ENDOGENOUS URIC ACID AND HEMATOPOIESIS.

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(Received for publication, May 18, 1929.)

Following the classification of Burian and Shur (1900), two sources of uric acid in the blood and urine are generally recognized; the exogenous, or that resulting from the purines of the food, and the endogenous, or that derived from tissue metabolism. The exact origin of the latter, however, is not known, nor is the rôle of the uric acid in the body economy established.

The more generally accepted view of the origin of endogenous uric acid is that of nuclear disintegration. This is based on the initial observation of Horbaczewski (1887) that uric acid may be produced in vitro from splenic pulp, secondly, that uric acid is increased upon the ingestion of tissues rich in nuclear material such as liver, pancreas, and thymus (Umber, 1896); that nucleic acid contains two purine components (Levene and Jacobs, 1912); and that all of the enzymes necessary for the destruction of nucleic acid are present in the body (Jones, 1920).

Burian and Shur (1900), however, oppose this theory on the ground that Horbaczewski's assumption of leucocyte destruction failed to account quantitatively for the results in disease, and also failed to explain the practically constant level established for every individual in health. They concluded that uric acid was an end-product of muscle metabolism derived from the hypoxanthine of the acid in birds, and by the partial recovery of hypoxanthine as uric acid after injection. Siven (1901), however, was unable to demonstrate a correlation between muscular exercise and uric acid output. Kennaway (1909) showed a gradual decrease of output with a repetition of equivalent exercise on successive days.

Mares (1910) attempted to account for the endogenous uric acid on the basis of increased "wear and tear" or activity on the part of the digestive cells, since it was shown by Folin (1905) that a pro-
tein diet increased the uric acid output. This interpretation has been questioned by Lewis, Dunn, and Doisy (1918) on the basis of their observations of an increase in hourly output after the administration of amino acids, and the observation of Smetanka (1911) that there is also an increase after the ingestion of honey, which requires little or no digestion. Furthermore, Zwarenstein (1928) found no increase after the ingestion of 200 gm. of Cheddar cheese or boiled egg white. Gibson and Doisy (1923) showed that while pyruvic acid increased the uric acid output, lactic acid decreased it.

Graham and Poulton (1913), observing a fall in uric acid on a protein-fat and a carbohydrate-fat diet, advanced an explanation involving a balanced carbohydrate-protein synthesis.

These various hypotheses, including the one of a general cell stimulation dependent upon the calorific values of the food taken in, are rendered untenable by the observation of Lennox (1924) who has shown a marked increase in uric acid output during periods of prolonged fasting. For a general review of the subject reference may be made to the papers of Benedict (1916), Rose (1923), and Folin, Berglund, and Derick (1924).

**Theoretical Considerations.**

On the hypothesis that endogenous uric acid may arise from the extruded nuclei of the normoblasts at the maturation of the erythrocytes, a series of calculations was made dealing with the quantitative relations of the substances involved. The results indicate a large and constant source of uric acid sufficient in amount to account for the observed outputs.

The total blood volume of man is generally placed at 5.5 liters (Keith, Rowntree, and Geraghty, 1915). The corpuscles represent 35 per cent of this by volume, or 1,925 cc. Blood destruction rate, based on the bilirubin output, is placed at 6.6 per cent by Brugsch and Yoshimoto (1910), 2.9 per cent by Eppinger and Charnas (1913), and 1.5 per cent by Abderhalden. Based upon this, the lowest estimate, the total volume of red corpuscles destroyed daily would be 28.9 cc. or 31.4 gm. Since the red blood cell count remains practically constant over long periods of time, the rate of production must equal the rate of destruction.
Measurements on the size of the pycnotic normoblast nucleus at the time of extrusion give an average diameter of 5\(\mu\), and an estimated volume of 65.44 cubic \(\mu\). This is approximately equal to the volume of the erythrocyte with an estimated value of 71 cubic \(\mu\). This would then indicate that 28.8 gm. of nuclear material are available for destruction daily. Of the chromatin of this pycnotic nucleus approximately half is nucleic acid, or 14.4 gm. Nucleic acid yields both adenine and guanine, which thus provide 2 molecules of uric acid. Uric acid with a molecular weight of 213 is 14.7 per cent of the nucleic acid molecule (molecular weight, 1443) (Levene and Jacobs, 1912). 4.23 gm. of uric acid may thus be theoretically produced daily from the destruction of the extruded nuclei of the normoblasts in the process of erythrocyte formation. This figure is of interest when compared to the amount of 0.3 gm. to which Folin was able to reduce his uric acid output on a purine-free diet. It would still be in excess if it be considered that the nucleus contained 50 or 75 per cent water, or that adenine and guanine might be reutilized in nuclear construction in adjacent cells.

