EFFECT OF A LYSINE-POOR DIET ON THE COMPOSITION OF HUMAN PLASMA PROTEINS*

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It has long been known that loss of body weight, negative nitrogen balance, and hypoproteinemia constitute the first signs of protein deficiency in man and experimental animals. However, in a series of studies sponsored by the Bureau of Biological Research of Rutgers University, in which six reference proteins were evaluated by different methods of assay, paradoxical findings were obtained in regard to the nutritional value of wheat gluten. Mitchell (1) reported that, by the nitrogen balance method, wheat gluten had a biological value of 40 as compared to 97 for egg albumin in the immature rat. Frost (2) by the rat depletion method found a value of 9 for wheat gluten as compared to 38 for egg albumin. Chow (3), on the other hand, by dog repletion tests obtained a value of 135 for total circulating proteins with wheat gluten as compared to 117 with egg albumin after 2 weeks, and 135 and 132 respectively after 4 weeks of repletion with these proteins. It is at once clear from the findings of these investigators that there may exist a lack of correlation between the nitrogen balance maintenance and plasma protein regenerative properties of protein foods.

Since, in the evaluation of protein nutrition of population groups, the only chemical test which has been widely applied has been the determination of total serum or plasma protein levels, it seemed to us worth while to attempt the resolution of the aforementioned nutritional paradox if it existed in the human (4). The need for such a study can be readily appreciated when it is realized that wheat gluten constitutes the principal, and sometimes the only, dietary protein of the major segment of the world’s population. The investigational details of this biochemical phenomenon as it occurs in the human infant are described in this report.

EXPERIMENTAL

Diets and Procedures—The composition of the wheat gluten diet employed in this study is shown in Table I. The wheat gluten product (In-
EFFECT OF LYSINE ON PLASMA PROTEIN
terchemical) contained 87 per cent gluten by Kjeldahl analysis and 1.38 per cent lysine by microbiological assay. The level of dietary protein given, i.e. 3.2 to 3.5 gm. per kilo of body weight, was determined by an evaluation of the available data in the literature (5), and by our own experience, as an intake required for optimum N retention in infants of this age. As in previously reported studies, this synthetic formula was given in five daily feedings and was supplemented daily with 50 mg. of ascorbic acid and 15 drops of oleum percomorphum. Owing to uncertainties regarding the complete human requirement of B complex vitamins, brewers'

**Table I**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gm.</td>
</tr>
<tr>
<td>Wheat gluten*</td>
<td>3.50</td>
</tr>
<tr>
<td>Brewers' yeast</td>
<td>1.00</td>
</tr>
<tr>
<td>Olive oil</td>
<td>4.00</td>
</tr>
<tr>
<td>Dextrimaltose No. 2</td>
<td>9.60</td>
</tr>
<tr>
<td>Arrowroot starch</td>
<td>2.30</td>
</tr>
<tr>
<td>Salt mixture†</td>
<td>1.60</td>
</tr>
<tr>
<td>Water</td>
<td>78.00</td>
</tr>
<tr>
<td>Total</td>
<td>100.00</td>
</tr>
<tr>
<td>Estimated lysine content</td>
<td>150 mg. per 100 gm.</td>
</tr>
</tbody>
</table>

* Kindly supplied to us by the Biochemical Division of the Interchemical Corporation. The additions of this product were corrected for water and ash content which equaled 13 per cent.
† The salt mixture employed had the following composition, measured in gm.: FeSO₄ 0.9, NaCl 6, Ca gluconate 48, Ca(OH)₂ 12, KH₂PO₄ 7, KCl 6, MgO 0.1.

yeast was employed instead of a mixture of the synthetically available vitamins. The quantities of lysine derived from this source appear to be approximately 16 mg. per gm. (6). In the precontrol period an evaporated milk formula was fed at levels which were isocaloric and isonitrogenous with the wheat gluten diet. In the postcontrol periods, the wheat gluten diet, which contained approximately 150 mg. of lysine per 100 gm., was supplemented stepwise from 1 to 5 per cent of L-lysine of the protein moiety as L-lysine hydrochloride (\(\left[\alpha\right]_{D}^{25} +20^\circ\) in 1 N HCl).

The diet periods were of 7 days duration and consecutive, and the children were weighed daily. The average daily N retention was determined from Kjeldahl measurements of daily 24 hour urine collections, analyses of pooled feces for each period, and computation of the daily N intake.
The plasma proteins were determined weekly by the Kjeldahl technique and the colorimetric procedure based on the Sakaguchi reaction for arginine described by us (7). These determinations were made by both methods on aliquots of the same plasma protein solutions or fractions as obtained by the Howe procedure.

