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Efficacy of methionine and choline administration in the treatment of liver cirrhosis

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THE EFFICACY OF METHIONINE AND CHOLINE ADMINISTRATION IN THE TREATMENT OF LIVER CIRRHOSIS

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I. Introduction.

The treatment of liver cirrhosis has until very recent times been one of the enigmatic problems of medical science. At the present time however, after over a decade of intensive investigation, progress is being made towards a better understanding of the etiological cause of liver cirrhosis, the progression of the pathological lesion, its physiological accompanyments, and its therapy; all of which offer the promise of a better prognosis for a heretofore fatal disease. This investigation, in truth is in its infancy, and it is probable that the entire aspect of the disease, especially that as regards therapy, will be changed within a short time as more investigative work is done.

The part that methionine and choline play in this repacement therapy is definitely controversial therefore the importance that is attached to their administration varies considerably. By considering all the known facts of choline and methionine an evaluation of their effectiveness in cirrhosis of the liver will be made. With this evaluation an attempt will be made to determine their most effective administration.

A. Evolvement of the Etiology and Therapeutic Regimen for Liver Cirrhosis

1. Nutritional Basis for Liver Cirrhosis.

Until the start of the investigative work it was generally considered that alcohol was the prime etiological factor in cirrhosis of the liver, and the therapy of the condition was centered about the abolition of alcoholic beverages from the diet. The patients were placed upon a high carbohydrate and low protein diet, and the

ascites was combatted in selected patients with diuretics and paracentesis. Then in 1937, Patek, (1) noted the frequency of nutritional deficiencies in patients with Laennec's cirrhosis and suggested that malnutrition might play a causative role, and therefore there might be an analogy between the occurrence of alcoholic cirrhosis and alcoholic beriberi or pellagra. Added weight was given to this theory when it was noted that the prevalence of cirrhosis in countries where nutritional deficiencies were endemic was very high. Patek, suggested that the effect of alcoholism in cirrhosis of the liver was on the basis of a secondary nutritional deficiency, and therefore such patients should be treated by being placed on a high protein, carbohydrate and vitamin diet. He reported clinical improvement in patients with cirrhosis given such a diet. This observation placed alcoholic cirrhosis on the basis of a nutritional deficiency instead of a toxic state.

2. Substantiation of such a basis by animal experimentation.

Pathologically the hobnail or fibrotic liver of Laennec's cirrhosis is preceded by the fatty enlarged liver of early cirrhosis. In this early stage the changes are essentially those of fatty infiltration and degeneration. Microscopically, fat droplets are seen in the hepatic cells; the droplets usually being of sufficient size to press the cytoplasm and nucleus aside. In rat experiments it was found that cirrhosis of the liver could be produced when these rats were fed large quanities of fat (2). The production of this cirrhosis, which was preceded by prolonged fatty infiltration, seemed to depend on a deficiency of protein

in the diet aided by a high fat content. It had been shown several years before that the fat content of the liver is known to increase under these conditions, and in the absence of sufficient choline (3). The pathogenesis of this liver injury appeared to be combatted by the effect of casein, choline and methionine when they were added to the diet (4,5). Such findings in animal experiments were corroborated when it was reported that patients with liver cirrhosis showed an increased period of survival, signs of general bodily improvement, and presumptive evidence of arrest of the disease process when put on a highly nutritious diet which included a high protein, carbohydrate, low fat content and high intake of vitamin B concentrate (6).

3. Introduction of the concept of lipotropic action.

Allan in 1924 (7), had shown that depancreatized dogs soon died even though they were adequately supplied with plenty of insulin, and a diet of lean meat, sucrose and bone ash. Upon autopsy their livers showed fatty infiltration. He found that if he gave depancreatized dogs in addition raw pancreas that their death could be prevented and their livers would not show fatty infiltration. It was postulated from this observation that there were certain substances, lipotropic in action, that might have a bearing on the prevention of fatty livers. Upon the administration of certain components of raw pancreas it was found that it was lecithin which prevented the development of such fatty livers, and that the active component of lecithin was choline (3). In both rats and dogs the amount of choline which might be derived from an adequate amount of lecithin was found to prevent the fatty

