very dilated and tortuous with prominent collaterals. Whenever adequate radiographic visualization of intrahepatic branches is achieved, they appear narrow with sudden tapering or truncation, giving a cut off appearance.[9]

The pathologic features have been described in detail recently.[6,9,21] The livers vary considerably in size and usually show some shrinkage of the left lobe and enlargement of the right. The surface may be smooth or wrinkled or uneven with fine granularity or even gross nodularity (Fig. 1A). Nodularity is particularly prominent over the inferior surface of the liver so that at surgery a mistaken diagnosis of cirrhosis may be made. The capsule is slightly thickened and shows lacy white streaks. On cut section, variable degrees of scarring, irregularly distributed but prominent around large portal tracts, may be seen. Small regenerating nodules may be present in a few areas but there is no cirrhosis.

Microscopically a mild to moderate degree of fibrosis involves portal tracts; the fibrous trabeculae may extend for a variable distance into or around the lobule (Fig. 1B). The lobular architecture is not disturbed. Morphologic changes of the greatest interest are seen in the intrahepatic branches of the portal vein.[6,9,21] The large and medium sized branches show a conspicuous thickening of their walls with considerable narrowing of their lumina (Fig. 1C). The thickening is intimal in location consisting of collagen fibers and fibroblasts along with some smooth muscle cells (Fig. 1D). It is patchy and segmental in distribution. The thickening may be so prominent that portal vein branches may have thicker walls than the corresponding hepatic artery branches (Fig. 1E). The large and medium sized branches of the portal vein may show recanalized thrombi with scarring in the surrounding area. These changes in the larger intrahepatic branches are conspicuous and readily observed in adequately sampled autopsy material. They are usually demonstrable in deep wedge biopsies of the liver removed at surgery. Superficial wedges may fail to show this lesion altogether and only show a subcapsular nodular distortion to be mistaken for cirrhosis by the uninitiated. The smaller branches of the portal vein are quite inconspicuous and often replaced by multiple tiny vascular channels embedded in scar tissue (Fig. 1B). This is all that one usually sees in needle biopsies.

