Commentary

Will the real Indian childhood cirrhosis please stand up?[1]

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Indian childhood cirrhosis (ICC), so named to reflect its ethnic origins, was found in 4 Caucasian siblings in the United States who died during the period 1958–1962. Since these children had not been exposed to copper (either endogenous or exogenous) and had no Indian ancestry, the disease at that time was classified as "cryptogenic cirrhosis." Many years later, pathologic review suggested that the true diagnosis should have been ICC. Hence, Indian childhood cirrhosis is probably a misnomer. Because of the large influx of immigrants from the Indian subcontinent, Western pathologists should become more familiar with the true histologic and gross picture of ICC. The authors differentiate cryptogenic cirrhosis and cirrhosis of Indian childhood from ICC (which is not a true cirrhosis) with illustrative gross specimens and photomicrographs. Historical background and a comprehensive review of the literature are offered.

Index terms: Liver cirrhosis, in children • Liver diseases

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Until recently, "Indian childhood cirrhosis (ICC)" was of only academic interest to the Western World. Two events have changed this situation: (1) the massive migration of Indians (citizens of the Indian subcontinent) to various developed countries of the world, especially the United Kingdom, the United States, and Canada, and (2) the recent report of ICC in 4 white siblings (who died between 1958 and 1962) in New Jersey, by Lefkowitch et al[1] in 1982. Four generations of ancestors of these children had

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never left the country. The children had no Indian ancestry and had never been exposed to copper (exogenous or endogenous), which is currently considered a risk factor for ICC. The 4 white siblings from New Jersey, of whom 3 were autopsied, had been coded as cases of cryptogenic cirrhosis for more than 20 years, illustrating that what the mind does not know, the eyes do not see. These cases provide additional evidence for the hypothesis of one of us (A.G.B.), who for years has contended that ICC is a misnomer.[2]

Historical perspective

The term *Indian childhood cirrhosis* was first suggested by Jellife et al[3] in 1957 for two reasons: (1) Working in Jamaica on veno-occlusive disease (VOD) in children drinking "Bush tea," they had the opportunity to see cases of "infantile biliary cirrhosis" (IBC), as ICC was then called. Although they found certain similarities between the IBC and VOD of Jamaicans, they were convinced that IBC was a different entity. (2) In 1956, the Pan-American Congress of Gastroenterology in Havana[4] defined the clinicopathologic criteria for cirrhosis. Since IBC did not fit this definition, with characteristic British ingenuity, the Congress[3] compromised on the term "Indian childhood cirrhosis." The term caught the fancy of Achar et al[5] in his classic paper in 1960 and became generally accepted. However, in an equally classic paper, Chaudhury et al[6] in 1960 advocated the name "Sen's syndrome," since they believed the disease to be a multifactorial syndrome, first clinically described by Sen in 1887[7] in Calcutta as "infantile cirrhosis" peculiar to children in India. Thus 1887 marked the first recognition of ICC in modern times, although some Sanskrit medical scholars of India believe that the condition was known to Sushruta in 1000 BC.[8–10] He defined this condition as "Mukhamandika graha" in which the child has a yellow complexion, edema over the face and limbs, a network of veins on the abdomen, a voracious appetite, a urinelike smell to the body, fever, and dyspepsia. A year after Sen's clinical description, Gibbons[11] in 1888 performed the first autopsy and, impressed by the proliferation of biliary ducts in the liver and scarring (+ cholestasis), he called the disease, "infantile biliary cirrhosis." The matter rested until 1933 when Ramachandra Rao[12] wrote his dissertation on the subject in London calling it, "subacute toxic cirrhosis" (STC). Two years later, Radhakrishna Rao[13] gave a meticulous histologic description of what he called, "infantile cirrhosis of the liver," and briefly commented that such a disease had been seen in North China and probably Mexico. In 1955, the dean and doyen of Indian pathologists, Professor V. R. Khanolkar convened a national workshop on infantile cirrhosis comprising a committee of about a dozen eminent workers in liver disease. They described the clinicopathologic criteria of early, intermediate, and late stages, describing, for the first time, the presence of Mallory's fibrillar hyaline (now called Mallory body) in the liver.[14] Until then Mallory hyaline was considered the sine qua non of alcoholic liver disease. Since then publications on the subject, variously called IC, IBC, and ICC began mushrooming, and as of today from 1887 to 1983, one of us (A. G. B.) has reviewed 206 publications on genetic, metabolic, toxic, immunologic, virologic, and clinicopathologic aspects of ICC. The review began in 1974, and to the astonishment of one of us (A. G. B.), from 1887 to 1978, not a single publication pictured the liver completely in ICC. We remedied the situation by publishing three gross photographs of complete autopsied livers in 3 typical cases of ICC.[15] Subsequently we published a review[16,17] of about 150 publications on ICC to 1980 classified under various terms. Also included was an analysis of critical (selected) publications on the subject[17] in an attempt to pinpoint the deficiencies of earlier work and to discover the probable reasons for failure, after 94 years, to understand the pathogenesis of ICC.

Simultaneously, we undertook the analysis of 76 autopsies in the pediatric age group (0–16 years) of patients dying from primary liver disease and came to the conclusion that the minimum criteria of ICC had never been defined, with the result that every worker used criteria that best suited him, and that Mallory hyaline was considered pathognomonic of ICC. As we know, there are at least two dozen causes of Mallory hyaline in liver, and Mallory hyaline has been described in pneumocytes of asbestotic lungs.[18] We have seen it in the kidneys (proximal convoluted tubules) and pancreatic acini in ICC. The incidence of Mallory hyaline in ICC (despite being the diagnostic marker of greatest significance) has varied between 14% to 82% (100% if you considered Mallory hyaline as pathognomonic of ICC as some authorities[19,20] have done). The 14% figure is that of Gerber et al[21] and the

Table 1. Primary liver disease in pediatric age group (0–16 yr) at autopsy (to postmortem no. 8036), total cases-76, Jan 1964–Feb 1983

CCIC/ACIC macronodule/micronodule/mixed)	23
ICC	14
12 typical; 2 atypical	
Acute hepatitis (submassive and massive necrosis)	13
Neonatal hepatitis with or without fibrosis and cirrhosis	7
Toxic/hypersensitivity hepatitis	2
Miscellaneous	17
(NCPF, Reye's; NSRH, material not available, not examined)	

CICC = conventional cirrhosis of Indian childhood, ACIC = atypical cirrhosis of Indian childhood, ICC = Indian childhood cirrhosis, NCPF = noncirrhotic portal fibrosis, NSRH = nonspecific reactive hepatitis.

82% is ours. The difference between us is that we have laid down specific, minimal criteria on the basis of which we have classified pediatric primary liver disease (PPLD) into seven groups (*Table 1*): typical ICC (TICC), atypical ICC (AICC), conventional cirrhosis of Indian childhood cirrhosis (CCIC), acute fatal hepatitis (AFH) with submassive or massive (confluent) hepatic necrosis, neonatal hepatitis (NH) with fibrosis (NHF) or cirrhosis (NHC), toxic or hypersensitivity hepatitis (TH/HH), and a miscellaneous group. If we cannot classify the liver changes into any known category, we list it as unclassified liver disease of Indian childhood (ULIC), many cases of which overlap with nonspecific reactive hepatitis (NSRH).

On the basis of our autopsy material and review of the literature, we proposed ten clinicopathologic criteria for the diagnosis of ICC.[8] Since no single criterion (including Mallory hyaline in liver) was pathognomonic, we arbitrarily gave one point to each criterion. If the score was 8–10, we called it TICC; if the score was 5–7, we called it atypical ICC (AICC). Of course, these criteria have to be used in the proper context, namely pediatric liver disease. Subsequent discoveries of abundant copper-binding orcein-positive proteins[22] and copper[23,24] in the liver, confirmed by others and by us, made it necessary to alter our diagnostic criteria for ICC. Also we realized that the diagnostic criteria cannot be the same for autopsy, biopsy material, early disease, and in the siblings of those affected with ICC. The separate criteria for autopsy, biopsy, and early disease (siblings) are shown in *Tables 2–4.*

Table 2. Criteria for diagnosis of ICC in early stages including asymptomatic siblings

1. Age: 3–9 months
2. Firm, smooth hepatomegaly, more than 1 cm below the costal margin
3. Serum glutamic oxalacetic transaminase more than 65 IU
4. Serum bilirubin less than 2 mg/dl
5. Periportal coarse orcein-positive deposits in the hepatocytes
6. Nonfatty vacuolation of hepatocytes confirmed by electron microscopy (EM)
7. Wedging of single fibroblasts or fibrosis between two adjacent hepatocytes (EM)
8. Pleomorphic, bizarre hepatocytic mitochondria (EM)
9. Disruption of biliary canalicular microvilli and luminal dilatation (EM)
10. Excess of copper in liver with normal serum ceruloplasmin

