

NITROGEN AND NUCLEIN METABOLISM IN GOUT.*

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For more than a century the pathology of gout has been associated with disturbances of uric acid metabolism. When the first theories of gout were advanced, there existed very little exact knowledge of the chemistry of uric acid and still less of its physiology. Every step in the progress of our knowledge of the chemistry of purin bodies, and of the biology of nuclein derivatives, led to a revision of the older theories of gout. A critical review of the most important views on this pathological condition has been published by Brugsch and Schittenhelm¹ and need not be repeated in this place.

The work of these authors was done in the light of the latest achievements in the biochemistry of nuclein compounds, and as a result chiefly of their own experiments they proposed a new theory to explain the disease. The principal advance made by these investigators is due to the fact that they placed their patients on a purin-free diet, and owing to this they were able to differentiate the process of endogenous from that of exogenous nuclein metabolism. They arrived at a conclusion similar to that of older writers; namely, that the pathology of gout is closely associated with that of nuclein metabolism. According to their view the disease is characterized by three conditions: first, retarded uric acid formation; second, retarded uric acid disintegration; and finally, retarded uric acid elimination.

The considerations which led them to formulate their theory were the following: the uric acid output of a gouty individual on a purin-free diet was lower than the output of a normal man under the same conditions. On the other hand, in the course of the disease the average uric acid content of the blood was higher than in health. If, however, purin bases, or nuclein material, were added to the purin-free diet, the increase in the elimination of uric acid of the gouty individual was lower in quantity, and at the same time more protracted than in health. A normal individual, on a purin-free diet after the intake of nuclein material, responded with a prompt increase in the output of uric acid, but this increased output had a very short duration.

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¹ Brugsch, T. B., and Schittenhelm, A. S., *Der Nukleinstoffwechsel und seine Störungen*, Jena, 1910.

This difference in the reaction of the organism to ingested purin suggested to Brugsch and Schittenhelm the view that the process of uric acid formation in the gouty organism was retarded as compared with that in normal individuals. Nevertheless, the absolute quantity of uric acid destroyed by the patient was higher than that destroyed by the normal individual, for the reason that at any given time the tissues of the patient contained more uric acid, and although its destruction at a given place was progressing with a lower intensity, more uric acid was destroyed in the body as a whole in a given period of time. The fact that the tissues and the blood of gouty individuals do not contain more uric acid than is generally found in them is the result of this arrangement.

Although the views of Brugsch and Schittenhelm met with some opposition, still in the main they were accepted. However, these authors neglected to include in the sphere of their observation the course of elimination of nitrogenous substances of non-nuclein origin. Hence it is possible that the abnormalities which they found in connection with nuclein metabolism may exist as a general abnormality of metabolism of all nitrogenous substances. The present investigation was undertaken with a view of obtaining light on this point and also to extend the knowledge of the progress of nucleic acid disintegration in the course of gout.

In a previous study on chronic granular nephritis the authors² observed that in that disease all nitrogenous end-products of metabolism were retarded in their elimination when the daily intake contained more nitrogen than the diseased kidneys could conveniently eliminate. However, if the eliminating capacity of the kidneys was taken into consideration, and the nitrogen intake regulated on the basis of this capacity, then the character of elimination in nephritis had a course similar to that in health.

For this reason it seemed to us of importance to begin the study of metabolism in the following manner: first, to establish the normal eliminating capacity of the kidneys for nitrogenous end-products of metabolism; second, to place the patient on a diet not exceeding this eliminating capacity; third, to compare the normal progress of nitrogenous output with that obtained after administration of additional nitrogenous substances derived from nucleic acid, or from proteins.

²Levene, P. A., Kristeller, L., and Manson, D., *Jour. Exper. Med.*, 1909, xi, 825.

The observations recorded here were made on a patient in a very advanced stage of gout. Very large gouty deposits in nearly all joints prevented him from any active movements. The patient was at first placed on a daily diet containing about six grams of nitrogen. When the daily output became fairly constant (about five and one half grams), the experiments were begun. These consisted in the addition of urea to the normal diet. The urea was added to the first morning meal and the nitrogen output was followed in twenty-four hour periods, day by day. In a similar manner experiments were carried out with asparagin, plasmon, uric acid, and nucleic acid.