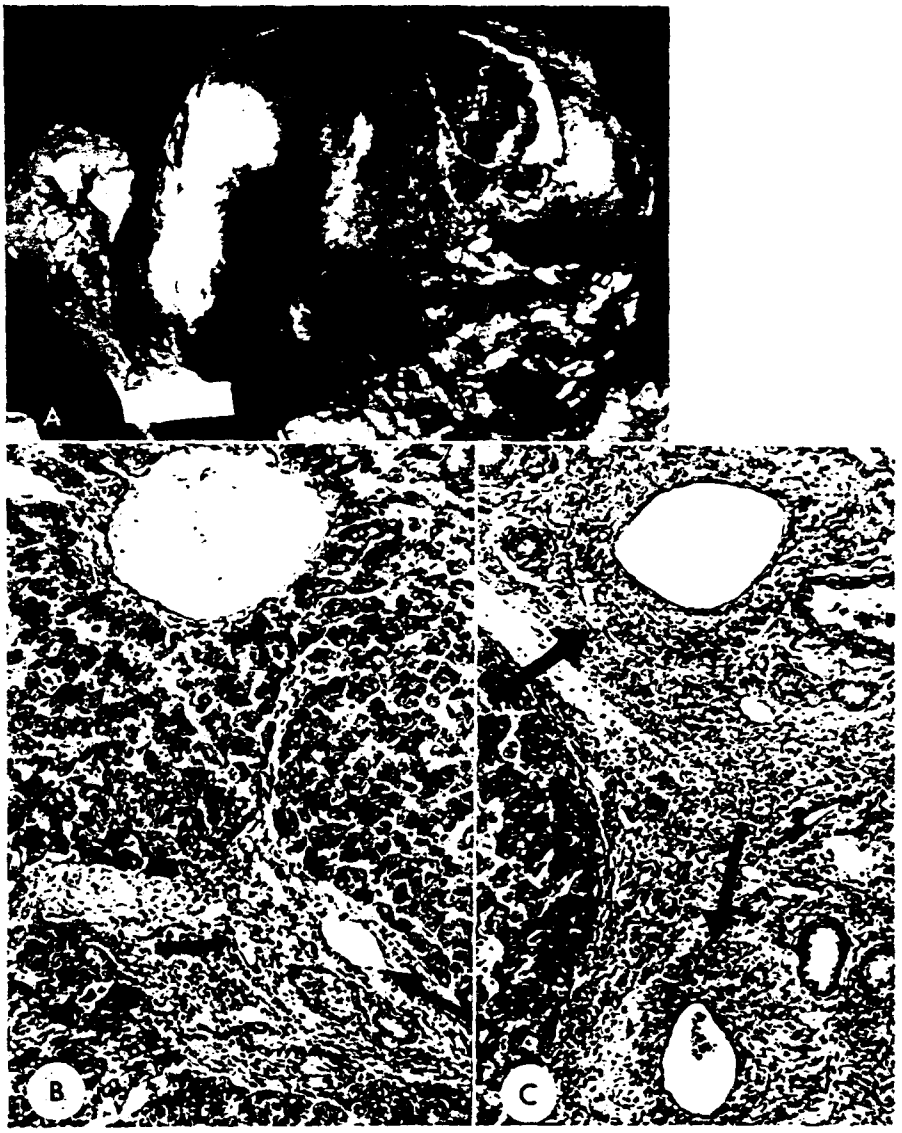

FIG. 1—Idiopathic portal hypertension. (A) External view of liver showing irregular humped surface with opaque white streaking of the capsule. (B) The prominent portal tract shows fibrosis, intralobular extension of septa and round cell infiltration. The portal vein branch is replaced by many inconspicuous channels (arrows). (Masson trichrome ×110.) (C) Medium-sized portal vein branches show severe luminal narrowing by intimal proliferation (arrows). (Masson trichrome ×110.) (D) A large intrahepatic branch of the portal vein. The conspicuous intimal thickening comprises fibroblasts, collagen fibers and a few smooth muscle cells. (Masson trichrome ×110.) (E) Pronounced intimal thickening in large portal vein branches in which the walls are thicker than in the accompanying artery. A strip of original muscle is seen at the periphery (arrow). (Masson trichrome ×160.)

ng irregu-
prominent
nfiltration.
(arrows).
w severe
e ×110.)
l thicken-
(Masson
branches
f original

The thickening and partial luminal obliteration of the intrahepatic branches of the portal vein are characteristic of the syndrome and so, at the risk of adding yet another name, we designated this condition "obliterative portal venopathy of the liver." [21] Mikkelsen and his colleagues described almost identical changes in the portal venous system in some cases of idiopathic portal hypertension in the U.S.A.[19] They designated the lesion as a "hepatoportal sclerosis." Such changes have not been observed by us in extrahepatic portal vein obstruction or in cirrhosis. The pattern of involvement of proximal and distal intrahepatic branches of the portal vein explains the observed splenoportographic pattern and the hemodynamic gradient. Have these vascular changes preceded or followed portal hypertension? Although we cannot answer this question categorically, they may be primary events and could account for the sustained portal hypertension. Portal fibrosis alone cannot be responsible for the hypertension since there is no direct relation between the degree of fibrosis and hemodynamic alteration.[5,21] Significant hepatic fibrosis may be present without portal hypertension. It is equally improbable that increased splenic effluent plays a significant part.

The pathogenesis of the obliterative lesion in the portal vein branches is a matter of conjecture at the present time. Schistosomiasis can be excluded as a factor in the Indian cases. Portal pyelophlebitis early in life has been suggested but without proof. We have been impressed by the recanalized thrombi in the intrahepatic portal vein branches in several of our cases.[21] In one patient, portal hypertension appeared to have followed repeated episodes of systemic thromboembolism and in another there was an almost complete obliteration of the superior mesenteric vein and its tributaries by organized thrombi. The hypothesis that the patchy eccenteric thickening of intrahepatic portal vein branches may arise from incorporation of thrombi or emboli deserves serious consideration.

INDIAN CHILDHOOD CIRRHOSIS

Indian childhood cirrhosis is an obscure malady, endemic to India, affecting an unknown number of infants and children and characterized by severe hepatic dysfunction and high mortality in the genesis of which a local pathogenic factor, so far elusive, must be involved. Since its first recognition in 1887,[31] it was described under various names such as "infantile cirrhosis," "infantile biliary cirrhosis," "intercellular hepatic fibrosis" and "subacute toxic cirrhosis." However, the term "Indian childhood cirrhosis," introduced by S. T. Achar whose sad demise earlier this year has deprived us of one of the keenest students of this disease, is now generally accepted.[1] A review of the historical aspects together with a critical account of our knowledge up to 1955 will be found in the Report of the Liver Diseases Sub-Committee of the Indian Council of Medical Research.[16]

Children between 1 and 3 years of age are commonly affected; males are reported to be affected more frequently than females. A predilection for the disease to attack certain castes such as the Agarwals of Northern India and to involve siblings has been reported.[32] There is a tendency for the disease to run in families but estimates of familial incidence vary wdely, 7–50 per cent of

reported cases revealing a positive family history. The disease has no clear-cut relation to climate and geography. It is not associated with extreme poverty and malnutrition as kwashiorkor is. It occurs predominantly among the middle income groups but there is no quantitative information on the nutrient intake of the afflicted children on the basis of accurate dietary analyses. Almost any kind of statement can be found in the literature regarding the role of dietary factors, a favorite theme of speculators, which includes the incrimination of breast milk as a possible etiologic factor.

