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METHIONINE IN THE TREATMENT OF ACUTE HEPATITIS

BY

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Experimental tests made on animals during the past ten years have shown the deleterious effect on the liver and its functions caused by insufficiency of protein in the diet. It has further been shown that the cause is a qualitative, not a quantitative, lack of protein. Liver necrosis and cirrhosis occurring in animals can therefore be prevented by giving sulphur-containing amino-acids, of which the most important is methionine. Damage caused by liver poisoning can also be prevented with methionine.

Even if the actual mechanism by which methionine protects the liver is unknown, it is natural to attempt to use it therapeutically in cases of acute hepatitis; for the damage to liver cells caused by virus may possibly be reduced, the processes of healing be speeded up, or both. The experience gained from such experiments has so far been insufficient and the results are contradictory. Wilson, Pollock, and Harris (1945) treated 50 patients with 5 g. of methionine daily until the urine had been free from bile pigments for five days. Comparing these cases with 50 simultaneous control cases, they found "no significant effect on the severity or duration of the disease." Nor did Higgins *et al.* (1945) in their tests on 18 patients, with an equal number of control cases, find any effect on the course of the disease or the duration of bilirubinaemia or bilirubinuria.

Beattie and Marshall (1944), on the other hand, briefly state that good results have been obtained in 450 cases of hepatitis and arsphenamine icterus, especially in cases of severe illness. They considered the effect "so striking as to leave no doubt." Peters *et al.* (1944) found that methionine had a definite effect (cited by Iversen, 1946). Barclay *et al.* (1945) claim dramatic results from the use of methionine intravenously (10 g. daily) in two cases. Eddy (1945) records beneficial results from methionine treatment of toxic hepatitis caused by trinitrotoluene and carbon tetrachloride.

Morrison (1947) obtained a considerable improvement when treating liver cirrhosis with choline and methionine; and Beams and Endicott (1947) used methionine alone with beneficial effects, shown both by biopsy of the liver and by tests of liver functions.

Present Investigation

The investigation began in October, 1947, and continued until the end of December, 1948. Every alternate case of acute hepatitis, with the exception of patients under

10 years of age, was put on methionine treatment (5 g. daily for 10 days), the other case serving as a control and receiving dummy tablets. Each series consisted finally of 125 cases—described as the C. (control) and M. (methionine) series. The average age in both was almost exactly identical (32.7 ± 1.1 and 32.8 ± 1.2 years). The diet was the same for all patients (about 90 g. protein, 90 g. fat, and 400 g. carbohydrate—2,850 calories).

No attempt was made to divide the material into epidemic and inoculation hepatitis. The former is the more common in our hospital. (An analysis of the hospital material by Gertzén and Ström in 1948 showed that at least 62% of the cases, and probably many more, were in the epidemic group.)

The material was tested once a week for the icterus index (Meulengracht), thymol and prothrombin content of the blood, bilirubin (after Hammarsten), bile acids (Hay), and urobilin (Schlesinger) in the urine.

With regard to the colour index of the blood it would have been more correct to follow the return of the index to the value of Meulengracht 10, but, as some patients had for various reasons left the hospital earlier, I took a value of 15 or less (≤ 15). Only three patients out of 250 were discharged with a higher value, and these are not included in the calculations. This fact is of no importance from the point of view of the material.

A calculation was made of the highest icterus index and the time in weeks for a return to ≥ 15 . In the same way the highest thymol reaction value was calculated, also the value at discharge, as the thymol content usually remains high longer than the bilirubinaemia and it has therefore been impossible to indicate when normal is reached. In the case of prothrombin the lowest value was calculated on an index obtained from the second week in hospital. It should be noted that all patients received vitamin K daily according to schedule. For bile pigments, bile acids, and urobilin in the urine I have calculated the time in weeks until negative tests were obtained.

The figures of different blood reactions in Table I show that the M. series had fewer cases in which bilirubinaemia increased after admission to hospital and a slightly smaller

TABLE I

Reaction	C. Series	M. Series
Meulengracht:		
Highest value	46.5 $\pm$ 2.9	44.3 $\pm$ 2.9
Cases increasing after admission	29	20
Time in weeks for decrease to ≤ 15	3.3 $\pm$ 0.19	2.9 $\pm$ 0.17
Thymol:		
Highest value	18.5 $\pm$ 0.9	20.0 $\pm$ 1.1
At discharge	11.5 $\pm$ 0.6	11.6 $\pm$ 0.6
Prothrombin:		
Lowest value	92.5 $\pm$ 1.4	94.5 $\pm$ 1.2

increase of bilirubinaemia than the C. series. In the C. series, also, the time was longer before the icterus index decreased to 15 or less. The thymol reaction shows slightly higher values in the M. series, but at discharge they were the same in both series. The prothrombin index has lower values in the C. than in the M. series. However, statistically proved differences were not obtained. Data concerning the secretion of bile products and their derivatives in the urine are shown in Table II. (Here I would point out that, because so many cases showed no bilirubin or urobilin in the urine, tests were made only once a week.) It will be seen that in the M. series more cases were free from bile pigments, that the duration of bilirubinuria was also somewhat shorter, and that the number of cases positive

at the time of discharge was smaller. The circumstances are the same with regard to urobilinuria, except that at discharge a slightly greater number of cases were positive in the M. series. Hay's test for bile acids showed a slight

