

hours. On theoretical grounds this dose was increased in later cases to a maximum of 400,000 units to obtain a concentration which should be bactericidal as well as bacteriostatic. When the infection appeared to be adequately controlled, the dose was reduced to a minimum of 100,000 units in twenty-four hours.

Two well-defined groups of cases were distinguished: (1) those admitted before the bone was seriously damaged and before pus had formed; and (2) those admitted with an abscess already present.

Group 1 could be treated successfully by systemic penicillin alone, provided the course was sufficiently long and intensive; the condition might resolve without

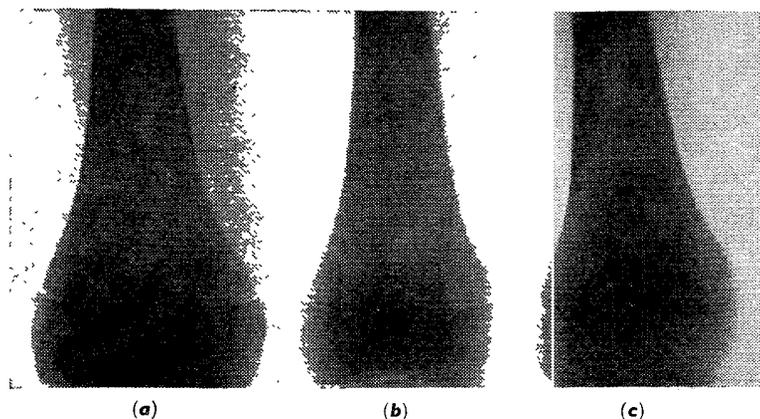


Fig. 3—Radiograms of a boy (case 6) admitted with osteomyelitis of femur and subperiosteal abscess. Treated with penicillin and by evacuation of abscess, bone drilling, primary suture, and immobilisation. Contrast with case 3. (a) Dec. 6, 1945, on admission, negative; (b) Jan. 4, 1946, localised area of decalcification, periosteum not separated from shaft; (c) Feb. 14, 1946 (9 weeks after onset), no further spread of the disease, clinically normal with full range of knee movement.

any radiographic bone changes; 7 out of 30 (1 in 4) cases admitted were suitable for this treatment. Group 2 must be treated surgically, as well as with penicillin, and surgery must include release of pus in the bone by drilling; after this, primary suture is safe and advisable to prevent secondary infection.

Cases in group 2 not treated by surgery as well as penicillin developed a spreading decalcification of the bone, the area of which increased over 1-5 months. Workers at other centres have confirmed this.

In this series there was no death, no joint involvement, and no secondary focus after admission. At the end of eighteen months, 4 cases still have a sinus, but 2 of these are nearly healed; 28 cases have normal function; one patient admitted with septic arthritis of knee has limited range of movement; one has a sinus which keeps her in hospital.

The importance of surgical drainage in these cases is discussed.

One case of infection with a penicillin-resistant organism was encountered early in this series. It is not included in the series, because at the time we had not sufficient penicillin for its adequate treatment. It was four times as resistant as the normal staphylococcus; it would have required at least 400,000 units of penicillin in twenty-four hours for bacteriostasis. The case serves as a reminder that the sensitivity of the organism must always be tested.

We wish to thank Prof. H. J. Seddon, whose interest initiated and made possible the investigation; Mr. G. R. Girdlestone and Mr. W. B. Foley, who allowed us to treat their cases with penicillin; Dr. E. S. Duthie, of the William Dunn School of Pathology, and Dr. W. J. D. Fleming, of the Radcliffe Infirmary bacteriological department, for valuable advice and assistance; and Sister Walker, whose help in the children's ward overcame many difficulties.

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DIET IN THE TREATMENT OF INFECTIVE HEPATITIS

THERAPEUTIC TRIAL OF CYSTEINE AND VARIATION OF FAT-CONTENT *

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In a previous paper¹ we reported on the therapeutic trial of methionine in 50 cases of infective hepatitis. The results indicated a slight beneficial effect, but on statistical analysis it did not appear that the differences observed between treated and control groups were significant. Subsequently, supplies of the sulphur-containing amino-acid cysteine were obtainable through the Ministry of Supply, and it was decided to carry out further trials with this substance.

The effects of dietary factors on the course of infective hepatitis have been studied by several workers, and the comparability of their results has sometimes been in doubt owing to the uncertain influence of other dietary constituents, particularly the amount of fat included. Though most observers have used a basic low-fat diet, others (including ourselves) gave a generous allowance of fat; and it was thought desirable to compare the effects of high-fat and low-fat diet on the course of the disease. It was therefore decided to combine a comparison of high-fat and low-fat diets with the therapeutic trial of cysteine.

