SOME KINETIC PRINCIPLES OF ERYTHROPOIESIS

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The tissues of the adult animal are in a state of dynamic equilibrium: dying cells are constantly being replaced by new, produced by cell division. The rate of renewal has now been measured for many organs and tissues of various mammals [3, 9, 10], and the results obtained experimentally by the use of different techniques are in most cases reasonably close. This information greatly simplifies the task of elucidating the nature of the processes of renewal and the qualitative analysis of their kinetic principles, which have received far less study.

The object of the present study was to investigate the changes in the hemoglobin concentration, the number of erythrocytes in the peripheral blood, and their distribution spectrum according to size in the course of recovery after blood loss. Since the size of the erythrocyte is directly related to its age, from analysis of the results of measurement we may draw certain conclusions regarding the rate of maturation of the erythrocytes and the character of the regeneration process as a whole.

EXPERIMENTAL METHOD

Male rabbits weighing 2200-2800 g were bled from the femoral artery to the extent of 2.2% of their body weight, equivalent to 40% of their total blood volume [1]. Blood samples were taken from the rabbits 1, 8, 15, 22, 29, 36, and 43 days after bleeding, and the hemoglobin concentration, erythrocyte count, and distribution spectrum of the erythrocytes according to size were determined. The hemoglobin concentration was determined colorimetrically from estimation of hematin hydrochloride by means of a type FEKM photoelectric colorimeter, and the erythrocytes were counted and graded according to size by means of a Celloscope apparatus manufactured by the Swedish firm of AB Lars Ljungberg Co. Since changes in the mass of the erythrocytes are not reflected in the blood volume [8], and the latter is normalized within a few hours after blood loss [7], the hemoglobin concentration and number of erythrocytes in the sample were characteristic of the total values for the whole of the circulating blood of the animals. The number of rabbits used in the experiments was 34.

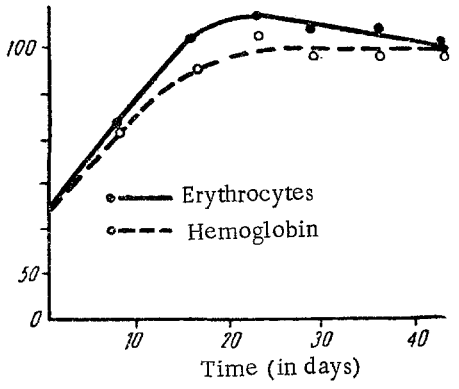

Fig. 1. Curves of recovery of the number of erythrocytes (1) and of the hemoglobin concentration (2).

EXPERIMENTAL RESULTS

The curves showing the restoration of the hemoglobin concentration and total erythrocyte count are shown in Fig. 1, from which it is clear that the process of restoration of the blood hemoglobin concentration fell to some extent behind the restoration of the number of erythrocytes. The hemoglobin concentration became normal only on the 20th day after bleeding, whereas the erythrocyte count reached normal values on the 15th day, and was 7% above normal on the 20th day. This demonstrates that the organism first regulates the biologically important parameter of the hemoglobin concentration, and that the greater rate of restoration of the erythrocyte count than of the hemoglobin concentration and the phenomenon of hyperregeneration observed in the process of restoration of the erythrocyte count are associated with the release of large numbers of young erythrocytes with a slightly lowered hemoglobin content into the blood stream.

Since we know that the mean diameter of the blood cells decreases with their age [4], investigation of the changes in the distribution spectrum of the erythrocytes according to size provided interesting information on the

process of maturation of the erythrocytes. By comparing the curves of restoration of the numbers of young and mature cells, we could determine which cells were being released into the peripheral blood from the hemopoietic organs, and we could examine the process of maturation of the erythrocytes in those organs. The recovery curve for the young cells, which were the largest, is illustrated in Fig. 2, a; the proportion of these cells in the blood of the control animals was 4.5%. The analogous curve for the mature cells, close in size to the mean erythrocyte diameter of the control animals, is shown in Fig. 2, b. The number of young cells rose sharply immediately after bleeding, reaching its maximum on the 23rd day after bleeding when it was 2.2 times larger than normal, after which it began to fall gradually. No corresponding increase in the number of mature cells could be observed immediately, but only

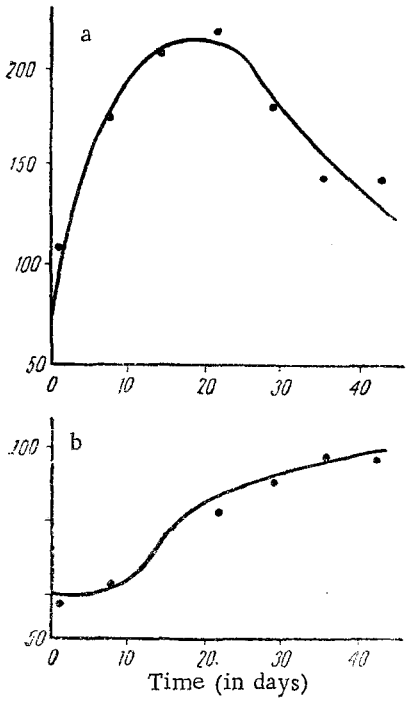

Fig. 2. Curves of recovery of the number of young (a) and mature cells (b).