Clinical features. The clinical course is customarily divided into three stages, recognizing that one stage merges imperceptibly into another. The speed of progression from stage to stage varies; while in the majority it runs a subacute course, in a few it may take a fulminant course. *The early stage or stage of onset* has vague symptoms with disturbances of appetite and bowel movements and low grade fever. Jaundice is not evident in the majority of patients. The liver is palpable and feels firm with a sharp edge. The spleen may be palpable. In the *intermediate or well established stage*, mild icterus, hepatosplenomegaly, ascites, edema and superficial abdominal veins are obvious. The liver has a sharply defined margin with a characteristic "leafy" edge. In the *late stage*, jaundice is deepening with clay colored stools, highly colored urine and ascites. The liver shrinks but is still palpable and feels hard with a sharp "knife" edge. Death supervenes generally as a result of hepatocellular failure, occasionally from gastrointestinal bleeding or secondary infection. The younger the child, the more fulminant the course.

Pathologic findings. The liver shows a spectrum of pathologic alterations which are highly characteristic of this condition.[22,34] Even in the early stages of the disease, there is a profound and progressive injury to liver cells associated with ineffective regeneration resulting in what Smetana so aptly called the "exhausted parenchyma with its dead and dying cells." [34]

Since death usually occurs from hepatocellular failure with jaundice, the liver at autopsy is usually bile-stained, green in color, very firm and presents a smooth or granular or finely nodular surface. The edges are sharp and the capsule thick and opaque. On cutting, one may see either an exaggerated lobular pattern only or small nodules varying in size from 0.5–2.0 mm. in diameter. Large irregular nodules are not seen. The gallbladder and biliary passages are normal.

Microscopic studies of needle biopsies of the liver at various stages and of autopsy specimens reveal a unique pattern. Even in the early clinical stages, there is a vacuolar and granular dissociation of cytoplasmic contents of individual hepatocytes. The affected cells are swollen with formation of intracytoplasmic hyaline masses, morphologically and tinctorially indistinguishable from Mallory's alcoholic hyaline (Fig. 2A). Satellitosis by neutrophils and mononuclears occurs around necrobiotic cells as a scavenger reaction. Around the individual or groups of necrotic liver cells, the reticulin network condenses. The combination of new fiber formation and collapse of the pre-existing framework gives rise to a striking increase of intralobular connective tissue (Fig. 2B). The portal tracts at this time are prominent and show inflammatory cell infiltration. There is no ductular cell proliferation.