METHODS

Five grammes of *dl*-cysteine was given daily by mouth in morning and evening doses of 2.5 g. The amino-acid has an objectionable taste, which may be accentuated by chemical changes following repeated exposure to the air. It was therefore stored in small nitrogen-filled containers holding a week's supply, and the requisite amount was made into solution immediately before administration. The solution was mixed with sweetened fruit juice to disguise the taste. Treatment started on admission of the patient to hospital and was continued until the urine became bile-free by the foam test. The mean period of administration was 11.1 days. A series of 103 Service cases was studied, alternate patients serving as controls. The effects of differences in the fat-content of the diet were studied in the same series of patients, alternate members of the control and treated groups being placed on high-fat or restricted-fat diet (approximately 200 g. and 70 g. of fat respectively) during the period of biluria. The protein content of the diet was similar in both groups and was maintained at approximately 100 g. after the appetite returned.

As in the methionine trials, a combination of clinical and biochemical criteria was used to assess the effects of treatment on the duration and severity of the disease.

Clinical observations included duration of anorexia, jaundice, liver enlargement, period in hospital, and frequency of relapses. A relapse consisted of a return of or increase in symptoms and biluria with a secondary rise in serum-bilirubin level; very occasionally a rise in serum-bilirubin level was the only manifestation of a relapse.

Biochemical tests included duration of biluria (with the foam test) and of hyperbilirubinæmia (elevation of serum-bilirubin level above 2.0 mg. per 100 c.cm.), and the improvement in hippuric-acid synthesis (with Quick's intravenous modification) during the first week of treatment. In the trial of methionine previously

* A report to the Medical Research Council.

1. Wilson, C., Pollock, M. R., Harris, A. D. *Brit. med. J.* 1945, **i**, 399.

reported, hippuric-acid synthesis was determined shortly before discharge. Since the rate of improvement of this liver-function test is greatest during the first week of treatment, it was decided to compare the values during this period in the present trial. Accordingly 20 unselected cases in the treated group and 20 in the control group were investigated. Hippuric-acid synthesis was determined on the day after admission and again seven days later; the results are expressed in g. of sodium benzoate detoxicated. All time intervals were measured from the day on which treatment started.

COMPARABILITY OF TREATED AND CONTROL GROUPS

All subjects were Service cases, and there was no significant difference in age-distribution between the control and treated groups. It is important that the groups studied should be comparable in severity and in the duration of the disease before treatment was started. The duration was taken as the interval between onset of symptoms and admission to hospital. A further indication of the stage of the disease was obtained by comparing the percentage of cases in each group admitted while the serum-bilirubin level was still rising. Criteria of severity of the disease on admission were provided by the initial serum-bilirubin levels (cases being divided into those with rising and those with falling serum bilirubin levels) and the admission values of the hippuric-acid synthesis test. Results of this analysis are included in table I, which shows that in both the cysteine and the dietary trials the control and treated groups were comparable in the criteria enumerated.

TABLE I—COMPARABILITY OF GROUPS

	Cysteine	Controls	High fat	Low fat
Duration before admission (days)	7.8	9.6	9.5	7.9
Percentage admitted with rising serum-bilirubin level	39	40	45	34
Serum-bilirubin (mg. per 100 c.cm.) on admission:				
(1) Cases with rising serum-bilirubin level	6.3	7.2	6.5	7.2
(2) Cases with falling serum-bilirubin level	6.3	7.8	7.2	6.9
Hippuric-acid synthesis on admission (20 cases in each group)	0.70	0.64	0.724	0.650

RESULTS OF CYSTEINE THERAPY

From table II it will be seen that for most of the criteria compared, the difference between the treated and untreated groups was about three times the standard error, which must be taken as a significant difference. Exceptions were the duration of anorexia and the length of stay in hospital. Length of stay of Service patients in hospital depends on many factors besides the duration of the disease, which probably explains this exception. The lack of any significant difference in the duration of anorexia is unexplained, but this is the only criterion which does not seem to depend directly on liver damage.

These results appear to indicate that cysteine exerts a beneficial effect on the recovery of liver function in infective hepatitis. It must, however, be pointed out that the differences between the treated and control groups are in the main due to the greater number of relapses among the controls. Even a minor relapse usually causes considerable delay in recovery; and, if all relapses are excluded from the analysis, the differences between the groups almost disappear; for instance, the D./S.E. for the duration of hyperbilirubinæmia in the two groups would drop from 3.38 to 1.29—i.e., the difference is no longer significant. Unfortunately, the number of relapses is too small to enable us to determine with a reasonable degree of certainty whether

