

# RES MEDICA

Journal of the Royal Medical Society



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### Abstract

Based upon a Dissertation on "Hepatic Cirrhosis" given before the Society on Friday, 31st January 1958.

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1. The Tropical and Subtropical Clinical Syndromes—The Kwashiorkor Syndrome.
2. Alcoholic Liver Injury.
3. Liver Injury caused by Protein Deficiency secondary to other disease.

The experiments carried out on rats in the field of nutritional liver damage are well known. For this reason, and also because their aetiological relationship to dietary liver injury in man seems to be limited, a brief resume of these will suffice.

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ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)

Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Spring 1958, 1(2): 23-28

[doi:10.2218/resmedica.v1i2.313](https://doi.org/10.2218/resmedica.v1i2.313)

# Some Aspects of Nutritional and Toxic Liver Injury

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By A. W. DELLIPIANI

The problem of nutritional liver damage and cirrhosis has been made easier and at the same time more difficult as a result of animal experiments and attempts to apply them to man. The clinical syndromes of nutritional liver injury are best classified according to the method of Sherlock:

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The experiments carried out on rats in the field of nutritional liver damage are well known. For this reason, and also because their aetiological relationship to dietary liver injury in man seems to be limited, a brief resumé of these will suffice.

It has been found that essentially two types of nutritional injury can be caused in the rat—

- (a) Fatty infiltration—This is of centrilobular distribution and is the result of lack of choline and its precursors, the so-called lipotropic substances.
- (b) Acute liver atrophy—This is the result of feeding diets low in sulphur containing amino-acids and especially cystine.

The first of these, if of sufficient severity, progresses to a Laennec cirrhosis, whilst the latter, if the animal survives, gives rise to post-necrotic scarring. Protein protects against these lesions and methionine, because of its content of labile methyl groups, plays an important dual role.

How are these findings to be applied to man? Let it be said straight away that there is no evidence that in man dietary deficiency is ever a direct cause of post-necrotic scarring subsequent to acute yellow atrophy. That it might be a conditioning factor has been suggested, especially by Himsworth and Glynn, in such conditions as the acute or sub-acute necrosis of pregnancy or in poisoning. This aspect will be discussed later, but firstly the relationship between fatty infiltration in animals and the kwashiorkor syndrome will be considered.

Many varieties of this syndrome have been described. These depend on factors superimposed on the basic syndrome, such as iron in the siderotic cirrhosis of South Africa, the hepatotoxic alkaloid senecio in senecio poisoning in the same region, and also possibly in veno-occlusive disease in the West Indies, and the effects of fruits such as the ackee in the vomiting sickness of Jamaica.

A fatty liver is characteristic of kwashiorkor but one of the striking features is that, unlike the nutritional lesions in animals, it is histologically of portal distribution. However, the fact that in man a fatty liver does result from protein deficiency provides an encouraging analogy with animal findings. Rigorous proof of the association between protein deficiency and fatty infiltration in man is, however, difficult to obtain. Moreover, it would seem that fatty liver is not necessarily the most important lesion in

kwashiorkor, since the degree of infiltration seems to bear little relation to the severity of the disease. Again though the syndrome will respond to an improved diet, and especially milk, there is no clearcut evidence that choline or methionine will improve or even arrest the established condition. Thus the cause of fatty liver in man does not seem to be deficiency of the known lipotropic substances that affects the rat. The different zonal distribution of fat would seem to emphasise this and recently several groups of workers in the U.S.A., Canada, and India have succeeded in producing fatty infiltration in the rat liver which, as in man, is also perilobular. This was done using low protein diets and shows that although deficiency of this substance can indeed promote excessive deposition of fat in the liver, the mechanism by which it occurs is unknown.

A new approach to the problem introducing the humoral element has been prompted by observations on the altered pancreatic secretions which are known to occur in kwashiorkor. In a recent paper Gillman and Gilbert are impressed by the rapidity of onset of the fatty liver in the disease which leads them to suspect hormonal imbalance as responsible for the changes. In the baboon the development of the lesion seems to be dependent on a dynamic equilibrium between adrenocortical steroids, insulin, and thyroxine. In the absence of the pituitary, the administration of cortisone will promote the development of fatty livers in these animals provided that insulin is inadequate; excessive thyroxine increases the fatty deposition. The lesions are similar to those seen in kwashiorkor. Though much has still to come from this line of research, dietary influences are known to have a marked effect on human endocrine secretions, and such factors might well be of importance in promoting fatty deposition in a liver already suffering from protein lack, even though the signs of this may not be histologically detectable. Many writers are nowadays of the opinion that the primary change in kwashiorkor may well be in the pancreas.

