THE AMINO ACID REQUIREMENTS OF MAN

XIII. THE SPARING EFFECT OF CYSTINE ON THE METHIONINE REQUIREMENT*

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In Paper XI of this series (1), consideration was given to the problem of the methionine requirement of man as measured by the maintenance of nitrogen equilibrium. Quantitative data obtained in six male subjects demonstrated that the minimal needs varied from 0.8 to 1.1 gm. daily. D-Methionine, in contrast to the behavior in man of the D isomers of all other indispensable amino acids, was found to be just as effective as DL-methionine for the purpose in question. From this observation, it follows that L-methionine does not possess a measurably greater metabolic activity than does the racemic compound, and that the methionine requirement of an individual is the same whether expressed in terms of the L- or the DL-amino acid.

In accordance with the practice followed in most of our human investigations, the diets employed in the above experiments contained the eight essential amino acids (cf. (2)), with added glycine and urea as sources of nitrogen for the synthesis of the non-essentials. Consequently, the subjects were deprived of cystine. In view of the metabolic relationship of methionine and cystine (3-6), one would anticipate that the inclusion of the latter in the food would affect the needs of the organism for the former. Indeed, the sparing action of cystine upon the methionine requirement of animals can be demonstrated readily. Several years ago, Womack and Rose (7) concluded that weanling rats require 0.6 per cent of DL-methionine for maximal gains when the diets are devoid of cystine, and that the addition to the food of moderate quantities of L-cystine reduces the methionine requirement to 0.5 per cent. These findings appeared to indicate that, in the rat, one-sixth of the minimal methionine needs for growth could be satisfied by cystine.

The experiments of Womack and Rose antedated the commercial pro-
duction of most of the vitamins of the B complex; consequently, at that time, the best available sources of these dietary factors were concentrates prepared from rice polishings, milk, or yeast. With the advent of abundant supplies of crystalline vitamins, the earlier tests were repeated under more ideal circumstances. Wretlind and Rose (8) showed that, with diets containing 0.2 per cent of L-cystine, maximal growth could be obtained with 0.4 per cent of L-methionine. Furthermore, in the growing rat as in the adult man, no significant difference could be detected in the effectiveness of the optical isomers of methionine. Unpublished experiments involving the use of rations which were devoid of cystine have served to verify the original finding of Womack and Rose; namely, that 0.6 per cent of methionine is the minimal amount which is capable of inducing maximal gains. In the light of the newer data, it is evident that approximately one-third of the methionine requirement of the growing rat can be satisfied by cystine.

The investigation herein described had as its objective a determination of the sparing effect of cystine upon the methionine requirement of adult man. This is a problem of more than passing interest since, in certain areas of the world, methionine is more likely than any other amino acid to be a limiting component of the foods commonly consumed (cf. Malhus et al. (9)). Therefore, to the extent that cystine is present in such dietaries, it may play an amazingly significant rôle, as will be revealed by the experiments outlined in the following pages.

EXPERIMENTAL

As in all of the investigations of this series, normal young men served as the subjects. The diets were analogous to those previously described and were composed of mixtures of highly purified amino acids, wafers, extra sucrose and butter fat, and Cellu flour to provide a residue in the alimentary tract. The amino acids were taken in aqueous solution flavored with filtered lemon juice and sucrose. The wafers furnished most of the energy and all of the inorganic salts. Vitamins were administered once or twice daily in the form of a concentrate of fish liver oil and supplements carrying the other accessory factors.¹ One-third of the daily allotment of amino

¹ A gradual change has occurred in the procedure followed in making the vitamin pills (10). In certain experiments, without modifying the kind and quantities of the active components, approximately 5 gm. of dextrin have been used each day as a diluent and binder. In later experiments, to disguise more completely the flavor of the liver concentrate, larger quantities of dextrin or sucrose, or both, have been used. Under these circumstances, the products have ceased to be pills and must be eaten rather than swallowed whole. The calories contributed by the carbohydrates have been included, of course, in calculating the energy intakes of the subjects. Obviously, this variation in the method of administering the vitamins has not affected the outcome of the experiments. The details are furnished merely as an aid to those who may conduct similar investigations.
acids, wafers, and extra sucrose and butter fat was consumed at each meal. The reader is referred to Paper I of this series (10) for the composition of the salt mixture and baking powder used in making the wafers, the daily intakes of the vitamins, and other pertinent information concerning the conduct of the experiments.

