WHAT IS IMPORTANT IN THE TREATMENT OF LIVER DISEASE *

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In the treatment of liver disease, clinicians in recent years have agreed rather well on the general value of rest, nutritious diet and, where there is a history of alcoholism, abstinence from alcohol. But this is a broad statement, and one can immediately ask the question, How strict should the rest program be and just what should constitute the nutritious diet? Further, one must determine the true importance of many other factors that have come on the scene: vitamins, lipotropic substances, adrenal hormones, testosterone, low sodium diet, intravenous amino acids, intravenous serum albumin, and various elective surgical procedures. With this rather imposing array of therapeutic measures available to him, the clinician must be critical in his thinking and selection to be certain that the truly important procedures are applied to his patient and that supplementary measures are used only in their appropriate places.

In terms of scientific research standards with adequate controls, it is not easy to prove just what is important in the treatment of liver disease. This point is illustrated in the experience of Klatskin and Yesner,[1] who observed patients with Laennec's cirrhosis during a control period of three to seven weeks under conditions of bed-rest, alcohol withdrawal and a minimal basic diet, all of which would exist in any such study of hospitalized patients. During this control period significant improvement occurred in the clinical status, liver function and histologic appearance of the liver by needle biopsy. The results allowed no conclusions as to the relative merits of the three factors known to be involved, but the study proved the merit of this basic treatment plan and illustrated clearly that care must be taken in assigning specific therapeutic value to a particular substance applied in the treatment of liver disease.

Rest and Activity

The importance of adequate rest in acute infectious hepatitis was best demonstrated in the Mediterranean campaign of World War II, when experience indicated that relapse was not uncommon among soldiers returned to duty early in convalescence, and that recovery was more likely to be complete if an adequate period of rest was allowed.[2] Although arbitrary criteria had to be established, it was difficult to determine the exact amount of rest necessary to obtain optimal results, and it was observed that the prescribed period of rest was growing steadily longer for a time because of fear of

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causing relapse, or of producing subsequent chronic hepatitis or cirrhosis. These patients were soldiers under the hardships of war, with strenuous physical exertion, excessive fatigue, and less than a totally desirable diet, and the disease was an epidemic variety.

Under the more desirable conditions of the postwar occupation of Germany from 1947 to 1949, the endemic viral hepatitis was apparently a milder disease than that observed in the Mediterranean area during World War II, and Swift and his associates [3] had the opportunity to observe the effect of exercise on the course of the disease during the acute period. Ninety-eight patients in various phases of viral hepatitis, but all with diminishing bilirubinemia, were divided into three groups of comparable character. One group was subjected to graduated exercises over a period of two weeks, beginning with bed exercises and progressing to standing calisthenics and ultimately terminating in a one-hour walk with 15 minutes of running. Another group was a control group kept at bed-rest for the two-week period, with bathroom privileges. The third group was composed of patients who were given strenuous calisthenics to the point of fatigue on the first day of the experiment, and thereafter were kept at bed-rest with bathroom privileges for the remainder of the two-week period. Except for activity, the patients in all three groups were given the same treatment in other respects, including a diet of 4,000 to 4,500 calories, consisting of 190 gm. of protein, at least 115 gm. of fat and 607 gm. of carbohydrates, with three multivitamin tablets daily. There was no significant difference in the over-all course and duration of the disease in the patients who were exercised and in those who were kept in bed. When the results were analyzed, however, according to the severity of bilirubinemia, those patients whose total serum bilirubin measured more than 3.0 mg. per 100 ml. at the time of exercise had a slightly longer period of convalescence. Likewise, there was no significant difference in the incidence of complaints or unusual physical signs in the various groups. In all the groups, occasional patients showed slight enlargement or increased tenderness of the liver at various times, and, in general, those patients who developed such findings during exercise and in whom exercise was continued had slightly longer convalescence. There were only minor differences in laboratory observations in the various groups. The final conclusions of these authors were that the specific exercise did not seriously alter the duration and severity of the disease process when the total serum bilirubin measured less than 3.0 mg., and that the only measurable effect of exercise in patients whose serum bilirubin measured 3.0 mg. or more was prolongation of the disease process by two weeks, with some increase in abnormal signs and symptoms.

While the specific exercise seemed innocuous in these patients, it is quite significant that all of these individuals were in a stage of viral hepatitis in which *the bilirubinemia was diminishing,* indicating that the patients had passed some peak in their disease process.

