Section of Experimental Medicine and Therapeutics

President—Professor H. P. HIMSWORTH, M.D.

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Nutritional Liver Disease in West Indian Infants

By J. C. WATERLOW, M.B.

A DISEASE occurs among babies in the West Indies, whose main features are œdema, gross muscular wasting, and fatty infiltration of the liver. The onset is usually in the second six months of life, within three months of weaning. The presenting symptoms are vomiting and œdema. The œdema is of the hypoproteinæmic type, without albuminuria. The mortality of the disease is high and death appears to be due to hepatic failure. Analysis of the liver in fatal cases shows a fat content of up to 50% of the fresh weight. Hepatic functional impairment may be demonstrated during life by the bromsulphalein test. Other liver function tests, such as the colloidal gold test, and measurements of serum phosphatase, have given negative results. The presence of fatty infiltration can be confirmed by histological examination of liver tissue removed by aspiration biopsy.

This syndrome resembles closely the disease known in Africa as kwashiorkor, or infantile pellagra. In the African cases there are typically severe lesions of the skin and mucocutaneous junctions, and depigmentation of the hair—changes attributable to deficiency of riboflavin and of other members of the vitamin B_2 complex. The condition has generally been looked upon as the result of a mixed deficiency of protein and of B vitamins, and it has been suggested that the fatty liver is a manifestation of pellagra (Gillman and Gillman, 1945*a*) or of ariboflavinosis (Hughes, 1946). However, in the West Indian babies lesions of the skin, hair and mucosæ were seldom severe and were sometimes absent. In no case would the diagnosis of infantile pellagra be appropriate. In spite of this, the condition, judged by the mortality rate and by the degree of fatty infiltration of the liver, was no less severe than in Africa. This suggests that fatty liver in infants should be regarded as a disease *sui generis*, which may or may not be associated with signs of vitamin deficiency. For simplicity's sake it will be called the "fatty liver disease".

Certain objections have to be met before fatty liver in infants can be accepted

as a specific entity. It is well known that severe fatty infiltration of the liver is found in infants dying of conditions such as gastro-enteritis or bronchopneumonia. But although the end-result may be the same in gastro-enteritis and in fatty liver disease, there may be a difference in the mechanism by which the fat accumulates in the liver. It is probable that in wasting diseases and in infections the fat in the liver is endogenous, derived from the body stores. It is suggested that in fatty liver disease the fat is exogenous, derived from the food. There is typically a history of feeding on a diet consisting mainly of starchy foods, low in protein and vitamins but with a high calorific value. Moreover, even in severe cases the fat depots are not entirely depleted; considerable quantities of subcutaneous fat are found at post-mortem. It is of interest that in the condition described by the German pædiatricians as "Mehlnährschaden" and attributed to overfeeding with carbohydrate, an intensely fatty liver has been observed (Huebschmann, 1921; Saito, 1924).

Overloading with calories is only one factor in producing fatty liver in these babies. It is generally agreed, and the evidence is very strong, that the underlying cause is a dietary deficiency of some kind. Experimentally the most widely studied type of dietary fatty liver is that produced by choline deficiency. The effects of choline deficiency can be prevented by methionine, which acts as a source of labile methyl groups. Inositol has a lipotropic action which is synergistic to that of choline. However, in babies with fatty liver, in the small number of cases tested in the West Indies, neither choline, methionine nor inositol appeared to have any effect in improving the condition of the liver or in saving life. Vitamin B_1, riboflavin, and nicotinic acid have been tried by workers in Africa with equally unsatisfactory results. On the other hand, good results have been obtained by the use of crude substances. Gillman and Gillman (1945*b*) in Johannesburg reported an excellent response to dried stomach. This has been both confirmed and denied (Trowell, 1946; Gelfand, 1946). In the West Indies it was found that a striking improvement occurred with no other treatment than an increased intake in milk. These results were controlled as far as possible by placing cases on a low milk intake for a preliminary period. On an intake of 7 to 8 oz. daily the condition remained more or less stationary; when the intake was increased to 30 oz. there was a rapid loss of œdema, a rise in serum protein concentration, and in dye clearance, and a more gradual decrease in the size of the liver. Serial biopsies showed a concomitant decrease in the severity of the fatty infiltration. No comparison is available between the effects of milk and of dried stomach. Our effort was directed to obtaining a base-line for the effects of milk alone, because all practical diets for babies must contain some milk. Until its action is known, it is impossible to investigate accurately the effectiveness of other substances. There is an urgent need for systematic fractionation and assay of the crude materials found effective. The isolation of an active substance which could be given parenterally would undoubtedly save many lives, since in severe cases oral treatment is made difficult by persistent vomiting.