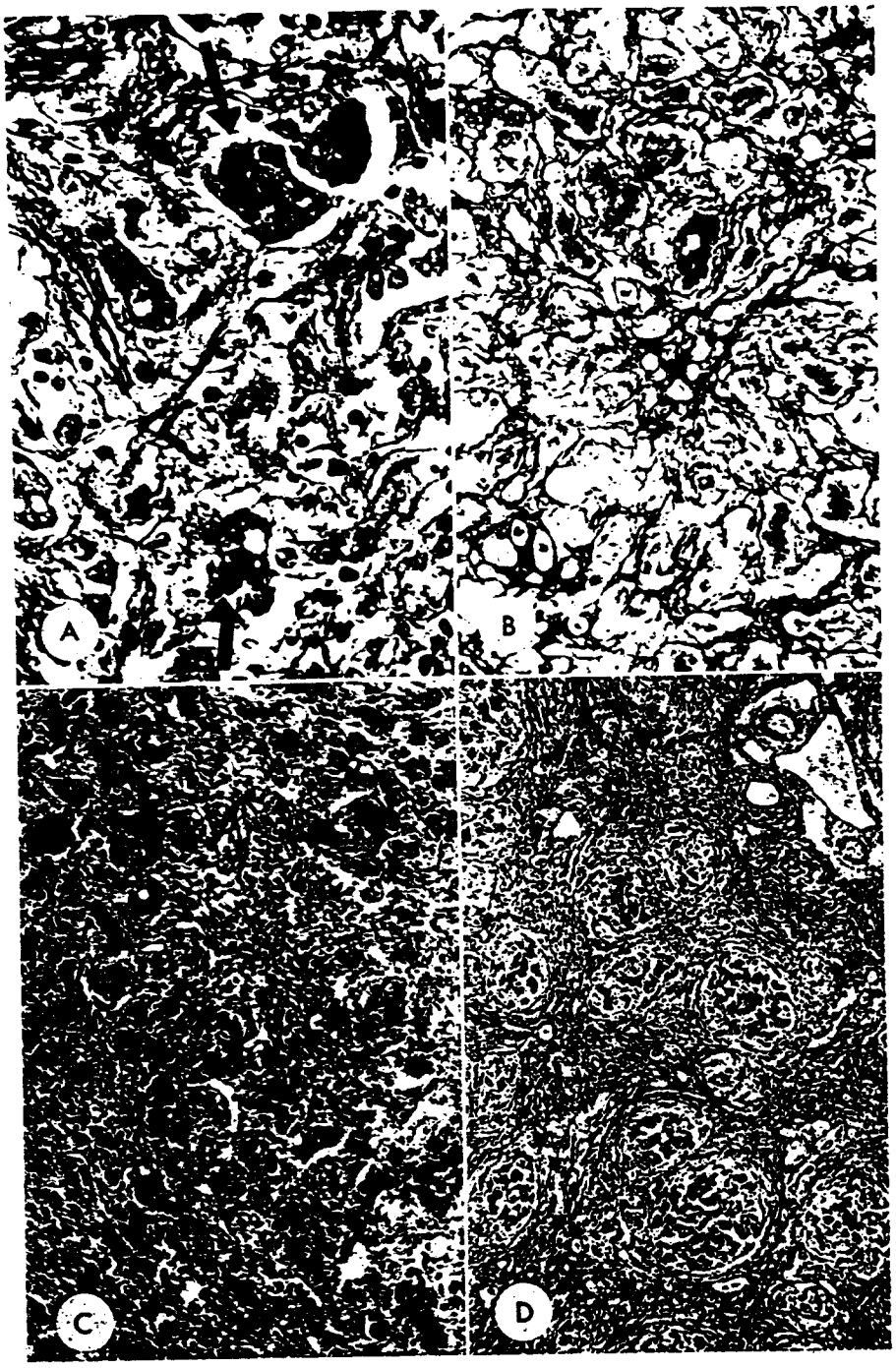

FIG. 2 A–D—*See legend with Fig. 2E, facing page.*

FIG. 2—Indian childhood cirrhosis. (A) Severe parenchymal damage and extensive interstitial fibrosis in the liver. Many of the hepatocytes contain characteristic Mallory's hyaline (arrows). (Chromotrope 2R aniline blue ×360.) (B) Intralobular reticulin condensation and new fiber formation in the liver, producing characteristic creeping or interstitial fibrosis reminiscent of experimental ethionine liver injury. (Gomori's silver impregnation ×100.) (C) Diffuse and extensive parenchymal damage, inflammation and fibrosis. The hepatocytes are not clearly delineated and many contain intracytoplasmic hyaline (Hematoxylin & Eosin ×110). (D) Liver in late stage showing extensive fibrosis, small nodules and ductular proliferation (Hematoxylin & Eosin ×30). (E) Marked intimal proliferation and luminal narrowing in a sublobular hepatic vein and its tributary (Chromotrope 2R aniline blue ×30).

In the established clinical stage of the disease, the injury to hepatocytes progresses relentlessly. The hyaline is usually abundant (Fig. 2), being seen in 80–90 per cent of all hepatocytes. The liver cells are disrupted and their contents merge imperceptibly with those of neighboring cells or with surrounding connective tissue. Some liver cells can only be recognized as a mass of hyaline and a pyknotic nucleus. The fibrosis becomes pronounced, creeping around single or small groups of liver cells. The whole picture is reminiscent of "florid cirrhosis" of alcoholic injury (Fig. 2C).

In the wake of such overpowering cell damage, liver cell regeneration is inadequate and nodular remodeling proceeds tardily. Foci of nodular regeneration are, however, seen here and there. The nodules are small, separated by large tracts of collapsed and proliferating stromal elements. In older children and in those in whom the course of the disease is prolonged, nodular regeneration is more prominent although, even here, the nodules are still small (Fig. 2D). In younger children, syncitial masses of regenerated liver cells are seen in the midst of reparative stromal reaction. Bile stasis and ductular proliferation are prominent at this stage.

Autopsy material from advanced stages of the disease frequently shows partial occlusion of the lumina of some of the efferent vein branches due to intimal proliferation (Fig. 2E). The parenchyma around these vessels is necrotic. This vascular lesion, however, is unlike that in veno-occlusive disease; it is probably a secondary phenomenon and resembles that seen in alcoholic hepatitis.