It was the practice at the Hepatitis Center [3] during the postwar occupation period to attempt to keep patients with viral hepatitis in bed, with bathroom privileges, for at least three weeks after the onset of symptoms, or until the patient was asymptomatic, without hepatic tenderness, and until the *one minute* serum bilirubin measured 1.0 mg.% or less. At this point in convalescence the patients were allowed out of bed, with the privilege of walking to the mess hall, theater or recreation rooms. When the one minute serum bilirubin measured less than 0.3 mg.%, and the retention of bromsulfalein was 5% or less 45 minutes after the intravenous injection of 5 mg./kg., and if the patient was asymptomatic, he was given a test of tolerance of exercise consisting of graduated calisthenics once daily for five days. If there was no clinical evidence of relapse, and if the retention of bromsulfalein remained normal, the patient was discharged to duty. Infractions against this regimen were common, even though it was considered somewhat lenient as compared to previous treatment.

The after-effect of such a therapy plan was partially investigated by Gardner and his associates,[4] who studied a number of patients, originally treated at this Hepatitis Center, after intervals varying from six months to one year following the acute hepatitis. There was no significant evidence of residual liver disease. When these patients were studied with particular reference to the strenuousness of physical exercise and the amount of alcohol consumed in the period between discharge and the follow-up examination, it appeared that neither factor played any significant rôle in the final outcome of the patients. A similar study by Nelson and his associates [5] on patients treated at the same center, two to three years after acute viral hepatitis, revealed a fair number of signs, symptoms and liver function abnormalities, but none of the liver biopsies on 40 patients showed any histologic evidence of incipient cirrhosis, chronic hepatitis or significant scarring of the liver. The authors assigned no clinical significance to the relatively mild subjective and objective findings, and their ultimate conclusion was that, on the amount of rest included in the original regimen, there was no evidence of residual hepatic disease two to three years later.

Kunkel and Labby,[6] on the other hand, reported five patients who developed definite evidence of severe cirrhosis two to six years after infectious hepatitis. They were definitely impressed by the fact that strenuous activity during the initial attack of the disease or during relapse was a contributing factor in the development of cirrhosis, as well as were such other factors as associated bacterial infection, alcohol and the age of the individual. Although rest and exercise were not the only factors involved, such observations are a warning to be cautious during the original attack of acute hepatitis.

In the case of chronic liver disease, rest has been considered of cardinal importance, but here there is more generalization about the subject and less specific evidence to prove the point. Basing their opinions principally on clinical experience and judgment, most clinicians [7,8] recommend an initial period of complete bed-rest as essential for lowering the general metabolic demands upon the liver. Prolonged and complete bed-rest is considered advisable for all patients with any acute exacerbation, or with such adverse findings as severe anorexia, digestive distress, jaundice, edema and ascites. Even when fibrosis has occurred and the pathologic process is thought to be relatively stationary, general restriction of physical activity, adequate rest and avoidance of fatigue are most important. These clinical opinions find good backing in the observation of Bradley and his associates [9] that a definite decrease in total hepatic blood flow occurs in the upright posture and during exercise in the form of bicycling against weights in the recumbent position. Both the horizontal position and the avoidance of physical exertion may be important factors.

With the evidence at hand, then, it would seem important to keep the patient with acute liver disease at complete bed-rest with reasonable bathroom privileges until there are definite clinical improvement and diminishing bilirubinemia. With good progress one might well lighten the restrictions by allowing simple diversions as the total serum bilirubin decreases significantly, with more privileges when the one minute serum bilirubin measures less than 1.0 mg.%, and, finally, test activities when bromsulfalein retention is 5% or less.

In chronic liver disease, admitting some empiricism, bed-rest is imperative in the initial portion of treatment and should be continued as long as there are such adverse signs as severe anorexia, digestive distress, jaundice, edema or ascites. As the patient progresses satisfactorily, such rest should be continued until all clinical abnormalities and serial liver function studies either return to normal or level off on a plateau with no further change. Finally, the individual should lead a life of restricted activity, avoiding strenuous physical exertion, avoiding fatigue and getting adequate sleep with rest periods in the horizontal position.