In order to determine the effect of cystine, it was necessary, first of all, to establish the minimal methionine requirement of each subject when cystine was absent from the food. Once this had been accomplished, a uniform daily dose of L-cystine was administered and the methionine requirement was again measured. Throughout, the total nitrogen intake of each subject was maintained at a constant level by suitable adjustments in the amount of glycine present in the amino acid mixture. DL-Methionine was used in all experiments since its effectiveness is not measurably different from that of the L isomer (1).

Three experiments were carried out, and the results obtained were in close agreement. Subject R. L. W. received initially a diet consisting of amino acid Mixture 205 (the composition of which was described in the preceding paper (11) of this series), Wafers IV (cf. Rose et al. (12)), 301.3 gm. of extra sucrose, and 42.4 gm. of extra butter fat. The daily intake of amino acid Mixture 205 furnished 9.70 gm. of nitrogen, of which 0.44 gm. was derived from the D isomers of valine, isoleucine, and threonine. The nitrogen intake from all sources was 10.10 gm. per day, of which 0.40 gm. was of an unknown nature. The latter originated largely in the starch of the wafers. Much smaller amounts were contributed by the butter fat, lemon juice, and liver concentrate present in the vitamin pills. The daily energy intake amounted to 55 calories per kilo of body weight. In this experiment, as well as in the other two, the ratio of calories derived from carbohydrates to those furnished by fats was maintained at 2.6.

Mention should be made of the fact that the amount of extra sucrose consumed by Subject R. L. W. was larger than has been used in other experiments. This subject weighed in excess of 80 kilos. In order to provide the desired energy intake, without modifying the customary ratio of calories originating in carbohydrates and fats, an increase was necessary either in the starch of the wafers or in the extra sucrose. The latter alternative was chosen by the subject in order thereby to avoid an increase in the bulk of wafers to be ingested. That the sucrose was completely utilized was demonstrated by frequent tests of the urines for reducing materials, before and after boiling the samples with acid. Invariably the tests were negative. Indeed, tests for sugar and protein were made routinely throughout all of our human experiments.

The findings in the experiment upon Subject R. L. W. are summarized in Table I. Starting with a daily dosage of 2.0 gm. of DL-methionine, a strongly positive nitrogen balance was established promptly and was main-
tained throughout the period. Distinctly positive balances also occurred during the two succeeding periods, when the daily methionine intakes were 1.0 and 0.9 gm., respectively. On the other hand, further decreases resulted in negative balances. Even during the fourth period, when the

### Table I

**Sparing Effect of Cystine on Methionine Requirement of Man**

<table>
<thead>
<tr>
<th>Period averages.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average daily N output</strong></td>
<td><strong>Average daily N balance</strong></td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td><strong>Feces</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject R. L. W.</td>
<td></td>
</tr>
</tbody>
</table>
| * The initial diet contained amino acid Mixture 205 (11).  
† Equivalent in sulfur content to 1.0 gm. of methionine.  
‡ The slight decrease in nitrogen intake during this period was due to the use in the wafers of a new shipment of starch which had a slightly lower nitrogen content. |  |  |
| **Period** | **Initial body weight** | **Daily N intake** | **Average N** | **Diet notes** |  |
|  | **kg.** | **gm.** | **gm.** | **gm.** |  |
| 6 | 81.9 | 10.10 | 8.82 | 0.92 | +0.36 | 2.0 gm. DL-methionine  
‡ 0.4 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 7 | 82.6 | 10.10 | 8.99 | 0.89 | +0.32 | 1.0 “ “  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 6 | 82.7 | 10.10 | 8.92 | 0.88 | +0.30 | 0.9 “ “  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 4 | 83.1 | 10.10 | 9.19 | 0.92 | -0.01 | 0.8 “ “  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 1 | 84.1 | 10.10 | 9.39 | 0.84 | -0.13 | 0.7 “ “  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 6 | 83.6 | 10.10 | 8.54 | 0.77 | +0.79 | 0.8 “  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 6 | 84.7 | 10.10 | 8.40 | 0.71 | +0.99 | 0.4 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 7 | 85.1 | 10.10 | 8.97 | 0.75 | +0.38 | 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 6 | 85.2 | 10.10 | 9.05 | 0.80 | +0.25 | 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
| 7 | 85.3 | 10.10 | 9.38 | 0.77 | -0.05 | No DL-methionine; 0.81 gm. L-cystine  
† No DL-methionine; 0.81 gm. L-cystine  
‡ No DL-methionine; 0.81 gm. L-cystine  
† No DL-methionine; 0.81 gm. L-cystine  
‡ No DL-methionine; 0.81 gm. L-cystine  
† No DL-methionine; 0.81 gm. L-cystine  
‡ No DL-methionine; 0.81 gm. L-cystine |  |
| 4 | 85.2 | 10.10 | 9.46 | 0.79 | -0.15 | No DL-methionine; 0.81 gm. L-cystine  
† No DL-methionine; 0.81 gm. L-cystine  
‡ No DL-methionine; 0.81 gm. L-cystine  
† No DL-methionine; 0.81 gm. L-cystine  
‡ No DL-methionine; 0.81 gm. L-cystine  
† No DL-methionine; 0.81 gm. L-cystine  
‡ No DL-methionine; 0.81 gm. L-cystine |  |
| 6 | 85.3 | 10.08 | 8.73 | 0.74 | +0.61 | 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
† 0.1 gm. DL-methionine; 0.81 gm. L-cystine  
‡ 0.1 gm. DL-methionine; 0.81 gm. L-cystine |  |
of 0.81 gm. of L-cystine. The latter quantity contains the same amount of sulfur as that present in 1.0 gm. of methionine. Thus, the cystine intake was more than equivalent to the methionine actually needed by the subject on a cystine-free diet. As the data in Table I indicate, the effect of this diet was extraordinary. Immediately, the nitrogen balance became strongly positive, with an average daily retention of 0.79 gm. This situation persisted during the next period, when the methionine content of the food was reduced to 0.4 gm. daily. But even more astounding is the fact that a daily methionine intake of only 0.1 gm. induced a distinctly positive nitrogen balance. To exclude the possibility that the apparent adequacy of this ration might be a transitory phenomenon, the test was continued for an additional period of 6 days. The result checked the previous finding, and showed definitely that 0.1 gm. of methionine, when accompanied by an abundant supply of L-cystine, was sufficient to meet the needs of this subject.