It was observed that after the administration of very simple nitrogenous substances, such as urea and asparagin, the patient did not remove the surplus nitrogen in the same manner as a normal individual, or even as the patient with granular nephritis who was placed on a low nitrogen intake. The increase in the nitrogen output was comparatively low during the first twenty-four hour period, and this slightly increased excretion usually continued for several days.

This suggested a comparison of the character of nitrogen elimination when the patient was placed on a daily diet containing about thirteen grams of nitrogen. On this diet, after administration of urea, the rise in the nitrogen output took place with greater rapidity and with greater intensity than on the low protein diet. Also the nitrogen output in the intervals between the experiments appeared to be more uniform than when the patient had been on a low protein intake.

For this reason it was decided to perform a new series of experiments, placing the patient on a diet abundant in nitrogen. But even under these conditions the increase in the output of nitrogen, after the administration of additional nitrogenous substances, was very low and protracted. This made it difficult to detect the differences in the output during the intervals between experiments and during the days of the experiments.

A new series of experiments was then performed, in the course of which the additional nitrogenous products were added, not during one day, but during three or four consecutive days, and the output of nitrogen was followed in twenty-four hour periods for a

number of days. But this change in daily nitrogen intake brought little change in the results of the experiments, for the increase in nitrogen output after the administration of nitrogenous substances was rather insignificant, and the excretion was very often protracted. For the sake of convenience, therefore, it was decided to estimate the increase in the nitrogen output during the days of the experiment and during the two days following the experiment.

While the patient was under observation, which was for three winter terms, Medigreceanu and one of us³ noticed that after the administration of purin bodies, the nitrogen output in animals had a more regular course if they received simultaneously considerable quantities of sodium bicarbonate. It was, therefore, decided to repeat the experiment on our patient, administering to him daily fifteen grams of this salt. It seemed that under these conditions the patient removed the surplus nitrogen intake with greater rapidity than without the bicarbonate of soda.

Together with the study of the character of the general nuclein metabolism an attempt was made to obtain information regarding the manner in which nucleic acid underwent disintegration in the organism of the gouty individual, with a view to ascertaining whether or not there existed any distinction in this regard between the gouty and the healthy organism.

It has been established in recent years that nucleic acids are composed of simple nucleotides, which in their turn consist of phosphoric acid and nucleosides. It has also been established recently that in the normal organism nucleic acid undergoes gradual decomposition, first into nucleotides, then into phosphoric acid and nucleosides, and finally into a base and a carbohydrate. Hence, it was planned to ascertain whether the complexity of the substance in which the purin bodies were administered to the organism had an influence on the rate and duration of the excessive nitrogen output. The patient received uric acid, hypoxanthine, inosine, guanosine, and nucleic acid in different experiments. For convenience of the analysis of the results of the experiments, the figures of the surplus output of nitrogen during the first twenty-four hours are presented in table I.

³Levene, P. A., and Medigreceanu, F., *Am. Jour. Physiol.*, 1911, xxvii, 438.

TABLE I.

Experiments.	N of standard diet in gm.	N of additional substance in gm.	Per cent. of N of additional substance eliminated in the first twenty-four hours.
First series.....	7.0	2.5 (urea)	65.0
	7.0	2.5 (asparagin)	59.0
	7.0	2.5 (uric acid)	26.0
	7.0	2.5 (uric acid)	29.0
	7.0	1.85 (nucleic acid)	50.0
Second series.....	6.0	2.0 (urea)	0
	10.0	2.0 (urea)	57.0
	13.0	2.0 (urea)	70.0
	13.0	2.0 (nucleic acid)	34.0
	13.0	2.0 (uric acid)	0
	13.0	2.0 (uric acid)	29.0
Third series.....	6.0	2.0 (urea)	0
	6.0	2.0 (urea)	17.5
	13.0	2.0 (urea)	69.0
	13.0	2.0 (hypoxanthine)	50.0
	13.0	2.0 (hypoxanthine)	15.5
	13.0	1.1 (inosine)	60.0
	13.0	1.5 (guanosine)	23.0
	13.0	2.0 (uric acid)	40.0

The figures presented in the table do not show a great regularity in the removal of the surplus nitrogen ingested. It is clearly seen, however, that the removal of nitrogen ingested in the form of nucleic acid derivatives is lagging behind the nitrogen output after the administration of urea. The nearest to urea in its behavior is inosine, then follow nucleic acid, hypoxanthine, and the most imperfect elimination follows the administration of uric acid and of guanosine.

