Of the many hypotheses advanced (1) to account for the origin of the endogenous uric acid of the urine, two, those of Burian and Schur and of Mareš, stand out as most satisfactory. Burian and Schur (2) first clearly distinguished between the two sources of the uric acid of the urine: that derived from the food or exogenous fraction, and that originating from tissue metabolism or the endogenous fraction. They held that the endogenous uric acid excretion might vary widely with different individuals, but that for any one individual it was a constant quantity, unaffected by the intake of purine-free food. Burian (3) has concluded from the analyses obtained in his earlier work (4) that only a small part of this endogenous fraction may be derived from the nucleoprotein of cellular origin. Such an origin would in his opinion involve far too extensive a catabolism of nuclear material to be considered as the main source of endogenous uric acid. Uric acid of endogenous origin, according to this view, is formed mainly from the hypoxanthine of the inosinic acid present in muscular tissue.

Mareš (5) considers that purine-free food may exert a marked influence on the endogenous excretion of uric acid. Others, notably Lambling and Dubois (6), Folin (7), Hopkins and Hope (8), Smetánka (9), Taylor and Rose (10), and Mendel and Stehle (11), have also shown that food free from purine precursors, particularly protein food, may markedly raise the level of endogenous uric acid excretion. Mareš (5, 12) has suggested that this influence on the uric acid excretion is the expression of the wear and
Uric Acid Metabolism. II

tear on the nuclear material of the secretory glands of the gastrointestinal tract in the work of secretion occasioned by the presence of food in the alimentary canal. Mendel and Stehle (11) in support of this hypothesis concluded that their data "offer no obstacle to the assumption that a portion, at least, of the endogenous uric acid may originate from the activity of the alimentary secretory apparatus." They point out however that the theory of Mares does not necessarily need to account for all the endogenous uric acid excreted, but may at least explain the source of some fraction of it. The experiments which offer most striking evidence of the rôle of the digestive glands were concerned with the influence of atropine and pilocarpine on uric acid excretion. Atropine, an inhibitor of glandular secretory activity, was shown to check the rise in uric acid output which normally followed ingestion protein food. After the administration of pilocarpine, which is known to stimulate secretion, there was a sharp rise in the uric acid output. Mares (12) has also reported similar results with pilocarpine. Increase in the mechanical work of the digestive tract (administration of bulky foods or laxatives) was not a factor in the stimulation of uric acid output.

The older methods for the determination of uric acid were hardly suited to the determination of small amounts of uric acid, such as are met with in studies of hourly elimination. The colorimetric method of Folin and Denis as modified by Benedict and Hitchcock is, however, very accurate for the determination of small amounts of uric acid in dilute urines. Moreover, the hourly elimination of uric acid in the fasting individual is subject to certain variations, due to a variety of factors (13), whose rôle is not clearly understood, and the proper control of which has frequently not been secured in former experiments.

The purpose of the experiments to be detailed was to study the influence of proteins and protein derivatives, on the endogenous uric acid excretion, with the use of the newer more accurate colorimetric methods for uric acid determination, and with as complete a control of the variable factors as possible. It was believed that a comparison of the influence of proteins with that of their digestive products, amino-acids, might indicate to what extent the work of the digestive glands is concerned with the increase in uric
acid excretion following ingestion of non-purine protein food. The study of the influence of carbohydrate and fat and their derivatives will be considered in a subsequent publication.

EXPERIMENTAL.

Methods.

The subject of the experiment was a healthy young man, 22 years of age, and about 58 kilos in weight. During a period of over 6 months, a meat-free low protein diet, free also from purine-containing beverages, which may be considered as a "purine-free" diet, was consumed with the exception of a few meals during the holidays, at which a small amount of meat was taken. No attempt was made to secure a quantitative uniformity of the diet. On the evening preceding the day of an experiment, a light supper was eaten and no further food was ingested until the completion of the day's experiment, except the substance whose influence on uric acid excretion was to be studied.

Some of the former experiments in which the hourly excretion of uric acid has been studied are open to the criticism that the volumes of urine collected are low, frequently less than 20 cc. In cases of such small volumes the error due to incomplete emptying of the bladder might be large, whereas in larger volumes this source of error would be inconsiderable. In order to insure reasonably large hourly volumes of urine and thus eliminate as far as possible the errors resulting from the inability to remove the urine quantitatively from the bladder, 200 cc. water were ingested hourly throughout the experimental periods. As a check on the errors from this source, creatinine was also determined in the hourly samples. Since creatinine elimination is uninfluenced by

1 Two other men also served as subjects. Many of the experiments were duplicated and similar results obtained with these other subjects, but inasmuch as the experiments with M. S. D. were more comprehensive and extended over a longer period of time, the data of these experiments alone are presented.

