

## Indian childhood cirrhosis

The frequency with which cirrhosis of the liver is seen in infants and children in India is in contrast to its relative rarity in temperate climates. Among this group of children with cirrhosis, and contributing largely to it, are those with Indian childhood cirrhosis (ICC).<sup>1</sup> Sen's original description of this condition in 1887 as 'a disease which grows worse in spite of all treatment eventually terminating in the death of the patient' remains true.<sup>2</sup> The recent demonstration<sup>3-7</sup> of an exceedingly high copper content in the liver in ICC has far-reaching implications and effective treatment, or even prevention, may become possible. The need for accurate definition and early diagnosis is also stressed. The efficacy of D-penicillamine in Wilson's disease<sup>8</sup> makes its attempted use in ICC inevitable, but widespread adoption of this treatment must await the results of properly conducted clinical trials, and a prerequisite for these is a clear definition of cases.

A typical child with ICC arrives at hospital between ages 9 months and 5 years, most commonly in the second year of life.<sup>9</sup> The history is of gradual and progressive abdominal distension. The liver has a characteristically hard consistency and a sharp edge. Jaundice is often the symptom precipitating admission, and usually heralds the terminal stage of the disease which ends within weeks or months in death from bleeding, anaemia, secondary bacterial infection, or hepatocellular failure. At this stage, a fairly confident clinical diagnosis of ICC can be made, particularly if the child is among the 30% who have a family history of the condition.<sup>9</sup> However, in the earlier stages of the disease, or in those children who present atypically with a hepatic illness, clinical diagnosis is unreliable. Standard liver function tests are not discriminatory, and serum copper and ceruloplasmin concentrations are normal.<sup>10-12</sup> Thus, the cornerstone of diagnosis is the liver biopsy.

The histological changes seen in advanced cases are well documented.<sup>9</sup> All of the hepatocytes look damaged, being ballooned, vacuolated, or necrotic; many contain hyaline inclusions identical with those seen in alcoholic liver disease, Wilson's disease, or late primary biliary cirrhosis. There is a variable inflammatory infiltrate. Aggressive intralobular pericellular fibrosis occurs, and, as there is poor regeneration, single cells or small groups of cells come to be surrounded by collagen, forming a 'micro-micro nodular cirrhosis'.

These appearances define ICC as we,<sup>3-4</sup> and others,<sup>9</sup> have used the term. In ICC so defined, almost every hepatocyte contains multiple, coarse, dark brown orcein-staining granules which represent copper-associated protein.<sup>13</sup> This appearance is seen in no other hepatic disorder in this age group. We suggest that in future studies of ICC, orcein-staining deposits should be a histological criterion for diagnosis.

Although advanced cases of ICC may therefore be clearly identified, these children have severe and probably irreversible liver damage. Attempts must be made to diagnose ICC at a much earlier stage, a formidable task. The early symptoms—such as malaise, sleeplessness, irritability, or abdominal distension—are nonspecific.<sup>14</sup> The only early physical sign is hepatomegaly, for which there are many other causes in Indian children. Histological diagnosis is also extremely difficult, for the changes which are described in infants who later developed ICC were nonspecific—namely, hepatocyte vacuolation and inflammatory infiltration.<sup>15</sup> If, as believed, hepatic copper accumulation is the primary abnormality in ICC, then copper-associated protein should be demonstrable by orcein staining at an early stage. However, this remains to be confirmed.

If it is indeed found that a group of infants exists in whom there is hepatic copper accumulation and minor histological abnormality, a further difficulty arises, for it is not known whether all such infants would proceed to advanced ICC, or only some of them.