change in their livers (8). Choline was therefore termed a lipotropic substance, the designation meaning a substance which decreases the rate of deposition and acclerates the rate of removal of liver fat. In the metabolism of fat, in the animal body, there is transportation of fat to the liver from the intestines and, or, the fat depots; thence from the liver the unmetabolized fatty acids are sent to the fat depots of the body again as neutral fats or as phospholipids, being replaced in the liver by the phospholipid lecithin. Phospholipids are therefore essential for fat mobilization from the liver, and the lipotropic effect of choline on the mobilization of fat from the liver is due to the formation of phospholipids (9,10). Experimental proof of such a concept was found by the observation that in rats the administration of choline would acclerate the rate of phospholipid turnover in the liver, this being demonstrated by the use of radioactive phosphorus as an indicator of phospholipid metabolism (11). Other substances, protein in nature, were found to have a similar lipotropic effect; proteins high in methionine were found to have a marked lipotropic action and proof of this was also obtainable by the use of radioactive phosphorus(11,12). It was also found that a liver high in lipid content and low in readily available protein is maximally suseptible to chloroform, while a liver low in lipid content and high in readily available protein is maximally resistant to injury by this agent (13). Methionine used as a dietary supplement will partially protect the livers of protein depleted animals from poisons such as chloroform, and excess choline has been found to give some measure of protection to animals

subjected to carbon tetrachloride (14,15). Such protection by these substances is most likely obtained by enhancing the mobilization of the fat which accumulates in large amounts in the liver as a result of toxic effects by such poisons.

4. The resulting clinical application.

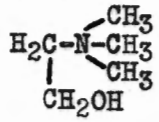
The establishment of cirrhosis of the liver on a nutritional deficiency basis and the subsequent work, as briefly outlined in the preceding paragraphs, resulted in an intensive type of replacement therapy. This therapeutic regimen consisted of a high protein, high carbohydrate, low fat diet, and high vitamin B intake both orally and parenterally. Somewhat later choline and methionine administration was incorporated in the regimen, and in addition parenteral liver extract was advocated (16). Liver extract was shown to be of benefit in combatting the severe anorexia of these patients. This therapy was combined with paracentesis when indicated by massive ascites. In addition some authorities advocated diuretics with fluid and salt restriction while others condemn their use (17,18,19). As was stated by Morrison (20), "The diagnosis of cirrhosis is an indication to push and force feed a nutritious 'liver diet' to the point of maximal tolerance," such a method has seemingly resulted in a sharp reduction of morbidity, mortality and disability rate in these patients.

B. Biochemical Data.

1. Choline

Chemically, choline is trimethyl ethanol ammonium hydroxide. It is a colorless, strongly alkaline liquid, and because of this property readily forms a series of salts. These choline

salts are the ones used in therapy instead of the substance choline itself. The structural formula of choline is:



Choline has been recognized for many years as a component part of the phospholipid lecithin, but it was only recently that its true importance in nutrition became apparent. Choline is now considered an important member of the vitamin B Complex, because most experimental animals, when placed on diets low in this compound and its precursors show characteristic signs. The most obvious changes include the development of fatty livers and hemorrhagic renal lesions (21,22). The function of choline therefore must be intimately tied up with fat metabolism in the body. That neutral fat is involved has been demonstrated in experiments with the dog and rat in which fatty livers produced by high cholesterol feeding did not respond to choline administration, but that livers containing large amounts of glycerides and small amounts of cholesterol did respond (10,22). McHenry (10), stated that there is now evidence that choline may function in at least one of three ways; to stimulate the formation of phospholipids, to make possible the production of acetyl choline and to supply labile methyl groups.

2. Methionine.

Methionine is a sulfur-containing, naturally occurring amino acid, alpha amino gamma methyl mercaptobutyric acid whose structural formula is : $H_3C-S-H_3C-H_3C-\underset{NH_2}{CH}-COOH$ Methionine is considered one of the essential amino acids in both the human and animal body. This essentiality resides in the fact that it is present in most body proteins, and that the body

cannot produce it through the metabolism of other amino acids. This latter fact was adequately proven when it was found that weight loss and negative nitrogen balance occur in the human on a methionine free diet, and that both of these phenomena can be corrected by supplying a methionine containing diet. (23)