TABLE II—EFFECT OF CYSTEINE AND OF HIGH- AND LOW-FAT DIETS ON SEVERITY AND DURATION OF INFECTIVE HEPATITIS

	Cysteine	Controls	Differ- ence	D./S.E.	High fat	Low fat	Differ- ence	D./S.E.
Number of cases ..	52	51	51	52
Duration of—								
anorexia (days)	8.0	10.2	2.2	1.16	10.0	8.3	1.7	0.89
jaundice (days) ..	14.1	21.2	7.1	3.0	17.2	18.0	0.8	0.32
liver enlargement (days) ..	16.5	26.4	9.9	2.73	19.9	22.1	2.2	0.59
biliruria (days) ..	11.1	15.8	4.7	3.14	13.8	12.9	0.9	0.56
hyperbilirubinæmia (days) ..	11.5	19.8	8.3	3.38	15.8	15.5	0.3	0.11
Period in hospital (days)	36.8	40.9	4.1	1.46	37.5	40.1	2.6	0.93
Improvement in hippuric-acid synthesis*	0.29	0.127	0.163	2.05	0.23	0.19	0.04	0.49
Number of relapses	2	10	8	..	6	6	0	..

* 20 cases in each group.

the difference in incidence between the two groups is likely to have arisen merely by chance, or whether cysteine acts mainly by preventing such relapses. Our conclusion that cysteine is of benefit in the treatment of infective hepatitis must therefore remain tentative.

EFFECT OF VARYING THE FAT-CONTENT OF THE DIET

It is traditional to feed jaundiced patients on a low-fat diet. The rationale for such a regime is not clear, but there are several reasons why reduction of fat in the diet may appear desirable. The most compelling reason is the repugnance often felt by the patient for fatty foods; there is also the consideration that absorption of fat is deficient in the absence of bile from the intestine, although, taken alone, this might be an argument for increasing rather than reducing the amount of fat ingested. Again, animal experiments have demonstrated that a high-fat diet predisposes to liver damage, but the proportion of fat in the animal diets has been excessive compared with the content of the normal human diet.

We have not found that patients with infective hepatitis are intolerant of fat. With few exceptions they prefer buttered bread to dry bread and rarely refuse milk drinks, cheese, or eggs. In fact the so-called fat-intolerance of these patients is largely an intolerance of greasy foods. If greasy dishes are avoided, fat in various forms is generally acceptable.

The main objection to a low-fat diet is the difficulty of restricting fat alone. Under present conditions it is not easy to maintain an adequate caloric intake when milk, cream, cheese, butter, eggs, and meat-fat are excluded. It appeared desirable to observe a controlled series of cases in which the fat-content of the diet was varied; for, if there is no virtue in the traditional low-fat diet, the patient may as well benefit from more palatable and nourishing food during his recovery, with the saving of much administrative labour.

The investigation was carried out concurrently with the cysteine trials, alternate cases in the cysteine-treated and control groups being admitted to separate wards for administration of high-fat or low-fat diets. Patients on the high-fat diet received the fat, cheese, and egg ration and the cream from the milk of patients on the low-fat diet. The protein content of both diets was adjusted to about the same value by adding skimmed milk and bread.

Sample analyses of the food consumed were made in 4 cases in each group at different stages of treatment and gave the following mean figures:

High-fat diet.—Fat 202 g., protein 99.5 g., carbohydrate 216.5 g., total calories 3056.

Low-fat diet.—Fat 68 g., protein 91.5 g., carbohydrate 279 g., total calories 2025.

Though there was no restriction of carbohydrate, the patients on low-fat diet did not eat enough to bring their caloric intake to the level of the high-fat diet.

With the criteria previously described, it will be seen from table I that the two groups were comparable except that the group on high-fat diet contained a rather higher percentage of cases admitted with rising serum-bilirubin level. This might be expected to lead to a rather longer recovery period for this group. In fact, however, the criteria of severity and duration of the disease after admission (table II) showed negligible differences between the two groups. These results therefore provide no evidence that a high-fat diet has a harmful effect on the course of infective hepatitis.

SUMMARY

The administration of 5 g. of cysteine daily by mouth to 52 patients with infective hepatitis produced a significant shortening of the period of recovery compared with 51 control cases. This appeared to be due to the smaller number of relapses in the treated group.

A comparison of the progress of 52 patients on a low-fat diet with that of 51 on a high-fat diet revealed no significant difference in the rate of recovery.

HÆMPOIETIC ACTION OF 5-METHYL URACIL (THYMINE) IN TROPICAL SPRUE*

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It has been shown that the administration of synthetic 5-methyl uracil (fig. 1) in large doses is followed by a striking hæmatological response in persons with Addisonian pernicious anæmia in relapse (Spies et al. 1946a and b, Frommeyer et al. 1946). Since it is impossible to distinguish the bone-marrow of persons with tropical sprue from that of Addisonian pernicious anæmia, it seemed worth while to test the effect of large doses of this substance in persons with the macrocytic anæmia of tropical sprue in relapse. The present report is concerned with our observations in 4 such cases.

