Protein Deficiency and Carbohydrate Tolerance of the Infant Squirrel Monkey (Saimiri sciureus) 

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ABSTRACT In order to investigate a syndrome of glucosuria, hyperglycemia, coma and death found in infant squirrel monkeys fed protein-deficient diets, 48 infants were studied in four experiments related to carbohydrate metabolism. In 12 infants fed a diet containing 2.3% of the calories as protein for a 12-day period, glucosuria and hyperglycemia appeared within 6 days. Animals prefed a commercial milk-based diet were more severely affected than those prefed a laboratory diet containing sucrose and dextrin as the carbohydrate source. Another 16 infants were given oral glucose tolerance tests following 3-week dietary periods during which three levels of dietary protein (2.3, 4.6, and 12.9% of calories) were fed. It was shown that glucose intolerance appeared when animals were fed the diet containing 2.3% of the calories as protein but not 4.6 or 12.9%. Glucose tolerance did not vary with the two levels of fat fed. In two additional experiments utilizing 21 and 6 infants, it was demonstrated that the caloric intake of malnourished infants was comparable to the control intakes and that a decrease in food consumption was not the cause of the observed symptoms. J. Nutr. 102: 1519-1528, 1972.

KEY INDEXING WORDS squirrel monkey • protein deficiency • carbohydrate metabolism • hyperglycemia • glucosuria

In preliminary studies in which low-protein diets were fed to three different species of infant monkeys, the infant squirrel monkey (Saimiri sciureus) responded uniquely when compared to other New World species, the capuchins or cebus (Cebus albifrons and apella) and an Old World species, the cynomolgus or Philippine macaque (Macaca fascicularis). When infant squirrel monkeys were fed a semipurified liquid diet containing only 2.3% of the calories as protein (lactalbumin), some of them developed postprandial hyperglycemia and a marked glucosuria within a few days. Some of the monkeys had previously been fed a commercial infant formula and others had been receiving a semipurified diet prepared in the laboratory which was thought to be adequate in all respects, including protein. It was evident that the animals which had previously received the commercial formula were more adversely affected by the low protein diet than those which had received the semipurified diet.

A comparison of the composition of the commercial formula and the laboratory diet showed that the commercial formula contained considerably more fat (47.2% of the calories) than the laboratory formula (21.0% of the calories). Also, the commercial formula was based upon milk and contained lactose, whereas the carbohydrate in the laboratory diet was a mixture of dextrin and sucrose. There were other obvious differences, such as the type of fat, but these were considered less likely causes of the peculiar response to the low protein diet. The studies reported herein were carried out to further define the cause of the abnormality in carbohydrate metabolism.

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1 Supported in part by Public Health Service Research Grants HE-10098, AM-09520, GM-00333 and KB-AM-18455 and the Fund for Research and Teaching, Department of Nutrition, Harvard School of Public Health.

2 Similar with Iron, Ross Laboratories, Columbus, Ohio. Composition of powder by weight (in %): fat, 26.85; carbohydrate, 53.40; protein, 13.75; minerals, 4.00; moisture, 2.0.
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TABLE I
Composition of semipurified liquid diets fed