The rate of elimination of the surplus nitrogen is controlled by two factors, the rate of absorption and that of oxidation, and it is possible that the low figures observed after uric acid and guanosine intake are brought about by the comparative insolubility of these substances. Both inosine and hypoxanthine possess a comparatively high degree of solubility, and it appears as if the elimination of inosine nitrogen proceeds with greater rapidity.

It is not improbable that the factors of purin metabolism discovered by Walter Jones come into play in this instance. Jones⁴ discovered that oxidation of the nucleosides and of purin bases is brought about by different enzymes, and it is possible that in this instance the nucleoside-oxidases were more active than the purin-

⁴Jones, W., *Jour. Biol. Chem.*, 1911, ix, 129, 169.

oxidases. This may also explain the reason for the more rapid nitrogen elimination after administration of nucleic acids. As a general rule, however, we noticed in our patient a comparatively slow rate of oxidation of nucleic acid derivatives, particularly of uric acid.

However, a review of the figures recording the surplus nitrogen output for the entire period of the experiments indicates that in the course of some days the greatest part of the nuclein nitrogen is removed from the body, although again in this respect there is noted a considerable irregularity.

The principal form in which the nitrogenous products of nucleic acid finally reappear in the urine seems to be urea. The increase in uric acid output and in the output of purin bodies is rather small, and the highest increase was noted after the administration of nucleic acid.

CONCLUSIONS.

Thus, our conclusions harmonize with those of Brugsch and Schittenhelm in so far as they are concerned with the nuclein metabolism. They add, however, the observation that the elimination of nitrogenous substances of protein origin has a protracted character, and that the oxidation of as simple a substance as asparagin proceeds at a subnormal rate.

The most striking peculiarity observed in our patient was the very imperfect elimination of ingested urea when the patient was placed on a diet containing only six grams of nitrogen per day, and a much more complete elimination when the diet contained thirteen grams of nitrogen.

EXPERIMENTAL PART.

Methods of Analysis.—Total nitrogen was estimated by the Kjeldahl-Gunning method; urea, originally by Folin's method, and later by the Levene and Meyer⁵ modification of Benedict's process; ammonia, by the method of Shafer-Folin; uric acid, by the method of Ludwig-Salkowsky. Purin bases were estimated by treating the mother liquor from uric acid with mercuric sulphate, decomposing the precipitate, and reprecipitating the purin bases with ammoniacal silver solution.

Food Analysis.—All cereals were obtained in large quantities and a sample of each new supply was analyzed. Milk, cream, butter, eggs, and bread were analyzed from time to time. Vegetables were not analyzed, their composition being calculated on the basis of figures given by Koenig.

⁵ Levene, P. A., and Meyer, G. M., *Jour. Am. Chem. Soc.*, 1909, xxxi, 717.

Diet.—The diet all through the experiments was purin-free. The patient was in charge of a special nurse who was familiar with the diet problem, and all meals were prepared by her personally. The diet consisted of eggs, milk, cream, butter, bread, cereals, vegetables, and fruit.

History.—The patient was Allen S., 44 years of age, a native of England. He had suffered from gout for twenty-seven years, and in the early period of the disease had frequent acute attacks. All his joints were deformed and stiff, and had been so since he had been under our observation.

The metabolism studies were carried out during the winter months of three consecutive years. With the beginning of warm weather the daily variations in nitrogen output were so great that the investigations had to be interrupted. Also in the course of the winter it generally required many weeks of a given diet before the nitrogen elimination approached a condition of equilibrium.

FIRST SERIES OF EXPERIMENTS.

During this series of experiments the additional substance was administered in one day periods and the nitrogen output was followed for several days after the administration. The standard output was calculated on the basis of an observation lasting eight days, from April 9 to April 16. The average output of total nitrogen was 6.72 gm. per day; of urea nitrogen, 5.68 gm., or 84.5 per cent. of the total; and of uric acid nitrogen, 0.081 gm., or 1.2 per cent. of the total.