**Results**

In previous studies the dietary lack of tryptophan (8), methionine (9), or isoleucine (10) was found to cause a drop in N retention as well as a
The effect of lysine on plasma protein levels within 10 to 16 days. It will be observed from the graphic representation of typical data secured in this investigation, shown in Fig. 1, that, although the wheat gluten diet caused a marked depression in N retention values, it did not affect the plasma protein levels, as determined by the Kjeldahl procedure. However, measurement of the plasma proteins in terms of their arginine content showed them to increase progressively with the duration of the wheat gluten diet. When this diet was supplemented stepwise with L-lysine, the arginine content of the total plasma proteins was slowly restored to the norm from aberrant values of 7 to 9.2 per cent arginine. No signifi-

Table II

<table>
<thead>
<tr>
<th>Subject</th>
<th>Periods</th>
<th>Diet</th>
<th>Estimated lysine intake</th>
<th>Kjeldahl method</th>
<th>Arginine method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mg. per kg. per day</td>
<td>Total plasma protein</td>
<td>Albumin to globulin ratio</td>
</tr>
<tr>
<td>R. A., 7 mos.; 6280 gm.</td>
<td>2</td>
<td>EM</td>
<td>200</td>
<td>6.26</td>
<td>2.30</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>WG</td>
<td>150</td>
<td>6.19</td>
<td>2.62</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>&quot; + 4% L-lysine</td>
<td>240</td>
<td>6.43</td>
<td>2.21</td>
</tr>
<tr>
<td>C. L., 6.3 mos.; 7407 gm.</td>
<td>2</td>
<td>EM</td>
<td>200</td>
<td>6.70</td>
<td>1.80</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>WG</td>
<td>150</td>
<td>6.62</td>
<td>2.05</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>&quot;</td>
<td>150</td>
<td>6.35</td>
<td>2.34</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>EM</td>
<td>200</td>
<td>6.40</td>
<td>1.67</td>
</tr>
</tbody>
</table>

* EM designates the evaporated milk formula, and WG, the wheat gluten diet.

significant alteration in the albumin to globulin ratios was observed throughout the course of these studies (Table II). From this it would appear that the compositional change involved both major plasma fractions.

The N retention of all the infants was restored to normal values when the wheat gluten diet was supplemented so that the lysine intake ranged from 185 to 220 mg. per kilo per day. Since the plasma protein levels were not altered by this dietary supplement, it must be concluded that measurements of these blood components do not constitute an adequate criterion of lysine intake in the infant.

DISCUSSION

The reported findings, which occurred in all six infants studied, suggest that in the face of an inadequate lysine intake the plasma proteins are formed at an apparently normal rate. This synthesis could be maintained by one of two processes, (a) the substitution of arginine for lysine in these
proteins or (b) an increase in a plasma protein fraction, or fractions, rich in arginine. In view of newer knowledge derived from electrophoretic studies, the latter mechanism might appear as the more likely one since, of the known plasma proteins, \(\alpha\)-globulin and fibrinogen have been reported to contain 7.7 and 7.9 per cent of arginine respectively (11). However, if this process prevailed, the observed arginine values could be attained only by changes, and probably inversion, of the albumin to globulin ratios. Since no significant alteration in the albumin to globulin ratios was noted, we are forced to consider the likelihood of the mechanism first mentioned.

Changes in the amino acid composition of serum proteins in health and disease have been the purpose of some investigations (6). Although the results on pathological sera are very meager, they appear to show that changes in basic amino acid content and especially in lysine do occur. Studies on Bence-Jones protein suggest that this protein may vary in basic amino acid composition in different cases. Some evidence of species differences has also been presented. Dolby, Hall, and Happold (12) have recently shown that protein fractions prepared from \textit{Bacterium coli} grown on different media possess different amino acid patterns. These observations have been questioned by those who would include constancy of amino acid composition as a criterion of protein purity. This thesis presupposes that biosyntheses of proteins are governed by the laws of organic chemistry. However, the present status of these problems has been neatly summarized by Tristram (13) as follows: "While it may be true that the physiological activities of proteins demand the presence of specific groupings, there is no evidence which would support the thesis that every unit is unchangeable in composition (\textit{i.e.}, alanine for glycine, etc.) or position."

Quite apart from these considerations, the observed discrepancy between the Kjeldahl and arginine values, if supported by further studies now under way, may serve as a criterion of lysine deficiency in man. In this connection it is of interest to note that we have obtained significant discrepancies between plasma protein values as obtained by Kjeldahl and arginine procedures in patients suffering from severe malnutrition resulting from chronic diseases.

SUMMARY

Evidence has been presented that plasma protein levels may not accurately reflect the protein nutritional state of the infant. The possible mechanism through which normal plasma protein synthesis may be achieved in the face of a lysine-poor diet is discussed.

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