2 Creatinine determinations were made in all the experiments reported in the tables. In order to condense the analytical data, the figures for creatinine are omitted in many cases except where variations in the volume of urine and in the uric acid excretion might throw doubt on the completeness of the collection of the urine (cf. Table VIII).
diet and tends to maintain a constant level, it was believed that any marked variation from the normal creatinine level in any period would indicate losses due to incomplete collection of the urine.

Uric acid was determined colorimetrically by the Benedict-Hitchcock modification of the Folin-Macallum-Denis method; creatinine by Folin's micro-colorimetric method; and total nitrogen by the method of Kjeldahl. The samples were preserved with chloroform in tightly stoppered bottles, until the analyses could be completed. In the greater number of the experiments the uric acid determinations were made on the experimental day and those of creatinine on the morning of the following day, although in a few cases this was impossible.

**Fasting Control Experiments.**

If changes in the excretion of uric acid following ingestion of various substances were to be of any significance, it was necessary to have accurate information as to the degree and kind of variations to be expected normally in the fasting subjects under the experimental conditions outlined above. Control experiments in which no food was ingested throughout the experiment were carried out at frequent intervals in order to make certain that the level of endogenous uric acid metabolism was not altered by the long continued "purine-free" diet. Protocols of three typical experiments of this sort are given in Tables I and II, these particular experiments being chosen from a considerable number as representing the uric acid level at the beginning and toward the end of the series of experiments respectively. In the majority of the experiments there was a tendency toward a diminished uric acid excretion at the end of the morning hours. This is in accord with the observations of previous investigators (11, 13).

On the basis of these control experiments it seemed reasonable to assume that a rise in the uric acid excretion to a level of 25 mg. per hour or above, following ingestion of some substance, resulted from the action of this substance and was not the result of a normal variation. It was not considered that a rise of a few mg. in any one experiment had necessarily any especial significance.
The following routine procedure was adopted for subsequent experiments. The uric acid excretion for the first 2 hours of the day was determined and if the results were comparable with those of the control days the substance, whose effect on the excretion of uric acid was to be studied, was ingested.

**TABLE I.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
<th>Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>122</td>
<td>20.7</td>
<td>61.0</td>
<td>386.7</td>
</tr>
<tr>
<td>7-8</td>
<td>210</td>
<td>19.9</td>
<td>58.8</td>
<td>425.8</td>
</tr>
<tr>
<td>8-9</td>
<td>291</td>
<td>18.5</td>
<td>64.2</td>
<td>416.1</td>
</tr>
<tr>
<td>9-10</td>
<td>150</td>
<td>15.0</td>
<td>63.0</td>
<td>355.5</td>
</tr>
<tr>
<td>10-11</td>
<td>92</td>
<td>16.5</td>
<td>59.8</td>
<td>345.0</td>
</tr>
<tr>
<td>11-12</td>
<td>122</td>
<td>15.5</td>
<td>59.7</td>
<td>339.1</td>
</tr>
<tr>
<td>12-1</td>
<td>311</td>
<td>17.1</td>
<td>62.2</td>
<td>441.6</td>
</tr>
</tbody>
</table>

**TABLE II.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Uric acid</th>
<th>Volume</th>
<th>Uric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>18.3</td>
<td>42</td>
<td>17.4</td>
</tr>
<tr>
<td>7-8</td>
<td>19.3</td>
<td>220</td>
<td>18.4</td>
</tr>
<tr>
<td>8-9</td>
<td>21.8</td>
<td>283</td>
<td>19.7</td>
</tr>
<tr>
<td>9-10</td>
<td>14.9</td>
<td>88</td>
<td>16.2</td>
</tr>
<tr>
<td>10-11</td>
<td>13.2</td>
<td>132</td>
<td>14.3</td>
</tr>
<tr>
<td>11-12</td>
<td>15.3</td>
<td>59</td>
<td>15.2</td>
</tr>
<tr>
<td>12-1</td>
<td>14.1</td>
<td>214</td>
<td>17.7</td>
</tr>
</tbody>
</table>

On 4 days in the series of some 40 experimental days the level of uric acid excretion was found to be greatly increased above the usual level and to remain at this level throughout the entire period. No satisfactory explanation of this variation could be found, and because of this, the fore period of 2 hours was determined upon. In no case where the excretion of uric acid was at the normal level (about 20 mg. per hour) in the earlier hours of the day did it rise abnormally in the later hours. The level of the early hours of the day was maintained whether it was abnormally high as in the four experiments referred to or at the normal level as in the majority of the experiments.
Protein.