The eliminating capacity of the kidney was determined by administration of urea. Two and one half gm. of nitrogen in the form of urea were given on April 26, 1909. During that day there were eliminated in excess over the standard days 1.63 gm. of nitrogen, and in the course of the three days that followed the administration, there were eliminated 3.67 gm. of nitrogen. The increase in urea nitrogen output for the same interval was 3.13 gm. and the average uric acid output per day was 0.078 gm. In previous observations on men and normal animals it was demonstrated that all of the urea administered is eliminated within the first twenty-four hours. In the present experiment during the same period only 65 per cent. of the excessive nitrogen intake was removed. Moreover, part of the excessive elimination was due to the diuretic effect of the substance. By this is explained the fact that of the excessive nitrogen output only 85 per cent. was in the form of urea. The daily output of uric acid for the same period did not differ materially from the normal.

Substances other than urea tested during this series were asparagin, uric acid, and nucleic acid.

Asparagin was given April 17, 1909. The additional nitrogen intake was 2.5 gm. The excessive output for forty-eight hours was 2.23 gm., the excessive output of urea nitrogen for the same period was 2.58 gm., and the daily output of uric acid nitrogen was 0.014 gm., which is not very significant. In previous observations on men and on normal animals it was found that the nitrogen of asparagin was removed with the same rapidity as urea; namely, all in the course of the first twenty-four hours. In this instance only 59 per cent. of the excessive intake was removed during that period.

Uric Acid was administered in two experiments. In the first experiment 2.5 gm. of nitrogen were given on May 6, 1909. During the following four days

there were eliminated 3.12 gm. of total nitrogen, 2.97 gm. of urea nitrogen, and 0.050 gm. of uric acid nitrogen in excess over the normal. The significant feature of this experiment is the fact that in the first twenty-four hours only 0.26 gm. of excessive nitrogen was removed, or 10 per cent. of the additional intake.

The second uric acid experiment was performed on May 10, 1909. The same quantity of uric acid was given. The excessive nitrogen output in the four days that followed was 3.23 gm., the excessive urea nitrogen was 3.63 gm., and the uric acid output 0.078 gm. per day, practically the same as on standard days. Again the significant feature of this experiment was the low nitrogen output in the first twenty-four hours; namely, only 29 per cent. of the excessive intake.

Nucleic Acid was administered on May 19, 1909. There were given 1.83 gm. of nitrogen in the form of nucleic acid. Following the second uric acid experiment the daily nitrogen output never came down to that of the original standard period. Therefore, the elimination after nucleic acid intake was compared, not with the first standard period, but with the average output of the five days preceding the nucleic acid intake. The daily average output for those five days was: total nitrogen 7.55 gm., urea nitrogen 6.61 gm., or 87.5 per cent. of the total, and uric acid nitrogen 0.0758 gm., or 1 per cent. of the total.

During the four days following the administration of nucleic acid there was an excessive output of 2.98 gm. of total nitrogen, 2.50 gm. of urea, and the uric acid nitrogen showed an increase of 0.0783 gm. It is noteworthy that in the first twenty-four hours the increase in the nitrogen output was over 50 per cent. of the excessive intake. Of course in part the increased nitrogen output during this period was occasioned by the diuresis produced by the absorption of nucleic acid.

SECOND SERIES OF EXPERIMENTS.

This series of observations lasted from November, 1909, to March, 1910. Again on this occasion an attempt was made to ascertain the most favorable conditions for the elimination of the nitrogen of the substances added in excess of the standard diet. The patient was placed in a condition approaching nitrogenous equilibrium on a diet containing less than 6 gm. of nitrogen. To this diet on the day of the experiment 2 gm. of nitrogen in the form of urea were added, but the nitrogen elimination remained unaffected by it. The nitrogen intake was then raised to 10 gm., and after the patient was placed in a condition of nitrogenous equilibrium, 2 gm. of nitrogen in the form of urea were added. But even then the increase in nitrogen elimination was very slow, and in one experiment the total increase in nitrogen output after an additional administration of 2 gm. of nitrogen was not much above 50 per cent. over the normal. The nitrogen intake was raised to 13 gm. per day and the urea administration proved satisfactory. Experiments were then performed with uric acid and with nucleic acid.

Experiments with an Intake of Six Grams of Nitrogen.—The normal output previous to the administration of urea was 5.98 gm. After the administration of an additional 2 gm. of nitrogen in the form of urea, on November 10, the nitrogen output was scarcely changed, being on the day of the experiment 6.13 gm. and on the day following 5.74 gm. The urea and uric acid output also remained little

changed. After this experiment the normal nitrogen output fell to 5.22 gm. as the average of seven days. The average urea output for the same days was 4.06 gm. Another experiment with the administration of 2 gm. of nitrogen in the form of urea was made. The nitrogen and urea output after this administration remained practically unchanged. Thus, on the low nitrogen intake there was a retention of nitrogen even when it was administered in the form of urea.