Nutrition

A nutritious diet is essential in the treatment of any form of liver disease. Again, experiences in World War II led to the conclusion that a high protein, high carbohydrate diet was an important part of the therapy of acute infectious hepatitis, and it was felt that the high protein constituent was the most important therapeutic factor.[2] In the case of chronic liver disease, there has been greater opportunity to analyze in more detail the importance of various factors in nutrition. Many investigators have reported over-all improvement in patients with chronic hepatitis and cirrhosis on a high protein, high carbohydrate diet.[7, 8, 10, 11]

The specific feature of protein has received great attention because studies have demonstrated a negative nitrogen balance in cirrhosis, with such severe nitrogen depletion that a high protein diet produces a striking, positive nitrogen balance that is maintained for many months of therapy. Cook and Van Auken [10] demonstrated daily nitrogen gains of 15 to 20 gm. by patients eating 150 to 250 gm. of protein per day, and this positive balance was often demonstrated for a year or longer after starting therapy. Morey and associates [11] had a similar experience with protein intakes of 2.5 gm. per kilogram of body weight, and were impressed by even greater nitrogen gain and more rapid clinical improvement when these diets were further supplemented by intravenous amino acids or salt-poor serum albumin.

Although it is slow, patients with cirrhosis receiving a high protein diet will show a progressive improvement in serum proteins and may revert to a practically normal electrophoretic pattern after treatment for many months.[12]

Eckhardt [13] studied the relationship of caloric intake and protein intake on patients with fatty alcoholic cirrhosis. Such patients were maintained on virtually protein-free diets but received adequate caloric intakes. Under these conditions there was definite clinical improvement, with decrease in liver size and tenderness and rapid fall in serum bilirubin, but throughout the study period nitrogen balance was persistently negative, and liver punch biopsies showed persisting moderate to marked fat content, initial low cellular protein content which further diminished, and moderate cellular glycogen content which progressively increased. When these same patients were then given high protein diet, a marked positive nitrogen balance was obtained and further improvement in clinical status and liver function continued but appeared less marked than the original. Liver punch biopsies then showed a progressive decrease in fat and a marked increase in protein content, and glycogen remained abundant. Thus it would appear that simple caloric intake will provide improvement in clinical status in liver disease, but only a high protein intake will overcome the serious nitrogen depletion. Such observations would provide adequate evidence in favor of the recommended carbohydrate intake of 300 to 500 gm. per day, to serve the various rôles of contributing to the total caloric intake, maintaining peak glycogen content in the liver cells, and exerting protein-sparing effect.

The question of optimal fat intake remains. In general, fat accomplishes the dual purpose of contributing heavily to the total calories of the diet and materially increasing the palatability of the diet to the average American. Colwell [14] demonstrated in acute hepatitis that where the total caloric intake, usually with a high fat intake, resulted in a striking gain of body weight, there was a significant increase in the accumulation of abnormal hepatic fat as demonstrated by needle biopsy. Although hepatic function was not additionally impaired by this accumulation of fat, and although it is impossible to state that such fat is harmful, its presence on histologic section in the liver is abnormal. On this basis this author concludes that dietary fat and caloric intake should be so controlled that excessive weight gain does not occur in the treatment of acute or chronic liver disease.

In the patient who is unable to eat satisfactorily because of anorexia, debility, vomiting, severe jaundice or ascites, initial requirements of protein, carbohydrate and calories can be met by intravenous amino acids or salt-poor human serum albumin, plus glucose infusions given daily for a period of several weeks if necessary. A number of investigators have shown such agents to be satisfactorily tolerated and to be definitely beneficial.[11, 15, 16] Though they should be applied only to chosen cases, their use in these patients will fill a most important rôle.

Other Substances

Vitamins have long been considered important in the treatment of liver disease. Evidence would indicate, however, that multivitamin preparations, including the relatively new vitamin B_{12}, have no specific curative effect in liver abnormalities.[17] In patients with severe anorexia, or any complication which prevents the prescribed food intake, such vitamins should be added to the therapeutic program not only to be certain of adequate supply but also to help stimulate the appetite for normal food intake. Furthermore, in spite of the surge of interest in lipotropic agents, clinical, laboratory and serial biopsy studies[17, 18, 19] have demonstrated that choline and methionine do not shorten the time required for disappearance of fat from the liver as long as patients are receiving even a normal, average diet. Similarly, choline and methionine do not favorably influence the nitrogen balance of patients with cirrhosis beyond the quantity of nitrogen the agents themselves contained. In like manner, testosterone propionate will produce, through its protein anabolic effect, an increase in nitrogen balance in patients with cirrhosis, but a positive nitrogen balance can be achieved most effectively by adequate dietary protein.[19]