Another problem is the relationship of the nutritional and the cirrhotic liver, and one would nowadays question the long accepted view that the one leads to the other. Though this is true of the experimental animal, Dible has pointed out that, if the same factors were to apply to man, more fat than is actually ever found in man's liver would have to act over a longer period of time than is actually the case. Thus, though the fibrous tissue might be a replacement fibrosis of cells killed by fat, as Hartroft showed in animals, it might also be that the fatty change found in such a liver is rather the result of disordered metabolism than the cause of the events which eventually lead to cell necrosis and subsequent cirrhosis.

Geographically there is, it is true, fairly close association between the incidence of kwashiorkor and Laennec's cirrhosis. Nevertheless in Brazil where fatty livers were until recently prevalent, the incidence of cirrhosis is low and the reverse is true in the Gambia. No one, it must be noted, has yet succeeded in showing a natural progression of fatty liver to cirrhosis by liver biopsy technique. In addition it must be remembered that though kwashiorkor is a childhood illness, cirrhosis is an adult one, and that though the incidence of kwashiorkor is equally distributed amongst the sexes, cirrhosis is five times commoner in the male. Though there might be some protective factor in the female the higher incidence of virus hepatitis in women, often with complicating massive necrosis in pregnancy, would, as Edington has pointed out, almost make one expect a higher incidence of cirrhosis in the adult female. In the three countries where true cirrhosis has been found to occur commonly in children—Jamaica, India, and the Gambia, in no case does the process seem to begin with fatty infiltration, and the stellate portal fibrosis which is often seen in kwashiorkor and which

many would consider the precursor of portal cirrhosis, has been seen in the absence of kwashiorkor, and indeed in the absence of fat. Dare one possibly suggest, therefore, that rather than the result of fatty change, cirrhosis itself is also a direct manifestation of alterations in the rhythm of the endocrine orchestra? However, in spite of these comments many would still favour the cause and effect association of fatty change and cirrhosis.

Nothing will be said about the third group in Sherlock's classification of aetiological factors in cirrhosis since, though liver changes are described in diseases involving primary pancreatic deficiency, ulcerative colitis and in such rare metabolic disturbances as the De Toni-Fanconi syndrome, extreme liver changes going on to cirrhosis are rare.

A note on the relationship of alcoholism and chronic liver change, a topic of much general interest, is more appropriate. One must accept that there is an association between the two. Sherlock quotes an 18 per cent. incidence of cirrhosis in alcoholics and the figures are said to be higher in America. If one accepts the association one must either postulate a direct effect by this drug, an indirect one via a nutritional mechanism, or even a combination of both. In favour of the first approach one recalls the disastrous effects which alcohol may have in a patient convalescing from infective hepatitis, or the precipitation of hepatic coma in a patient with cirrhosis.

It is well to recall at this point the experiments of Best and his associates carried out in 1949. As a result of very carefully controlled work, they concluded that there is no more evidence of a specific toxic effect for pure alcohol than there is for sugar. This conclusion was based on the observation that dietary supplements of sucrose given to rats on basal diets caused hepatic lesions identical to those caused by an isocaloric amount of alcohol. These results suggest that an imbalance between caloric intake and the supply of relative food factors is the cause of the hepatic lesions. There is, in other words, a relative lack of lipotropic agents. As has already been mentioned, these substances might not be of the same importance in man, but there is little reason not to suppose that a relative protein deficiency produced by alcohol in man might well condition a fatty liver going on to cirrhosis—that is if this latter association is accepted.

However, if the harmful effects of alcohol were due solely to the increased caloric intake then they should be abolished by restricting calories. When this is done in rats, one group of which is given alcohol and the other sucrose, the alcoholic rats show more advanced liver lesions than the sucrose fed animals. Thus Best's experiments do not tell the whole story.