Experiments with an Intake of Ten Grams of Nitrogen.—On a diet of 10 gm. of nitrogen the average daily output for six days was 8.82 gm. For the same period the urea output was 7.51 gm. per day, or 85.2 per cent. of the total nitrogen. The uric acid output was 0.0869 gm. per day and the nitrogen of the purin bases was 0.062 gm. per day.

Urea Experiments.—An experiment with the administration of an additional 2 gm. of nitrogen in the form of urea was made on December 14. During the first twenty-four hours after the administration there was an excessive output of nitrogen of 1.15 gm., or 57 per cent. of the total excessive intake. There was, however, a protracted increase in the output for four days, so that in this experiment the total increase in the output exceeded the intake, although the diuresis produced by the substance was insignificant.

On December 21 another experiment was performed with the administration of 2 gm. of nitrogen in the form of urea. During the first twenty-four hours of the experiment 0.36 gm. of nitrogen was removed, or 18 per cent. of the intake. The following day there was an increase of the nitrogen output of 0.59 gm., or 30 per cent. of the intake, and on the third and fourth days there was still a slight increase. The total increased output for four days exceeded the normal by 59 per cent. of the excessive intake.

Experiments with an Intake of Thirteen Grams of Nitrogen.—The nitrogen intake was again raised to 13 gm. per day and the additional substances were given on four successive days. The output was then followed for about eight days after the beginning of the administration of the additional substances. The average output for five days was 12.20 gm. The first experiment began on January 19. For four successive days 2 gm. of nitrogen in the form of urea were administered. During the first twenty-four hours 1.41 gm. of excessive nitrogen were removed, or 70 per cent. of the intake. The following day again 1.40 gm. of nitrogen were removed. In course of eight days from the beginning of the experiment 8.94 gm. of nitrogen were removed, of which 6.68 gm. were in the form of urea, 0.0751 gm. in the form of uric acid, and 0.0074 gm. in the form of purin bases.

It is seen from these figures that the elimination of the excessive nitrogen was most favorable on this diet and, therefore, experiments were performed with nucleic acid and with uric acid. The nucleic acid experiments began on January 31, 1910.

Nucleic Acid Experiments.—Two gm. of nitrogen in the form of nucleic acid were given on four successive days and the nitrogen output was followed for eight days after the beginning of the experiment. In the first twenty-four hours there was eliminated 0.68 gm. of nitrogen in excess of the normal output, and each following day the excessive nitrogen output increased in value reach-

ing on the fifth day 2 gm. The total excessive output for eight days was 8.09 gm. of nitrogen of which 5.91 gm. were in the form of urea, 0.500 gm. in that of uric acid, and 0.415 gm. in the form of purin bases.

Uric Acid Experiments.—On February 15, experiments with uric acid were begun. The experiments lasted four days. On each day the patient received 2 gm. of nitrogen in the form of uric acid. During the first twenty-four hours the nitrogen output remained unchanged. In the second twenty-four hours, 0.82 gm. of excessive nitrogen was removed; on the following day 1.50 gm., and in the course of nine days 7.15 gm. of nitrogen were removed, of which 5.22 gm. were in the form of urea, 0.381 gm. in the form of uric acid.

On March 7, the second experiment with uric acid was performed. Two gm. of nitrogen in the form of uric acid were given daily on four successive days. During the first twenty-four hours 0.59 gm. of excessive nitrogen was removed, on the second day 1.34 gm., and on the fifth day the nitrogen output came down to normal. In the course of the five days the total excessive nitrogen output was 5.39 gm., of which 5.17 gm. were in the form of urea, and 0.187 gm. in the form of uric acid.

It is seen from these figures that on a high nitrogen intake the removal of excessive nitrogen is more complete than on a low protein intake. But it is not so complete as in health, so that even urea is in part retained in the organism. The nitrogen of nucleic acid and uric acid is removed at a slower rate than that of urea. This, of course, occurs also in health. Comparing the character of nitrogen elimination after the administration of nucleic acid and of uric acid one notes that after uric acid administration the nitrogen output proceeded at a lower rate of speed, and was less complete. This is observed also in health. The increase in the uric acid output was 6.2 per cent. of the total in the nucleic acid period, and 5.3 and 3.5 per cent. respectively in the two uric acid periods.