The observations described thus far naturally suggested the possibility that in man, in contrast to the rat, cystine might be capable of replacing methionine entirely. That this is not the case is disclosed by the results obtained during the last three periods of the experiment upon R. L. W. With the exclusion of methionine, while the administration of 0.81 gm. of L-cystine was continued daily, a slightly negative balance ensued. If one neglects the 1st day of the period, when the balance was still positive because of a carry over effect of the preceding diet, and calculates the average balance for the last 6 days only, a figure of -0.10 gm. is obtained. This is quite comparable in magnitude to the value of -0.15 gm. observed with the same ration during the penultimate period. The final period again showed the adequacy of a daily intake of 0.1 gm. of DL-methionine when cystine also was being consumed.

The effect of L-cystine, as outlined in the above experiment, greatly exceeded our expectations. The decrease in methionine requirement from 0.9 to 0.1 gm. daily represents a sparing action of approximately 89 per cent. Furthermore, the data demonstrate that cystine, though incapable of meeting the full methionine needs of man, actually diminishes the severity of the negative balances which follow the consumption of diets devoid of both these amino acids (cf. Rose et al. (10)). On the other hand, attention should be called to the fact that the subjective symptoms associated with methionine deprivation (10) are not prevented by the ingestion of L-cystine. More will be said about this in connection with the next experiment.

Finally, mention should be made of the very slight decrease in nitrogen intake during the last period (Table I). As will be seen later, this occurred even earlier during the second experiment. In both instances, it came
about through the use in the wafers of a new shipment of starch having a slightly lower nitrogen content. The differences are too small to be significant; indeed, such quantities are well within the limits of accuracy of the nitrogen balance technique.

Subject A. A. S. served in the second experiment. This young man was quite slender and undoubtedly would be regarded by most authorities as being under weight. He was 27 years of age and 5 feet 7 inches in height. When first placed on the diet, he weighed 58.8 kilos. The "ideal" weight of a male of this height at age 25 years is said to be 66.0 kilos (cf. Sherman (13)). It has been the experience in this laboratory that very thin individuals do not attain nitrogen balance readily upon diets containing mixtures of amino acids unless the energy intakes are raised above the usual figure of 55 calories per kilo. Reference was made to this fact in an earlier paper (14).