Typical early ICC (TEICC) = score 8–10
Atypical early ICC (AEICC) = score 5–7

Table 3. Criteria for biopsy in established cases

1. Age 10–24 months
2. Firm, smooth hepatomegaly 3 cm or more below the costal margin
3. Sharp leafy edge of the liver
4. Splenomegaly less than liver below the costal margin
5. Serum glutamic oxalacetic transaminase more than 260 IU
6. Periportal to panlobular coarse orcein-positive deposits in liver
7. Mallory hyaline in the hepatocytes with satellitosis
8. Excess copper by qualitative (rubeanic acid or rhodamine), or quantitative histochemistry (atomic absorption spectrophotometry), in liver with normal ceruloplasmin levels in serum
9. Dissecting (helter-skelter fibrosis of liver lobules confirmed by Masson's or any other collagen stain
10. Macrovesicular and microvesicular fat demonstrated by oil-red-o in absence of recent steroid therapy or significant hypoalbuminemia

TICC—Score of 8–10; AICC—Score of 5–7

Table 4. Revised autopsy criteria for classification of ICC

1. Age between 12–36 months
2. Firm hepatomegaly, asymmetric involvement of lobes and random nodules of varying size and definition, with intervening flat scars
3. Sharp and/or "leafy" edge of left lobe and rounded and/or "loafy" edge of right lobe of the liver
4. Death within 3–33 months of onset in absence of d-penicillamine therapy
5. Dissecting (helter-skelter fibrosis of liver lobules demonstrated by Masson's stain of liver, or any other collagen stain
6. Periportal to panlobular presence of coarse orcein-positive deposits in liver
7. Mallory's hyaline in the hepatocytes, with satellitosis
8. Excess of copper in liver by qualitative (rubeanic acid or rhodamine) or quantitative determination (atomic absorption spectrophotometry), with normal serum ceruloplasmin levels
9. Predominantly ill-defined nodules and coarse or fine scars with variable number of regenerative nodules, micronodular macronodular or both
10. Moderate to marked amount of fat by oil-red-o staining in absence of recent steroid therapy

Score of 1 for each feature:
TICC = Score of 8–10
AICC = Score of 5–7

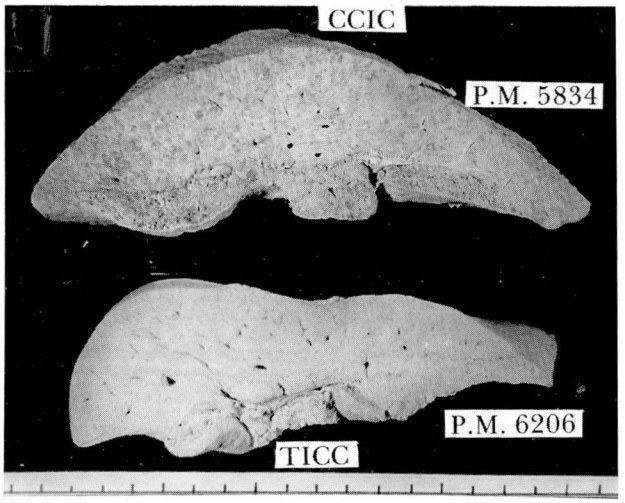

Fig. 1. Typical uniform nodular cut surface of CCIC in sharp contrast to apparent lack of nodularity in TICC.

Indian childhood cirrhosis versus cirrhosis of Indian childhood

The difference between ICC and CIC is graphically illustrated in *Figures 1–3* and *Table 5*. It is obvious from the figures that ICC is not a true cirrhosis. *Figures 4–6* show diagnostic microscopic features: grossly poorly visible and microscopically ill-defined parenchymal nodules in the liver (*Fig. 4*), confirmed by reticulin silver-impregnation techniques; Mallory's hyaline with satellitosis (*Fig. 5*); abundance of orcein-positive deposits in hepatocytes (*Fig. 6*), and high copper content, determined quantitatively.

It has been documented that whereas cases of ICC in India were invariably fatal between six and 36 months, almost all cases in the West (whether seen in Indians, Mexicans, or Bangladeshis) proved fatal in the much older age group between four and 11 years. We have hypothesized that whereas in underdeveloped countries, the children were exposed to numerous noxious agents such as viruses (hepatitis-B) and toxins (aflatoxin, copper, arsenic), in the West the more likely causes were genetic predisposition or genetically controlled metabolic error. (This is not to say that these causes were not operating in the underdeveloped countries). Likewise, in the developed countries the viruses and toxins could be of different nature, or exposure to toxins could be via a different route. On the basis of our own clinical, biochemical, biopsy, and autopsy experience of PPLD and review of the complete ICC literature, we have suggested a multifactorial etiology for ICC (*Diagram*) Achar et al[5] found that clinically typical ICC cases showed a spectrum of histologic changes (*Table 6*) including persistent hepatitis. He emphasized that from the clinical picture, it was almost impossible to predict what changes would be seen. In a similar vein, Aikat et al[25] described five patterns of histologic changes in cases clinically diagnosed as ICC. Twelve percent showed aggressive (active) hepatitis. Their group 2, according to them, was what should be called ICC. Their groups 3 and 4 were those cases of clear-cut cirrhosis with or without fat, macronodules or micronodules or both. Whereas in their group 2, Mallory hyaline was present in 70% of cases, and in their groups 3 and 4, it varied between 1% and 17%.

The search for etiologic agent(s)

The search for etiologic agents has proved illusory until recently. Among the agents suspected are these in order of importance: genetic, toxic, viral, metabolic (biochemical), and immu-

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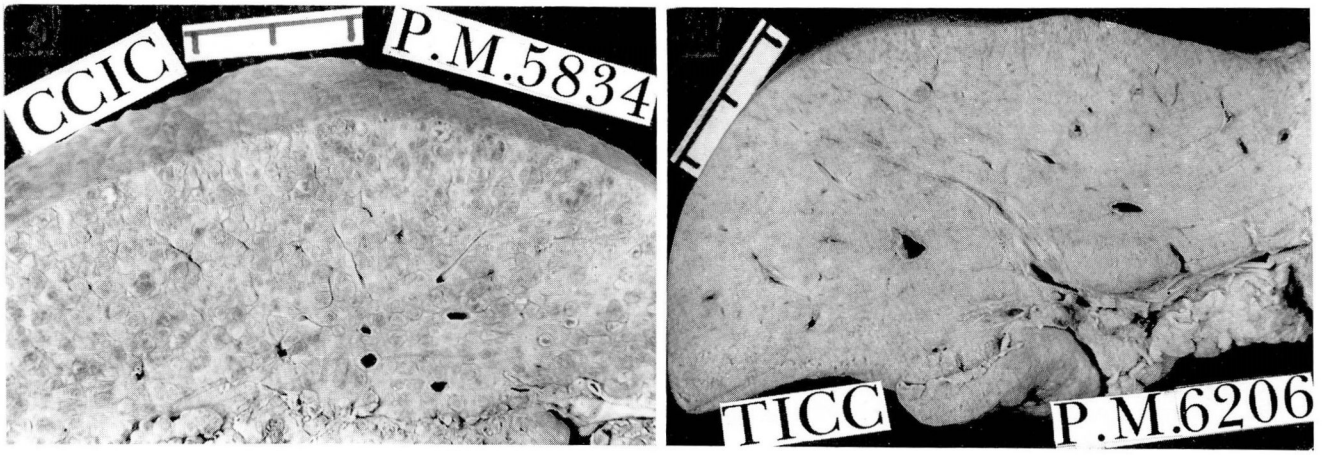


Figs. 2 and 3. Cut surfaces of the liver in CCIC and TICC.

Table 5. Features of ICC versus CCIC

Feature	ICC	CCIC
1. Age	6–24 mo	4–16 yr
2. Nutrition	Well nourished	Cachexia
3. Family history	+ (30%–50%)	(Significantly less)
4. Socioeconomic status	Middle class	Lower class
5. Liver at autopsy	Surface nodularity absent/sparse/random asymmetric	Uniform gross nodularity macronodular /micronodular /mixed symmetric
6. Liver edge		
Left lobe	Sharp, firm and "leafy"	Crumpled (particularly following confluent/submassive/massive hepatic necrosis)
Right lobe	Firm and rounded, "loafy"	Firm and rounded, "loafy"
7. Spleen	Liver much larger than the spleen below the costal margin	Splenomegaly, larger than hepatomegaly below the costal margin
8. Liver (cut surface)	Nodularity not apparent/indistinct/random/when present	Diffuse nodularity with predominance of macronodules or micronodules or equal number of macronodules or micronodules
9. Liver (microscopy)		
a. Mallory bodies	In 14%–100% livers and 10%–90% hepatocytes when present	Less than 20% up to 0%
b. Satellitosis	i.e., collection of mixed inflammatory (neutrodominant) cells around degenerate hepatocytes with Mallory bodies	Present only if Mallory hyaline is present; Mallory hyaline (body) has chemotactic influence on neutrophils
c. Dissecting fibrosis	Fibrosis breaks liver cell cords (intercellular and pericellular)	Fibrosis surrounds islands of hepatic cords resulting in nodules
d. Fat in hepatocytes	Characteristically minimal or absent in routine stains and if no steroids have been given	Amount of fat varies with degree of protein malnutrition, steroid therapy
e. Regenerative nodules	Absent/very few/sparse/random	Uniformly present and usually varying size
f. Orcein + deposits	Abundant and typically periportal in early cases	Moderate to minimum
g. Copper	Largest amount of in any human disease	Moderate to minimum

CCIC = conventional ICC.

nological. (For a detailed review see Bhagwat 1980).[16] Wide discrepancies in the findings of various workers on virtually every etiologic agent (except perhaps copper) indicate that ICC is a multifactorial syndrome rather than a disease caused by a single etiologic agent.