Etiologic considerations. On the basis of an antecedent history of jaundice

and some similarities believed to exist in the histologic sequences in the liver between childhood cirrhosis and endemic hepatitis in children, it has been suggested that Indian childhood cirrhosis is a form of chronic progressive hepatitis following viral hepatitis and culminating in cirrhosis.[1] However, the clinical picture at the onset of the disease in a majority of the cases is unlike that of acute viral hepatitis. The occurrence of the disease almost exclusively in India also is hard to explain on this hypothesis. The histologic picture bears no resemblance to any of the phases of viral hepatitis. The failure of the liver cells to regenerate promptly and the abundance of alcoholic hyaline in the degenerating hepatocyte are, in our opinion, not features of viral hepatitis. The large-scale epidemic of infective hepatitis that swept Delhi in 1955–56 was not followed by any significant increased incidence of Indian childhood cirrhosis in the various hospitals of Delhi.[11]

The hyaline bodies, the progressive destruction of hepatic parenchyma and the "portal" type of cirrhosis that eventually develops are believed to be indicative of a nutritional etiology in the same manner that alcoholic cirrhosis has been considered to be a nutritional cirrhosis. We believe that Indian childhood cirrhosis has remarkable similarities with alcoholic cirrhosis, particularly with the florid variety and with the diffuse interstitial cirrhosis of Mexico and Latin America [24] but we do not subscribe to the view that this necessarily implies a nutritional etiology. The disease rarely affects children of the lowest income groups in whom malnutrition, especially protein malnutrition, is widely prevalent. Fatty change in the liver, so characteristic in protein malnutrition in young growing children, is rare in Indian childhood cirrhosis. Finally, considerable evidence has accumulated in recent years both in man and experimental animals to indicate that the liver damage associated with excessive intake of alcohol is probably, at least in part, the result of direct toxic action of alcohol on liver cells and not, as was believed until recently, caused by secondarily induced malnutrition.[29] If malnutrition is a determining factor, the disease should be present in other countries where malnutrition is prevalent. This is not so.

Inherited metabolic defects have been incriminated on the basis of familial history and occurrence of the disease in siblings. A defect in maltose metabolism has been proposed.[12] However, chromatographic study of urinary sugars in a large series of our patients and in matched controls failed to confirm this.[33] Changes in the ocular fundi, usually seen in metabolic diseases of the liver, are not found in this condition.[33] Ceruloplasmin levels are normal.[1] No definitive pedigrees have been reported to which Mendelian laws can be applied. No chromosomal abnormalities have been found.[10] Transmission through symptomless carriers of recessive genes with low and irregular penetrance has been suggested and it is believed that toxic or infective factors may act on a sublethal milieu of an inherited abnormality to unmask the disease.[32]

In our opinion, the pattern of liver injury is like that of a toxic liver injury. Its close resemblance to florid cirrhosis of alcoholic injury has already been emphasized (Fig. 2A–2C). Unlike alcoholic injury, however, fatty change is rare in Indian childhood cirrhosis at any stage of the disease, but this may be an expression of an overwhelming and profound injury. The failure of liver cells

to regenerate effectively is also probably caused by this overwhelming injury which affects it diffusely but which does not lead to a massive hepatic necrosis (acute yellow atrophy) as in viral hepatitis or experimental nutritional injury. The fibrosis is characteristically creeping or interstitial, encircling individual or small groups of liver cells and with a fiber stain, the whole picture resembles ethionine-induced diffuse hepatic fibrosis in the experimental animal[30] (Fig. 2B). Fatty liver produced by ethionine appears to be a toxic effect rather than a conditioned amino acid deficiency.[13]

The hyaline bodies are a hallmark of the disease and, in a country where alcoholic liver disease is uncommon and in this age group, are diagnostic of it. Detailed morphologic and histologic studies of these bodies show that they are indistinguishable from Mallory's alcoholic hyaline [23] (Fig. 2A). They stain with phloxin, basic fuchsin, chromotrope 2R at strongly acidic pH, luxol fast blue and acetone-Sudan black B. They exhibit strong pyroninophilia, only part of which is removed by digestion with RNAase, or with acids. Stains for basic proteins give positive reactions while they react negatively with PAS and for acid and alkaline phosphatases, ATPase and dehydrogenases. From their staining properties, these structures appear to be composed of tightly bound phospholipid-protein complexes. We have not yet studied them in detail under the electron microscope. It has been suggested that they are derived from damaged and distorted mitochondria [34] but one cannot be certain of this unless detailed ultrastructural studies of the evolution of these bodies are made from the earliest stage.