It has repeatedly been shown that the excretion of endogenous uric acid is increased by purine-free protein food. The experiments recorded in Tables III, IV, and V are in agreement with previous work. After ingestion of each of three types of protein food, egg white, cottage cheese, and glidine, there occurred a rise in uric acid excretion.

### Table III

#### Experiment 4. Protein. Egg White. 200 Cc. of Water per Hour

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
<th>Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>136</td>
<td>21.7</td>
<td>58.6</td>
<td>484.1</td>
</tr>
<tr>
<td>7-8</td>
<td>273</td>
<td>21.8</td>
<td>57.5</td>
<td>455.4</td>
</tr>
<tr>
<td>8-9*</td>
<td>245</td>
<td>23.5</td>
<td>58.8</td>
<td>443.4</td>
</tr>
<tr>
<td>9-10</td>
<td>244</td>
<td>24.4</td>
<td>58.5</td>
<td>470.6</td>
</tr>
<tr>
<td>10-11</td>
<td>166</td>
<td>28.2</td>
<td>58.1</td>
<td>489.7</td>
</tr>
<tr>
<td>11-12</td>
<td>75</td>
<td>29.2</td>
<td>57.7</td>
<td>453.0</td>
</tr>
<tr>
<td>12-1</td>
<td>332</td>
<td>19.9</td>
<td>59.2</td>
<td>574.3</td>
</tr>
</tbody>
</table>

* 300 gm. of egg white, poached, eaten at 8 a.m. N content = 5.85 gm.

### Table IV

#### Experiment 12. Protein. Cottage Cheese. 200 Cc. of Water per Hour

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
<th>Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>156</td>
<td>19.3</td>
<td>56.2</td>
<td>429.0</td>
</tr>
<tr>
<td>7-8</td>
<td>207</td>
<td>19.8</td>
<td>59.2</td>
<td>459.5</td>
</tr>
<tr>
<td>8-9</td>
<td>303</td>
<td>20.0</td>
<td>58.5</td>
<td>478.7</td>
</tr>
<tr>
<td>9-10*</td>
<td>58</td>
<td>15.2</td>
<td>55.7</td>
<td>281.5</td>
</tr>
<tr>
<td>10-11</td>
<td>96</td>
<td>24.1</td>
<td>62.4</td>
<td>579.8</td>
</tr>
<tr>
<td>11-12</td>
<td>96</td>
<td>23.2</td>
<td>58.5</td>
<td>595.2</td>
</tr>
<tr>
<td>12-1</td>
<td>200</td>
<td>18.0</td>
<td>56.0</td>
<td>628.0</td>
</tr>
</tbody>
</table>

* 200 gm. of cottage cheese taken at 9.15 a.m. N content = 4.8 gm. (approximately).

Glidine is a commercial "pure vegetable protein food, prepared wholly from wheat." The preparation used in these experiments contained 15.1 per cent nitrogen. According to the analyses of Street (Connecticut Agric. Exp. Station., Ann. Rep., 1913, 25) glidine contains no starch and 91.4 per cent protein.
in uric acid excretion clearly above the basal level, a rise which usually reached its maximum during the 3rd or 4th hour after administration of the protein. The two experiments with glidine (Table V) show some sort of a quantitative relationship, for in Experiment 32, 66.6 gm. of glidine increased the excretion more markedly than did half the amount, as in Experiment 31. It was not possible to continue Experiment 32 long enough to determine whether the maximum effect had been reached. No clearly defined differences between the three types of proteins in their action on the uric acid output could be observed.

TABLE V.
Protein. Glidine. 200 Cc. of Water per Hour.

| Time | Experiment 31 | | Experiment 32 |
|------|---------------|---------------|
| Volume | Uric acid | Volume | Uric acid |
| cc. | mg. | cc. | mg. |
| 6-7 | 42 | 14.1 | | | |
| 7-8 | 218 | 17.1 | 51 | 17.5 |
| 8-9 | 265* | 16.6 | 245 | 19.2 |
| 9-10 | 170 | 23.6 | 266† | 19.8 |
| 10-11 | 208 | 22.2 | 156 | 27.9 |
| 11-12 | 200 | 16.6 | 99 | 26.7 |
| 12-1 | 53 | 16.1 | 70 | 29.2 |

* 31.7 gm. of glidine taken dry at 8.00 a.m. N content = 4.8 gm.
† 66.6 " " " " " " 9.00 " N " = 10.1 "

Amino-Acids. Alanine and Glycocoll.