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Diet 1</th>
<th>Diet 2</th>
<th>Diet 3</th>
<th>Diet 4</th>
<th>Diet 5</th>
<th>Diet 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/100 g nonaqueous diet</td>
<td>g/100 g nonaqueous diet</td>
<td>g/100 g nonaqueous diet</td>
<td>g/100 g nonaqueous diet</td>
<td>g/100 g nonaqueous diet</td>
<td>g/100 g nonaqueous diet</td>
</tr>
<tr>
<td>Lactalbumin</td>
<td>16.17</td>
<td>16.17</td>
<td>19.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>28.37</td>
<td>28.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextrin</td>
<td>35.08</td>
<td>63.45</td>
<td>44.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soybean–cottonseed oil</td>
<td>9.45</td>
<td>9.45</td>
<td>25.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt mix</td>
<td>4.73</td>
<td>4.73</td>
<td>4.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin mix</td>
<td>0.47</td>
<td>0.47</td>
<td>0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choline chloride</td>
<td>0.28</td>
<td>0.28</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulose</td>
<td>4.73</td>
<td>4.73</td>
<td>4.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrageen</td>
<td>0.38</td>
<td>0.38</td>
<td>0.38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tween 80</td>
<td>0.34</td>
<td>0.34</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% calories as protein</td>
<td>12.90</td>
<td>12.90</td>
<td>12.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% calories as fat</td>
<td>21.00</td>
<td>21.00</td>
<td>47.20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Diet 2: 2.94 g lactalbumin; 41.60 g sucrose (2.3% calories as protein).
2 Diets 4 and 5: 5.88 and 2.94 g lactalbumin; 73.74 and 76.68 g dextrin (4.6 and 2.3% calories as protein).
3 Diets 7 and 8: 7.03 and 3.52 g lactalbumin; 56.60 and 60.11 g dextrin (4.6 and 2.3% calories as protein).
4 The dietary ingredients are mixed and stored in plastic containers for periods up to 2 weeks. The premixed dry ingredients, oil and Tween 80 were mixed in a commercial Waring blender with sufficient water to yield a dilution providing 1 kcal/ml of liquid diet.
5 The lactalbumin contained 12.9% nitrogen by Kjeldahl analysis.
6 Wesson Oil, Hunt-Wesson Foods, Inc., Fullerton, Calif.
7 The salt mix contained (in g/kg): CaCO3, 300; KH2PO4, 322; CaHPO4 · 2H2O, 75; MgSO4 · 7H2O, 102; NaCl, 167; Fe(C6H5O7)2 · 2H2O, 57.5; KI, 0.8; MnSO4 · 5H2O, 50; ZnCl2, 0.25; CuSO4 · 5H2O, 0.30.
8 The vitamin mix contained (in mg): thiamin hydrochloride, 80; riboflavin, 160; pyridoxine hydrochloride, 80; calcium pantothenate, 150; niacinamide, 800; folate acid, 20; biotin, 4; cyanocobalamin, 3; menadione, 100; dl-alpha-tocopherol acid succinate, 690 IU; retinyl acetate beadlets, 250,000 IU; cholecalciferol beadlets, 25,000 IU. Made to 100 g with dextrin.
9 Alphacel, Nutritional Biochemicals, Cleveland, Ohio.
10 Irish Moss, Nutritional Biochemicals, Cleveland, Ohio.
11 Nutritional Biochemicals, Cleveland, Ohio.

MATERIALS AND METHODS

The studies comprised four experiments utilizing 48 infant squirrel monkeys over a period of 2.5 years. In all cases the infant monkeys were removed from their dams at birth and hand-raised in an infant nursery (1). Animals are usually fed a commercial formula until 8 weeks of age at which time they are assigned to different experimental liquid formulae of our own design.

Experiment 1. This experiment was designed to reproduce and define the evolution of the observed hyperglycemia and glucosuria by measuring the blood glucose concentration and the appearance of glucose in the urine. Twelve infant male and female squirrel monkeys were available who had received the commercial formula until 8 weeks of age. Five of the 12 had continued to receive the commercial formula whereas seven had been fed a semipurified liquid diet of our own composition containing an adequate amount of protein as lactalbumin (diet 1, table 1). Feeding was ad libitum from a fresh bottle of food offered at 2- to 3-hour intervals from 8:00 AM until 12:00 PM. The animals were 11 to 19 weeks of age when they were fed for a 12-day experimental period the low protein diet (diet 2, table 1), containing 2.3% of the calories as protein. The animals were divided into two groups of six each to provide a mean age of 15 weeks and a balanced sex distribution. One group of animals was tested on days 0, 6, and 10 and the other group on days 0, 8, and 12. Day zero (the day before the low protein diet was started) was considered base line for each group of animals.

On each test day blood glucose was determined at 8:00 AM after an 8-hour fast and postprandially at 10:00 AM and at 9:00 PM. Four tests for urinary glucose were made throughout the day. Blood samples in this and later experiments were obtained on unanesthetized monkeys by femoral or jugular venipuncture. Fifty microliters of whole blood was pipetted into 0.95 ml of a NaCl:NaF solution (0.9: 1.35%) for analysis of blood glucose on an autoanalyzer according to the ferri-
cytamine reduction procedure of Hoffman (2).

In retrospect, the 12 infants in experiment 1 also comprised four subgroups according to the diet they had received previously, diet 1 or the commercial formula, and the days of testing, 0, 6, 10 or 0, 8, 12. For reasons that will become obvious, the data were analyzed on this basis. Each of the four subgroups was analyzed by a three-way analysis of variance (time × day × animal). Due to wide variations in glucose concentrations, a logarithmic transformation was necessary to equalize variances for statistical testing (3).