On the analogy of alcoholic hyaline believed to be of ergastoplasmic origin on the basis of electron microscopic studies,[8] there is an implication of a severe injury to cellular structures in childhood cirrhosis also, particularly to ribosomes. With the shift in the concept of alcoholic liver injury from nutritional to toxic, the concept that the Mallory body is a special and specific type of expression of nutritional injury is no longer tenable. The identity of hyaline material described in rats and mice in experimental dietary cirrhosis with the Mallory body has not been established.[3] Although we cannot be certain whether the hyaline bodies in childhood cirrhosis are an expression of a primary and distinctive injury to liver or are secondary phenomena, they appear at some stage or other in the course of the disease, generally in the intermediate or established stage and their appearance is a sign of grave prognosis.

We believe that the possibility of an as yet unknown hepatotoxic agent being involved in the etiology of Indian childhood cirrhosis merits serious study. As in human disease one often deals with a constellation of factors, the contributory role played by other factors such as malnutrition and heredity requires examination. It is doubtful if the etiologic tangle can be resolved fully by merely studying hospitalized patients in the terminal stage.

CIRRHOSIS OF THE LIVER IN ADULTS

There is a large volume of literature in India on cirrhosis in adults which is stated to be a common disease. It is true that large city hospitals, particularly teaching hospitals, attract many patients. But how common is it? Is it more or less common than in, say, England or the U.S.A.? It is hazardous to make any

comparisons with respect either to frequency among hospital admissions or to frequency among autopsies. It is impossible to relate hospital admissions in this country to the size of the population that the hospital serves. The proportion of deaths autopsied is, in general, low and it varies considerably from one part of the country to another.

With regard to the morphologic types of cirrhosis, the pattern described has varied over the years. Portal cirrhosis, hallowed by tradition, was the most frequent type reported in earlier years but since 1950, postnecrotic and post-hepatitic types have been reported with increasing frequency. This would seem to be a reflection, not of a true change in morphologic pattern but rather of the impact of new ideas of morphogenesis and new systems of classification. Cirrhosis in northern India is usually not accompanied by significant fatty change [27] while in the South, where protein malnutrition is more prevalent, over a third of the cirrhotic livers may contain excess of fat.[28] Three possible etiologic factors, protein malnutrition, hepatitis virus and hepatotoxins, are discussed.

Protein malnutrition. The relationship between protein deficiency, fatty liver and cirrhosis has been reviewed recently.[25] The liver changes of acute kwashiorkor are entirely reversible by protein supplementation. Long-continued protein deficiency rarely, if ever, leads to progressive fibrosis and cirrhosis. Monkeys maintained over prolonged periods on protein deficient diets, fail to develop cirrhosis even though their livers may be severely fatty.[26] Rats on a protein deficient diet do not develop cirrhosis on repeated administration of CC14, whereas control animals on adequate protein intakes with similar doses regularly do so.[7]

Hepatitis virus. It has been reported that a past history of jaundice suggestive of viral hepatitis can be elicited in 26–41 per cent of cases of cirrhosis.[2,3,20] In the absence of specific methods of isolation and demonstration of the virus and in view of the long time interval that may elapse between the onset of hepatitis and the discovery of cirrhosis, the precise role of this factor cannot be ascertained. Our experience in Delhi suggests that it is only in a minority of cases that a previous attack of viral hepatitis can be clearly incriminated.[12]

In 1955–56, an explosive outbreak of infectious hepatitis occurred in Delhi by accidental pollution of water supply with sewage. Approximately 30,000 persons suffered icteric disease over a short period of 6 weeks. The epidemic reached a peak in less than two weeks and declined equally rapidly. A follow-up study of a sample of the affected population and their family contacts, 304 and 1,070 persons respectively, did not reveal evidence of persistent liver damage to any significant extent.[11]

Aflatoxins. Clinical studies in recent years in India have drawn attention to the possible role of hepatotoxic agents as etiologic factors [15] but none have been identified. Two cases of veno-occlusive disease have been reported from Delhi [14] but this type of liver disease is distinctly uncommon in India.