In order to test the validity of the theory that increases in the excretion of endogenous uric acid after ingestion of protein result from the secretory activity of the glandular tissue of the alimentary canal, occasioned by the work of digestion, the influence of amino-acids, the ultimate cleavage products of protein in the tract, was studied. The results of two typical experiments with alanine and glycocoll are shown in Table VI. It is evident from the results of these and a number of other experiments of the same kind that glycocoll and alanine, amino-acids representing the final products of the digestion of proteins, stimulate the endogenous uric acid metabolism in a manner similar to the proteins themselves,
although the effect is produced more rapidly and is more marked. Thus in Experiment 10 (Table VI), glycocoll equivalent to 1.94 gm. of nitrogen caused an increased uric acid excretion the 2nd hour after ingestion of much the same order of magnitude as that produced by egg white equivalent to three times the above amount of nitrogen, 5.85 gm., during the 3rd and 4th hours after ingestion. The effect of the amino-acid is manifested sooner than

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>150</td>
<td>21.6</td>
<td>56.4</td>
</tr>
<tr>
<td>7-8</td>
<td>300</td>
<td>21.9</td>
<td>58.8</td>
</tr>
<tr>
<td>8-9</td>
<td>117</td>
<td>23.4</td>
<td>57.3</td>
</tr>
<tr>
<td>9-10</td>
<td>294</td>
<td>30.2</td>
<td>57.9</td>
</tr>
<tr>
<td>10-11</td>
<td>210</td>
<td>21.2</td>
<td>55.8</td>
</tr>
<tr>
<td>11-12</td>
<td>65</td>
<td>19.7</td>
<td>53.3</td>
</tr>
<tr>
<td>12-1</td>
<td>166</td>
<td>19.4</td>
<td>59.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>100</td>
<td>18.9</td>
<td>57.0</td>
</tr>
<tr>
<td>7-8</td>
<td>201</td>
<td>17.6</td>
<td>56.4</td>
</tr>
<tr>
<td>8-9†</td>
<td>108</td>
<td>21.5</td>
<td>58.8</td>
</tr>
<tr>
<td>9-10</td>
<td>291</td>
<td>25.9</td>
<td>55.3</td>
</tr>
<tr>
<td>10-11</td>
<td>79</td>
<td>17.1</td>
<td>54.9</td>
</tr>
<tr>
<td>11-12</td>
<td>57</td>
<td>17.8</td>
<td>54.2</td>
</tr>
<tr>
<td>12-1</td>
<td>36</td>
<td>14.4</td>
<td>47.8</td>
</tr>
</tbody>
</table>

* 10.4 gm. of glycocoll eaten at 8.00 a.m. N content = 1.94 gm.
† 12.1 " alanine " 8.00 " N " = 1.90 "

in the case of the proteins, the excretion of uric acid reaching its maximum the 2nd hour after ingestion and as a rule returning to normal the following hour.

It seemed possible that the effects observed might be due to a stimulation of the processes of elimination of uric acid under the influence of the amino-acids, rather than to increased uric acid formation; that they might be the result of the removal of preformed uric acid and uric acid precursors from the tissues, an
exaggerated elimination of purine reserve stored. If this were the case, ingestion of a second dose of amino-acid after the effect of the first had reached its maximum should not further affect the uric acid elimination, since the increased elimination as a result of the first dose should have caused the removal of any excess present in the system. In Table VII are presented the results of such an experiment, the influence of the administration of successive doses of glycocoll on the same experimental day. The figures clearly demonstrate that the effects of amino-acids on uric acid excretion are not the result of stimulation of excretory processes leading to a removal of preformed uric acid from the body since the administration of a second dose of glycocoll gives rise to an increased uric acid excretion comparable in all respects to the increase produced by a single dose.

**Dicarboxylic Amino-Acids. Glutaminic and Aspartic Acids.**

The work of Lusk (14) has clearly proven that the phenomena of the specific dynamic action of protein are associated with the amino-acids or their cleavage products (15). It seemed probable that the increased elimination of uric acid, presumably the result of a stimulation of the metabolism of the nuclear material...
of the cell, might be associated with these phenomena of increased heat production under the influence of the amino-acids. According to Lusk no increased heat production follows ingestion of the dicarboxylic amino-acid, glutaminic acid (and presumably also its analogue, aspartic acid). Grafe more recently has maintained that these two amino-acids do exert a specific dynamic action (16), as do also ammonium chloride and several other substances. In view of these considerations it seemed of interest to observe the influence of the dicarboxylic amino-acids on the uric acid metabolism.