Corticotropin and cortisone have both been used in the treatment of liver disease. Evans and associates,[20] in studying patients with viral hepatitis of average severity, recorded symptomatic improvement and prompt, often dramatic initial drop in serum bilirubin on treatment with corticotropin. Comparison with a similar control group, however, did not reveal sufficient advantage gained from the corticotropin therapy to justify its routine use. In like manner, cortisone[21] speeded up the return of clinical, laboratory and pathologic features toward normal and shortened the recovery period by about two weeks, but significant relapses occurred, and again it was the judgment of the authors that cortisone should not be used in the average case. However, in the instance of severe, fulminant cases of viral hepatitis, and in those whose course is progressively downhill in spite of conventional therapy, both corticotropin and cortisone have a place in treatment. While they do not alter the fundamental disease process, they may well provide support to the patient that might mean the difference between life and death.[22, 23]

Alcohol is a common problem in liver disease. Some feel there is no evidence that the moderate use of alcohol is deleterious if the patient at the same time eats an adequate diet,[24] but others feel it can well be a significant factor in the development of chronic liver disease.[6] The fact remains that many patients with cirrhosis are chronic alcoholics, and in such individuals moderation is extremely rare. Thus, from the practical point of view, these patients should be urged to become teetotalers.

Ascites

Prentice and associates[25] using tritium-labeled water, demonstrated that the water content of ascitic fluid enters and leaves the peritoneal cavity at a very rapid rate, showing that ascitic fluid then is a rapidly circulating medium rather than a static, segregated reservoir. This fact is quite in keeping with the observation made by a number of investigators that careful restriction of dietary sodium to 500 mg. daily or less, coupled with the improvement of plasma protein levels by protein repletion, will often provide complete relief from this distressing complication.[8, 26–29] One must be careful that over-zealous sodium restriction does not lead to the low-sodium syndrome of weakness, prostration, nausea, oliguria and increasing nitrogen retention in the blood, and should be particularly careful if abdominal paracenteses have to be performed repeatedly. In fact, if ascites returns promptly following paracentesis, it is probably true that any severe sodium restriction program should be abandoned in order to avoid the low salt syndrome.[29]

Hepatic Coma

Coma is one of the serious complications of either acute or chronic liver disease and carries an extremely high mortality rate. While coma can supervene in the course of any liver disease illness, it is more commonly observed in situations where there is further deterioration of underlying liver pathology, such as excessive bleeding from esophageal varices or peptic ulcer, surgery and anesthesia, severe infection and acute alcoholic bouts. It is particularly important to recognize impending hepatic coma, the signs and symptoms being of three general characters: first, changes in mental status, with clouding of consciousness, mental confusion and grossly inappropriate behavior; second, a characteristic tremor described as "flapping," with coarse, irregular, flexion-extension movements of the metacarpophalangeal joints and wrists, and even at times of the elbows and shoulders; and third, a characteristic abnormality in the electroencephalographic pattern.[30] These findings should be sufficient warning to institute full therapy for hepatic coma. It is interesting that the syndrome of impending hepatic coma has been observed in patients with cirrhosis while receiving ammonium-containing medications or a high protein dietary intake, and their signs and symptoms were completely relieved by discontinuing these substances.[31]

The management of hepatic coma, in the first place, is similar to the management of coma for any other reason, demanding careful attention to general nursing, fluid intake and output, electrolyte levels and general nutrition. Tube feeding by slow, constant drip is recommended, the danger of bleeding or pneumonia not being considered serious when compared with the advantage gained by the procedure. Just how much protein should be administered is not known, but large quantities probably should be avoided. A daily intake of about 50 gm. for a short time will help to decide whether protein plays any rôle in the pathogenesis of coma, and if it does seem to, complete omission of protein is in order. Large amounts of glucose, parenteral vitamins, corticotropin and cortisone may be beneficial.[30-32]

Hemorrhage

One of the most serious complications in liver disease is massive hemorrhage from dilated veins in the lower esophagus and upper stomach. Some 85% of patients will die of recurrent hemorrhage within two years of their initial hemorrhage, indicating that it is important to take some definitive step in regard to this complication.[33] With newer advances in visualization of the portal circulation by splenic portagrams and portal portagrams, the surgeon now has the opportunity to plan a definitive approach with a little more certainty prior to the operation itself. While balloon compression or, occasionally such emergency surgery as transesophageal ligation of varices has to be applied in the acute episode, ultimate elective surgery is definitely to be preferred. The procedures of choice are those that specifically lower portal hypertension, namely, portacaval or splenorenal shunts, with or without splenectomy, depending on the situation. Rousselot[33] reports an operative mortality of 10% and a resulting protection from further hemorrhage of some 75% of patients.