All the evidence—the history, the associated lesions (hypoproteinæmic œdema and dermal and mucosal changes) and the response to treatment—suggests that the underlying deficiency in this fatty liver disease is either of protein or of some member of the vitamin B_2 complex; but it is not yet possible to choose between these alternatives. Reasons have already been given to suggest that neither riboflavin nor nicotinic acid is involved. Little is known about the possible rôle of the other B vitamins, apart from choline and inositol: but it is significant that good results in treatment have not been obtained with yeast. On the other hand, œdema is very constant in severe cases. There is gross macroscopic and micro-

scopic wasting of muscles. Analyses of the liver in five fatal cases show a 20% decrease in the non-fatty solids, which are mainly protein. There is thus evidence of depletion in the three most important protein reservoirs of the body. Recent work on dogs (Fouts, 1943; Li and Freeman, 1946) has suggested a relation between protein deficiency and fatty liver. This type of fatty liver does not depend upon deficiency of methyl groups, since it is neither prevented nor cured by choline.

The cause of the fatty liver disease in infants is therefore still unknown. There is also much to be learnt about its natural history. In the course of the field investigations in the West Indies the question arose of how to recognize the disease in its early stages. In established cases that were responding successfully to treatment, it was found that the liver remains enlarged and, as shown by biopsy, still contains some fat for some time after the disappearance of the œdema and the restoration of normal serum protein concentration and dye clearance. It therefore seemed logical to suppose that in the development of the disease the reverse sequence occurs: that the first stage is a gradually increasing fatty infiltration and enlargement of the liver. Cases were found with enlargement of the liver but without other clinical or biochemical abnormalities, and with no evidence of malaria or

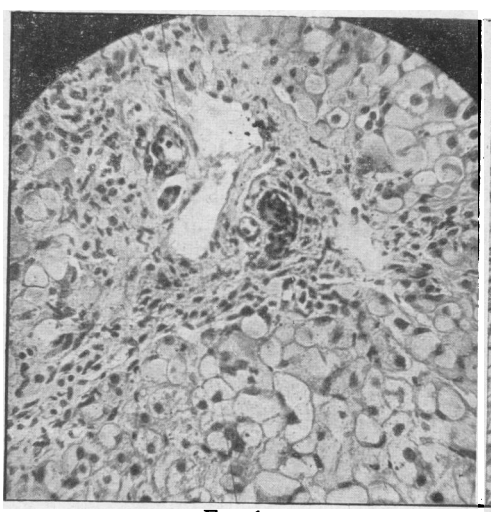

FIG. 1.

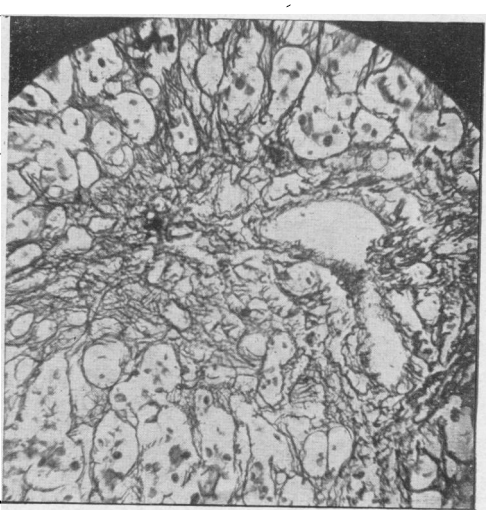

FIG. 2.

FIG. 1.—Liver. Biopsy specimen. Hæmatoxylin and eosin. × 187. There is cellular infiltration of the portal tract, and an increase of connective tissue. The liver contained no fat at the time that this biopsy was taken. The vesicular appearance of the hepatic cells is caused by the presence of glycogen. This specimen was taken from an infant aged 16 months, with enlargement of the liver, reduced hepatic function, œdema, and ascites.

FIG. 2.—As fig. 1. Silver impregnation (Gömöri's method) × 187. There is an increase of silver-staining fibres in the portal tract, and an outgrowth of fibres into the parenchyma, to form a fine network, surrounding some liver cells at the edges of the lobules.

syphilis. Biopsy of the liver in two such cases showed a moderate degree of fat, which was much decreased after one week on a high milk intake. This response to improved diet suggests that, in spite of the good clinical condition of the babies, fatty infiltration of the liver cannot be regarded as normal. It seems probable that such infants represent early or larval cases of the fatty liver disease, many of which become spontaneously cured. Babies with symptomless enlargement of the liver were common in the West Indies: they were more common in the second than in the first six months of life, which suggests that the enlargement was not merely an exaggeration of the physiological condition of the liver in the newborn.

In the age-group 6 to 18 months, definite enlargement of the liver (liver edge one fingerbreadth or more below the costal margin), not associated with signs of syphilis or enlargement of the spleen, was found in 10% of unselected infants. If the hypothesis outlined above is correct, then the fatty liver disease, at any rate in mild grades, must be regarded as a common condition in the West Indies. From the practical point of view, as regards prevention and treatment in infant welfare clinics, it might be said that enlargement of the liver without enlargement of the spleen is an indication for a supply of extra milk.