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
<th>Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>200 Cc.</td>
<td>19.1</td>
<td>50.9</td>
<td>219.1</td>
</tr>
<tr>
<td>7-8</td>
<td>293</td>
<td>19.1</td>
<td>50.9</td>
<td>219.1</td>
</tr>
<tr>
<td>8-9*</td>
<td>44</td>
<td>27.8</td>
<td>54.1</td>
<td>256.0</td>
</tr>
<tr>
<td>9-10</td>
<td>40</td>
<td>44.4</td>
<td>54.6</td>
<td>394.0</td>
</tr>
<tr>
<td>10-11</td>
<td>71</td>
<td>46.8</td>
<td>54.6</td>
<td>394.0</td>
</tr>
<tr>
<td>11-12</td>
<td>527</td>
<td>23.7</td>
<td>49.7</td>
<td>548.0</td>
</tr>
<tr>
<td>12-1</td>
<td>165</td>
<td>19.9</td>
<td>47.8</td>
<td>396.0</td>
</tr>
</tbody>
</table>

* 20 gm. of glutaminic acid (N = 1.9 gm.) taken at 8.00 a.m. Solution was facilitated by heat and the addition of 7 gm. of Na₂CO₃. The solution obtained still retained an acid reaction to litmus. After 30 minutes general dizziness and nausea without vomiting, which continued for 4 to 5 hours, and increased with ingestion of water at each hourly period.

Ingestion of glutaminic acid (Table VIII) resulted in an increased excretion of uric acid, more marked than in the previous experiments with glycoecoll and alanine. The effect was more prolonged as the normal level was not reached until the 5th hour after ingestion of the amino-acid. The effects on the volume of urine and on the nitrogen elimination were also noteworthy. During the 3 hours of maximum elimination of uric acid the urinary volume was very low, falling below 50 cc. during two periods. This was followed by a marked diuresis with the extraordinary hourly volume of 527 cc. the 4th hour when the uric acid excretion had returned to normal. That these low volumes of urine
were not the result of incomplete voiding is evidenced by the constancy of the creatinine excretion. During this period of decreased urinary volume, a marked diminution in the excretion of total nitrogen occurred. As noted in the protocol, the subject suffered from nausea and general malaise following ingestion of the glutaminic acid. It seemed possible that the factor of gastrointestinal irritation might contribute to the increased uric acid elimination. Aspartic acid, a second dicarboxylic amino-acid, and asparagine, its acid amide, however, resulted in increases (Table IX) comparable to those observed in the glutaminic acid experiment. Neither of these substances produced gastrointestinal irritation or ma-

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>75</td>
<td>17.2</td>
<td>56.4</td>
</tr>
<tr>
<td>7-8</td>
<td>310</td>
<td>21.5</td>
<td>53.0</td>
</tr>
<tr>
<td>8-9*</td>
<td>53</td>
<td>22.0</td>
<td>53.5</td>
</tr>
<tr>
<td>9-10</td>
<td>37</td>
<td>45.2</td>
<td>56.9</td>
</tr>
<tr>
<td>10-11</td>
<td>102</td>
<td>29.7</td>
<td>57.2</td>
</tr>
<tr>
<td>11-12</td>
<td>42</td>
<td>17.7</td>
<td>55.3</td>
</tr>
<tr>
<td>12-1</td>
<td>52</td>
<td>16.7</td>
<td>50.2</td>
</tr>
</tbody>
</table>

Experiment 17. Aspartic acid.

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>162</td>
<td>20.2</td>
<td>55.1</td>
</tr>
<tr>
<td>7-8</td>
<td>303</td>
<td>22.2</td>
<td>60.6</td>
</tr>
<tr>
<td>8-9†</td>
<td>63</td>
<td>25.3</td>
<td>57.8</td>
</tr>
<tr>
<td>9-10</td>
<td>85</td>
<td>38.6</td>
<td>56.1</td>
</tr>
<tr>
<td>10-11</td>
<td>474</td>
<td>22.5</td>
<td>57.3</td>
</tr>
<tr>
<td>11-12</td>
<td>78</td>
<td>18.5</td>
<td>57.7</td>
</tr>
<tr>
<td>12-1</td>
<td>152</td>
<td>15.0</td>
<td>54.7</td>
</tr>
</tbody>
</table>

Experiment 21. Asparagine.

* 18.4 gm. of aspartic acid (N = 1.9 gm.) at 8.00 a.m. 7 gm. of Na₂CO₃ were added to effect solution. No nausea. Mild diarrhea lasting several hours.

† 18.4 gm. of asparagine (amino N = 1.9 gm.) taken at 8.00 a.m., dissolved in hot water and ingested while solution was still warm. No abnormal symptoms.
laise, a fact which would seem to rob these of their significance as causative factors in the previous experiments. The diminution of urinary volume was noted in these experiments also. The experiment with asparagine is of interest as showing that masking of one carboxyl group does not alter the power to stimulate uric acid excretion, and that an amide of this type resembles the dicarboxylic amino-acids in its effects rather than the monocarboxylic amino-acids. This is not surprising in view of the ease with which asparagine loses its amide group and is converted to aspartic acid.