Experiment 2. In the second experiment, another 16 infant squirrel monkeys were utilized to define the effect of dietary protein and fat on the impaired glucose metabolism described in the first experiment. The monkeys were reared from birth with the commercial formula (12 animals) or diet 1 (four animals) until 12 weeks of age. They were then divided into two groups according to sex and previous diet. One group was fed a low fat diet (21.0% of the calories) and the other group a high fat diet (47.2% of the calories) with protein (lactalbumin) supplying 2.3, 4.6, or 12.9% of the calories. The diets were fed for 3-week periods beginning with an adequate level of protein (12.9% of the calories as protein) followed by one of the low protein diets (2.3 or 4.6% of the calories as protein). The normal diet was again fed for 3 weeks followed by the other low protein diet. Dextrin was the only source of carbohydrate in these diets. Description of the diets (diets 3 through 8) and their preparation are given in table 1.

An oral glucose tolerance test (4 g/kg, 8-hour fast) in conscious animals was made at the conclusion of each 3-week dietary period. Animals were fed a 25% dextrose in water solution which they drank in 1 to 3 minutes. Blood was drawn at fasting, 30, 60, and 120 minutes after glucose loading for glucose determinations. A log transformation was again necessary for the statistical analysis of glucose values in experiment 2. The glucose tolerance curves were evaluated by summing the logs of the one-half and the one-hour blood glucose concentrations to give a Tolerance Index (4) which was analyzed by a two-way analysis of variance with a nested design (3).

Experiment 3. In order to determine whether the symptoms might be related to low caloric intake or partial starvation, total food intake and total urine and feces collections were made on seven 6-month old control monkeys (fed diet 3), and fourteen 6-month old infant squirrel monkeys maintained on long-term protein deprivation (2.3 to 6.1% of the calories as protein) from 8 weeks of age. Feces and urine were collected together over a 7-day period and dried, weighed and analyzed for total fat. Since the diet contained cellulose, which is expected to be excreted in the feces, the cellulose consumed during the collecting period was subtracted from the weight of the excreta. The weight not accounted for by fat or dietary cellulose was assumed to represent carbohydrate or protein. This was assumed to yield 4 kcal/g and the fat 9 kcal/g in calculating the total calories lost in the excreta. Total food intake was corrected by collecting spilled liquid formula in drip pans and, after drying, calculating its caloric value. Net calories were expressed as the difference between those eaten and those in the excreta. Tukey's t test for all possible comparisons of treatment means was applied to the data (5).

Experiment 4. In order to determine if simple caloric deprivation could cause glucose intolerance and glucosuria, six healthy infant squirrel monkeys, 4 to 5 months in age receiving diet 3 (with safflower or coconut oil substituted for the soybean–cottonseed oil) were restricted to an intake of 70 or 85% (three each, respectively) of the kilocalories/kilogram body weight/day that they had been consuming previously. Caloric intake for these restricted animals ranged from 200 to 250 kcal/kilogram body weight/day within the range of the lowest intakes among protein-deprived monkeys. After 8 weeks this restricted intake was further reduced by 50% to only 100 to 125 kcal/kg body weight/day for 2 days. Urine samples were measured after meals for the presence of glucose.

RESULTS

Experiment 1. Animals in experiment 1 consuming the two control diets (diet 1
and the commercial formula) prior to the start of the experiment had similar baseline glucose values. Although these two groups had individual monkeys that demonstrated marked impairment when fed the low protein diet (diet 2), the mean blood glucose concentrations for all animals previously fed the commercial formula increased significantly during the 12-day test period, whereas the concentrations of those previously fed diet 1 did not (fig. 1). In animals previously fed a commercial formula, a multiple range analysis (6) for the significant sources of variation indicated that they were impaired by day 6 and remained unchanged through day 12. The blood glucose concentrations were significantly elevated at 10:00 AM and occasionally at 9:00 PM. In contrast, those infants preferred the semipurified diet (diet 1) demonstrated, as a group, no significant variation in blood glucose concentration due to the day of testing or time of day.

The mean glucose levels were generally lower at 9:00 PM than at 10:00 AM (fig. 1), presumably due to the pattern of food consumption. On day zero, all animals consumed the entire bottle of food (25 ml) offered 2 hours prior to the 10:00 AM and 9:00 PM sampling. However, animals consuming the low protein diet and found hyperglycemia at 10:00 AM often consumed less than half the bottle offered at 7:00 PM and were normoglycemic and without glucosuria at 9:00 PM. Although the total caloric intake for the entire 12-day period was not decreased, the animals consumed their food more slowly rather than as distinct meals.