3. Lipotropic Action.

Lipotropic substances are those that decrease the rate of deposition and accelerate the rate of removal of liver fat (24). Two substances that have a lipotropic action are methionine and choline. Choline constitutes one of the main factors in mobilization of liver fat by increasing the rate of phospholipid activity(9,10). Production of a fatty liver is due to either a failure in transportation of fat from the liver or to a rapid withdrawal of fat from body stores at a rate so great that the liver is unable to cope with the fat brought to it (9). If there is an inadequacy of choline or choline producing substances then there results a breakdown of this phospholipid activity. It should be stated however that choline does not change the total content of the phospholipid fraction, it only increases the phospholipid turnover in the liver by being available, and thus causing an increased fat transportation; it literally sweeps out fat from the liver (24). However choline has shown some specificity in the type of fat that it will mobilize by the phospholipid route. All types of fat can make up the composition of a fatty liver, therefore all fatty livers are not alike, and thus the action of a lipotropic agent is conditioned by the characteristics of the fat in the liver (10). Choline has been found to be effective

for thiamin (glycerides)fatty livers, partially effective with cholesterol fatty livers, but shows little activity with biotin fatty livers by animal esperimentation (10,25)

Methionine is the other lipotropic substance of great importance, yet its lipotropic activity does not have the same mechanism as does choline except insofar as it too facilitates the removal of liver fat. It accomplishes this by the formation of choline by the process of transmethylation.

4. Transmethylation.

According to du Vigneaud, (26) there is a very close metabolic interrelationship between methionine and sulfur metabolism, and choline and fat metabolism. He also states that the metabolism of methionine, choline, and creatine are interrelated. This relationship revolves about the metabolic transference of labile methyl groups; methyl groups which the body is incapable of generating and therefore must be supplied in the diet. Choline and methionine are two very important substances in the diet that act as donors for the labile methyl groups involved in this process of transmethylation. By methylation methionine is formed from homocystine, the necessary methyl groups being donated by choline. The body is also able to synthesize choline by the methylation of ethanolamine with the methyl groups of methionine; a reversal of the above mentioned methylation. Creatine, is another example of the metabolic transmethylations of which the body is capable. Creatine is formed from guanido acetic acid and labile methyl groups. These labile methyl groups are obtained either directly from methionine or from choline through the formation of methionine.

In this metabolic process methionine is about ten times as powerful a methyl donator as is choline. Therefore the ability of methionine to donate methyl groups for the formation of choline from ethanolamine is the basis of its lipotropic action.

II. Establishment of the Efficacy of Methionine and Choline Therapy

A. Animal Experimentation.

Clinical worth of choline and methionine in the treatment of Laennec's cirrhosis was first indicated in the experiments with animals (4,5). Such evidence will be presented to show that these two substances form an integral part of the therapy of liver cirrhosis.

Best and associates in 1932 (27) found that even small amounts of lecithin were sufficient to prevent the deposition of large amounts of fat in the liver of a rat. Best and Huntsman subsequently in 1932 (28) conducted rat experiments to study the effects that various components of lecithin would have upon the accumulation of fat in the liver of normal rats. Of the substances tried oleic acid, other unsaturated fatty acids, glycerophosphate, and choline, it was found that only choline chloride would inhibit such fat accumulations in the livers. According to these investigators this constituted evidence that choline was the active component of lecithin in preventing fatty livers. Best and associates in 1935 (29) showed that choline's action was on the "neutral" fraction of liver fat. Proof was shown by the fact that this neutral fraction was responsible for the increased amount of fat in the liver when poisoned by phosphorous and

other chemical substances. They also found that choline exerted an effect on the rate of the disappearance of this excess neutral fat. They stated however that whereas choline increased the rate of disappearance of fat from the liver during the recovery phase of phospherous poisoning it did not inhibit the deposition which took place after the injection of large amounts of phospherous. The only degenerative change in the liver in phospherous poisoning which was affected by choline was this accumulation of excess fat.

Channon, et al. (30) in 1940, demonstrated that there was greatly increased fat deposition in the liver when rats were fed cystine in combination with diets low in caseinogen and high in fat. These investigators also obtained results which showed that dietary caseinogen exerts its normal lipotropic action on fat deposition caused by cystine. Similarly small amounts of choline added to the diet each day would also prevent this cystine action. In these studies methionine had also such a preventive action which increased as the amount of methionine was increased, up to a certain percentage level of the diet. From the latter finding it was stated that at its optimum the intensity of methionine, in such lipotropic action, is one fifth that of choline. These investigators concluded that the effect from methionine was probably due to it supplying methyl for the formation of choline, or an active compound derived from choline. Hence they believed that methionine could not be solely responsible for the action of the high protein diet in preventing liver fat deposition. This last conclusion therefore opened up two possibilites; either

some other amino acid exerts a lipotropic action, or alternatively, added methionine is incapable of exerting its full action in the absence of some other protein constituent.