Since no digestive processes are required for the utilization of amino-acids it can hardly be considered that the rises in endogenous uric acid observed following the ingestion of four different amino-acids can be attributed to the work of the digestive glands. The effect is more probably due to a direct stimulation of the body cells by amino-acids or their catabolism products, a stimulation of nuclear metabolism. It is known that amino-acids disappear very rapidly from the blood stream and are stored temporarily in the tissues. If the stimulating influence on nuclear metabolism common to at least four amino-acids is inherently a property of amino-acids as such, substituted amino-acids might be expected to exert a similar influence. If on the other hand, the stimulation is due not to amino-acids as such, but either to the cellular work of their catabolism or to the intermediary products

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>31</td>
<td>17.4</td>
<td>51.4</td>
</tr>
<tr>
<td>7-8</td>
<td>172</td>
<td>24.1</td>
<td>63.6</td>
</tr>
<tr>
<td>8-9*</td>
<td>168</td>
<td>20.3</td>
<td>58.8</td>
</tr>
<tr>
<td>9-10</td>
<td>210</td>
<td>23.9</td>
<td>61.3</td>
</tr>
<tr>
<td>10-11</td>
<td>317</td>
<td>22.2</td>
<td>62.7</td>
</tr>
<tr>
<td>11-12</td>
<td>58</td>
<td>17.2</td>
<td>53.7</td>
</tr>
<tr>
<td>12-1</td>
<td>30</td>
<td>14.1</td>
<td>54.5</td>
</tr>
</tbody>
</table>

* 10 gm. of sarcosine taken at 8:00 a.m. N content = 1.6 gm. No ill effects.
of their breakdown, a substituted amino-acid which does not follow the normal path of amino-acid catabolism would in all probability be devoid of the power of stimulation. Sarcosine, methyl glycocoll, was selected to test out the effect of a substituted amino-acid (Table X), since it has been observed to pass unchanged through the organism for the most part, although the possibility of its conversion to some extent to creatine has not been entirely excluded. The experiment was not altogether satisfactory, but lack of further material made it impossible to repeat the trial. It is hardly probable that the slight rise the 2nd hour after ingestion was a true rise, the effect of the sarcosine. In any case the effect is too slight to be compared with that of the closely related substance, glycocoll. From this one experiment it would seem that amino-acids as such do not stimulate uric acid metabolism, and that an amino-acid which is not broken down in catabolism is without effect on uric acid excretion.

Ammonium Chloride.

The first step in the catabolism of the amino-acids within the body is deaminization, a reaction which yields as products ammonia and α-ketonic or hydroxy acids. In order to secure further information as to what reaction or product of reaction is responsible for the effects of amino-acids and proteins on uric acid metabolism, ammonium salts were studied. The ammonia, in amount comparable as to the content of nitrogen with the amino-acids fed, was administered as the chloride, which is less toxic than other ammonium salts. Inorganic ammonium salts are not converted to urea (17, 18), so that this type of ammonium salt should show whether ammonia as such is the factor influencing the changes in purine metabolism observed. No rise in the uric acid excretion above the normal level occurred as a result of the ingestion of ammonium chloride (Table XI). This offers direct evidence that the ammonia from the deaminization of the amino-acid plays no rôle in stimulating the output of endogenous uric acid. The ammonia formed by the processes of deaminization is normally converted to urea and excreted as such. It would have been logical at this point to have studied the influence of ammonium carbonate, citrate, or the ammonium salt of some other organic
TABLE XI.

Experiment 18. Ammonium Chloride. 200 Cc. of Water per Hour.

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
<th>Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cc.</td>
<td>mg.</td>
<td>mg.</td>
<td>mg.</td>
</tr>
<tr>
<td>6-7</td>
<td>32</td>
<td>20.4</td>
<td>54.2</td>
<td>340.4</td>
</tr>
<tr>
<td>7-8</td>
<td>120</td>
<td>22.7</td>
<td>55.8</td>
<td>458.4</td>
</tr>
<tr>
<td>8-9*</td>
<td>55</td>
<td>16.5</td>
<td>53.8</td>
<td>395.4</td>
</tr>
<tr>
<td>9-10</td>
<td>59</td>
<td>18.2</td>
<td>56.7</td>
<td>454.3</td>
</tr>
<tr>
<td>10-11</td>
<td>330</td>
<td>20.1</td>
<td>55.0</td>
<td>607.2</td>
</tr>
<tr>
<td>11-12</td>
<td>247</td>
<td>17.0</td>
<td>53.1</td>
<td>553.2</td>
</tr>
<tr>
<td>12-1</td>
<td>273</td>
<td>15.5</td>
<td>55.4</td>
<td>543.2</td>
</tr>
</tbody>
</table>

* 7.4 gm. of NH₄Cl (N = 1.94 gm.) at 8.00 a.m. No toxic symptoms except slight feeling of nausea the first 2 hours.