Genetic aspects

Indian childhood cirrhosis has been described in twins.[16] In 30% to 50% of the cases of ICC, there is a history of sibling disease and death due to ICC, although it must be emphasized that often a biased historian may merely consider evidence of jaundice or ascites in a dead sibling as sufficient evidence of ICC. Nevertheless, the masterly study[1] of Lefkowitch of 4 white siblings (3 autopsied) showing unequivocal evidence of ICC (micromicronodular cirrhosis, abundant orcein-positive, copper-binding proteins, high copper content of the liver and presence of Mallory's fibrillar/dendritic hyaline (Mallory body) has strongly suggested a genetic basis for ICC. About 30% of ICC children are firstborn.[17] There are now three definitive studies available in which siblings of ICC patients were followed for several years clinically and/or by serial liver biopsies to determine how many eventually develop typical ICC. The largest of these studies is that of Patel et al.[26] In a village of 11,000 in Vapi District (Gujerat, India), they followed asymptomatic and symptomatic siblings of ICC patients over a period of two to three years by serial liver biopsies.

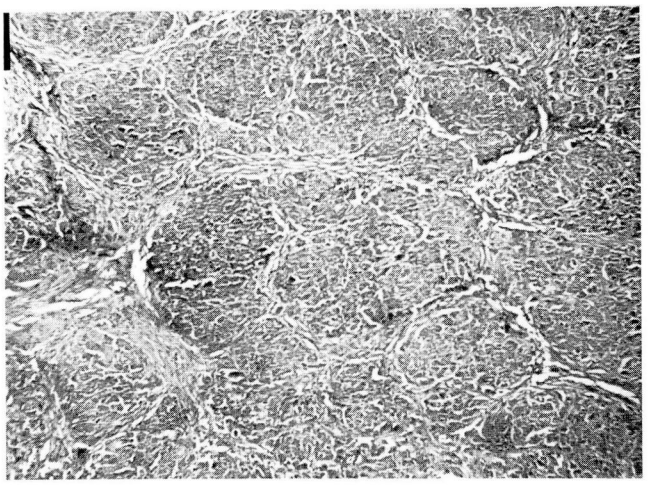


Fig. 4. Ill-defined nodularity of the liver in TICC (hematoxylin-eosin × 44).

They found that approximately 25% of the 76 siblings followed up developed ICC. The sequence of histological events seen by them from the earliest to the fatal stage was: nonfatty vacuolation of hepatocytes, portal fibrosis and scarring, and typical ICC. Although no one has repeated their work on that scale, Nayak et al[27] followed 200 siblings of ICC patients clinically (by palpation of liver and liver function tests) and by liver biopsy in 29 siblings studied by light and electron microscopy. *Not a single* case developed ICC. We studied[28] 29 siblings of ICC patients (with 15 age-matched controls); 24 boys and 5 girls below the age of four years. Of 29, 12 (40%) had early or late ICC, and only 4 of these (14%) had clearly established ICC. Of these, we followed 5 cases by serial liver biopsies (two or three) for as long as 19 months. Only one showed some progression, but this too was highly equivocal. Chromosomal studies (karyotypes) and dermatoglyphics in ICC have proved inconclusive.[16]

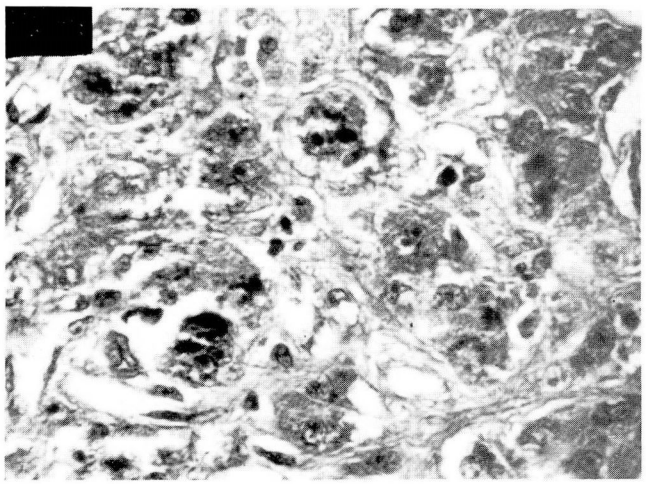


Fig. 5. Extensive Mallory hyaline in hepatocytes (hematoxylin-eosin × 440).

Toxic aspects

As early as 1933[12,13] it was suspected on the basis of histologic evidence that some toxic factor (superposed on genetic predisposition) might be operative in the genesis of ICC, and, in fact, these authors[12] called it "subacute toxic cirrhosis" of Indian children. Among the toxins suspected were aflatoxins, arsenic, and copper. Although cirrhosis was produced experimentally by administration of aflatoxins and by various dietary manipulations,[16] it had little resemblance to ICC. In our study of siblings of ICC patients,[28] we found that during pregnancy, 16 of 29 mothers had been imbibing a concoction called "janam ghutti" in the belief that they would have a male child (a traditional belief for centuries in North India). Chemical analysis of this concoction, as well as autopsy liver samples of ICC victims, showed high arsenic content.[29,30] Drinking water collected from various sources in the villages of Punjab and Haryana and opium were also sources of high arsenic content. He also found the copper content of these autopsy livers to be high as well.

Tanner et al[23] and Popper et al[24] in collaboration with Indian workers who supplied the raw material) showed for the first time that copper content of the livers of ICC patients was several times higher than in any disease known so far such as Wilson's disease and primary biliary cirrhosis. Lefkowitch et al[1] studied the copper content of the liver in 10 groups including controls. Their figures, expressed as $\mu g/g$ of tissue dry weight, were as follows: normals, 58 $\mu g/g$; newborn, 295 $\mu g/g$; primary biliary cirrhosis, 411 $\mu g/g$; primary sclerosing cholangitis, 244 $\mu g/g$; Wilson's disease, 744 $\mu g/g$; Indian childhood cirrhosis, 1832 $\mu g/g$; extrahepatic biliary duct obstruction, 128 $\mu g/g$; paucity of interlobular bile ducts, 271 $\mu g/g$; chronic active hepatitis, 40 $\mu g/g$; alcoholic and cryptogenic cirrhosis. We have confirmed these observations (Fig. 8).[31] It is our educated guess that ICC in India has a stronger environmental component (copper vessels for cooking), whereas in the West, disordered copper metabolism may be a more dominant factor. However, it must be stressed that in con-

trast to Wilson's disease, serum ceruloplasmin levels in ICC are either normal or slightly higher but never low.

Metabolic aspects

Among the metabolites incriminated (genetic disorder of the metabolism of a particular substance) are maltose, tryptophan, sulphur-containing aminoacids, zinc, magnesium, iron, α^1, antitrypsin, ketoacids, vitamin B_{12}.[16] None has stood the test of time, and no purpose is served by elaborating on them. If one considers genetically determined disorder of copper metabolism as an important etiologic aspect, this is the only metabolite that deserves more than cursory interest, and it has already been discussed earlier.