Daft and associates in 1941, (5) demonstrated that liver cirrhosis in rats, produced by a low protein and low fat diet with added cystine and alcohol, could be prevented by the administration of methionine, choline or casein, singly or in combination. Lowry, et al, also in 1941, (31) presented evidence that the administration of choline or a high casein diet to rats with experimental dietary cirrhosis resulted in regeneration of liver cells, disappearance of degenerative fatty changes and a decrease in liver size. Earle and Victor, 1941, (32) confirmed the reports of severe liver damage and fatty infiltration resulting from excessive dietary cystine, and found also that cirrhosis developed on a more prolonged cystine feeding. These authors state that such a diet produced histologically an acute lesion of hemorrhagic necrosis which had a tendency to localize in the portal area, and that later there was connective tissue and bile duct proliferation which lead to portal type of cirrhosis. It was noted that these lesions were very similar to those found in rats with selenium poisoning, but tests on the cystine showed it to contain no selenium.

Earle and associates in 1942, (33) investigated the hypothesis that if the formation and excretion of large amounts of sulfate resulting from the metabolism of l-cystine were the cause of the liver lesions (portal cirrhosis) then dl-methionine fed in excess amounts would also result in liver damage. Under such

a theory therefore cysteic acid, because of its sulfur being excreted in the neutral sulfur fraction of the urine, should have no liver damaging effect. They found in rats that l-cystine caused development of liver necrosis and cirrhosis, but dl-methionine did not cause liver damage. Cysteic acid also caused liver necrosis and cirrhosis, and therefore it was their conclusion that there is no apparent correlation between the amount of sulfate formed and the development of liver damage in rats fed these substances. This observation offered substantial evidence that the contained sulfur in the amino acids methionine and cystine had no relation to the production or prevention of hepatic cirrhosis. Instead it was probably the lack of labile methyl groups in the cystine molecule that accounted for the hepatic necrosis and cirrhosis when large amounts of it were fed in the diet.

Engel, in 1943 (34) and again in 1947 (35), reported on rat experiments in which, cirrhosis being produced consistently with a choline deficient diet, the histologic lesions consisted of mild to extensive periportal fibrous tissue proliferation. This resulted in the liver parenchyma being divided into sharply circumscribed lobules of varying size and shape. This investigator also observed that the cirrhosis was entirely prevented in other rats recieving the same diet by the administration of choline chloride daily. These observations are noted to closely correspond to those by Earle (32) and emphasize the fact that nutritionally produced fatty infiltration of the liver and subsequent proliferation of connective tissue and bile ducts result in a portal type of cirrhotic liver. It is against this type of lesion, in

the initatory stage of fatty infiltration and degeneration, that choline and methionine administration experimentally is effective.

Horning and Eckstein (36) in evaluating the influence of methionine, casein and cystine on the lipid content of the livers in rats state that methionine is as effective as its equivalent content in casein. Hemsworth and Glynn (37) also showed that in rats, on a protein-deficient diet, massive hepatic necrosis can be prevented by adding casein, or an amount of dl-methionine equivalent to that of the casein to the diet. Therefore from these observations it can be stated that the lipotropic effect evidenced by casein was due to the contained methionine.

Handler and Dubin (38) found that as more and more of the fat accumulated the physical organization of the cytoplasm and nucleus became disrupted with subsequent loss of function and death; the resulting disintegration of the cell releasing the fat, which is removed by phagocytosis, and scar tissue develops in its place. They state that this is suggestive that liver necrosis of choline deficiency may be the obligatory consequence of massive fatty infiltration of the liver cells. They postulated that only the lipotropic activity of choline is involved in maintaining the integrity of the liver. These authors also observed that the ingestion of an adequate quanity of good protein protects the liver from the deleterious effect of chronic fatty infiltration. They state that this protective capacity of protein is not based upon lipotropic activity alone.

Experimentally therefore it has been proven that progression of portal cirrhosis stems from the initial lesion of fatty infiltration, subsequent hepatic necrosis, and finally proliferation

of connective tissue. This can be produced by a high fat and low protein diet, and this process can be intensified by the addition of cystine to the diet. Experimental evidence has also established that the sulfur content of a substance or compound has nothing to do with the production of such a type of cirrhosis. Instead the lesion probably is the result of a deficiency of labile methyl groups which result in a breakdown of fat transportation by phospholipids from the liver to the fat depots. Subsequently it was then indicated that lecithin by virtue of its choline content when administered would prevent the initial lesion of such a cirrhotic process.