TABLE XII.

Urea. 200 Cc. of Water per Hour.

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cc.</td>
<td>mg.</td>
<td>mg.</td>
</tr>
<tr>
<td>6-7</td>
<td>59</td>
<td>18.7</td>
<td>61.7</td>
</tr>
<tr>
<td>7-8</td>
<td>229</td>
<td>18.3</td>
<td>56.1</td>
</tr>
<tr>
<td>8-9*</td>
<td>330</td>
<td>17.1</td>
<td>58.7</td>
</tr>
<tr>
<td>9-10</td>
<td>127</td>
<td>20.6</td>
<td>57.5</td>
</tr>
<tr>
<td>10-11</td>
<td>177</td>
<td>22.1</td>
<td>60.4</td>
</tr>
<tr>
<td>11-12</td>
<td>177</td>
<td>22.1</td>
<td>58.9</td>
</tr>
<tr>
<td>12-1</td>
<td>213</td>
<td>13.7</td>
<td>57.5</td>
</tr>
</tbody>
</table>

Experiment 14.

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Uric acid</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>59</td>
<td>18.7</td>
<td>50.9</td>
</tr>
<tr>
<td>7-8</td>
<td>29</td>
<td>15.4</td>
<td>50.9</td>
</tr>
<tr>
<td>8-9</td>
<td>192</td>
<td>18.2</td>
<td>55.5</td>
</tr>
<tr>
<td>9-10†</td>
<td>96</td>
<td>20.0</td>
<td>56.6</td>
</tr>
<tr>
<td>10-11</td>
<td>260</td>
<td>19.5</td>
<td>56.1</td>
</tr>
<tr>
<td>11-12</td>
<td>132</td>
<td>16.3</td>
<td>50.9</td>
</tr>
<tr>
<td>12-1</td>
<td>209</td>
<td>20.0</td>
<td>57.7</td>
</tr>
</tbody>
</table>

* 6.6 gm. of urea taken at 8.00 a.m. N content = 3.14 gm. No ill effects.
† 6.6 " " " 9.00 " No ill effects.
acid, which is capable of further transformation to urea in the organism. Such an experiment should show whether the conversion of ammonia to urea is a factor related to the problem of the stimulation of uric acid metabolism. Because of the greater toxicity in the required dosage experiments with this type of ammonium salts were not carried out.

Urea.

The ingestion of urea, the end-product of the catabolism of the nitrogenous fraction of the amino-acid molecule, resulted in an excretion of uric acid (Table XII) which did not vary appreciably from the normal. Urea is, therefore, probably not responsible for the rises in uric acid excretion after ingestion of amino-acids and proteins.

DISCUSSION.

The experiments reported are believed to offer direct evidence against the hypothesis of Mareš that the origin of the increased amounts of endogenous uric acid following the ingestion of protein food is to be attributed mainly to the activity of the secretory glands of the gastrointestinal canal. There is no evidence that the presence of amino-acids in the digestive tract stimulates secretion of the juices. On the other hand, data, which indicate that the presence of amino-acids in the system stimulates to a marked degree cellular activity, have been presented by Lusk (14, 15). The increased uric acid excretion which results from the intake of protein food, hitherto explained as a result of stimulation of the secretory glands, can be accounted for equally well as a result of a general stimulation of cellular metabolism by the products of digestion of proteins, the amino-acids. Moreover, the extent of nuclear breakdown necessary to account for the marked increases in the uric acid of the urine reported by many observers would be far too great to be the result of stimulation of so small a proportion of the cells of the body as the cells of the digestive tract. Quantitatively the production of the amounts of uric acid concerned appears possible with a less extensive destruction of the nuclear material of any one set of cells, if the effect is considered the result of a general stimulation of all
cells. It is not necessary to assume that all the endogenous uric acid arises from nuclear breakdown. This as pointed out by Burian (3) would involve too extensive a destruction of nuclear material. A part may originate from the hypoxanthine of muscle tissue. The fact that there is no conclusive evidence that an increased uric acid output follows muscular work is not necessarily a convincing argument against the muscular origin of a part, at least, of the endogenous uric acid. Urinary creatinine is generally considered as a derivative of the creatine of the muscles, yet muscular work does not increase the creatinine content of the urine, nor cause the appearance of creatine. It is believed, however, that the increases in uric acid of the present series of experiments can be considered as originating from nuclear catabolism if the stimulation is considered a general one involving all cells rather than a limited one.