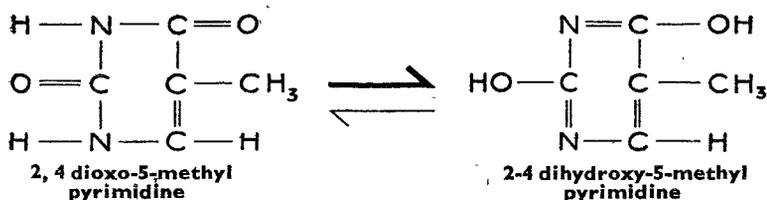


Fig. 1.—Methyl uracil (thymine).

In the selection of patients for this study the following criteria were used: (1) the patient must have glossitis; (2) he must have diarrhoea, characterised by voluminous foul-smelling frothy liquid yellow stools, with an increased fat content as determined by chemical analysis; (3) a body-weight loss of at least 20 lb. must have taken place during the six months preceding the initiation of this study; (4) he must have a macrocytic hyperchromic anæmia with a red-cell count of 2,500,000 or less per c.mm. and a colour-index of 1.0 or more; (5) there must be megaloblastic arrest of the sternal bone-marrow; (6) there must be free hydrochloric acid in the gastric juice on fractional analysis after histamine stimulation; (7) he must have a flat oral glucose-tolerance curve as determined by an increase in blood-glucose of no more

than 10 mg. per 100 c.cm. in subsequent blood samples compared to the fasting specimen, no sample being greater than 105 mg. per 100 c.cm.; (8) the blood-calcium level must be low, but not below 8.5 mg. per 100 c.cm.; (9) the serum amylase and lipase activity must be normal; (10) the intestinal pattern on radiography must have a "moulage" appearance; and (11) the patient must not have had specific therapy within the five weeks preceding the initiation of the study.

METHOD

The patients thus selected were admitted to hospital. A complete dietary and medical history was obtained, and complete physical and neurological examinations were made in each case, as were base-line laboratory and hæmatological studies. The hæmatological studies included a packed cell volume (p.c.v.) with blood indices and daily reticulocyte, erythrocyte, and hæmoglobin determinations as previously described (Spies et al. 1945). Sternal bone-marrow was obtained by aspiration before treatment and on the day after the peak reticulocytosis. Gastro-intestinal X-ray examinations were made before treatment and on the fifteenth day of therapy. Glucose-tolerance tests were done before and after treatment. The stool (the laboratory findings will be reported separately) was examined for parasites, cultured for bacteria, and analysed chemically for total fat, neutral fat, and fatty acids. The diet of each patient was standardised and rigidly controlled throughout the study and contained no meat, meat products, fish, fowl, milk, or eggs. All other foods were allowed in any amount desired.

After the base-line studies had been made, each patient was given a total of 15 g. of synthetic 5-methyl uracil daily, which was weighed on an analytical balance and given in two 7.5-g. doses, one at 10 A.M. and one at 3 P.M. Each dose was suspended in half a glass of hot water immediately before administration; and, after the patient had drunk this mixture, the glass was rinsed thoroughly with water, which the patient also drank to ensure his getting as much of the substance as possible.

The results of the base-line laboratory studies are shown in table I. Table II shows the p.c.v. and blood indices obtained before therapy. In table III the hæmatological effect of synthetic 5-methyl uracil in each of the 4 patients is shown.

Examination of the sternal bone-marrow obtained on the day after the peak reticulocytosis showed that in each case the marrow consisted largely of normoblasts, with almost complete obliteration of the megaloblastic arrest seen in the preparations obtained before therapy. Radiography of stomach and intestines showed a substantial decrease in intestinal motility as well as a decrease in the spasm and dilation and in the amount of "puddling" of barium in comparing the films taken after therapy with those taken before therapy. The glucose-tolerance tests indicated that intestinal absorption improved after therapy.

CASE-RECORDS

CASE 1.—A white man, aged 34, was admitted to the Calixto Garcia Hospital on March 14, 1946, with four months' history of anorexia, diarrhoea, and loss of weight. He had begun to have 4-6 liquid voluminous yellow foul-smelling stools daily four months before admission. Fifteen days later he had noted soreness of the mouth and tongue, aggravated by hot or cold foods, and a sensation of epigastric fullness and great abdominal distension after meals. The anorexia and weakness had become progressively worse, and in four months he had lost 40 lb. in weight. His diet had been inadequate in protein and in the vitamin-B complex before his illness, and since his illness it had been inadequate in all the essential nutrients.

He was an emaciated pale man, with diffuse generalised fine desquamation of the skin of the entire body. The buccal mucosa was oedematous and reddened, but there were no ulcers. No other abnormality was found.

* University of Cincinnati studies in nutrition at the Calixto Garcia Hospital, Havana, in cooperation with the Institute of Nutrition of Cuba and the University of Havana.