It was also proven that this fatty infiltration and degeneration could be prevented whenever substances such as methionine and choline, which supply labile methyl groups, were added to such a cirrhotic producing diet. Then it was shown that the lipotropic action of casein on this initial phase of cirrhosis was due to the contained methionine. On such an experimental basis it is concluded that methionine will provide labile methyl groups for the formation of choline and that choline is necessary for the formation of phospholipids. Therefore through the formation of necessary phospholipids for fat transportation choline and methionine provide the lipotropic action that is involved in maintaining the integrity of the liver. It must be emphasized that methionine and choline effect only the initial or preliminary phase of portal cirrhosis, the phase of the fat engorged liver, and that these substances will not or cannot affect the other phases of the cirrhotic process. These facts have been established

only on an experimental basis, but it would seem that according to such experiments methionine and choline should form the integral part of therapy for cirrhosis in humans. However it is also indicated that the main effect that could be obtained from these substances in clinical cases is during the fatty infiltration stage.

Experimentally there is also an indication that the condition of the liver plays a part in portal cirrhosis; that it is the debilitated liver, the one that is low in protein due to a low protein diet, in which the fatty infiltrative phase of the cirrhotic process starts. This factor must also be evaluated, and thus it should be stated probably that the effect of the high protein diet manifests itself in two ways in providing protection for the liver; one, in providing amino acids, methionine, which have labile methyl groups, and two, in preventing a negative nitrogen balance in which the fat metabolism of the liver would be accentuated thus facilitating increased fat deposition.

B. Clinical Studies

By animal experimentation it would seem that the efficacy of methionine and choline administration in portal cirrhosis had been established. The subsequent question is how does this apply clinically, what have been the results from such treatment clinically, and how valuable is methionine and choline in the clinical therapy?

Snell (19), in 1940, after reviewing the literature at that time which had resulted from Patek's adjuvant therapy, stated that until more was known of the specific requirements for the various

protective substances of the liver such treatment would have to be on an emperic basis. This statement characterizes the majority of opinion on methionine and choline therapy at that time. Since then there have been many investigators that have diligently followed this therapy in series of controlled cases, and subsequently reporting them. Review of these reports will be made.

Patek and Post (6), in 1941, state that the treatment of cirrhosis by a highly nutritious diet supplemented with vitamin B concentrate is of therapeutic value. They make the observation that the co-existence in these patients of a nutritional deficiency and cirrhosis of the liver is striking; this relationship may be either cause or effect. It is possible that the lack of certain food factors leads directly to the development of cirrhosis. Clinically therefore these investigators noted a suggestion that there was a part of the therapy that was supplying the agents that had been markedly deficient. Butt and Snell, 1942 (39), state that according to their results the initial lesion in cirrhosis of the liver involves fatty degeneration, necrosis and subsequent atrophy, and that choline, methionine and betaine appear to prevent fatty deposition in the liver. These conclusions were made after a three year observation of patients with cirrhosis who had received the adjuvant therapy; 60% of these patients were dead, 55% of the living had improved markedly, and 45% of the living had no evidence that the course of the disease had been altered.

Fagin and Zinn, in 1942 (40), attacked the problem more directly by using parenterally administered amino acids. Their series of five patients was small, but they noted subjective

improvement of great or moderate degree in four of the five patients during the one month when the amino acids were used. From these results they postulated that the decrease in size of the livers of the patients was due to the resorption of fat through the lipotropic action of the amino acids.

Broun and Meuther (41), in 1942, reported that they had observed the development of a fatty liver, in rabbit experiments on the production of atherosclerosis by means of a diet high in cholesterol. Under these conditions choline was found to markedly inhibit this liver change. On this basis these investigators treated patients with hepatic cirrhosis for two years with choline chloride and a diet low in fats and cholesterol. Their observations were that a number of patients with cirrhotic livers responded well to this form of therapy, whereas use of a similar diet without choline was only slightly beneficial.