Virologic aspects

In a country where viral hepatitis is endemic (both A and B types), its role in the genesis of ICC cannot be altogether ignored. As mentioned earlier, Achar et al[5] found the typically firm enlarged liver of ICC showed a spectrum of histologic changes in liver biopsy, including persistent hepatitis. Aikat et al,[25] in their 100 clinically diagnosed cases of ICC (80 biopsies and 20 autopsies), found that 12% had features of aggressive hepatitis. In India there is a tendency to assume that any histologically proved acute or chronic hepatitis is viral. But this is not necessarily true because several drugs and toxins and immunological interactions can produce acute or chronic hepatitis, which, in turn, may produce cirrhosis. A statement quoted from paper to paper (originated by the New Delhi group)[32,33] that the massive epidemic of viral hepatitis in New Delhi in 1955–1956 was not followed by increase in the incidence of ICC in Delhi, does not really explain why viral hepatitis cannot be the cause or one of the causes of ICC. *In no part of India has the incidence of ICC been determined* with the possible exception of Vapi District and a few small isolated pockets of the country where epidemiologic studies were done.[16,34,35]

Immunologic aspects

Evidence or the immunologic basis of ICC is mostly indirect, such as depressed cell-mediated immunity,[36] and reduction of T-lymphocytes. These appear to be a result rather than the cause of ICC.[16,35]

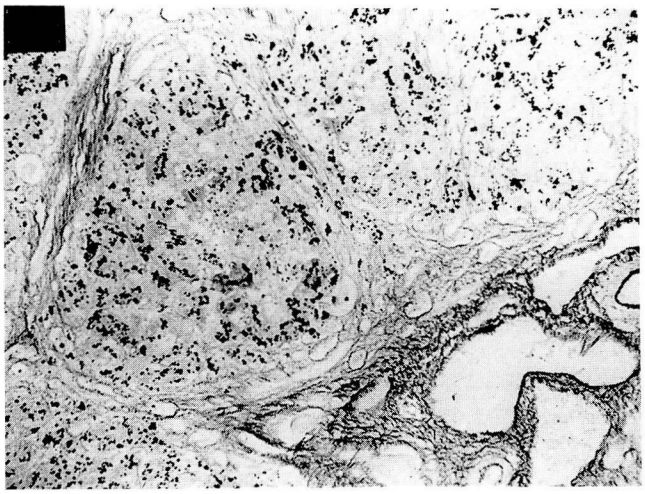
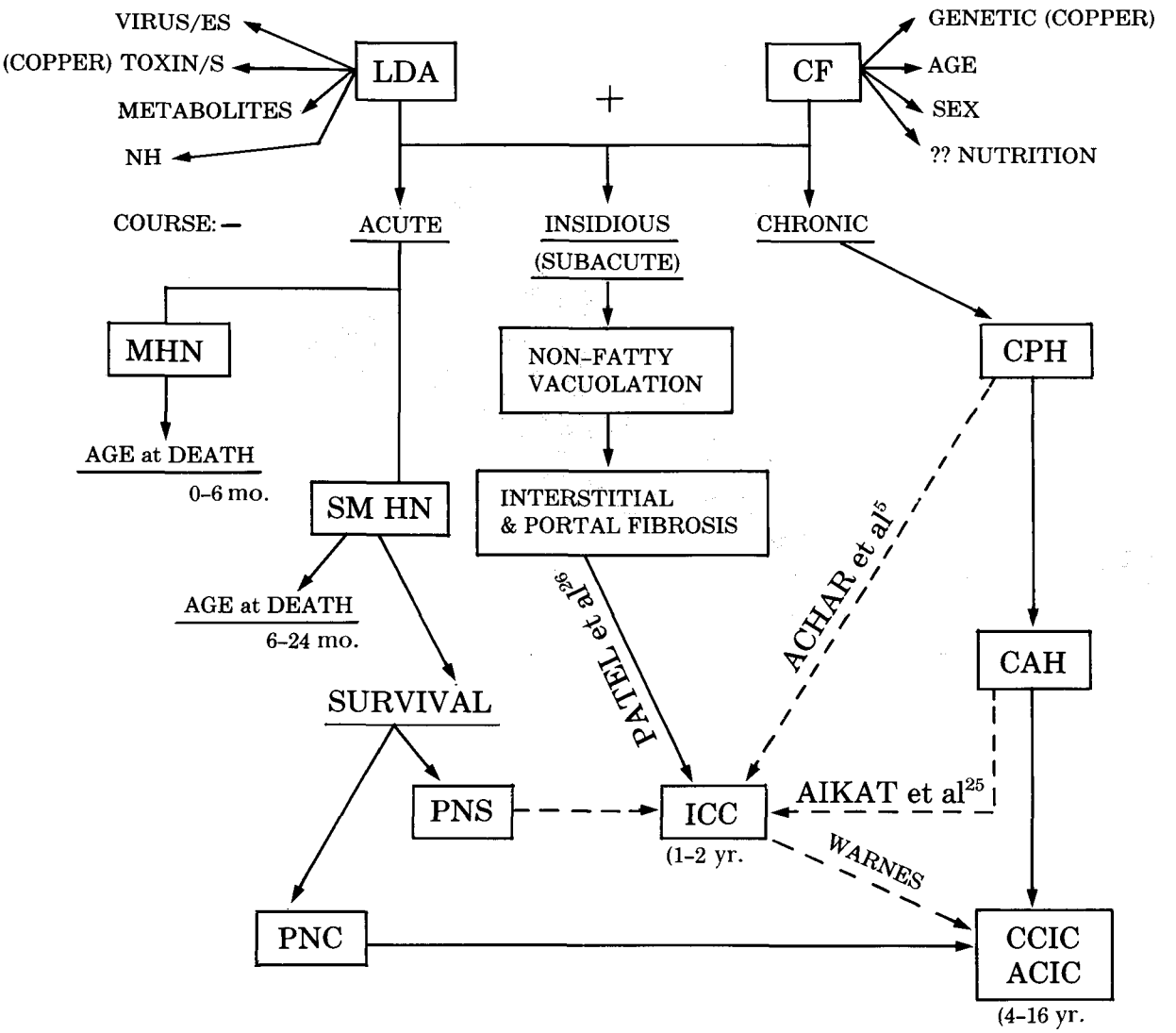


Fig. 6. Abundance of orcein-positive deposits in liver in a case of TICC. Note periportal distribution extending to periphery (orcein stain × 44).

Indian childhood cirrhosis: the crux of the matter

It is almost 100 years since Sen described infantile cirrhosis peculiar to Indian children. Since then we have reviewed critically 206 publications on various aspects of the subject. There is more disagreement than agreement, and yet ICC is regarded as a subject that everyone knows about. Why this paradox? The diagnostic criteria have never been clearly defined. What are the minimum criteria for ICC, and if these are not met, what are borderline cases to be called? The criteria (age-old) have become outdated, and relevant new information is ignored to maintain the illusion of ICC as a distinct disease of India. Until 1979, 93 years after ICC was first described by Sen,[7] more than 100 papers had been published (including symposia and workshops) but not a single paper showed how the entire liver of an ICC patient looked. For the first time we showed three autopsy livers of ICC patients in 1979.[15] Furthermore, ICC is a misnomer.[2] It has been seen in at least 17 countries including Africa (West), Bangladesh, Britain (in Indian children), Burma, Canada (in a Mexican child), Ceylon (Sri Lanka), China (North), Costa Rica, Egypt, Indonesia, Israel, Mexico, Malaya, Pakistan, and in the United States (in 4 white American siblings) and Australia. Indian childhood cirrhosis is not Indian exclusively, whatever else it might be. The vast majority of patients (until the recent introduction of d-penicillamine therapy) died between eight and 36 months, most less than 15 months of age. Thus, the true genesis of the disease



LDA = liver-damaging agent; *CF* = conditioning factors; *NH* = neonatal hepatitis; *MHN* = massive hepatic necrosis; *CPH* = chronic persistent hepatitis; *SMHN* = submassive hepatic necrosis; *CAH* = chronic aggressive hepatitis; *PNS* = postnecrotic scarring; *ICC* = Indian childhood cirrhosis; *PNC* = postnecrotic cirrhosis; *CCIC* = conventional cirrhosis of Indian childhood; *ACIC* = atypical cirrhosis of Indian childhood:— = established link: – – – = probable link.

occurred in infancy or perhaps the intrauterine (postzygotic) stage 1 if not in prezygotic stage (genetic predisposition) stage. As *Figures 1–3* show, the disease is not true cirrhosis. At best it is occult (micromicronodular) cirrhosis. We have the most extensive autopsy experience of ICC in the world, and virtually all of the livers are grossly nonnodular or sparsely nodular (see Pathology) sometimes even soft with confluent hepatic necrosis. We therefore like to use the morphologic classification of "soft ICC" and "hard ICC."

Of the many etiologic agents, copper is the most acceptable, but even here acute or chronic copper administration in various species of animals has failed to produce changes even remotely resembling ICC. We believe this to be further support for our multifactorial etiology.