THIRD SERIES OF EXPERIMENTS.

This series lasted from November, 1910, to April, 1911. In this series of experiments it was again aimed to ascertain whether the quantity of nitrogen in the standard diet influenced the rate of elimination of excessive nitrogen added to the standard diet. The patient was again placed on a diet containing about 6 gm. of nitrogen. He came to a condition approaching nitrogenous equilibrium when the average daily output for five days was 6.29 gm. of nitrogen.

Urea Experiments.—On December 3 an experiment was begun with the administration of urea. Two gm. of nitrogen in the form of urea were given on three consecutive days. There was no increase in the nitrogen output during the first twenty-four hours. During the second twenty-four hours the increase of nitrogen output was 0.076 gm., and on the third day 0.072 gm. After this the output came down to normal. In December the daily nitrogen output on

the standard diet was lower, reaching an average of 5 gm. per day. On December 13 an experiment was begun with the administration of 2 gm. of urea per day on three consecutive days. The excessive output for the first day was 0.35 gm., the second day 1.30 gm., the third day 1.65 gm., and for five days following the beginning of the experiment 4.54 gm. of nitrogen were removed.

Again it follows from these observations that on a low nitrogen diet the elimination of the excessive nitrogen was very incomplete. Hence the diet was changed so as to contain 13 grams of nitrogen per day. On this diet the daily output was 10.50 grams of nitrogen per day.

On January 23 an experiment was performed with urea. Two gm. of urea were administered per day on three consecutive days. The excessive output during the first twenty-four hours was 1.38 gm., or 69 per cent. of the intake. The following day the output was 2.36 gm., and in five days after the beginning of the experiment the excessive nitrogen output was 6.31 gm.

It is seen from these figures that again on this occasion the increase in the nitrogen intake brought about a condition which permitted the nitrogen added in the form of urea to be removed more completely and in a shorter period of time. Experiments were then performed with hypoxanthine, inosine, guanosine, and uric acid.

Hypoxanthine Experiments.—1. Two gm. of nitrogen in the form of hypoxanthine were given on three successive days beginning January 30. On the first day of the experiment 1.02 gm. of excessive nitrogen were removed, and in five days following the beginning of the experiment there were removed 4.17 gm. of nitrogen in excess over the normal, or 69.5 per cent.

2. The second experiment with hypoxanthine was performed on February 13, when 2 gm. of nitrogen in the form of hypoxanthine were given daily for three days. During the first twenty-four hours there was an excessive elimination of 0.23 gm. of nitrogen, the second day 0.84 gm. of nitrogen, and in the course of six days from the beginning of the experiment 4.47 gm. of nitrogen were removed, or 74.5 per cent. of the excessive intake.

The daily output of nitrogen on the standard diet changed at about this period, reaching 10.85 grams per day.

Inosine Experiments.—One gm. of nitrogen in the form of inosine was given on three consecutive days beginning February 24. The excessive nitrogen output on the first day of the experiment was 0.65 gm. of nitrogen, and in three days of the experiment there were removed 2 gm. of excessive nitrogen, or 60 per cent. of the excessive intake.

The nitrogen output on the standard diet changed again, giving an average of about 10.17 grams of nitrogen.

Uric Acid Experiments.—Two gm. of nitrogen in the form of uric acid were given on three consecutive days beginning March 6. The excessive output during the first twenty-four hours of the experiment was 0.81 gm., on the second day 1.31 gm., and in five days after the beginning of the experiment there were eliminated 6.43 gm. of excessive nitrogen, or 100 per cent. of the excessive intake.

After this period the condition of the patient was such that the physician deemed it advisable to prescribe diuretin for him. The daily output on the normal diet then rose to 11.96 grams per day.

Guanosine Experiments.—One and a half gm. of nitrogen in form of guanosine were given in two days beginning April 7. In the first twenty-four hours there was an excessive nitrogen output of 0.46 gm.; in three days after the beginning of the experiment there was an increase of nitrogen output of 2.36 gm., or 78.6 per cent. of the total intake.

In order to facilitate the analysis of the behavior of the different derivatives of nucleic acid after their administration the figures of the excessive nitrogen elimination are presented in the following tables (tables II, III, and IV).