A study of the peanut crop grown in the eastern districts of the Indian peninsula showed that nearly 3–5 per cent of samples of freshly harvested peanuts were contaminated with aflatoxin. The toxigenic strains of *Aspergillus flavus*

dmissions or to
l admissions in
rves. The pro-
siderably from

tern described
ı, was the most
rotic and post-
y. This would
tern but rather
of classification.
ignificant fatty
nore prevalent,
Three possible
patotoxins, are

ency, fatty liver
f acute kwashi-
-continued pro-
and cirrhosis.
nt diets, fail to
.[26] Rats on a
ministration of
th similar doses

aundice sugges-
of cirrhosis.[2,3,20]
ion of the virus
en the onset of
actor cannot be
n a minority of
riminated.[11]
curred in Delhi
ximately 30,000
. The epidemic
idly. A follow-
ly contacts, 304
stent liver dam-

wn attention to
none have been
reported from
ı India.
the Indian pen-
rvested peanuts
spergillus flavus

FIG. 3—Liver of a Rhesus monkey given 32 bi-weekly doses of Aflatoxin at 0.25 mg./Kg. body weight. There is striking ductular proliferation and fibrosis (Masson trichome ×110).

isolated from peanut kernels in this region produced only aflatoxin B, the more toxic of the aflatoxin family when grown on healthy ground nuts.[33] Under the climatic and storage conditions existing in India, there are opportunities for man and cattle to be exposed to significant levels of aflatoxin through food. Biologic studies of aflatoxins have shown that, in primates, the toxins produce severe hepatocellular injury accompanied by severe ductular cell proliferation and periductular fibrosis, giving the appearance of biliary cirrhosis.[15] The susceptibility of primates and rats to the toxin is reported to be enhanced in the presence of protein deficiency.[17] Our own studies on this toxin carried out with Dayal, Deo and Wogan and as yet unpublished, deal with over 60 Rhesus monkeys to whom high and low doses of pure toxin have been given for varying periods of time. They too reveal the profound effects. There are, however, great variations in the response of the monkey liver to the toxin making it imperative to use many animals in characterizing responses. Hepatocellular damage and ductular cell proliferation occurred (Fig. 3) but there was no cirrhosis; the differences between the protein deficient and control animals in their response to the toxin were not clear-cut. No tumors were produced up to 5 months of feeding the toxin. The whole problem of the effect of mycotoxins on malnourished populations in developing countries has opened the flood-gates of enquiry in which crucial experiments with penetrative vision are needed.

In the end, we are forced to conclude that cirrhosis of the liver among adult Indians is cryptogenic in the vast majority of patients.

REFERENCES

1. Achar, S. T., Raju, V. B. and Sriramachari, S.: Indian childhood cirrhosis. J. Pediat. *57*:744, 1960.

2. Anklesaria, X. J. and Koshy, T. S.: Cirrhosis of the liver in south India. Indian J. Med. Sci. *15*:866, 1961.

3. Banerjea, J. C. and Das Adhikary, C. R.: Observations on hepatic cirrhosis in the state of West Bengal. J. Ass. Physicians India *11*:769, 1963.

4. Basu, A. K. and Aikat, B. K.: Tropical Splenomegaly. London, Butterworths, 1963.

5. —, Boyer, J., Bhattacharya, R., Basu Mallik, K. C. and Sengupta, K. P.: Non-cirrhotic portal fibrosis with portal hypertension: A new syndrome. Part I. Clinical and functional studies and results of operations. Indian J. Med. Res. *55*:336, 1967.

6. Basu Mallik, K. C., Sengupta, K. P., Basu, A. K., Biswas, S. K., Pal, N. C. and Boyer, J.: Non-cirrhotic portal fibrosis with portal hypertension: A new syndrome. Part II. Histopathological studies. Indian J. Med. Res. *55*:451, 1967.

7. Bhuyan, U. N., Nayak, N. C., Deo, M. G. and Ramalingaswami, V.: Effect of dietary protein on carbon tetrachloride—induced hepatic fibrogenesis in albino rats. Lab. Invest. *14*:184, 1965.

8. Biava, C.: Mallory alcoholic hyaline: A heretofore unique lesion of hepatocellular ergastoplasm. Lab. Invest. *13*:301, 1964.

9. Boyer, J. L., Sen Gupta, K. P., Biswas, S. K., Pal, N. C., Basu Mallik, K. C., Iber, F. L. and Basu, A. K.: Idiopathic portal hypertension, comparison with the portal hypertension of cirrhosis and extrahepatic portal vein obstruction. Ann. Intern. Med. *66*:41, 1967.

10. Chaudhuri, A., Chaudhuri, K. C.: The karyotype in Sen's syndrome (infantile cirrhosis of the liver). Indian J. Pediat. *31*:309, 1964.

11. Chuttani, H. K., Sidhu, A. S., Gupta, D. N. and Ramalingaswami, V.: Follow-up study of cases from the Delhi epidemic of infectious hepatitis of 1955–56. Brit. Med. J. *2*:676, 1966.