Myth of Mallory hyaline in ICC

In 1911 Mallory (Boston) first described the presence of perinuclear filamentous eosinophilic material in the cytoplasm of hepatocytes in chronic alcoholics suffering from alcoholic liver disease (ALD). Subsequent workers called it Mallory's hyaline (*Fig. 5*), and it became a diagnostic

landmark of ALD. In 1955, the liver disease subcommittee of the Indian Council of Medical Research, New Delhi, India,[14] conclusively demonstrated that ICC livers contained Mallory's hyaline, which was histologically and histochemically indistinguishable from alcoholic Mallory hyaline. In the years to come, Mallory hyaline was described in the liver in numerous hepatic and nonhepatic diseases, as well as in organs other than liver such as lungs, kidneys, and pancreas.[18] In fact, medical students in the late fifties and early sixties were taught that ICC livers show changes of "acute alcoholic hepatitis" but without fat. A complete review of the ICC literature (1887–1983) shows wide variations in the incidence of Mallory hyaline in liver, ranging from 14%[21] or less[25] to 70%,[25] 82%,[18] and 100%.[19,20] The authors,[19,20] while not categorically stating that incidence of Mallory hyaline, in livers of ICC patients is 100%, have implied it by saying that they found Mallory hyaline in 1% to 80% hepatocytes[19] (not livers) and 10% to 90% hepatocytes. Clearly, these various authors are not speaking the same language about what constitutes ICC. To remedy this situation we first proposed[10] ten clinicopathologic criteria (including minimum standards) to define what we called typical ICC (TICC) with a score of 8–10 (each criterion carrying one point), and atypical ICC (AICC) with a score of 5–7. These criteria were based on retrospective analysis of our autopsy material. However, when we applied these criteria to biopsy material or ICC siblings (early disease, nonspecific changes, or no changes) we ran into problems. Also by this time the presence of abundant coarse orcein-positive deposits in livers and kidneys[22] of ICC cases and massive amounts of copper in livers of ICC patients[23,24] had been well established. We therefore incorporated these criteria at the cost of less important criteria, keeping the total to ten (*Tables 2–4*). We propose that these criteria be accepted universally for a reasonable period of time to bring some semblance of uniformity in the various parameters of ICC, failing which we have the spectacle of Mallory hyaline incidence varying from 14% to 100%, smooth muscle antibodies from 17% to 80%,[37] serum alpha fetoproteins from 0% to 45%,[38–40] and reduction of beta$_1$ C complement fraction in 0% to 73% of cases.

Clinicopathologic picture of typical ICC

This has already been shown in *Table 6* and *Figures 1–4*. This is slightly out-of-date, but the essential features remain the same. Only the modifications and reasons for doing so will be discussed briefly here.

Table 6. Classical clinicopathologic picture of ICC

Clinical	A moderately nourished two-year-old Brahmin or a Bania boy from middle-income family; irritable, restless, not growing well, passing sticky clay-colored stools; gradually bulging belly; family history of sibling death due to similar illness; PE: firm hepatomegaly with sharp "leafy" edge, splenomegaly; later progressive ascites and icterus
Laboratory	Deranged liver function test, raised total conjugated bilirubin, anemia, raised transaminases and alkaline phosphatase, hypoalbuminemia, biliuria, prolonged prothrombin time
Death due to:	Hepatic failure (by far the commonest)
Liver pathology (autopsy)	Firm, enlarged, deeply icteric random surface distribution of coarse, fine, and ill-defined "lumps and bumps," smooth scarred streaks or bands and wrinkles
Histology	Intercellular (creeping) fibrosis, pseudolobulation, and generally poorly formed (ineffective) regenerative nodules, florid ductular proliferation, Mallory's hyaline and satellitosis (polymorphs), cholestasis, absence of fat, hepatic venous sclerosis, muscular hyperplasia of hepatic arteries in the portal tracts
Other organs	Esophageal varices; bile casts in renal tubules (cholemic nephrosis); bronchopneumonia; T-cell depletion of the lymphoid organs; bile-stained viscera

Clinically, the uniqueness of ICC consists in the patient's voracious appetite (most liver diseases produce anorexia), irritability, extremely sticky stools, and firm hepatomegaly. Parekh and Patel[41] have designated it as "pre-cirrhotic symptom complex" (PCSC). However, in a recent international seminar on ICC in Pune, India,[31] 10–11 November 1982, most pediatricians consider PCSC as nonspecific. The other feature, sharp, knife-edge of the liver called "leafy" because it curls under the palpating fingers, has also proved unreliable. We have found that a sharp, knifelike leafy edge is restricted to the left lobe of the liver and can be seen in neonatal hepatitis with fibrosis and/or cirrhosis, inspissated bile-plug syndrome, and posthepatitic cirrhosis. Consistency is produced by replacement of hepatic parenchyma by fibroelastic tissue. The right lobe of the liver in typical ICC is rounded, and we have designated it as "loafy." But again this is by no means specific of ICC.

Grossly at autopsy, in the vast majority of cases the liver is firm, asymmetric, and either shows flat scars (especially in the left lobe and on the visceral surface) with no nodules or very sparse randomly distributed nodules, usually micronodules. In contrast, the right lobe shows either

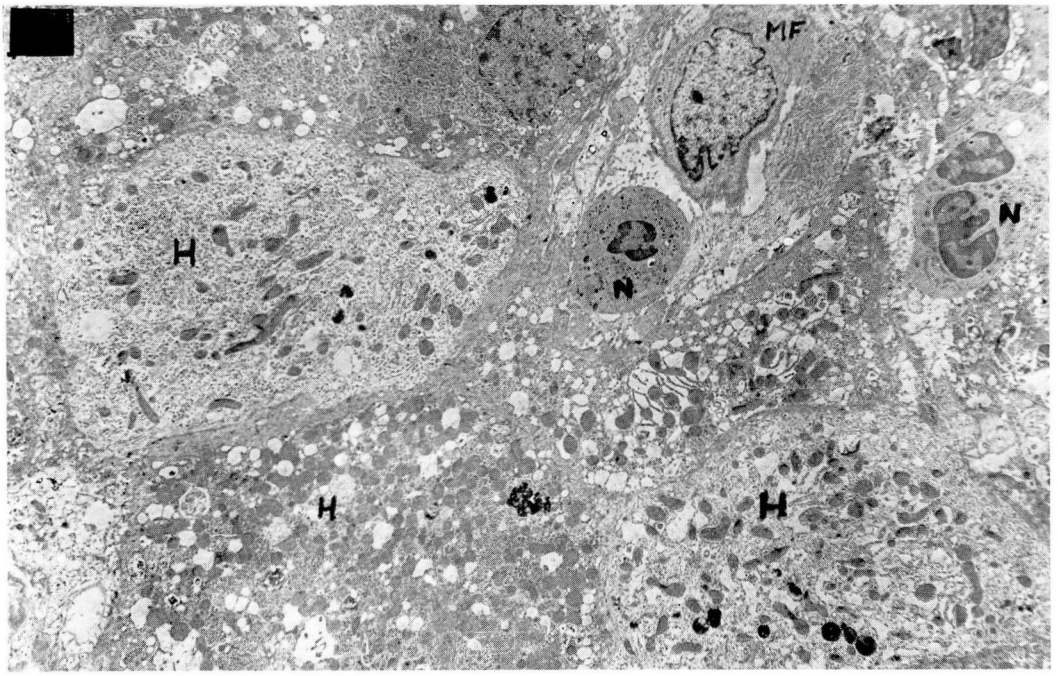


Fig. 7. Electron micrograph of liver in TICC. At least three hepatocytes (H) show crowding of pleomorphic mitochondria and dilated rough endoplasmic reticulum (RER). Hepatocytes are in close contact with two neutrophils (*N*) and possibly a myofibroblast (*MF*) (uranyl acetate and lead citrate × 1500).

no nodules or poorly delineated macronodules. If one compares typical ICC livers with cirrhotic livers in age-matched cases, one gets the impression that the child died before the liver had time to become fully cirrhotic. This impression is supported by the observation that as age at death in ICC increases, the resemblance to true cirrhosis becomes closer. Whereas typical ICC patients die between 6 to 36 months of age in the underdeveloped countries, patients from the well-developed countries tend to be much older, about 5–10 years of age at the time of death.[1,41] To date the oldest patient with ICC seen by us at death was two years old. By contrast the youngest patient with typical cirrhosis was four years old, the so-called CCIC according to our definition. D-penicillamine therapy, which is now being given a trial in several centers in this country and abroad, undoubtedly modifies the picture. What we have described so far is "hard ICC," but there are cases of ICC that run a rapid course (between 0 to 12 months of massive/submassive/confluent hepatic necrosis) but show histologic features of ICC. In such cases, the livers are soft, shrunken and resemble "spleen" on the cut surface due to massive necrosis of hepatic parenchyma with pooling of blood by confluence of sinusoids. Such cases we grossly term "soft ICC" (subject to histologic confirmation).

Histology

The critical histologic features have been illustrated in *Figures 4–6.* In our hands, the histochemical stain for copper is rubeanic acid, and we rely entirely on quantitation of copper in liver expressed as $\mu g/g$ of dry weight of the liver.

In the siblings of ICC patients one may not see any change histologically nor perceive nonfatty vacuolation of hepatocytes and orcein-positive coarse deposits in the hepatocytes periportally in the initial stages, progressing centrifugally with passage of time.