TABLE II. *Fresh Series.*

Date	April, 1939.										May, 1939.																				
	9	10	11	12	13	14	15	16	17	18	20	27	28	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
Inhale:																															
Nitrogen in gm.	7.08	7.22	7.08	7.12	7.16	7.16	7.12	7.00	6.92	7.10	7.08	7.20	7.04	7.06	6.96	7.18	7.00	7.00	7.02	6.88	6.66	6.94	7.00	7.00	7.06	7.06	7.00	7.06	7.12	7.10	7.10
Water in cc.	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00	2,350.00
Carbon dioxide in gm.	2.09	2.10	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09
Additional N in hake.									2.5 gm. N					2.5 gm. N					2 gm. N									1.83 gm. N			
Output:																															
Urine in cc.	1,878.00	2,088.00	1,790.00	2,235.00	1,833.00	1,665.00	2,041.00	2,079.00	2,230.00	1,795.00	2,650.00	2,320.00	2,370.00	1,965.00	1,995.00	2,375.00	1,880.00	2,165.00	2,310.00	1,935.00	2,140.00	2,040.00	1,870.00	1,870.00	2,010.00	2,255.00	2,295.00	2,600.00	2,300.00	2,265.00	2,225.00
Urea N in gm.	6.71	6.93	6.49	6.73	6.26	6.45	7.24	7.24	8.10	7.48	8.35	7.83	7.65	6.98	7.62	7.90	7.50	7.44	7.88	7.40	7.33	7.42	6.90	6.90	8.04	7.59	7.59	8.52	8.39	8.39	7.98
Fece N in gm.	1.74	2.45	1.65	0.49	1.70	0.83	1.11	1.76	1.33	1.27	1.76	1.16	1.10	1.08	1.27	0.74	1.33	1.43	1.37	1.66	1.16	1.43	1.08	1.08	1.14	1.43	1.43	0.72	0.72	1.17	0.97
Total N in gm.	8.45	9.38	8.14	7.22	7.96	7.28	7.99	9.00	9.43	8.75	10.11	8.99	8.75	8.06	8.90	8.64	8.83	8.87	9.25	9.15	8.52	8.89	8.07	8.07	9.18	9.02	9.02	9.24	9.11	9.46	8.95
Urea N in gm.	5.76	6.05	5.33	5.83	5.45	5.45	5.88	6.10	7.30	6.64	7.20	6.39	6.38	6.16	6.58	6.90	6.65	6.63	7.17	6.56	6.50	6.50	6.30	6.30	7.15	6.33	6.33	7.50	7.46	7.19	6.79
Percent of total urine N	0.15	0.18	0.34	0.13	0.17	0.18	0.22	0.34	0.31	0.19	0.27	0.23	0.21	0.17	0.18	0.10	0.15	0.26	0.10	0.18	0.15	0.15	0.13	0.13	0.16	0.10	0.10	0.18	0.20	0.24	0.15
Ammonia N in gm.	3.30	2.60	3.90	2.09	2.70	2.80	3.00	3.40	2.60	2.60	3.20	3.00	2.90	2.20	2.30	1.40	2.20	3.50	2.50	2.90	2.10	2.20	2.00	2.00	2.00	2.00	2.00	2.40	2.50	3.00	2.00
Percent of total urine N	0.80	0.80	0.9913	0.6877	0.697	0.683	0.689	0.6714	0.6988	0.6907	0.6736	0.6945	0.6848	0.6816	0.677	0.6517	0.6890	0.6813	0.677	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833
Uric acid N in gm.	1.30	1.30	1.40	0.6877	0.697	0.683	0.689	0.6714	0.6988	0.6907	0.6736	0.6945	0.6848	0.6816	0.677	0.6517	0.6890	0.6813	0.677	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833	0.6833
Creatinin N in gm.	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277	0.277
Creatinin + urea N in gm.	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455	0.455
Albumin gm. per 1000 cc.	0.3	0.2	0.3	0.3	0.2	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Body weight in kilos.	83.46	83.46	83.46	83.46	83.91	83.91	83.91	83.80	83.91	83.57	83.48	83.46	83.68	83.72	83.78	83.78	83.66	83.23	83.12	83.12	83.00	83.23	83.00	83.00	83.23	83.00	83.23	83.00	83.12	83.12	83.12