The ration which Subject A. A. S. first received furnished 55 calories per kilo. It was composed of amino acid Mixture 205 (11), Wafers V (described previously (12)), 190.2 gm. of extra sucrose, and 26.0 gm. of extra butter fat. After an adjustment period of 9 days, the subject was still in negative nitrogen balance, although his body weight had increased by about 1.0 kilo. At this point, his energy intake was raised to 58 calories per kilo, on the basis of his original weight, by the daily addition to the previous diet of 32.0 gm. of sucrose and 5.3 gm. of butter fat. No alteration was made in the amino acid mixture or wafers. The effect of this change in energy intake is shown by the figures representing the first period of the experiment as summarized in Table II. As will be observed, an average daily nitrogen balance of +0.04 gm. occurred. Since this was so slightly positive, the test was continued for the next period without dietary modification. An average retention of 0.20 gm. of nitrogen daily resulted. However, a fact which is not disclosed by the average is that on 2 of the 5 days of the period the subject was in slightly negative balance. An occurrence of this sort introduces uncertainty in the interpretation. To overcome this, the energy intake was further raised, beginning with the third period, to the unusual figure of 60 calories per kilo. This induced perfectly consistent results; consequently, the fuel value of the food was maintained at this level for the remainder of the experiment. Of the 10.03 gm. of nitrogen furnished by the final diet, 0.33 gm. was of an unknown nature. During the last four periods of the experiment, the use of the new shipment of starch, as mentioned above, reduced the unknown nitrogen to 0.30 gm.

Parenthetically, it is of interest to note that the highest energy intake of Subject A. A. S., if expressed in terms of the so called "ideal" or "normal" weight of 66.0 kilos for a young man of his age and height, amounted to
slightly in excess of 53 calories per kilo. No satisfactory explanation can be offered to account for the enhanced energy requirement of an unusually thin individual. Possibly it is associated with the greater body surface per unit of body weight, and the greater heat loss resulting therefrom. In

**Table II**

Sparing Effect of Cystine on Methionine Requirement of Man

| Period | Initial body weight | Daily N intake | Average daily N output | Average daily N balance | Diet notes*
|--------|---------------------|----------------|------------------------|------------------------|------------------------
|        | kg. | gm. | kg. | gm. | gm. | kg. | gm. | gm. |
| 7      | 59.8 | 10.03 | 9.20 | 0.70 | +0.04 | 2.0 gm. D,L-methionine |
| 5      | 60.1 | 10.03 | 9.12 | 0.71 | +0.20 | 2.0 " " |
| 6      | 60.1 | 10.03 | 9.00 | 0.67 | +0.36 | 2.0 " " |
| 6      | 61.1 | 10.03 | 9.07 | 0.71 | +0.25 | 1.0 " " |
| 6      | 61.1 | 10.03 | 9.39 | 0.73 | -0.09 | 0.9 " " |
| 6      | 61.1 | 10.00† | 9.11 | 0.73 | +0.16 | 0.2 " " 0.81 gm. L-cystine‡ |
| 4      | 61.0 | 10.00 | 9.70 | 0.61 | -0.31§ No D,L-methionine; 0.81 gm. L-cystine |
| 4      | 60.5 | 10.00 | 9.24 | 0.73 | +0.03 | 0.3 gm. D,L-methionine; 0.81 gm. L-cystine |
| 5      | 61.1 | 10.00 | 9.71 | 0.74 | -0.45 | 0.1 gm. N L-methionine; 0.81 gm. L-cystine |

* The initial diet contained amino acid Mixture 205 (11). During the first two periods, the subject received 58 calories per kilo of body weight; thereafter, the energy intake was increased to 60 calories per kilo.

† The slight decrease in nitrogen intake during this and subsequent periods was due to the use in the wafers of a new shipment of starch which had a slightly lower nitrogen content.

‡ Equivalent in sulfur content to 1.0 gm. of methionine.

§ Averages represent first 2 days only of the period. As a result of the deficiency, the subject experienced a severe loss of appetite and vomited part of the diet on the 3rd day. See the text.

any event, the phenomenon is one to be reckoned with in nitrogen balance studies, at least when the diets contain mixtures of amino acids in place of proteins.

As pointed out above, a consistently positive nitrogen balance occurred throughout the third period of the experiment upon A. A. S. (Table II). At that time, the methionine dosage was 2.0 gm. daily. During the next two periods, the intake of methionine was decreased, first to 1.0 gm. and
then to 0.9 gm. per day. The results indicate that 1.0 gm. daily was the smallest amount which was capable of maintaining a distinctly positive nitrogen balance. Therefore, this quantity represented the minimal requirement of Subject A. A. S. when cystine was absent from the food. The diet was then supplemented with 0.81 gm. of L-cystine daily, and, in view of the experience gained in the preceding experiment, the methionine dosage was dropped to 0.2 gm. daily. A distinctly positive balance resulted, with an average daily nitrogen retention of 0.16 gm.