All of the replacement therapy diets for liver cirrhosis feature a high protein, low fat diet as well as vitamins, and orally administered lipotropic substances, choline and methionine. Many of the effects of the high protein diet are explainable on the basis of the increased intake of methionine which make methyl groups available for the formation of choline (16). Fagin and associates, in 1943 (42), after the use of parenterally administered amino acids compared the total lipid and total nitrogen content of the livers of patients who had died with cirrhosis and had received amino acids from those cirrhotic patients from whom amino acids had not been administered. Specimens from the former group of patients contained a greater percentage of protein and a lesser percentage of fat than

specimens from the latter groups. Thus these investigators postulated that these results indicated a lipotropic activity of the amino acid mixture, probably due to their methionine content. They also found that good results could be obtained in treating cirrhosis of the liver with high protein, high carbohydrate, low fat diet, with vitamin supplements. Therefore in their opinion it remains to be seen whether the prognosis can be influenced still more favorably by the additional use of choline, methionine or amino acid mixture. Russakoff and Blumberg (43), were not of the same opinion when they reported a series of cases to record the efficacy of choline as an adjuvant to the already highly recommended high caloric, high protein and low fat type of diet. It was their observation that patients manifested little or no change when treated first for several weeks with the high protein diet alone, but showed distinct improvement within a week after the beginning of choline therapy. They state that there seems to be justification for the use of choline as an adjuvant to the dietary therapy of cirrhosis, particularly of the fatty alcoholic type. Wade, in 1945 (44), after a review of the literature, also supports the administration of choline and methionine in addition to the rest of the replacement therapy. He states that choline, methionine and a low fat type of diet have brought about the aforementioned changes in experimental animals, and that clinical evidence suggest strongly that these observations are applicable to human cirrhosis. He also states that if liver fat can be mobilized and further deposition prevented there is sufficient improvement

in the patients appetite to permit correction of the dietary effects. This is perhaps one of the functions or results of methionine and choline.

Chaikin and Schwimmer (45) made a comparative evaluation of the effects of the replacement type of therapy in 112 patients, the results being compared with the results in 134 patients treated with diuretics, paracentesis and general supportive treatment. They state that the best results were obtained in the former group, and of these, the patients who showed the best clinical response were those in the early phase of the disease where multiple liver function tests had shown minimal impairment. That the best response would be obtained when this pathological process was attacked early is logical, however it should be stated good clinical response may be obtained in the late stages of the disease as well. Morrison, (20) after using the dietary regimen and choline, methionine, and casein states that there was improvement in the majority of patients with decompensation, and almost unbelievable improvement in patients with severely decompensated cirrhosis. Patek (17) also supports this conclusion for it was his finding that even though the milder the case of cirrhosis the better the response to therapy the duration of life after the onset of ascites was lengthened. Beams (46) states that since the combined administration of choline and cystine was effective only in the patients with large livers, where fatty changes were suspected, a lipotropic action of choline and cystine is the logical explanation. He maintains that the favorable results in the treatment of cirrhosis of the liver

reported by Patek and Post (6), and by Fleming and Snell (18) using high protein diets and vitamin supplements must be attributed to certain factors in the proteins which arrest or reverse the process in the liver. Beams draws the conclusion that up to the present there has been no treatment which has been found that alters fibrosis of the liver, and therefore recovery of liver function must depend on the arrest or reversibility of the other pathological changes which are found in cirrhosis.

On the basis of the investigations up until 1947 it was the opinion of the profession, in general and in particular those men that were treating liver cirrhosis, that the therapy advocated was of the shotgun type. The therapy is highly valuable and should be used, but more controlled clinical evidence is needed to evaluate the specific status of methionine and choline in the treatment and prevention of liver injury (47,48). Beams and Endicott (49), in 1947, reported a series of cases which had been treated with a replacement diet and daily methionine, and from which liver biopsies before and one to two months after the beginning of treatment had been obtained. In this series, it was stated that in one half of the cases the improved histologic picture was accompanied by improvement of the clinical course and in some of the liver function tests. In the other half, there was no correlation between the histologic changes and the clinical course or liver function. They and others believed there was good suggestible evidence that methionine was responsible for the histologic changes which occurred in the cirrhotic livers after treatment (49,50). Steigmann, (51) also observed in 166