All animals previously fed the commercial formula began excreting glucose in the urine 1 or 2 days after the low protein diet (diet 2) was started, whereas those previously fed the laboratory formula were more resistant. Nonetheless, most of them were also excreting glucose by the experimental day 12. Thus, even though the mean blood glucose values of this group (fig. 1) were not elevated at the time the samples were taken, the urinary threshold was often exceeded, presumably associated with postprandial hyperglycemia. Table 2 summarizes the data for urinary glucose at 3-day intervals during experiment 1 and for 4 days following the test period.

Experiment 2. Experiment 2 was designed to evaluate glucose tolerance when diets containing various levels of dietary protein were fed. The animals were fed a diet with a level of protein adequate for normal growth (12.9% of the calories as protein) prior to each of the low protein diets (2.3 and 4.6% of the calories as protein). These two levels of low protein diets were, respectively, less than the amount needed for weight maintenance, or approximated the weight maintenance requirement of the infant squirrel monkey under normal consumption. As the low protein diets were not fed consecutively, a replication of the measurements for the control diet was obtained. Similar tolerance curves were obtained in animals consuming either the control diets or the diet containing 4.6% of the calories as protein, whereas the diet with the least protein

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TABLE 2

Glucosuria recorded during feeding of low protein test diet and subsequent refeeding of two different control diets (experiment 1)

<table>
<thead>
<tr>
<th>Control diet</th>
<th>Glucose excretion in the urine</th>
<th>Low protein (diet 2)</th>
<th>Recovery on control diets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of animals</td>
<td>Experimental days</td>
<td>Experimental days</td>
</tr>
<tr>
<td>Diet 1</td>
<td>7</td>
<td>0 1 1 0 3</td>
<td>3 0 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 3 2 3 3</td>
<td>3 2 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 0 3 0 1</td>
<td>0 0 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 0 0 0 0 3</td>
<td>0 0 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 0 0 0 0 3</td>
<td>0 2 0</td>
</tr>
<tr>
<td>Commercial formula</td>
<td>5</td>
<td>0 3 3 2 3</td>
<td>3 1 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 0 2 0 3</td>
<td>0 0 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 3 3 3 3</td>
<td>2 0 0</td>
</tr>
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<td>0 0 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 3 3 0 3</td>
<td>0 0 0</td>
</tr>
</tbody>
</table>

1 Clinistix (see text footnote 3). Possible values range from 0 (no urinary glucose) to 3 (extreme urinary glucose).

Fig. 2 Glucose tolerance curves are presented for two groups of eight animals fed low or high fat diets with three different concentrations of protein. The lowest protein diet, irrespective of dietary fat content, produced a marked impairment of the glucose tolerance in eight animals with blood glucose elevations at 1 hour ranging from 64 to 298 mg/100 ml. (2.3% of the calories) resulted in weight loss and induced an abnormal glucose tolerance (fig. 2). The order in which the low protein diets were fed did not appear to affect the results.

Statistical analysis of the Tolerance Index (the sum of the log glucose levels at one-half hour and one hour) indicated that the lowest protein diet produced a significantly elevated glucose response ($P < 0.01$) compared to the other two diets and that the results produced by the control diet and the 4.6% protein diet were not different. Although the analysis of variance indicates marked differences in the response of individual animals ($P < 0.01$), especially in those consuming the high fat diet, the overall differences in the high
and low fat diets were not statistically significant.

The possibility that the low protein diet may have caused a reduction in food intake in the infant squirrel monkey leading to the hyperglycemia and glucosuria associated with "starvation" or "hunger diabetes" was explored. The data are presented in figure 3 as a scatter diagram comparing the average caloric intake of each monkey with its Tolerance Index for each test period. It is apparent that many of the animals receiving the low protein diet and having an elevated Tolerance Index were consuming at least as many kilocalories/kilogram/day as unaffected animals. Glucosuria appeared only in animals fed the 2.3% protein diet and appeared to be independent of caloric intake and weight change. Occasional glucosuric animals consumed more kilocalories/kilogram/day and gained weight when fed the lowest protein diet.

