3774

Analysis of Morphological Blood Changes in Pernicious Anemia Following Administration of Liver.

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The introduction by Minot and Murphy[1, 2, 3] of the liver diet in the treatment of pernicious anemia has supplied experimental medicine with a hitherto unequalled method of studying blood formation. Three general types of anemia have been produced experimentally, secondary anemia due to hemorrhage, the aplastic anemia due to destruction of the blood forming element of the bone marrow, and the hyperchromatic anemia produced by certain poisons. The fact which differentiates the condition in pernicious anemia from the types of anemia which have been experimentally produced, is that in pernicious anemia a blood is available which shows a low spontaneous regenerative activity and yet the bone marrow is not aplas-

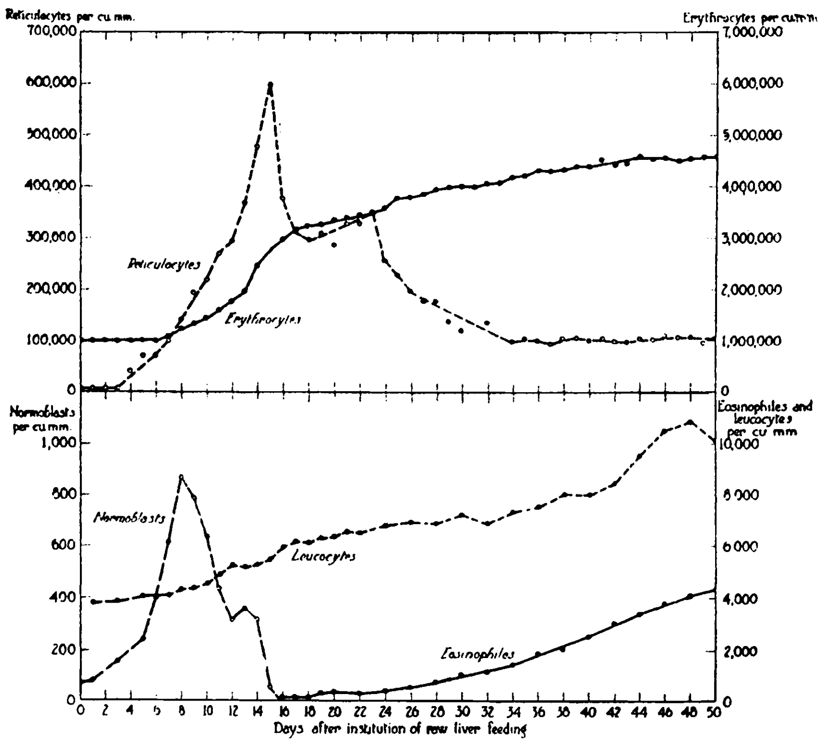

CHART 1.

tic. Minot and his co-workers have shown that after about two months of the liver treatment, the morphological blood picture of pernicious anemia has returned to practically normal.

A detailed study of the morphological blood features in a case of pernicious anemia is presented in figures 1 and 2. The patient is a married woman 52 years of age presenting the classical picture of the disease. Before the liver diet (all liver given raw) the morphological picture was observed for 5 days, ascertaining that no signs of blood-forming activity were present. There is in our graphs no curve for megaloblasts. Whether they occur or not is a question of more than momentary interest. The megaloblast is a cell which is normally produced in the blood islands around the yolk sac and in the connecting stalk of the embryo, and pathologically occurs only occasionally in pernicious anemia and severe toxic anemias. It was first fully described by Ehrlich,[4, 5] who also sharply differentiated between the megaloblast and the normoblast. Later investigators seem to have overlooked the finer morphological characters which distinguish the two types of cells and base their differentiation chiefly upon size, which is no criterion, for normoblasts frequently

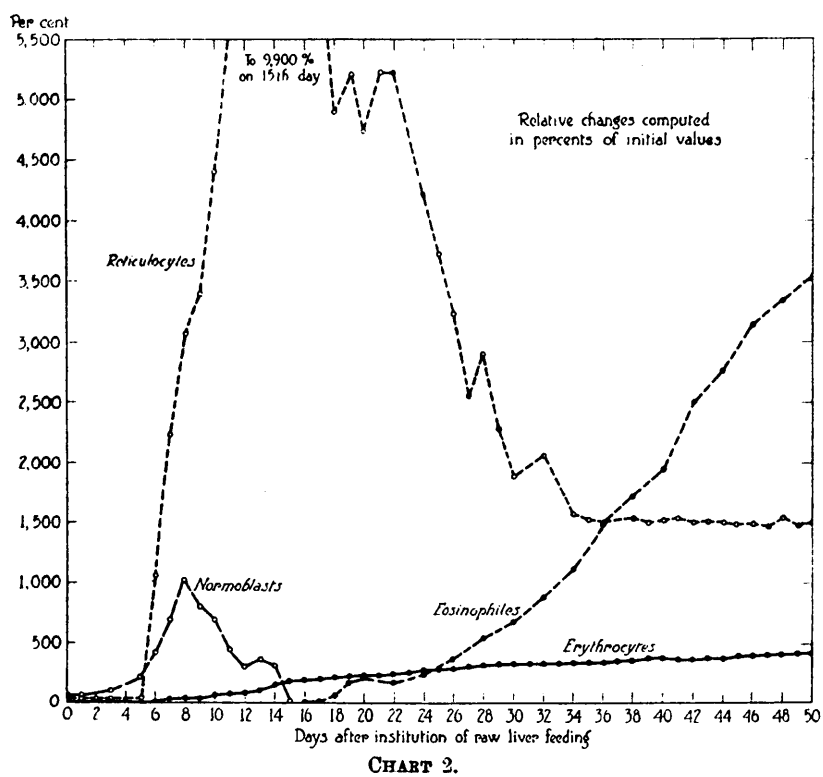

CHART 2.