Electron microscopy[42–44]

In *established* cases, a spectrum of changes in the liver is shown: dilated channels of rough endoplasmic reticulum (RER), pleomorphic mitochondria with tendency to binary fission, massive intercellular fibrosis, occasional myofibroblasts, dilated bile canaliculi with "fractures" of lining microvilli followed by disappearance, neutrophils adjoining necrobiotic hepatocytes, clumps of nonmembrane-bound fibrillar Mallory hyaline, and numerous (but varying from cell to cell) electron-dense irregular bodies (? cuprosomes or copper-binding orcein-positive proteins) *Figs. 7–9).* Three types of Mallory hyaline have been seen.[44]

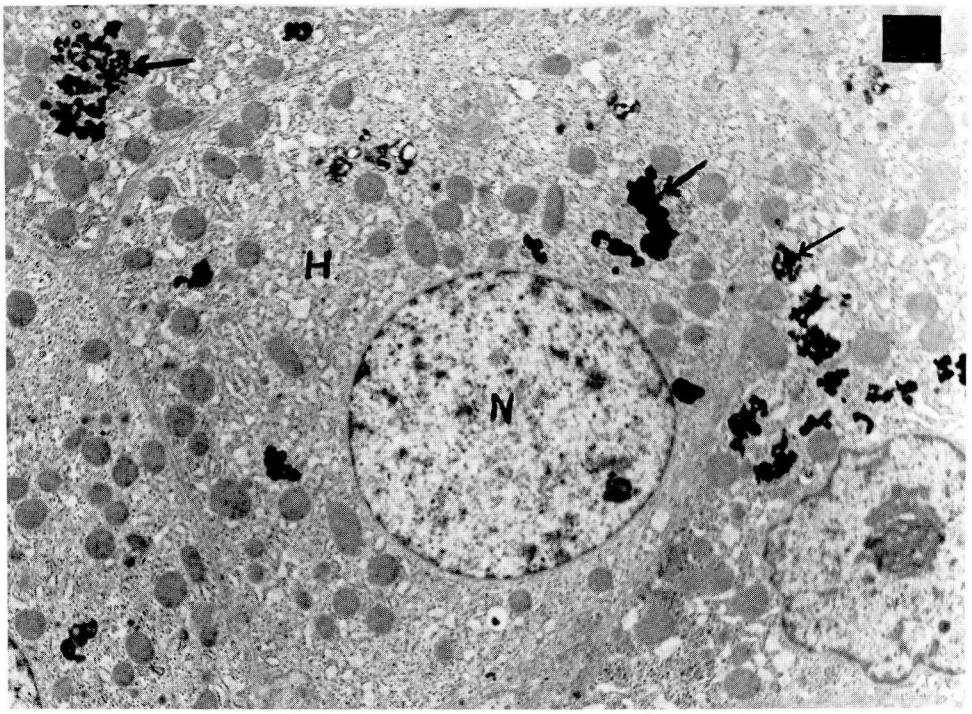


Fig. 8. Electron micrograph of liver in TICC. Hepatocyte (*H*) showing numerous electron-dense deposits, possibly copper-binding proteins or cuprosomes (uranyl acetate and lead citrate × 3000).

In *early cases* (clinically asymptomatic or symptomatic siblings), there is considerable controversy regarding the changes. We have reported[42] glycogen depletion in nonfatty vacuolated hepatocytes, "wedging" of single fibroblasts between two adjacent hepatocytes, intracellular collagen bundles in apparently normal or degenerated glycogen-depleted hepatocytes, pleomorphic mi-

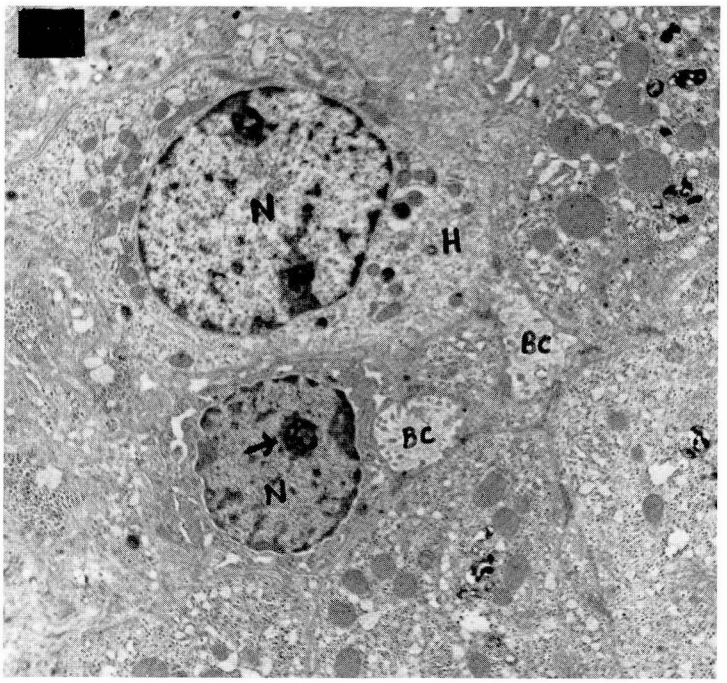


Fig. 9. Electron micrograph of liver in TICC. Hepatocytes with two intervening dilated bile canaliculi (*BC*) with sparsity or absence of microvilli (uranyl acetate and lead citrate × 3000).

tochondria, dilated bile canaliculi with "disrupted" microvilli but no Mallory hyaline (*Figs. 10–13*). Nayak et al[27] have stated that changes are inconsistent, varying from case to case (we agree), but they particularly emphasize the presence of clusters of microtubules, which they interpret as precursors of Mallory hyaline. Patel et al,[26] claiming excess glycogen in the hepatocytes, have gone to the extent of proposing that ICC is a disorder of glycogen metabolism. Other workers[27,45] totally disagree with their claim and believe that what they have shown are normal glycogen-rich hepatocytes consequent to sampling error, since the changes in ICC sibling livers are extremely patchy.

Future study of Indian childhood cirrhosis

Of first and foremost importance for the future of ICC research is the standardization of diagnostic criteria in siblings, both for early and late

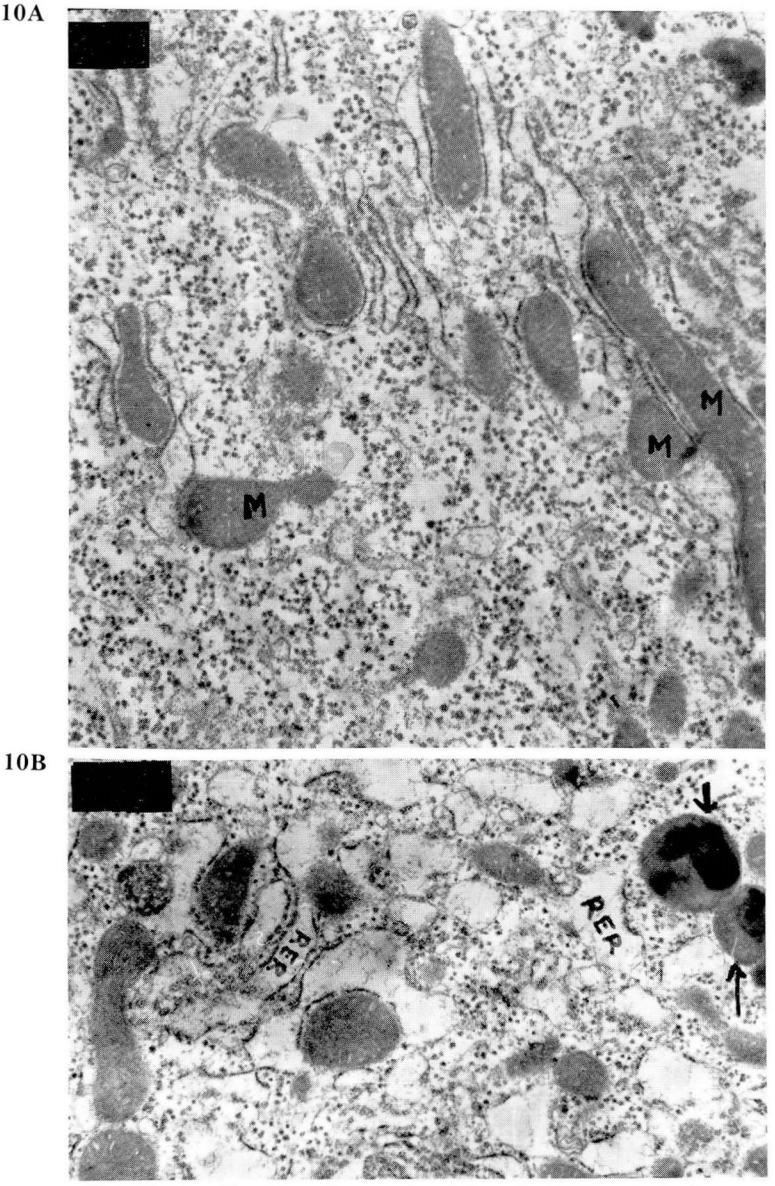


Fig. 10. A. Electron micrograph of liver in TICC. Markedly pleomorphic mitochondria and abundance of beta-granules of glycogen are seen (uranyl acetate and lead citrate × 7000).