Finally, there is evidence that there may be late sequelæ in cases which neither die nor recover completely. In Jamaica cirrhosis of the liver in childhood is not uncommon. A series of cases was described by McFarlane and Branday (1945) with an average age of 5 years. Experimentally it has been shown both in rats (Lillie *et al.*, 1942) and in dogs (Chaikoff *et al.*, 1938) that fatty infiltration of the liver may proceed to cirrhosis. In human pathology, a similar sequence has been described in diabetes and in chronic alcoholism (Connor, 1938). It therefore seemed probable that cirrhosis of the liver in children in the West Indies might be the result of preceding fatty infiltration in infancy. An attempt was made to collect by means of liver biopsy pathological material to demonstrate this sequence of events. This material is as yet far from complete. The earliest change that has been seen is a thickening of the portal tracts, with round-cell infiltration and some proliferation of fibrocytes. This has been found in an infant 1 year old with a fatty liver of at least three months' standing. The next stage appears to be an outgrowth of reticulin fibres into the parenchyma from the portal tracts; these fibres penetrate between the hepatic cells at the edge of the lobule, and surround them. This has been seen in a child of 16 months (figs. 1 and 2). At a still later stage, some of the ingrowing fibres develop the histological characteristics of collagen, forming bands traversing the liver lobule. At this point the normal architecture of the liver begins to be destroyed. This pathological picture has been found in a child of 18 months with signs of portal destruction.

In rats, Himsworth and Glynn (1944) have described two types of dietary cirrhosis: in the first the fibrosis is diffuse, follows fatty infiltration and is caused by choline deficiency; in the second the fibrosis is coarse, follows massive necrosis, and is caused by deficiency of sulphur-amino-acids. In the infants described, the fibrosis was diffuse, with no sign of necrosis; there is therefore no resemblance to the second of the two sequences in the rat, and no reason to look upon sulphur-amino-acid deficiency as a possible cause.

Cirrhosis of the liver is much commoner in tropical than in temperate countries, with a high incidence in the fourth decade of life. Reports from all parts of the world show that this cirrhosis is predominantly of the diffuse Laennec type, often accompanied by fat. There is at present no evidence that "tropical cirrhosis" is a dietary disease: but the sequence of events that has been described in infants and children in the West Indies, which leads to an identical pathological picture may help to throw some light on its pathogenesis and cause.

The suggestions put forward in this paper are based on the preliminary findings in a small number of cases, and are therefore to be regarded as tentative, until supported by further evidence.

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Dr. P. Ellinger: I fully agree with Dr. Waterlow that the condition he has described has nothing to do with real pellagra and I regret that by some authors it has been called infantile pellagra. Amongst hundreds of pellagra cases which I saw in Egypt in 1937 and 1938, as far as I can remember, there were no children below 4, the critical age of the nutritional liver disease. I examined in numerous villages of the Delta parts of the population selected at random. Amongst the people examined were numerous small children below 4 all of whom were free but pellagra was very frequent amongst children between 4 and 10 years.

I was also allowed to examine the post-mortem reports of the Department of Pathology of the Faculty of Medicine of the University of Cairo for reports on pellagrins. They were not very numerous but I could not find any remark on liver damage found in these pellagra post-mortems.

Some Renal Effects of Experimental Dietary Deficiencies

By H. HELLER, M.B., Ph.D., and S. E. DICKER, M.D.

Dr. H. Heller: Liver lesions may be produced experimentally by feeding protein-deficient diets and it has been recently suggested (Himsworth and Glynn, 1944) that hepatic poisons act ultimately by reducing the supply of protective protein derivatives to the liver. Now many of the toxic factors which produce liver damage also give rise to lesions of the kidneys. The question arose, therefore, whether chronic protein deficiency may damage the kidney as well as the liver.

Following this idea it was decided to investigate the kidneys and the water metabolism of animals fed on various protein-deficient diets. The diet first used was modelled on the type of food which, in concentration and prison camps, has frequently been reported to lead to hypoproteinæmia and œdema, namely a protein-deficient vegetable diet of low calorific value. The supply of this diet which consisted essentially of raw turnips, starch, fat and adequate amounts of vitamins, was not restricted but its calorie value was so low that the amount eaten per animal per twenty-four hours provided only one-third of the number of calories supplied by the control diet. Other rats received a diet of the same composition but with fresh carrots taking the place of fresh turnips. These diets, while containing less than 0·9% of vegetable protein, contained sufficient amounts of choline to eliminate a deficiency of that substance.

Adult rats fed on the protein-deficient vegetable diets lost weight rapidly (about 35% of the initial body-weight in forty days). The mean plasma protein level fell from 7·6 to 4·7 grammes/100 c.c. in the same time. Externally there was little amiss. There was no diarrhœa. A sudden increase in body-weight occurring after a period of steady loss of weight was interpreted as due to accumulation of œdema fluid. The presence of ascites was subsequently verified in some of these animals. Ascites could also be frequently induced by giving 5% of the animal's weight of water by stomach tube. Diuresis experiments showed that only about half of the normal amount of water was excreted in the urine, thus confirming this tendency to water retention. Measurements of urinary specific gravity showed