Clearly the cause of the increased hepatic copper concentration in ICC requires urgent elucidation. The simplest, and clinically most desirable, explanation would be an excessive copper intake. The hepatotoxicity of ingested copper in animals is well recognised, both experimentally and in sheep grazing on copper-contaminated pastures.<sup>16</sup> Acute copper poisoning in man is sufficiently well known for Chuttani *et al.*<sup>17</sup> to be able to collect 53 cases of suicidal copper sulphate ingestion in New Delhi, but there are only scattered reports of chronic copper ingestion in man. For example, the liver disease of Portuguese vineyard sprayers has been attributed to the inhalation of Bordeaux mixture.<sup>18</sup> A single case report of an Australian boy who died at age 14 months with cirrhosis and with a very high hepatic copper content (3360  $\mu\text{g/g}$  dry tissue) is of great interest because the histological appearances were

identical with those of ICC; in his case, copper poisoning was attributed to a high copper content in the drinking water.<sup>19-20</sup> Since the newborn has a modestly increased hepatic copper concentration,<sup>21</sup> and (in the rat) an impaired ability to excrete a copper load,<sup>22</sup> it is possible that the newborn infant and fetus may exhibit increased hepatic copper storage and hepatotoxicity when subjected to a copper load which is tolerated by the older animal, and this might provide an explanation for the age incidence of ICC.

An explanation is also required for the familial clustering of ICC. There are three possibilities. Firstly, if ICC is due simply to excessive copper ingestion, siblings sharing the same diet and environment are equally likely to be affected.

Secondly, ICC may be another inherited abnormality of copper metabolism, resembling Wilson's disease or the copper toxicosis of Bedlington terriers.<sup>23-24</sup> The fact that no clear pattern of inheritance is demonstrable<sup>25</sup> may be due to poor 'penetrance', either of the genotype in causing copper storage or of the copper storage in causing hepatic damage. Against this hypothesis is the geographical restriction of ICC to India, and its apparent absence in Indian expatriates in the UK, Africa, or North America.

Environmental factors must be at least partially responsible, and the third possibility therefore is that both an inherited abnormality and an increased copper load are necessary to produce ICC. The fact that animals may vary with respect to their predisposition to copper toxicosis is illustrated by the variation between species. Whereas the rat is fairly resistant, the sheep and the dog are more susceptible; in the dog, this susceptibility has been attributed to a reduced affinity of serum albumin for copper.<sup>26-27</sup> A more bizarre example of genetic variation is provided by sheep of the Orkney breed from North Ronaldsay, which survived for many generations on a copper-poor diet consisting largely of seaweed; when given a normal diet they succumbed to copper poisoning.<sup>28</sup>

Even if children with ICC are genetically normal with respect to their copper metabolism, there may not be a simple relationship between copper intake and copper absorption. For example, other trace elements—such as zinc or molybdenum—impair copper absorption.<sup>29-30</sup> The availability of dietary copper varies between different foods, and it is of great interest that copper is well absorbed from milk. Suttle<sup>31</sup> found that the availability of copper in suckling lambs might be as high as 70%, decreasing to only 10% on weaning. Many infants with ICC have been fed entirely on milk, either breast, bottle, cows', goats', or a mixture of these. (The con-

dition was said in 1887 not to occur in 'cases brought up by a healthy wet nurse',<sup>2</sup> but this remains to be confirmed.) These considerations provide a further possible explanation for the age incidence of ICC.

A final theoretical possibility is that the ingestion of another agent might interfere with the hepatic excretion of copper. Such a mechanism has been suggested to explain the hepatotoxic effects of pyrrolizidine alkaloids of the plant *Heliotropium europaeum*.<sup>32-33</sup>

Thus, the finding of a raised hepatic copper concentration in ICC poses many questions. The hypothesis is advanced that, whether it results from excessive copper ingestion, or from increased copper availability in the food, or from an inherited or acquired abnormality of copper metabolism, hepatic copper accumulation is of pathogenetic importance in ICC. Such a hypothesis must stimulate further research in this disease.

We thank colleagues in India who allowed us to study their patients.

Financial support was provided by Action Research for the Crippled Child, H J Heinz Company Limited, the Wellcome Trust, and the Wates Foundation.

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