Experiment 3. Results of experiment 3 are shown in table 3. Low protein levels of 2.3, 3.8, 5.2, 5.6, and 6.1% of calories were fed, but the data from the last four groups were pooled as animals fed these levels generally grew slightly or maintained their body weight and were not glucosuric. The data confirm the observation made in experiment 2 that glucosuric animals consuming the lowest protein diet (2.3% of protein calories) ate approximately the same amount of kilocalories/kilogram/day (corrected for spillage and loss through the urine and feces) as those receiving the higher protein diets. The data indicate a modest degree of malabsorption at the lowest protein intake. However, the total calories metabolized (expressed as kcal/kg/day) were not different for animals fed the lowest protein diet as compared to the control group. Net metabolized calories (kcal/kg/day) for animals fed medium protein diets (3.8 to 6.1% of the calories) were significantly greater than those fed the control diet. As this may be caused by the difference in body size of the animals in each of the two groups, net metabolized calories were also computed in terms of kcal/kg²/day.

Experiment 4. Caloric restriction of the control diet to 220 to 250 kcal/kilogram body weight/day in six healthy infant squirrel monkeys did not result in post-prandial glucosuria, even though this level
of consumption approximated the lowest intake of the protein-restricted monkeys in experiment 2 and depicted in figure 3. These six animals also maintained or increased body weight while remaining free of glucosuria. When intakes of only 100 to 125 kcal/kilogram/day were allowed, glucosuria did not appear during the 2-day restriction but was observed in one animal upon refeeding ad libitum on day 3. This disappeared within 24 hours.

**DISCUSSION**

This series of experiments demonstrates that normal carbohydrate metabolism of the infant squirrel monkey is dependent upon adequate protein intake and that acute alterations in carbohydrate utilization evidenced by postprandial hyperglycemia, glucosuria, and an impaired response to oral glucose loading may develop when a diet sufficiently low in protein is fed. The amount of protein consumed is a critical factor as shown by the data of experiment 2 in which a moderately low protein diet (4.6% of the calories) limited the rate of weight gain, yet produced no abnormality in glucose tolerance or glucosuria, whereas a 2.3% protein diet generally resulted in weight loss, abnormal glucose tolerance, and, with rare exceptions, glucosuria. Even though the 2.3% protein diet was usually inadequate for weight maintenance during the 3-week period, a few animals consumed such a large quantity of food that they increased or maintained their weight. They were tolerant to a glucose load, although occasionally glucosuric.

The composition of the diet fed prior to the low-protein diet also affected the severity and time of onset of the postprandial hyperglycemia and glucosuria as shown in experiment 1. Animals prefed a commercial formula were more severely affected than those fed a semipurified laboratory diet (diet 1). The composition of the two diets differed in many respects, among them the concentration of fat and the type of carbohydrate they contained. The type of carbohydrate, fat diet which has been shown to produce high blood glucose levels and an impaired glucose tolerance (7) and man (8, 9), a high protein diet has produced high blood glucose levels and an impaired glucose tolerance (10). Protein intake during the 3-week period also affected the severity of the postprandial hyperglycemia and glucosuria, whereas a 2.3% protein diet generally resulted in weight loss, abnormal glucose tolerance, and, with rare exceptions, glucosuria. Even though the 2.3% protein diet was usually inadequate for weight maintenance, a few animals consumed such a large quantity of food that they increased or maintained their weight. They were tolerant to a glucose load, although occasionally glucosuric.

The composition of the diet fed prior to the low-protein diet also affected the severity and time of onset of the postprandial hyperglycemia and glucosuria as shown in experiment 1. Animals prefed a commercial formula were more severely affected than those fed a semipurified laboratory diet (diet 1). The composition of the two diets differed in many respects, among them the concentration of fat and the type of carbohydrate they contained. In experiment 3, these six animals indicated in figure 3. It was observed during the 2-day restriction but was not observed in one animal upon refeeding ad libitum on day 3. This disappeared within 24 hours.

**TABLE 3**

<table>
<thead>
<tr>
<th>No. of</th>
<th>Dietary protein</th>
<th>Calorie intake</th>
<th>Calorie content of excreta</th>
<th>Total fat in excreta</th>
<th>Net metabolized calories</th>
<th>Net metabolized calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>animals</td>
<td>% of calories</td>
<td>kcal/kg/day</td>
<td>% of intake</td>
<td>g</td>
<td>kcal/kg/day</td>
<td>kcal/kg·day</td>
</tr>
<tr>
<td>7</td>
<td>12.9</td>
<td>282 ± 20</td>
<td>14.6 ± 2.3 *</td>
<td>0.82 ± 0.12 *</td>
<td>241 ± 16 *</td>
<td>190 ± 16</td>
</tr>
<tr>
<td>6</td>
<td>6.1</td>
<td>320 ± 40</td>
<td>13.7 ± 2.7 b</td>
<td>1.62 ± 0.66</td>
<td>278 ± 32 *</td>
<td>204 ± 24</td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>5.2</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>3.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2.3</td>
<td>318 ± 54</td>
<td>23.2 ± 3.8 **</td>
<td>4.56 ± 1.72</td>
<td>244 ± 43</td>
<td>184 ± 35</td>
</tr>
</tbody>
</table>

*Values represent mean ± sp.