**Experimental Methods and Results.**

In order to test the hypothesis of a relationship between endogenous uric acid and hematopoiesis, a thoroughbred Dalmatian coach dog was obtained from a reliable kennel; the uric acid level was established over a period of 12 days; the dog was then bled and the posthemorrhagic level determined. The dog was a young male, born July 24, 1928. He weighed at the time of bleeding, 15 kilos. He was kept in an animal cage and the urine was collected through a floor drain. Toluene was used as a preservative. The specimens were collected every morning at 9 a.m. At that time the dog was taken from the cage, while the latter was thoroughly cleaned. He was returned to the cage and given a light breakfast of eggs, grits, or Wheatena. At 1 p.m. he was given a fairly heavy meal of freshly cooked beef, and vegetables, such as rice, carrots, peas, cowpeas, cabbage, or turnip greens. The first 3 days he was on beef and dog biscuit, but this proved too constipating. No trouble was had after the freshly cooked vegetables were substituted for the dog biscuit. The animal remained in excellent condition throughout the experimental period.
Uric Acid and Hematopoiesis

Uric acid determinations were made by the Benedict-Franke method. The values of the prehemorrhagic period varied from 66.6 to 256 mg. with an average of 154 mg. for the 12 days. The dog was bled April 30 at 4 p.m. by Dr. Ralph Chaney of the Department of Surgery. 350 cc. of blood were withdrawn from the femoral artery under local anesthesia. This represents 2.5 per cent of the total body weight and approximately one-third of the total blood volume. The animal withstood the operation readily and ate a hearty meal at 5 p.m. The uric acid determinations for the succeeding 15 days are given in Table I.

If the value for the 1st day be excluded, and it very evidently belongs to the prehemorrhagic period, the average for the post-hemorrhagic period is 302 mg. In an extensive analysis of the relation of regeneration to hemorrhage, Dawson (1901) has shown that approximately half of the number of erythrocytes

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After readings for Apr. 30 were taken the dog weighed 15 kilos and was bled 350 cc. at 4 p.m.

* Increased volume due to dilution by drinking water.
† Exclusive of the 129 mg. of May 1.
removed by severe hemorrhage, are replaced between the 4th and 15th day. Thus with an estimated 33 per cent removal and 50 per cent of this amount replaced, the average daily replacement would be approximately 1 per cent. On the hypothesis of one and one-half per cent destruction and replacement under normal conditions, the uric acid levels before and after bleeding are markedly consistent. The high posthemorrhagie level represents the normal 1.5 per cent plus an additional 1 per cent due to compensation.

The extremely high level on the 2nd day is of interest, since it precedes the increase in reticulocytes as ordinarily observed following hemorrhage. It is further indicative of a marked stimulation of the bone marrow while the subsequent sharp drop would indicate a rapid fatigue.

**DISCUSSION.**

While the hypothesis of the production of endogenous uric acid from the extruded nuclei of the normoblast is supported by a single experiment only, the results are clear cut and fit the theoretical considerations. Food ingestion can hardly account for the results, since the animal was given the same diet throughout the experiment. Exercise is not a factor since the animal was confined to a cage, free to move, but limited in activity. With a direct correlation between erythrocyte count and uric acid output, the results receive their simplest explanation on the foregoing hypothesis.

That erythropoiesis is the only factor in the production of uric acid is of course not shown. A nuclear metabolism for all tissues is generally assumed, but nuclear destruction in quantities sufficient to account for the daily output of uric acid in normal conditions has no histological support, except in the instance of the bone marrow.

In disease, the increase in uric acid in leukemia, anemia, lead poisoning, and pneumonia may be accounted for in the erythrocyte behavior.

The high uric acid output by the new-born (Schloss and Crawford, 1911), the increase during pregnancy (Slemons and Bogert, 1917), the return to a lower level after parturition (Williams, 1921), and the increased variations during menstruation (Okey and Erikson, 1926) are suggestive of the soundness of the hypothesis.
Uric Acid and Hematopoiesis

SUMMARY.

1. The average daily output of uric acid for a Dalmatian coach dog for a period of 12 days was 154 mg.

2. The average daily output of uric acid for the same dog on the same purine-free diet, but after the removal of 350 cc. of blood, was 302 mg., for the first 15 days, exclusive of the 1st day.

3. This increase in the output of uric acid after hemorrhage is considered to arise from the increased activity of the hematopoietic tissue in producing red blood cells, with the concomitant destruction of the nuclei of the normoblasts.

4. The source of endogenous uric acid from the nucleic acid of the normoblast nuclei is indicated on experimental and theoretical grounds.

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