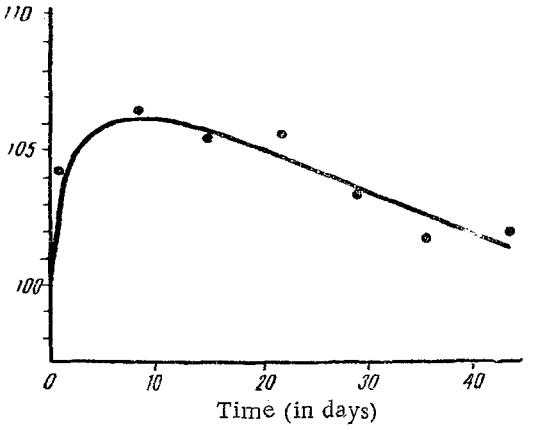

Fig. 3. Changes in the mean erythrocyte diameter during recovery after bleeding.

after the lapse of 8-10 days after bleeding, and in this case no hyperregeneration was present. This means that in the course of regeneration mainly young cells were released from the hemopoietic organs, and the number of mature cells rose as a result of maturation of young cells, while themean duration of maturation of the rabbit's erythrocyte was approximately 8-10 days. The increase in the number of young cells in the peripheral blood, the result of a sharp rise in the intensity of their release from the hemopoietic organs, led to an increase in the mean erythrocyte diameter and to a decrease in the mean hemoglobin content of the erythrocytes. It may be seen from Figs. 1 and 3 that the mean content of hemoglobin per cell fell to 94% of normal, while the mean erythrocyte diameter increased to 107%. These changes in the age spectrum were normalized only on the 43rd day after bleeding, i.e., 20 days after normalization of the hemoglobin concentration in the blood.

The experimental findings described above give some idea of the changes in the rate of renewal of the erythrocytes during regeneration. The mean life span of the erythrocytes of the normal rabbit is 68 days [2, 3, 5, 6, 11, 12], corresponding to a renewal of approximately 1.5% of erythrocytes in 24 h. It is easy to understand that the change in the number of erythrocytes in unit time is equal to the difference between the number of erythrocytes released into the blood stream during this time and the number of erythrocytes leaving the blood. If we assume that the relative proportion of young cells in the blood is a measure of the relative intensity of erythropoiesis (like the reticulocyte content in the blood), then by using the curves given in Figs. 1 and 2 we can calculate the intensity of erythropoiesis as a function of time. By comparing the latter with the change in the number of erythrocytes illustrated in Fig. 1, we can determine the intensity of decay of the erythrocytes as a function of time, and compare it with the normal intensity of decay, amounting to 1.5% in 24 h.

Analysis of the experimental curves shows that bleeding caused a marked stimulation of erythropoiesis, the intensity of which reached its maximal value (approximately 2.1 times greater than normal) in the 8-22 days following bleeding, thereafter falling to the normal level gradually. The intensity of cell decay at the beginning of the regeneration period was lowered, reaching only 1% of the cells in 24 h on the 8th day after bleeding, after which it

rose to 2.9% of cells in 24 h on the 22nd day after bleeding, when it began to fall gradually again. At the end of the experiment, on the 43rd day after bleeding, the intensity of cell decay still remained well above the normal level, however, amounting to 2% in 24 h. It is interesting to note that the lowering of the intensity of cell decay coincided in time with the period of acute deficiency of cells, and its increase with the end of the process of recovery and with the appearance of hyperregeneration.

The facts we have described indicate that the life span of the erythrocyte in the peripheral blood is determined not only by its internal structure, but also by the conditions of the environment. The level of the blood hemoglobin concentration is established as a compromise between, on the one hand, the conflicting demands of the maximal supplying of oxygen to the tissues and, on the other hand, the minimal expenditure of energy on the maintenance of this process. Deviations from this optimal level towards an increase or a decrease lower the efficiency of the system; special regulating mechanisms exist to maintain its constancy in the face of outside influences. These mechanisms are based on the stimulation of erythropoiesis when there is a deficiency of hemoglobin and on the removal of the excess of cells from the blood when there is a surplus of hemoglobin. The mechanism of removal of the excess of cells probably consists of the limiting action of an insufficient supply of energy [13], and it leads to an increase in the intensity of cell decay should the hemoglobin concentration in the blood be restored normal and the intensity of hemopoiesis is still increased on account of the inertia of the system of stimulation of erythropoiesis.

SUMMARY

Changes occurring in the hemoglobin content, erythrocyte count, and the spectrum of the red corpuscles distribution according to sizes were studied in the peripheral blood of rabbits during the restorative process after blood letting. The mean size of erythrocytes increased whereas the content of hemoglobin in them diminished, which corresponded to the ejection into the blood of considerable numbers of insufficiently mature cells. As demonstrated, blood letting greatly stimulated the erythropoiesis, which in turn increased the intensity of cellular degeneration after the normalization of the blood hemoglobin content.

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