B. Electron micrograph of liver in TICC. Some mitochondria are wrapped by a ribosomal wreath of rough endoplasmic reticulum (*RER*). Note dilated tubules of RER and two electron-dense membrane-bound bodies containing crystalloids (? microbodies) (uranyl acetate and lead citrate × 7000).

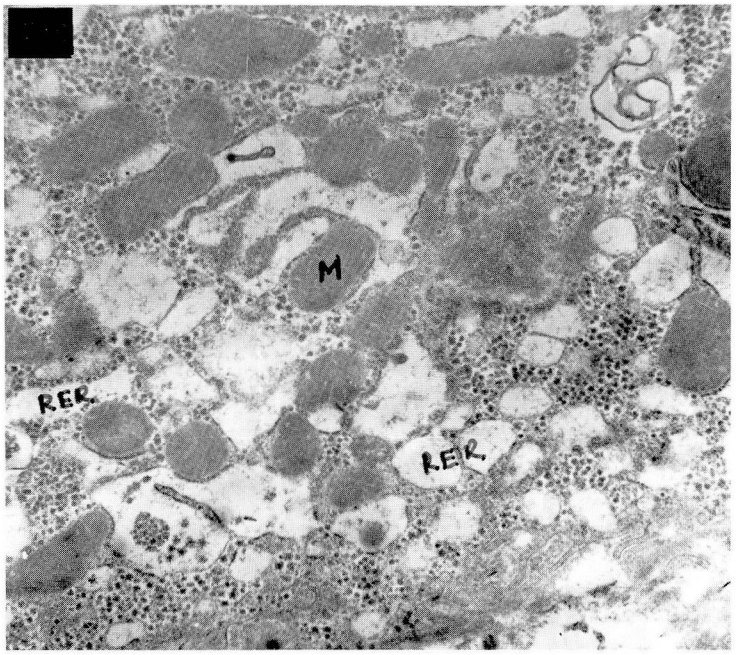


Fig. 11. Electron micrograph of liver in TICC. Severe dilatation of RER, and pleomorphic mitochondria are seen. Note myelin figure in right top corner and fibrillar Mallory hyaline (*arrows*) (uranyl acetate and lead citrate × 7000).

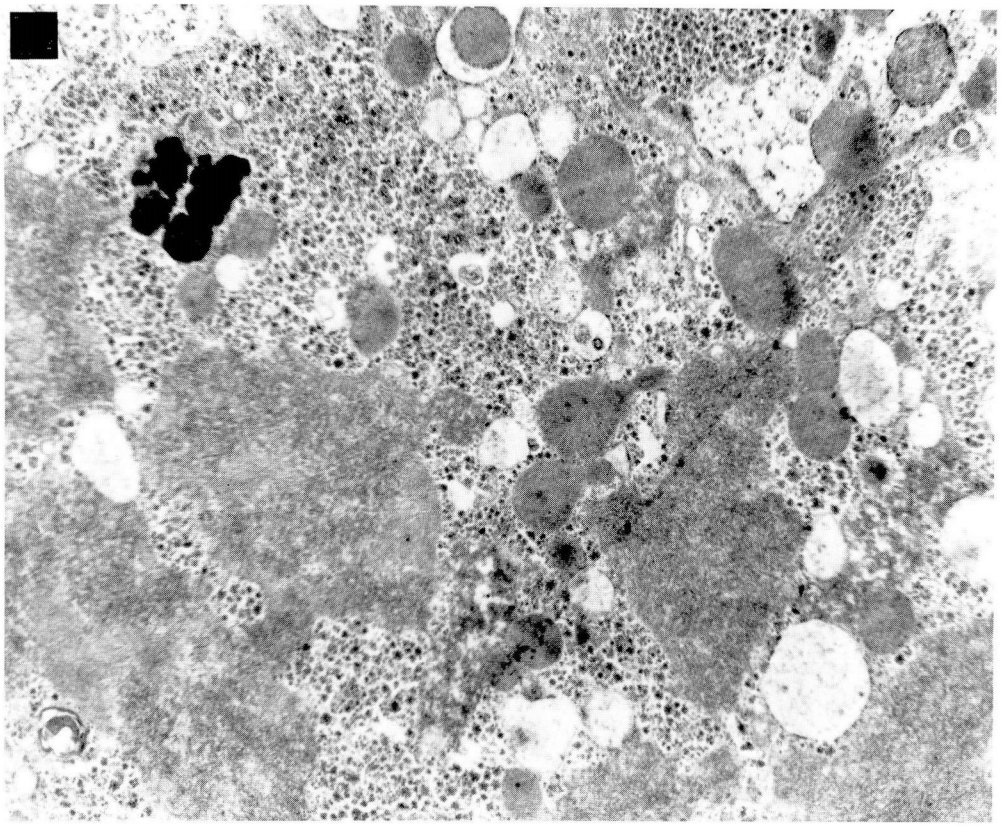


Fig. 12. Electron micrograph of liver in TICC. Note three large irregular nonmembrane bodies containing crisscross fibrillary pattern of Mallory hyaline (uranyl acetate and lead citrate × 7000).

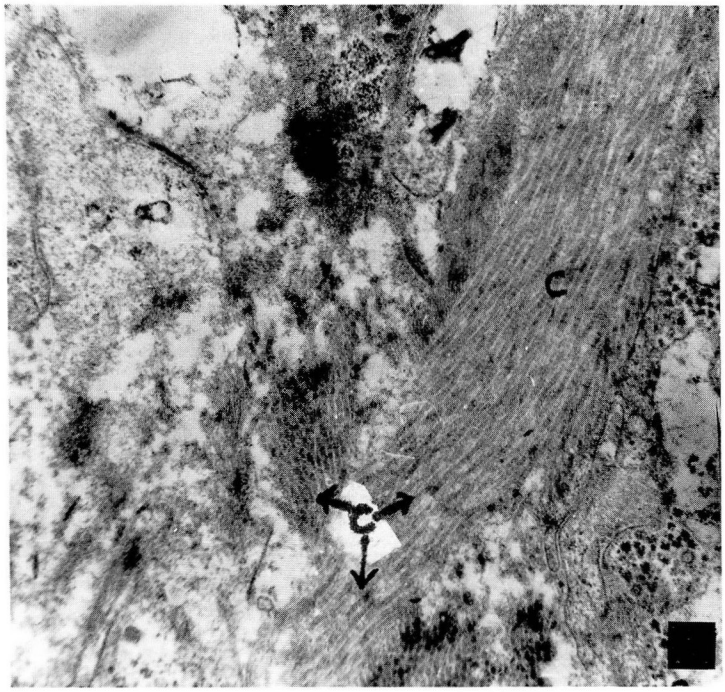


Fig. 13. Electron micrograph of liver in TICC. Thick bundles of banded collagen fibril (*C*) are "invading" the hepatocyte, identified by glycogen granules at bottom right corner (uranyl acetate and lead citrate × 10,000).

stages of the disease. Failure to define minimum diagnostic criteria in every group has led to perpetually conflicting findings with the result that nearly 100 years (1887–1983) after ICC was first described, the final answer is not forthcoming. To achieve standardization we should reject the impression that ICC is exclusively an Indian disease, and incidence of ICC in various parts of India and the world (where Indians have massively emigrated) should be compared and ICC should be sought in all races. The discovery of Lefkowitch et al[1] of ICC in 4 white siblings (21–25 years after death) clearly shows that ICC must be sought. Lefkowitch in a personal communication (1982) to one of us has admitted that he became aware of ICC during his stay in England where he saw many cases of ICC material being sent from India. Like diagnostic criteria, sampling of tissue (at autopsy) and stains (minimum number) should be standardized. Thus we take a minimum of four blocks (two from the right lobe, one subcapsular and the other from a deeper region and rectangular shaped; two from the left lobe, triangular shaped) and embed them in a single paraffin block, so that staining is done under identical conditions. The battery of stains we employ is: hematoxylin and eosin, reticulin by silver impregnation technique, periodic acid- Schiff (PAS) following diastase digestion, Masson's trichrome stain, Shikata's orcein stain, and stain for copper (rubeanic acid or rhodamine). In the biopsy material, we use the same stains unless the biopsy is inadequate. In ICC siblings (asymptomatic or mildly symptomatic), we take a 5-mm-long portion of liver biopsy for electron microscopy. The minimum liver function tests include total and differential proteins, transaminase, hepatitis-B surface antigen (HBsAg), bilirubin, alkaline phosphatase, and sulfobromophthalein (Bromsulphalein) retention test in selected cases.