TABLE II.—Results of Test for Bile Products and Their Derivatives in the Urine

Reaction	C. Series		M. Series	
	No. of Cases	No. of Weeks	No. of Cases	No. of Weeks
Hammarsten:				
Neg. whole time in hospital ..	31		42	
Pos. → neg. while in hospital ..	85	1.7	77	1.6
Pos. whole time in hospital ..	9		6	
Schlesinger:				
Neg. whole time in hospital ..	12		24	
Pos. → neg. while in hospital ..	71	2.6	53	2.3
Pos. whole time in hospital ..	42		48	
Hay:				
Neg. whole time in hospital ..	16		18	
Pos. → neg. while in hospital ..	99	1.9	91	2.0
Pos. whole time in hospital ..	10		16	

tendency to the contrary, with a somewhat longer positive reaction in the M. series. There were no significant statistical differences in the urine reactions.

The length of stay in hospital in the control cases was 27.5 ± 1.4 days and in the methionine cases 25.0 ± 1.4 days.

The essential facts obtained from these tests are that the cases treated with methionine tend to show a smaller increase in bile pigments in the blood and a quicker return to normal values, and consequently that the secretion of bile pigments and urobilin in the urine also ceases earlier. But, compared with the untreated cases, the difference is very small, and statistically is not significant. Definite effects cannot therefore be claimed for treatment by this method. If, however, methionine treatment had been given during the whole course of the illness the results might probably have been better; but this is problematical.

While these attempts to treat acute hepatitis with methionine have not been very encouraging, I certainly think that amino-acids should be used in the treatment of pre-comatose and comatose cases. Though I am unable to present a scientific basis for this opinion, our experience tends to show that a course of amino-acids given intravenously is of value in severe cases.

Summary

In experiments on animals several investigators have proved that the amino-acid methionine affords excellent protection to the liver against damage caused both by toxins and by lack of protein in the diet. Attempts to use methionine in the treatment of acute hepatitis have been made by several authors, with contradictory results.

Methionine treatment was given in 125 slight and semi-severe cases of acute hepatitis and an equal number served as control cases. The group treated with methionine showed fewer cases with increasing bilirubinaemia after admission to hospital, a slightly smaller increase in bilirubinaemia, and a somewhat quicker return to normal values, as well as an earlier cessation of secretion of bilirubin and urobilin in the urine as compared with the cases not receiving treatment. Thymol reaction and secretion of bile acids showed a more uncertain tendency. The prothrombin index decreased slightly more in the untreated cases. The differences, however, were small and were not proved statistically.

The investigation shows that a marked effect is scarcely to be expected from the use of methionine in the treatment of acute hepatitis of average severity. In more severe cases of hepatitis, however, clinical experience suggests that amino-acids may be of value when given intravenously.

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THE RATE OF EXCRETION OF A LARGE DOSE OF PENICILLIN

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For some years past it has been a common practice in this country, although not elsewhere, to administer aqueous penicillin in only two daily intramuscular doses. The convenience of this system in private patients and hospital out-patients needs no emphasis, and the experience of many has been that it gives satisfactory therapeutic results, at least in certain conditions. In so far as it is likely to be superseded by the administration of slowly absorbed preparations containing procaine penicillin at even longer intervals, its effects will cease to be of interest. There is nevertheless some advantage in knowing how long a given large dose in water continues to exert an effect, and it seemed to us that in one important particular knowledge on this subject is incomplete. This is the rate of disappearance of penicillin from the blood after an intramuscular dose of 500,000 units, the largest dose commonly given at long intervals.

Many authors report the results of blood assays at intervals after various smaller doses, and it is well recognized that duration of effect is not directly proportional to the dose given. Reports of assays after a dose of 500,000 units are few and usually refer to control observations made in a small or unstated number of subjects during a study of some slowly absorbed preparation. May (1948) gave this dose to four subjects at rest in bed, and regards the results as indicating that it will be followed by a "therapeutic level" for 12 hours and "complete disappearance" in 16 hours; but this conclusion is based on only one positive titration after the ninth hour in each of three cases, while in the fourth no assay made after the third hour was positive, those intermediate between this and the twelfth hour having been omitted.

Miller and Boger (1948) gave 500,000 units at intervals of three hours and found the average blood content when the next dose was due to be 1.89 units per ml. Wayne *et al.* (1949) gave 600,000 units to three patients, and the blood level is shown as near zero at 10 hours. Loewe *et al.* (1949) state that 500,000 units in saline "gave no detectable blood levels at eight hours or thereafter," but in an accompanying table the level at eight hours is stated as 0.012 unit per ml. and *nil* at 12 and 16 hours.