12. Dhatt, P. S., Gupta, H. L. and Saini, A. S.: Disaccharide intolerance and Indian childhood cirrhosis: A possible aetiological factor. Indian J. Med. Res. *56*:39, 1968.

13. Farber, E., Schull, K. H., Villa-Trevino, S., Lombardi, B. and Thomas, M.: Biochemical pathology of acute hepatic adenosine triphosphate deficiency. Nature (London) *203*:134, 1964.

14. Gupta, P. S., Gupta, G. D. and Sharma, M. L.: Veno-occlusive disease of liver. Brit. Med. J. *1*:1184, 1963.

15. Kasliwal, R. M., Sharma, B. M. and Chaturvedi, G. C.: Aetiological factors of cirrhosis of the liver in adults in India. J. Indian Med. Ass. *44*:407, 1965.

16. Liver disease sub-Committee of the Indian Council of Medical Research. Report on infantile cirrhosis of the liver in India. Indian J. Med. Res. *43*:723, 1955.

17. Madhavan, T. V., Suryanarayana Rao, K. and Tulpule, P. G.: Effects of dietary protein level on susceptibility of monkeys to aflatoxin liver injury. Indian J. Med. Res. *53*: 984, 1965.

18. —, Tulpule, P. G. and Gopalan, C.: Aflatoxin induced hepatic fibrosis in Rhesus monkeys. Arch. Path. (Chicago) *79*:466, 1965.

19. Mikkelsen, W. P., Edmondson, H. A., Peters, R. L., Redeker, A. G. and Reynolds, T. B.: Extra and intrahepatic portal hypertension without cirrhosis (hepatoportal sclerosis). Ann. Surg. *162*:602, 1965.

20. Misra, S. S., Misra, R. N. and Jhingram, S. C.: Cirrhosis of the liver—incidence, etiology and natural history. J. Ass. Physicians India *11*:755, 1963.

21. Nayak, N. C. and Ramalingaswami, V.: Obliterative portal venopathy of the liver associated with so-called idiopathic portal hypertension or tropical splenomegaly. Arch. Path. (Chicago) *87*:359, 1969.

22. — and —: To be published.

23. —, Sagreiya, K. and Ramalingaswami, V.: The hyaline in Indian childhood cirrhosis. To be published.

24. Pérez-Tamayo, R.: Diffuse interstitial cirrhosis. Amer. J. Clin. Path. *29*:226, 1958.

25. Ramalingaswami, V.: Perspectives in protein malnutrition. Nature (London) *201*: 546, 1964.

26. —, Deo, M. G. and Sood, S. K.: Protein deficiency in the Rhesus monkey. *In* Progress in Meeting Protein Needs of Infants and Preschool Children. Proceedings of an International Conference. Publication No. 843. Washington, National Academy of Sciences, 1961.

27. —, Wig, K. L. and Sama, S. K.: Cir-

rhosis of the liver in Northern India—a clinicopathological study. Arch. Intern. Med. *110*:350, 1962.

28. Reddy, D. G. and Sriramachari, S.: Histological changes in cirrhosis of the liver. Indian J. Med. Sci. *10*:944, 1956.

29. Rubin, E. and Lieber, C. S.: Malnutrition and liver disease—an overemphasized relationship. Editorial. Amer. J. Med. *45*: 101, 1968.

30. — and Popper, H.: The evolution of human cirrhosis deduced from observations in experimental animals. Medicine (Balt.) *46*: 163, 1967.

31. Sen, B. C.: Infantile cirrhosis. Indian M. Gaz. *22*:338, 1887.

32. Singh, A., Jolly, S. S. and Kumar, L. R.: Indian childhood cirrhosis. Lancet *I*:587, 1961.

33. —, Meherban, Visalakshi, S., Nayak, N. C., Deo, M. G. and Ghai, O. P.: Urinary sugar chromatography in Indian childhood cirrhosis. Indian J. Med. Res. In press.

34. Smetana, H. F., Hadley, G. G. and Sirsat, S. M.: Infantile cirrhosis. Pediatrics *28*:107, 1961.

35. Suryanarayana Rao, K., Madhavan, T. V. and Tulpule, P. G.: Incidence of toxigenic strains of Aspergillus flavus affecting ground nut crop in certain coastal districts of India. Indian J. Med. Res. *53*:1196, 1965.

36. Wig, K. L., Ramalingaswami, V., Guleria, J. S., Tandon, B. N. and Sama, S. K.: Clinical features of cirrhosis of liver and non-cirrhotic portal hypertension in adults. *In* Wahi, P. N. (Ed.): Liver-cirrhosis—Proceedings of Symposium. Indian Acad. Med. Sci. 1966.