One cannot therefore rule out a direct toxic effect by alcohol though it would seem that this is probably small and not as important as the relative protein deficiency induced by the substance. A true protein deficiency is often an additional factor since its cost makes it a luxury. Chronic gastritis and pancreatitis may produce a vicious circle. Alcoholics often show the signs of general dietary deficiency and on the whole alcoholic portal cirrhosis falls into place alongside pellagra, beri-beri, and Wernicke's encephalopathy as a dietary deficiency conditioned by chronic alcoholism.

Even more interesting than nutritional liver damage, and not entirely unassociated with it, is the problem of toxic liver injury. The importance of this as a causative factor in cirrhosis has probably been exaggerated in the past. Himsworth, subsequent to animal observations, divided the hepatotoxic agents into two groups. The first contains those which produce zonal necrosis and the other those agents which produce massive necrosis conditioned by dietary deficiency.

1. *Producing Zonal Necrosis.*

(a) Chemicals—Industrial carbon tetrachloride, chloroform, phosphorus, and tannic acid.

(b) Intoxications—e.g. Eclampsia.

(c) Infections—The yellow fever, I.H. and S.H. viruses.

2. *Producing Conditioned Massive Necrosis.*

(a) Industrial Chemicals—Trinitrophenol, dinitrophenol, dinitrobenzol, trinitrotoluol, tetrachloroethane.

(b) Drugs—Cincophen, plasmoquin, mepacrine.

(c) Toxic Grain—Selenium poisoning.

Taking this classification in conjunction with the pathology makes it unlikely that toxic liver injury should be a common cause of cirrhosis.

The characteristic finding in the first group is the tendency for the reticulum to remain patent so that even in severe zonal degeneration cirrhosis does not occur, recovery being complete in about two weeks in animals. This is due partly to the maintained reticulum, the preservation of the blood supply and the zonal distribution of the lesion which leaves a sufficiently large number of cells in the lobule to permit regeneration. Repeated doses of the irritant acting at intervals which are so short that they impose a new lesion on one which is not yet healed, however, result in a fine and typically uniform fibrosis. At this point it must be stressed that Himsworth believes that zonal necrosis is a pure lesion because all the evidence suggests that massive necrosis is not a severe and fulminating variety of the zonal type.

This introduces the importance, if any, of virus hepatitis as a causative factor of cirrhosis. This has been discussed often and at length with the object of trying to fill the gap in the aetiological classification of the cirrhoses. In this country where diet and alcohol play but a minor role in the aetiology of chronic hepatitis, it would be not only convenient, but also of considerable satisfaction to explain away most of the cryptogenic group as post-hepatic. Ratnoff and Patek and Sherlock give figures of 6.5 per cent. and 33 per cent. respectively for the incidence of a history of previous jaundice in their groups of cirrhotic patients. In the same group Sherlock found that 49 per cent. of the patients gave no history which might indicate an obvious aetiology. The cryptogenic group is indeed large. It has, however, been pointed out that in an epidemic of virus hepatitis, a large number of cases occur in which jaundice is not manifested and which are difficult or impossible to recognise clinically. Needle biopsy studies reveal that in these subjects obvious lesions occur and that these cases may take as long, if not longer, to recover complete good health as those in which jaundice is great. One is therefore tempted to suggest that a non-icteric lesion might rarely lead to cirrhosis.

Looking at the pathology more closely, the human lesion is typical of the zonal type which Himsworth observed in animals. Mild cases show a predominantly central zonal lesion by liver biopsy technique, whilst in severer cases the lesion is more extensive but still zonal, the incidence of acute yellow atrophy being rare. The fascinating tendency for a maintained reticulum is marked and recovery, which is complete, is said to be the rule in 99.8 per cent. of cases.

In those cases where cirrhosis supervenes, the mechanism might be, as Himsworth suggests, repeated attacks of hepatitis before healing from a previous attack has been completed, this resulting in a disorganised reticulum with subsequent fibrosis. In any zonal lesions its exact distribution, whether mid, central or peripheral zonal, is a mystery though the presence of definite vascular territories has been suggested as an explanation.

Though fibrosis might depend on the original zonal location, it would seem impossible to forecast which part of a regenerating nodule would be most vulnerable to the repeated destructive action of the same irritant and hence where fibrosis might begin. Eventually, however, the picture would be indistinguishable from that of the typical Laennec cirrhosis.