Although we have arbitrarily assigned one point for every diagnostic criterion of ICC in siblings, early and late stages, common sense suggests that all criteria cannot have equal weight, and hence we have developed a statistical model of ICC.[46,47]

Acknowledgments

We acknowledge with appreciation Prof. P. L. Wahi, Chairman, Editorial Board, Bulletin of the Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India, for permitting us to reproduce Tables 2–4 and Figures 1–3 from Bhagwat et al.[10,46]

References

1. Lefkowitch JH, Honig CL, King ME, Hagstrom JWC. Hepatic copper overload and features of Indian childhood cirrhosis in

an American sibship. N Engl J Med 1982; **307:**271–277.
2. Bhagwat AG. Indian childhood cirrhosis. Br Med J 1982; **284:**194.
3. Jellife DB, Bras G, Mukherjee KL. Veno-occlusive disease of the liver and Indian childhood cirrhosis. Arch Dis Child 1957; **32:**369–385.
4. Harrison CV. Diseases of the liver. [In] Recent Advances in Pathology. 7th ed. London: JA Churchill, 1960, p 181.
5. Achar ST, Raju VB, Sriramachari S. Indian childhood cirrhosis. J Pediatr 1960; **57:**744–758.
6. Chaudhuri A, Chaudhuri JN, Chaudhuri KC. Infantile cirrhosis of the liver (Sen's syndrome) with particular reference to sulphur-containing amino acids. J Pediatr 1960; **57:**230–247.
7. Sen BC. Infantile cirrhosis of the liver. Indian Medical Gazette 1887; **22:**338–340.
8. Majumdar DK, Kapoor UK, Sharma NL. Infantile cirrhosis of the liver in twins. Indian J Pediatr 1969; **36:**39–43.
9. Sur AM, Bhatti A. Indian childhood cirrhosis: an inherited disorder of tryptophan metabolism? Br Med J 1978; **2:**529–531.
10. Bhagwat AG, Walia BNS, Banerjee CK. A unifying hypothesis for Indian childhood cirrhosis (ICC). Bulletin of Postgraduate Institute of Medical Education and Research 1980; **14:**146–151.
11. Gibbons JB. Infantile biliary cirrhosis in an 11 months old boy. Indian Medical Gazette 1888; **23:**148–149.
12. Ramachandra Rao P. *Cirrhosis of liver—its morbid anatomy, pathogenesis and aetiology*, thesis. London, 1933.
13. Radhakrishna Rao MV. Histopathology of liver in infantile biliary cirrhosis. Indian J Med Res 1935; **23:**69–70.
14. ICMR liver disease subcommittee report. Infantile cirrhosis of the liver in India. Indian J Med Res 1955; **43:**723.
15. Bhagwat AG. Indian childhood cirrhosis. Lancet 1979; **2:**640–641.
16. Bhagwat AG. Indian childhood cirrhosis; a complete classified review (1887–1980). Indian Pediatr 1980; **17:**581–585.
17. Bhagwat AG, Walia BN. Indian childhood cirrhosis; a commentary. Indian J Pediatr 1981; **48:**433–437.
18. Bhagwat AG, Pandit VL. Manifold mystic of Mallory's alcoholic hyaline. Bulletin Postgraduate Institute Medical Education Research 1979; **13:**204–208.
19. Nayak NC, Visalakshi S, Singh M, Chandra RK, Ramalingaswami V. Indian childhood cirrhosis; a re-evaluation of pathomorphologic features and their significance in the light of clinical data and natural history of disease. Indian J Med Res 1972; **60:**246–259.
20. Marwaha N. *Ultrastructural study of liver in the siblings of Indian childhood cirrhosis*, thesis. All-India Institute of Medical Sciences, New Delhi, 1980.
21. Gerber MA, Orr W, Denk H, Schaffner F, Popper H. Hepatocellular hyaline in cholestasis and cirrhosis. Gastroenterology 1973: **64:**89–98.
22. Tanner MS, Portmann B, Mowat AP, Williams R. Indian childhood cirrhosis presenting in Britain with orcein-positive deposits in the liver and kidney. Br Med J 1978; **2:**928–929.
23. Tanner MS, Portmann B, Mowat AP, et al. Increased hepatic copper concentration in Indian childhood cirrhosis. Lancet 1979; **1:**1203–1205.
24. Popper H, Goldfischer S, Sternlieb I, Nayak NC, Madhavan TV. Cytoplasmic copper and its toxic effects—studies in Indian childhood cirrhosis. Lancet 1979; **1:**1205–1208.
25. Aikat BK, Bhattacharya T, Walia BN. Morphological features of the Indian childhood cirrhosis; the spectrum of changes and their significance. Indian J Med Res 1974; **62:**953–963.
26. Patel BD, Parekh SR, Chitale AR. Histological evolution of Indian childhood cirrhosis with emphasis on criteria of early diagnosis. Indian Pediatr 1974; **11:**19–28.
27. Nayak NC, Marwaha N, Kalra V, Roy S, Ghai OP. The liver in siblings of patients with Indian childhood cirrhosis; a light and electron microscopic study. Gut 1981; **22:**295–300.
28. Bhagwat A, Vashisht KK, Walia BN. Clinicopathologic and ultrastructural studies in the siblings of Indian childhood cirrhosis (Abst). Fed Proc 1980; **39:**877.
29. Datta DV, Narang AP, Arya P, et al. Indian childhood cirrhosis. Lancet 1979; **2:**641.
30. Datta DV, Narang AP, Sahni MM, Bannerjee CK, Walia BN. Role of arsenic and copper in Indian childhood cirrhosis. Indian Pediatr 1981; **18:**53–57.
31. Bhagwat AG, Koshy A, Walia BNS. Indian childhood cirrhosis. Proceedings of the workshop on Indian childhood cirrhosis held at KEM Hospital, Pune, India. Indian Pediatr 1983; **19:**1051–1062.
32. Chuttani HK, Sidu AS, Wig KL, Gupta DN, Ramalingaswami V: Follow-up study of cases from the Delhi epidemic of infectious hepatitis. Br Med J 1966; **2:**676–679.
33. Ramalingaswami V, Nayak NC. Liver disease in India. [In] Popper H, Schaffner F, eds. Progress in Liver Disease. vol 3. New York: Grune-Stratton, 1970, pp 222–235.
34. Nayak NC, Roy S. Ramalingaswami V, Sachdeva R. Hepatitis-B virus and Indian childhood cirrhosis. Lancet 1975; **2:**109–111.
35. Srivastava JR, Devi PS. Virological basis of Indian childhood cirrhosis. Indian Pediatr 1977; **14:**167–168.
36. Chandra RK, Chawla V, Verma IC, et al. Hepatitis-associated antigen and depressed cellular immunity in Indian childhood cirrhosis. Am J Dis Child 1972; **123:**408–409.
37. Sehgal S, Aikat BK, Bhattacharya T, et al. Immunological studies in Indian childhood cirrhosis. Indian J Med Res 1977; **65:**89–94.
38. Nayak NC, Chawla V, Malaviya AN, Chandra RK. Alpha fetoprotein in Indian childhood cirrhosis. Lancet 1972; **1:**68–69.
39. Agarwal SS, Mehta SK, Bajpai PC. Alpha fetoprotein in Indian childhood cirrhosis. Lancet 1974; **2:**175–176.
40. Sehgal S, Walia BN. Alpha fetoprotein in Indian childhood cirrhosis. Lancet 1975; **2:**1144–1145.
41. Parekh SR, Patel BD. Epidemiologic survey of Indian childhood cirrhosis. Indian Pediatr 1972; **9:**431–439.
42. Bhagwat AG, Medline A. Indian childhood cirrhosis in a 10-year-old Mexican boy in Canada? (To be published)
43. Bhagwat AG, Walia BN, Koshy A, Banerjee CK. Ultrastructural spectrum of liver in Indian childhood cirrhosis. (To be published)
44. Ramalingaswami VV, Roy S, Nayak NC. An ultrastructural study of the liver in Indian childhood cirrhosis with particular reference to the structure of cytoplasmic hyaline. Gut 1971; **12:**693–701.
45. Parekh SJ, Patel BD, Dempo K, Mori M, Onoe T. Electron microscopy of Indian childhood cirrhosis. Bulletin of Jaslok Hospital and Research Centre 1981; **6:**42–46.
46. Bhagwat AG, Koshy A, Deshpande JV, Walia BN, Pendharkar VG. A statistical approach to Indian childhood cirrhosis—why and how? A preliminary communication. Bulletin of Postgraduate Institute of Medical Education and Research 1982; **16:**99–107.
47. Bhagwat AG, Koshy A, Deshpande JV, Walia BNS, Pendarkar VG. A proposed statistical model for Indian childhood cirrhosis (ICC) (abst). Fed Proc 1983; **42:**510.