It is also possible as suggested by Taylor and Rose (10) that nuclear anabolism as well as catabolism may be stimulated by the presence of large amounts of amino-acids, in the last analysis, the sources of the nitrogen of the purines of the nucleic acids. A chemical reaction involving the direct synthesis of purines from the four amino-acids ingested in the present series is difficult of conception. Ackroyd and Hopkins (19) have suggested that in the growing rat arginine and histidine may function as purine precursors. The experiments of Lewis and Doisy (20), however, offer no evidence that in man a diet high in protein and high in its content of arginine and histidine increases the uric acid excretion over that eliminated on a high protein diet low in these amino-acids.

It might seem surprising that the difference in time between maximum stimulation of cellular activity, as shown by the changes in the uric acid excretion, by proteins and by amino-acids, is not more marked. The rate of protein metabolism as determined by the excretion of “extra nitrogen” and “extra glucose” in the phlorhizinized dog (21) is nearly as rapid as that of amino-acids. The time required to digest the protein to amino-acids, and to absorb and metabolize these, is only slightly longer than that required for the absorption and metabolism of the amino-acids alone. But slight differences in the time element would accordingly be anticipated between the effects of proteins and amino-
acids on endogenous uric acid metabolism if the influence of the amino-acids is responsible for the changes.

It has been shown in the attempt to find what factor is responsible for the increased uric acid excretion after protein food that the amino-acids are similar in their action to the proteins, and that the ammonia and urea, products of the catabolism of the nitrogenous rest of the amino-acid, are without influence. This would seem to limit the causal agents to two, either the amino-acids or their non-nitrogenous rest, α-ketonic or hydroxy acids. It was not possible to study the effect of these non-nitrogenous intermediary catabolism products of the amino-acids. Lusk (15), however, concluded that, in the case of glycocoll and alanine, the chemical stimulation of protoplasm, which is responsible for the phenomena of increased heat production (specific dynamic action), results from the action of their intermediary products, glycollic and lactic acids, rather than from the amino-acids themselves. The phenomena of the stimulation of uric acid metabolism by amino-acids run parallel to those of the specific dynamic action of the amino-acids (except in the case of the dicarboxylic amino-acids?) and it is possible that the same chemical factors are responsible for both.

SUMMARY.

1. Ingestion of purine-free protein food resulted in an increased uric acid output in the fasting subject, which reached its maximum the 3rd and 4th hours after ingestion of the food. No quantitative differences in the action of three types of protein food, cottage cheese, egg white, and glidine (a wheat protein preparation), in their effect were observed.

2. Amino-acids (glycocoll, alanine, aspartic, and glutaminic acids) also increased uric acid excretion, the maximum effect being produced within 2 hours after ingestion, more rapidly than in the case of the proteins. The stimulation of uric acid metabolism caused by the dicarboxylic amino-acids was more marked than with glycocoll or alanine. Asparagine, the acid amide of aspartic acid, resembled aspartic acid in its action.

3. The effect of the amino-acids is considered to be the result of a stimulation of uric acid production rather than of a more rapid excretion of the uric acid already present in the system,
Uric Acid Metabolism. II

since successive doses of glycocoll on the same experimental day resulted in an increased elimination of uric acid in each case.

4. Sarcosine, methyl glycocoll, an amino-acid which does not pass through the same path of catabolism as do the other amino-acids, did not influence uric acid excretion.

5. Ammonium chloride and urea, products of deamination of the amino-acids, were also without effect on endogenous uric acid excretion.

6. Since the secretory activity of the digestive tract is not stimulated by amino-acids, it is believed that the experiments as a whole speak against the hypothesis of Mareš that the secretory activity of the alimentary glands is mainly responsible for the increased uric acid excretion observed after protein ingestion. It is suggested that the effect is to be considered rather as one due to a general stimulation of all cellular metabolism by amino-acids, the products of the digestion of protein. The relation of the increased uric acid metabolism to specific dynamic action of proteins and amino-acids is discussed.

BIBLIOGRAPHY.

STUDIES IN URIC ACID METABOLISM:
II. PROTEINS AND AMINO-ACIDS AS FACTORS IN THE STIMULATION OF ENDOGENOUS URIC ACID METABOLISM
Howard B. Lewis, Max S. Dunn and Edward A. Doisy


Access the most updated version of this article at http://www.jbc.org/content/36/1/9.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC’s e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/36/1/9.citation.full.html#ref-list-1