

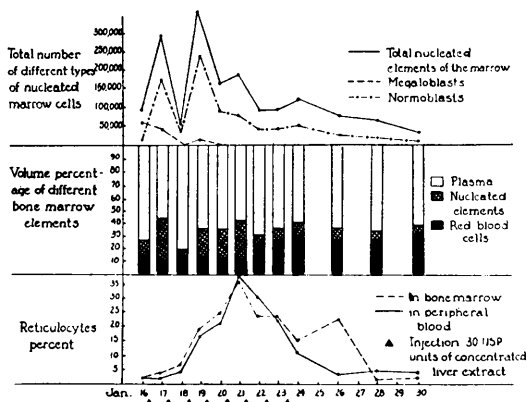


FIG. 1.

Illustrates the changes in the number and volume of the nucleated elements of the marrow following large doses of liver extract.

the first liver dose showed again a marked decrease in the number and volume of the total nucleated cells which was due to an almost complete depletion of the normoblastic cells in the marrow. This was again

followed by marked normoblastic proliferation.

With these data we confirmed and elaborated the observations made by others using a similar technic.^{4,8,9} These authors also noticed a fluctuation of the total number of the nucleated marrow cells.

Summary. Serial sternal marrow studies at 24-hr intervals before and after liver induced remission in 16 patients with Addisonian pernicious anemia, revealed a marked fluctuation of the total number and volume of the nucleated elements. Six to 24 hr after the first injection of liver the majority of the cases showed a marked decrease in the total number of nucleated cells. This was followed by a periodic increase and decrease of the absolute number of the normoblasts. During the period from 96 to 168 hr after the institution of liver therapy there was at times an almost complete depletion in the marrow of these normoblasts.

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Serial Bone Marrow Studies in Pernicious Anemia. II. Nucleated Cells and Blood and Urine Uric Acid.

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Because of an increase of the uric acid levels in the blood in pernicious anemia, early observers assumed that a primary purine disturbance was present in this disease.¹⁻³ Increased amounts of uric acid in the blood and urine simultaneous with a rise in the blood reticulocytes has been observed in pernicious anemia during liver induced remission,^{4,5} in iron deficiency anemias,⁵ and in experimentally produced anemias.^{6,7} Few authors reported acute attacks of gout following liver administration in patients with pernicious anemia.⁸⁻¹⁰ The

increased amount of uric acid in these conditions was regarded as a disintegration product of the nucleic acid portion of the extruded nuclei of the normoblasts.

In the previous communication there was evidence of marked fluctuation in the number of nucleated marrow cells during the early phases of liver induced remission. This fluctuation was due to irregularly

⁴ Riddle, M. C., *J. Clin. Invest.*, 1929-30, **8**, 69.

⁵ Cotti, L., and Balestrieri, F., *Gior. di clin. med.*, 1939, **20**, 628.

⁶ Krafka, J., Jr., *J. Biol. Chem.*, 1929, **83**, 409.

⁷ Krafka, J., Jr., *J. Biol. Chem.*, 1930, **86**, 223.

⁸ Sears, G. W., *Lancet*, 1933, **224**, 24.

⁹ Opsahl, R., *Acta Med. Scand.*, 1939, **102**, 611.

¹⁰ Broechner-Mortensen, K., *Medicine*, 1940, **19**, 161.

¹ Rosenquist, E., *Z. f. klin. Med.*, 1903, **49**, 193.

² Gettler, A. O., and Lindeman, E., *Arch. Int. Med.*, 1920, **26**, 453.

³ Gibson, R. B., and Howard, C. P., *Arch. Int. Med.*, 1923, **32**, 1.

periodic proliferation and depletion of the normoblasts in the bone marrow. In the present study an attempt has been made to trace these normoblasts disappearing from the bone marrow by finding a concomitant increase of the uric acid level in the blood and urine.