are as large as, or larger than megaloblasts. Naegeli[6] claims that megaloblasts can be found in practically all cases of pernicious anemia and other investigators believe that the megaloblasts must be present in order to establish the diagnosis of pernicious anemia. Out of a series of 14 cases presenting a typical clinical, as well as morphological picture of pernicious anemia, megaloblasts were found in only two cases and in these instances none were found after the liver treatment had been instigated. It would seem surprising if a regenerative process leading to a normal blood picture were ushered in by an exaggeration of the most unusual pathological feature of the erythrocyte.

At the time the liver diet was started the total number of normoblasts per cu. mm. of blood was 78. Immediately after the liver was started they increased rapidly so that by the 8th day the total number was 870 per cu. mm., after which there was a gradual decline, until by the 16th day they had practically disappeared. Figure 2 represents a graph of the percentage increase, using the value before liver was started as unity and from this calculating the increase in percentage over unity. The highest percentage for the normoblasts is 1015 on the 8th day.

The reticulocyte curve began to rise 4 days after treatment was started and reached its peak on the 15th day, at which time the normoblasts had practically disappeared. The increase was 9,900% on the 15th day. This represents the highest percentage increase of any of the formed elements, giving a mathematical expression of the happy stroke of Minot and Murphy in choosing the reticulocyte count as the chief check on the effect of the liver feeding. There was a slight secondary rise in the normoblast curve on the 13th day and a similar one occurred for the reticulocytes on the 23rd day. At first this was thought to be an individual variation. However, a similar rise has been found in other cases, but as yet its significance is not established.

The total red count remained relatively constant until the 6th day after the diet was started and then there was a marked increase up to the 18th day. From this time on the count rose more slowly up to normal. The increase in erythrocytes was about 410%, which was reached 50 days after liver was started. Comparing these curves with the graphs of the reticulocytes, it will be found that at the time of the most rapid increase in reticulocytes there is also the most rapid increase in total red cells. It is also shown that, although the reticulocytes offer a good means of estimating the regenerative activity of the bone marrow, they do not represent the only method of erythrocyte production. Thus the total reticulocytes increase to slightly over 600,000 per cu. mm., while at the same time the total red cells increase from below 1,000,000 up to more than 3,000,000 cells per cu. mm. Therefore, many mature erythrocytes are being released from the bone marrow along with the less mature reticulocytes. The rate of increase of erythrocytes is correlated with the reticulocyte production, for after the peak of reticulocytes is reached there is a slowing down of the rate of red cell production.

From the time the liver treatment started, up to the 18th day, the percentage of eosinophiles remained relatively constant. From this time on they increased from approximately 2% to about 48% of the total number of leucocytes. Since the eosinophilia begins just after the peak of reticulocytes has been reached and at the time the rapid increase in the red count has diminished, this may possibly be regarded as a reaction of the body to an overdose of liver.

Although the morphological blood picture returned to normal following the liver treatment it was found that the so-called "pernicious anemia neutrophiles" remained. This has likewise been observed in other cases. Whether this deviation from normal will ultimately disappear has not been established, but it is of aid in the diagnosis of pernicious anemia after the blood picture has become essentially normal.

Conclusions—1. Megaloblasts and normoblasts are morphologically different types of cells. 2. Megaloblasts are not essential in the establishing of the diagnosis of pernicious anemia. 3. The liver diet causes a response in the circulating blood in the form of an appearance of (a) normoblasts, (b) reticulocytes, (c) mature erythrocytes, (d) eosinophiles. 4. The progressively increasing eosinophiles may be an expression of an overdosage of liver.

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[1] Minot, G. R., and Murphy, W. P., *J. Am. Med. Assn.*, 1926, lxxxvii, 470.

[2] Minot, G. R., and Murphy, W. P., *J. Am. Med. Assn.*, 1927, lxxxix, 759.

[3] Minot, G. R., and co-workers, *Transact. Ass. Amer. Phys.*, 1927, xlii, 83.

[4] Ehrlich, P., De- und Regeneration roter Blutscheiben. Verhandl. d. Gesellsch. d. Charite'ärzte. 1880, June 10 and December 9. Quot. fr. Lazarus.

[5] Lazarus, A., *Nothnagel's Handbuch d. Spez. Path. u. Ther.* Vol. viii. Die Anaemie p. 1 und 107. Wien, 1913.

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