This, however, is not the whole story, and many pathologists would prefer to believe that post-hepatitis cirrhosis is really the result of acute yellow atrophy, and that the post-necrotic scarring which results eventually becomes histologically indistinguishable from the classical Laennec type, via progressive fibrosis and contraction of fibrous bands. There is little doubt that as a result of the regeneration and fibrosis which constitute post-necrotic scarring, there is a tendency for freer communication between the hepatic and portal veins than exists in the normal liver, this change occurring especially at the periphery of the regenerating nodules and in the fibrous septa. The portal blood is therefore shunted past the nodules which come to rely more and more on the arterial supply. There is therefore likely to be further necrosis, a diminution in the size of the nodules, a rearrangement so as to provide a more favourable distribution of blood supply, and, in general, a maintenance of the cirrhotic process which will tend to alter the picture of post-necrotic scarring through time to one approximating to that of the Laennec variety. This would explain the variability in size of the nodules and in the width of the fibrous bands which is sometimes seen in post-hepatitis cirrhosis and which would seem to indicate that the cirrhosis had its origin as a post-necrotic scarring.

One is therefore left with the possibility that post-hepatitis cirrhosis is: (a) the result of organised sub-acute liver atrophy, or (b) the result of repeated attacks of zonal necrosis.

That a non-icteric attack of hepatitis might give rise to cirrhosis is of course inconsistent with the first view, but not unlikely if the second is accepted. Sherlock seems to be in favour of the first view, but also points out that even in a zonal lesion where there is much centrilobular loss of liver cells, there is condensation of reticulum. This might conceivably go on to cirrhosis and is a convenient way of steering between the above groups. The problem is therefore involved, and one might further suggest that there is no reason why both methods should not operate in the causation of post-viral cirrhosis. Dible does in fact suggest that a massive necrosis is merely a farther step in the process of zonal necrosis. As has been mentioned, however, Himsworth prefers to believe that each lesion is one in its own right and that when massive necrosis occurs in man, it is a lesion conditioned by nutritional factors. This introduces the second group of substances in Himsworth's classification. (See Table.)

There is some evidence that these substances produce their lesion when conditions are rendered suitable by dietary deficiency. Thus though 25 per cent. of industrial workers exposed to TNT develop symptoms other than in the liver, only 0.2 per cent. develop acute yellow atrophy, and a nutritional basis is the most likely. In animals there is some evidence that this substance acts by raising the B.M.R. thus possibly outrunning the liver's demand for cystine. Similarly it is suggested that selenium produces its toxic effects by replacing sulphur in cystine which is rendered unavailable. There is of course the danger of applying these results from animals too dogmatically to man without sufficient direct evidence. However, whatever the mechanism, if such a view as to the aetiology of massive necrosis in man is correct in respect to chemical agents, it is tempting and perhaps not totally unjustified to apply the same to infective agents. Thus pregnant women seem particularly liable to develop massive necrosis subsequent to virus hepatitis.

Although it is true that cases have been described in which recovery from the disease has been noted in spite of proteinaemia and although massive necrosis has been observed in well nourished people, it is difficult to refute the evidence of the occurrence of that complication in Denmark during the late war years, or in central Europe between 1915-20, as not indicative of a predisposing nutritional element.

Before ending this article, the probable importance of multiple factors operating in the causation of hepatic injury must be emphasised. Himsworth is of course the protagonist of this view and it has been brought to the fore recently by Waterlow and Bras. In the animal liver, at least, nutrition is important in determining the susceptibility of the organ to the effects of irritants. Waterlow and Bras stress the fact that the liver may show no histological evidence of this in the early stages. Thus in animals, even before fat appears in the cells, there occurs a loss of several cytoplasmic constituents, protein, phospholipids and ribonucleic acids as a result of protein-deficient diets. This must involve some compromising loss of liver enzymes. There is no reason why this should not apply to man also. Thought along these lines has led to the recent revival of the concept that malaria might after all be a cause of cirrhosis, in the Gambia for example, where cirrhotic livers are found in children in the presence of malnourishment though fatty livers are uncommon.

Thus it seems that toxins and infections, whether bacterial, viral or parasitic, or even, as we have seen more recently, humoral agents, when combined with malnutrition might play an important role in the causation of chronic liver damage, but there is still much to be learnt about the pathogenesis.

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