Material. In patients with Addisonian pernicious anemia, in addition to the previously detailed bone marrow and blood studies, daily uric acid of the blood was determined in 15 cases, using the method of Folin.¹¹ The amount of uric acid of the

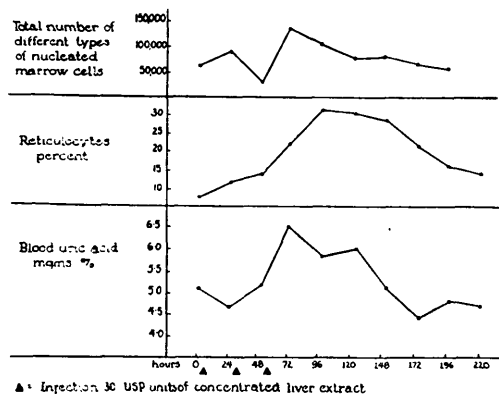


FIG. 1.

A composite chart of 7 cases illustrates that the depletion of nucleated cells in the marrow precedes the rise in reticulocytes and in the level of the uric acid of the blood.

24-hr urine was also determined in 3 of these cases.¹¹ Three of the patients were on a purine poor diet over a period of 20 days while the others were on the regular hospital diet.

Observations. With the above technic, 2-4 mg % was considered the normal range of the uric acid level in the blood. There were 24 observations on patients with pernicious anemia in relapse. In 8 instances the values were from 4.2 to 8.9 mg %, giving an average of 5.28 mg %; in two instances the values were 1.4 and 1.6 mg %.

Fig. 1, a composite graph of 7 cases, illustrates that when the bone marrow showed a depletion of the nucleated elements, there was a concomitant increase in the amount of uric acid in the blood preceding but roughly paralleling the rise in the reticulocytes.

These cases, with an average of uric acid in the blood already above normal, showed more elevated levels varying from 5.3 to 10 mg % within 72-120 hr after the first liver extract injection. In 9 instances the peak of the uric acid in the blood was 24-48 hr prior to, and in 5 instances, it was simultaneous with, the peak of the reticulocytes.

Fig. 2 illustrates a typical response of a patient on a purine poor diet for 20 days who received 30 U.S.P. units of liver extract. It shows that when there was a fall in the total nucleated elements in the bone marrow there was a simultaneous rise in the blood reticulo-

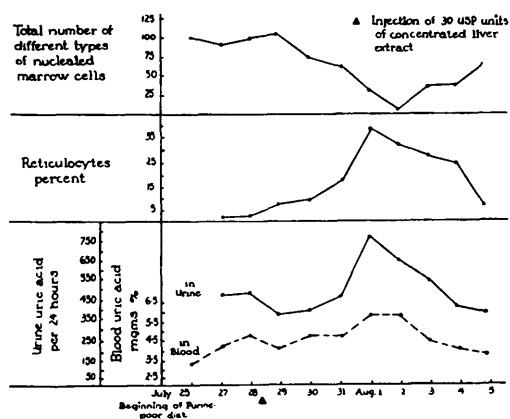


FIG. 2.

Illustrates the changes in the total number of nucleated marrow cells, reticulocyte percentage of the blood, and the level of the uric acid of the urine and blood, following the administration of 30 USP units of liver extract in a patient with pernicious anemia.

cytes and in the level of the uric acid of the blood and urine.

In 14 patients, during the period of observation from 12-30 days, there was no significant elevation in the uric acid level of the blood other than that corresponding to the rise of the reticulocytes. In 2 cases of macrocytic hyperchromic type of anemia, which did not respond to liver injection with a marked increase of reticulocytes, there was no increase in the uric acid level.

Summary. There was a definite increase of the uric acid level in the blood and urine simultaneous with the diminution of the normoblasts in the bone marrow and with the increase of reticulocytes in the peripheral blood.

¹¹ Folin, O., *J. Biol. Chem.*, 1933, **101**, 111.