*Means in each column given the same superscript are significantly different (P < 0.05). Means without a common superscript are not significantly different.

*No statistical tests were done as the variances in the three groups were significantly different. However, values in the group fed 2.3% protein ranged from 1.90–7.17 and did not overlap the range of the group fed 12.3% protein (range 0.50–0.97).
utilization of carbohydrate. The influence of dietary fat on this syndrome was tested in experiment 2 in which two concentrations of fat were fed in combination with three levels of protein. Although animal variation among the high fat group in experiment 2 was significant by the analysis of variance, the mean glucose concentrations of this group during oral glucose tolerance testing were not significantly different from those fed the low-fat diet. Thus, the difference in fat concentration between the commercial formula and diet 1 was not sufficient to account for the difference in severity of symptoms produced by the low protein diet in the two groups of animals in experiment 1. The difference in the carbohydrate of the commercial formula and diet 1 may have been responsible for the differences in the severity of symptoms observed in the first experiment. Since diet 1 contained sucrose and dextrin, rather than lactose, the animals receiving it were probably accustomed to more rapid rates of glucose delivery from the gastrointestinal tract due to both previous enzyme induction (10) and the more proximal site of digestion of sucrose and dextrin as compared to lactose which is more slowly digested (11). The preconditioned, accelerated synthesis and release of insulin by pancreatic beta cells (12) may have been a factor as well.

Although glucose intolerance and glucosuria can result from the effects of starvation (13) or prolonged fasting (14), this does not appear to explain the effect of the low protein diet. Intolerant animals did not necessarily have smaller food intakes than control animals. In addition, the control infant monkeys deliberately restricted to food intakes as low as those found among the protein-deficient monkeys did not become glucosuric. It is concluded that at the lowest level of protein intake some hormonal, absorptive or metabolic change occurred which affected the animals' ability to metabolize glucose.

Oral glucose tolerance tests demonstrated that the animals fed the low protein diet were abnormal compared to control animals, even though the mean blood glucose levels were only 137 and 164 mg/100 ml one hour after the glucose load for low and high fat animals, respectively, and normal levels were reached after 2 hours. The actual levels achieved in such tests depend, of course, upon the amount of glucose given. In pilot studies, an 8 g/kg dose produced blood glucose levels as high as 250 mg/100 ml in control animals with marked glucosuria. Thus, the 4 g/kg dose used in these studies seemed a reasonable compromise.

The blood glucose levels achieved postprandially in animals receiving various diets are not accurately known. The values shown in figure 1 were obtained at an arbitrary time 2 hours after food was offered. However, it must be assumed that the blood glucose level exceeded the renal threshold at some time during the day in animals showing glucosuria whatever that threshold level may be.

Inadequate levels of circulating insulin, impaired synthesis or delayed release of pancreatic insulin and/or insulin resistance are known factors associated with glucose intolerance and may be involved in this syndrome. These aspects of insulin metabolism are discussed in reports of impaired carbohydrate metabolism during protein deficiency in pigs (15), dogs (16-21), rats (7), rabbits (22), and humans (23-25). However, each of these studies involved animals or humans exposed to chronic protein deficiency. The severe and immediate hyperglycemia and glucosuria found in these protein-deficient infant squirrel monkeys has apparently not been demonstrated in other species. Brown et al. (26) have demonstrated a high resting cortisol concentration in the adult squirrel monkey which increases markedly under stress or restraint. As cortisol is a known diabetogenic hormone, and is associated with stress and tissue breakdown, protein catabolism, and gluconeogenesis, measurement of this steroid as well as estimations of circulating immunoreactive insulin and insulin sensitivity are needed to further define this impairment in these infant squirrel monkeys. A lack of sufficient quantities of amino acids for the stimulation of insulin excretion (27) may be another factor worthy of consideration.

Lang (28) and Davidson et al. (29) reported that in randomly selected adult squirrel monkeys approximately one-half responded abnormally to glucose tolerance
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LITERATURE CITED