patients that results seemed more favorable in the presence of a large liver (which indicated mainly fatty infiltration rather than fibrosis) than in a small one. He noted that the presence of ascites decreased the therapeutic effect which, too, would suggest that pronounced fibrosis in the liver as manifested by portal hypertension is not likely to be influenced by replacement diet as well as methionine and choline. Therefore the sooner a patient with cirrhosis recieves intensive therapy, the better is his chance of improvement and eventual recovery. He empahsized that not only were the effects of these substances lipotropic, especially methionine, but the addition of these lipotropic substances enhances the beneficial effects of the high protein and high vitamin regimen. Eckhardt, and co-workers (52), in reporting a series of patients in which parenteral amino acids had been the only source of protein and lipotropic substances concluded that not only are such amino acids well tolerated in patients with active liver disease, but also that clinical improvement may occur when amino acids are the only source of nitrogen and lipotropic substances except for small amounts of choline.

Patek, and co-workers, (53) from their investigations sound a note of warning on placing too much value on the assumed specificity of lipotropic substances in bringing about a clinical response in portal cirrhosis. They state that according to their observations there has not been suggestion that these substances alone are adequate for repair or regeneration of the cirrhotic liver. It would seem that their field of greatest

usefulness might be in the precirrhotic fatty stage of the disease since they are lipotropic agents. It was their opinion that when the diagnosis of cirrhosis of the liver can be made in the incipient stages the mortality rate should become materially reduced, for, unlike most other vital organs of the body, the liver has the capacity to regenerate.

III. Summary

Experimental evidence has adequately proven that liver cirrhosis in animals is a nutritional deficiency disease or more specifically a labile methyl groups deficiency disease. The lipotropic substances, methionine and choline, have been shown in animal studies to directly supply this lack and cause the regression of the pathological process and the signs due to cirrhosis. In such experiments it has been found that methionine and choline possess a high degree of specificity in the prevention of liver cirrhosis by reversing the fatty infiltration of the liver. This fatty stage in the uncontrolled or untreated condition progresses to the subsequent stages of hepatic necrosis and connective tissue proliferation. Against the latter two stages of the cirrhotic process methionine and choline have no effect; their lipotropic action being only manifested in the phase of fat engorgement of the liver. These animal experiments therefore may indicate that liver cirrhosis, of the portal type, in man is on a nutritional deficiency basis. Secondly, that the disease can be prevented if caught in its early stages by the administration of lipotropic substances, and that these substances should evidence a high

degree of specificity in the prevention of the cirrhotic process. According to experimental evidence then by means of these lipotropic agents the transmethylation metabolism of and fat mobilization from the liver will be supported until the liver is again in a physiologic state.

In some aspects clinical results support the experimental evidence, and in some ways it does not. Clinically, there is basis for the belief that portal or alcoholic cirrhosis in man is due to a nutritional deficiency. The treatment therefore evolved includes components which would accomplish the replacement of the deficiency. But of this therapy there has not been enough clinical evidence as yet presented to support the experimentally indicated belief that methionine and choline, per se, accomplish this purpose. The replacement therapy of a high protein diet, high carbohydrate and low fat intake, high vitamin B administration, methionine, choline, and liver extract has been shown clinically to materially reduce the morbidity and mortality of patients with portal cirrhosis. There is also good suggestible clinical evidence that methionine and choline very adequately accomplish their lipotropic action, but that this action is mainly manifested during the early stage of cirrhosis, that of the large fatty engorged liver. Methionine and choline, by means of this lipotropic action, have been shown to enhance the beneficial effects of the high protein, low fat and high vitamin regimen.

The conclusion is that methionine and choline are highly necessary components of the replacement therapy of portal cirrhosis. The diagnosis of liver cirrhosis calls for the institution of an

intensive therapy, all components included, for these patients can be both subjectively and objectively benefited even if in one of the later stages of the pathological process. Therefore the earlier liver cirrhosis can be diagnosed the earlier treatment can be instituted, and by this means only will the mortality and morbidity rate be further decreased.

IV. Conclusion

1. Methionine and choline, as part of the high protein, high carbohydrate, low fat diet, high vitamin B and liver extract therapy, are essential in the treatment of liver cirrhosis.

2. Clinical evidence as yet does not support the experimental evidence that methionine and choline are, per se, responsible for the beneficial effects of the present day treatment of portal cirrhosis in man.

3. Early diagnosis and early use of the replacement therapy are essential for further reducing the morbidity and mortality which result from portal or alcoholic cirrhosis.

4. Cirrhosis complicated by decompensation is no contraindication for the intensive use of all components of the replacement regimen.

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