During the next period, the exclusion from the food of the small quantity of methionine being ingested exerted a remarkable effect. On several occasions (cf. Rose et al. (10, 15)), the fact has been emphasized that depriving a human subject of one of the eight essential amino acids leads to a profound failure in appetite, a sensation of extreme fatigue, and a marked increase in nervous irritability. In the present experiment, these symptoms followed methionine deprivation even though cystine was being consumed. So marked was the appetite failure that A. A. S. found it necessary to force himself to eat the food. This he courageously contrived to do for 2 days, but, following breakfast on the 3rd day, part of the meal was lost by vomiting. During the remainder of the 3rd and all of the 4th day the subject was unable to ingest part of his ration. Obviously, this régime could no longer be maintained. The figures for the period (Line 7, Table II) represent the first 2 days only, during which all of the ration was consumed and retained. The average daily nitrogen loss is shown as 0.31 gm., but really was increasing quite rapidly and amounted to 0.51 gm. on the 2nd day.

To reestablish nitrogen equilibrium and restore the appetite of Subject A. A. S., 0.3 gm. of methionine was administered daily, along with 0.81 gm. of L-cystine, during the penultimate period. The effect was just as dramatic as that resulting from the exclusion of methionine. The average nitrogen retention for the period was only 0.08 gm., but the figures for the 4 days were -0.60, +0.07, +0.20, and +0.44 gm., respectively. Along with the change in nitrogen balance came a restoration of appetite, so that no further difficulty was experienced in consuming the ration until late in the final period, when a decrease in the methionine intake to 0.1 gm. daily occasioned a steadily increasing negative balance. The experiment was discontinued on the 5th day of lowered methionine consumption in order thereby to avoid the possibility of vomiting. The data demonstrate unequivocally that 0.2 gm. of methionine was the minimal daily requirement of the subject when cystine was present in the food. Thus, an abundance of cystine in the food reduced the minimal methionine needs of A. A. S. from 1.0 to 0.2 gm. daily. This represents a sparing action of approximately 80 per cent. On the contrary, in this subject, as in the preceding
experiment upon Subject R. L. W., L-cystine was incapable of replacing all of the methionine of the food.

**Table III**

_Sparing Effect of Cystine on Methionine Requirement of Man_

<table>
<thead>
<tr>
<th>Period</th>
<th>Initial body weight</th>
<th>Daily N intake</th>
<th>Average daily N output</th>
<th>Average daily N balance</th>
<th>Diet notes*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject A. G.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>days</th>
<th>kg.</th>
<th>gm.</th>
<th>gm.</th>
<th>gm.</th>
<th>gm.</th>
<th>0.6 gm. DL-methionine; 0.81 gm. L-cystine†</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>78.8</td>
<td>10.10</td>
<td>9.04</td>
<td>0.71</td>
<td>+0.35</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>79.4</td>
<td>10.10</td>
<td>8.83</td>
<td>0.74</td>
<td>+0.53</td>
<td>0.5 gm. DL-methionine; 0.81 gm. L-cystine</td>
</tr>
<tr>
<td>6</td>
<td>79.4</td>
<td>10.10</td>
<td>9.02</td>
<td>0.69</td>
<td>+0.39</td>
<td>0.4 gm. DL-methionine; 0.81 gm. L-cystine</td>
</tr>
<tr>
<td>8</td>
<td>79.2</td>
<td>10.10</td>
<td>8.97</td>
<td>0.76</td>
<td>+0.37</td>
<td>0.3 gm. DL-methionine; 0.81 gm. L-cystine</td>
</tr>
<tr>
<td>8</td>
<td>79.8</td>
<td>10.10</td>
<td>9.06</td>
<td>0.73</td>
<td>+0.31</td>
<td>0.2 gm. DL-methionine; 0.81 gm. L-cystine</td>
</tr>
<tr>
<td>7</td>
<td>80.4</td>
<td>10.10</td>
<td>9.21</td>
<td>0.80</td>
<td>+0.09</td>
<td>0.1 gm. DL-methionine; 0.81 gm. L-cystine</td>
</tr>
<tr>
<td>8</td>
<td>81.3</td>
<td>10.10</td>
<td>9.46</td>
<td>0.77</td>
<td>−0.13</td>
<td>No DL-methionine; 0.81 gm. L-cystine</td>
</tr>
<tr>
<td>4</td>
<td>81.9</td>
<td>10.10</td>
<td>9.80</td>
<td>0.86</td>
<td>−0.56</td>
<td>&quot;</td>
</tr>
<tr>
<td>5</td>
<td>81.5</td>
<td>10.10</td>
<td>9.32</td>
<td>0.63</td>
<td>+0.15</td>
<td>0.1 gm. DL-methionine; 0.81 gm. L-cystine</td>
</tr>
<tr>
<td>5</td>
<td>82.6</td>
<td>10.10</td>
<td>9.08</td>
<td>0.77</td>
<td>+0.25</td>
<td>0.1 gm. DL-methionine; 0.81 gm. L-cystine</td>
</tr>
</tbody>
</table>