Summary

1. The most important features in the treatment of liver disease are rest and the successful administration of a high protein, high caloric diet.

2. In acute infectious hepatitis, bed-rest with bathroom privileges should be observed at least until there is evidence of diminishing bilirubinemia, and preferably until the one minute serum bilirubin is 1.0 mg.% or less. In chronic liver disease, similar bed-rest probably should be continued as long as the patient is showing evidence of improvement.

3. While adequate caloric intake alone will provide improvement in liver disease, the most striking improvement in chronic liver disease results from a high protein intake over a period of many months to combat the serious nitrogen depletion. Alcohol should be omitted entirely. Vitamins, lipotropic agents, testosterone and adrenal hormones offer no additional advantage in average cases of liver disease.

4. The complication of ascites can be managed best by strict sodium restriction in addition to the basic treatment program.

5. The clinician should be alert to the earliest signs of impending hepatic coma: mental disturbance and characteristic tremor. Protein should be administered with caution in such instances, and corticotropin and cortisone may be beneficial.

6. Massive hemorrhage from varices of the upper gastrointestinal tract deserves definitive surgical therapy in most instances to ward off subsequent fatal hemorrhage.

Summario in Interlingua

Reposo, dieta nutritive, e non-uso de alcohol (in casos de historia de alcoholismo) es ben-acceptate factores cardinal in le tractamento de morbo hepatic. Tamen, le clinico require datos inequivoc pro determinar a qual grado ille debe insister que le programma de reposo es strictemente observate e etiam pro definir plus detaliatemente le composition del "dieta nutritive." In plus, il es necessari evalutar le importantia de un impressionante serie de mesuras therapeutic secundari.

Observationes colligite pro acute hepatitis infectiose durante le occupation postguerral de Germania indica—sin diminuer le importantia fundamental de reposo—que un limitate activitate non es nocive, providite que illo es permittite solmente post un periodo initial de allectamento (con privilegio de visitar le W.C.) e post que le bilirubinemia se ha diminuite, preferibilemente quando le total de bilirubina seral es 3 mg o minus. Examines post-tractamental in un gruppo de patientes subjicite a un programma de iste genere revelava nulle significative effecto del activitate super le resultatos final a periodos de inter sex menses e tres annos post le acute hepatitis.

Le rolo del nutrition ha recipite le melior analyse in casos de chronic morbo hepatic in que le valor de dietas ric in proteina e hydratos de carbon es ben demonstrate. Con un tal dieta un positive balancia nitrogenic es mantenite durante multe menses, e le nivellos de proteina seral se meliora progressivemente. Durante que le ingestion de un dieta simplemente ric in calorias resulta in melioration clinic, solmente le ingestion de un dieta ric in proteinas pote producer un positive balancia nitrogenic, reducer le contento de grassia del hepate, e augmentar le contento proteinic del cellulas hepatic. Le ingestion de un dieta tanto ric in calorias (usualmente con un alte contento de grassia) que illo causa un frappante augmento in le peso corporee del patiente de hepatitis resultara in le accumulation de anormalmente alte quantitates de grassia hepatic determinabile per biopsia a agulia. On debe concluder que il es desirabile includer in le dieta satis grassia pro augmentar le palatabilitate del alimentos sed que il es indesirabile permitter augmentos excessive del peso corporee del patiente.

Le uso intravenose de amino-acidos o albumina seral es a restringer a seligite patientes cuje requirimentos dietari non pote esser satisfacite per le via oral. Sed il non existe multe datos a demonstrar que vitaminas, cholina, methionina, o testosterona resulta in effectos que non es effectuabile per un dieta nutritive. Corticotropina e cortisona es a considerar como disponibile pro provider supporto general a patientes qui es criticamente malade. Alcohol deberea esser eliminate completemente.

Le restriction de natrium es le plus importante mesura additional in le tractamento de ascites. In coma hepatic le factores cardinal es prompte recognition, bon sollicitude, nutrition adequate, e probabilemente restriction de proteina con appropriate augmento additional del ingestion de glucosa. In casos del discoragiante complication de sanguination massive, le alte mortalitate debite a hemorrhagias recurrente parla in favor de definitive therapia chirurgic post le prime serie episodio.

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