* In an earlier experiment, the minimal DL-methionine requirement of this subject had been shown to be 0.3 gm. daily when the ration was devoid of cystine. In the present test, the initial diet contained amino acid Mixture 205 (11), except for the indicated quantities of methionine and cystine.

† Equivalent in sulfur content to 1.0 gm. of methionine.

‡ During this period only, the subject received 1.22 gm. of L-tyrosine daily for the reason explained in the text.

The results of the third experiment are summarized in Table III and require very little discussion. Several weeks earlier, the minimal methionine requirement of this young man (Subject A. G.) had been shown to be 0.8 gm. daily when the diet was devoid of cystine. The experiment in Table III is concerned only with the effects of the latter amino acid. During the interval between the two tests, the subject was at his home for the Christmas vacation and had gained about 1 kilo in body weight. On the
basis of the initial weight given in Table III, his energy intake was slightly under 54 calories per kilo. His initial diet was composed of amino acid Mixture 205 (11), except for the indicated quantities of methionine and L-cystine, Wafers IV (cf. Rose et al. (12)), 255.3 gm. of extra sucrose, and 41.6 gm. of extra butter fat. The nitrogen intake from all sources amounted to 10.10 gm., of which 0.40 gm. was of an unknown nature.

The data in Table III demonstrate clearly that, in the presence of L-cystine, the minimal methionine requirement of Subject A. G. was 0.1 gm. daily. The figures also reveal that cystine, as in the other subjects, was incapable of replacing the entire methionine needs, and show further that the exclusion of both methionine and cystine (Line 8, Table III) greatly intensified the negative nitrogen balance. This latter observation was, of course, anticipated from the findings in our previous studies (10). Throughout, Subject A. G. was unaware of the character of the dietary alterations. During the period when both methionine and cystine were removed, finely powdered L-tyrosine was incorporated each day in the amino acid solution, just as the sulfur-containing amino acids were added during other periods. The limited solubility of tyrosine was sufficient to disguise its true nature. Despite this precaution against psychological influences, the deficiency symptoms were intense. The subject experienced a loss of appetite, complained of headache, nervousness, and insomnia, and threatened to discontinue the experiment. For these reasons, the period was shortened to 4 days. As always, the symptoms disappeared with the return of the missing amino acid to the diet.

It is evident from the above that the inclusion of L-cystine in the food diminished the minimal methionine requirement of A. G. from 0.8 to 0.1 gm. daily, or exerted a sparing action of approximately 87 per cent. Thus, in the three subjects, the replacement value of L-cystine varied from 80 to 89 per cent. This observation should prove to be of considerable importance from the nutritional point of view. In those areas of the world in which native diets are low in methionine, little consideration appears to have been given to the beneficial effects of cystine. In the light of our experience, such rations should be reevaluated in so far as they contain significant amounts of the latter amino acid.

SUMMARY

Experiments have been conducted in normal young men for the purpose of ascertaining the sparing effect of L-cystine upon their minimal methionine needs. To accomplish this, the methionine requirement of each subject was first established in the absence of dietary L-cystine. An excess of the latter amino acid was then incorporated in the food, and the methionine requirement was again determined. The results demonstrate
that L-cystine is capable of replacing 80 to 89 per cent of the minimal methionine needs of adult man, as measured by the maintenance of nitrogen equilibrium. Attention is called to the significance of this finding, particularly in those areas of the world in which methionine appears to be the limiting amino acid in the native diets.

BIBLIOGRAPHY

THE AMINO ACID REQUIREMENTS OF MAN: XIII. THE SPARING EFFECT OF CYSTINE ON THE METHIONINE REQUIREMENT

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