Studies on the Radiosensitivity of Bone Marrow

III. The Dynamics of Erythrocyte Regeneration after Hemorrhage and Irradiation

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Since the introduction of liver therapy in the treatment of pernicious anemia, various charts and formulas have been constructed to compare observed regeneration of red blood cells with predicted values. Interest in erythrocyte regeneration has centered primarily in pernicious anemia where an accurate evaluation of the adequacy of therapy is of great importance. Less attention has been paid to the response of hypoferremic anemia to iron and to the spontaneous recovery from acute hemorrhage.

Isaacs et al. have plotted idealized recovery curves of 129 patients with pernicious anemia. These curves have a logarithmic form, reaching the normal level eight weeks after the start of therapy. Inspection of the data of Murphy shows a similar curve. Riddle has compared the early rise in erythrocyte counts after a single massive liver injection with the “law of growth” described by Robertson:

\[
\frac{dx}{dt} = kx(a - x)
\]

which is an expression for autocatalyzed monomolecular reactions. The curve fitting this formula goes to the normal value of \(a\) as an asymptote, but cannot overshoot this value. Further, the equation implies that the erythrocyte in the circulating blood is itself an active producer of new cells.

Della Vida has proposed the formula: average weekly increase = 0.93 - 0.214 \(x\) pretreatment RBC for calculating the expected increase in erythrocytes during the first two weeks of effective parenteral therapy in cases of pernicious anemia. This equation implies that the rate of increase is linear and proportional to the severity of the anemia. A functional analysis of regeneration is not presented, however.

Schiödt, in a series of papers on blood regeneration and the life span of the erythrocyte in pernicious anemia, iron deficiency anemia and recovery from bleeding peptic ulcer, first assumed that regeneration followed the “law of growth.” Later he adopted a linear rate of regeneration with the curve bending to a slope of zero at about thirty days, the rate of regeneration being proportional to the severity of anemia. He deduced the life span of the red blood cell to be about thirty days because if his dynamics were correct then the curve...
must have become horizontal when all of the pretreatment red cell population had disappeared.

Robscheit-Robbins and Whipple,12 using their standardized anemia technic, found that severely anemic dogs produced significantly more hemoglobin per week than moderately anemic animals. Ponder,13 who has written extensively on the mechanics of hemolytic systems, believes it to be advantageous to consider the normal blood count a balance between production and destruction, so

\[ \frac{dN}{dt} = (p - q) \]

he directs his attention to red cell destruction in various systems.

Apparently there have been no evaluations of regeneration kinetics in the light of current knowledge of the formation and destruction of red blood cells. It is now well established that the life span of the human erythrocyte is about one hundred and twenty days and that disappearance is normally a function of cell age.14

To establish a "law of regeneration" which is in better agreement with current information, blood regeneration after a single hemorrhage will first be considered. To simplify the analysis blood volume will be considered constant. Assuming that erythrocytes die as a function of their age, a fraction \( Q \) of the original population \( N_0 \) will be left after hemorrhage and this fraction will disappear in a linear fashion so that the number of cells remaining from the original population at any given time \( t \) after the hemorrhage can be expressed

(Equation 1)

\[ N_t = Q \cdot N_0 \left(1 - \frac{t}{t_m}\right) \]

where \( t_m \) is the known life span of the erythrocyte. The erythrocyte count at any time \( t \) after hemorrhage is the number remaining \( (N_t) \) plus the number born between the time of hemorrhage and time \( t \) so

(Equation 2)

\[ N = Q \cdot N_0 \left(1 - \frac{t}{t_m}\right) + \int_0^t b(t) \, dt \]

where \( b(t) \) is the number of new cells entering the blood stream at any time after hemorrhage. Solving for \( b(t) \)

(Equation 3)

\[ b(t) = \frac{dN}{dt} + \frac{Q \cdot N_0}{t_m} \]

In the case of pernicious anemia where erythrocytes remaining from the pretreatment population are destroyed at random rather than as a function of their age15 the number of the remaining population can be expressed

(Equation 4)

\[ N_t = N_0 e^{-t/T} \]

when \( T \) is the average life span of the red cells before treatment. Then

(Equation 5)

\[ N = N_0 e^{-t/T} + \int_0^t b(t) \, dt \]

and

(Equation 6)

\[ b(t) = \frac{dN}{dt} + \frac{N}{T} e^{-t/T} \]
The formulas presented above make it possible to calculate the birth rate from known data, but they do not allow for predictions in terms of known dynamics. To establish the latter it will be assumed that: (1) the “precursor” cells producing erythrocytes in the bone marrow and the erythrocytes in the peripheral blood stream are the components of a two compartment system, (2) the productivity of the marrow varies directly with the deficiency in the peripheral red cell count and (3) the peripheral red cell count varies according to the difference of the number of new cells released by the marrow and those dying. Then

\[
\frac{dP}{dt} = K_2(N_0 - N) + b - K_2 P
\]

and

\[
\frac{dN}{dt} = K_2 P - D
\]

where

- \(dP\) = rate of formation of erythrocyte producing precursors in the marrow
- \(dT\) = rate of change in red cell count
- \(N_0\) = normal red cell count
- \(N\) = observed red cell count
- \(b\) = birth rate of precursors when the system is in equilibrium
- \(K_2P\) = those precursor cells maturing to erythrocytes and being released to the peripheral blood
- \(K_1\) and \(K_2\) = time constants in reciprocal days

Solving Equations 7 and 8 for \(N\)

\[
\frac{d^2N}{dt^2} + K_2 \frac{dN}{dt} + K_1K_2N = K_1K_2N_0 + K_2(b - D)
\]

This has the solution

\[
N = Ae^{\alpha_1 t} + Be^{\alpha_2 t} + N_0 + \frac{b - D}{K_1}
\]

where

- \(\alpha_1 + \alpha_2 = -K_2\)
- \(\alpha_1\alpha_2 = K_1K_2\)
- \(A + B = N_0 - N\) (at start of experiment)

Equation 10 allows the blood count to overshoot the baseline and then to return toward it. If data were sensitive enough to show further oscillations about the baseline other “precursors” could be linked to give higher order differential equations.

**EXPERIMENT**

In order to compare the relative radiosensitivity of erythroid and myeloid elements adult cats were bled 24 ml per Kg body weight and the blood loss replaced with saline. Regeneration of erythrocytes and hemoglobin was compared with the leukocyte count in nonirradiated cats and in animals subjected to 200 r whole body irradiation with the following factors: 250 KV, 15 ma, inherent filtration equivalent to 0.21 mm. Cu, 0.5 mm. Cu parabolic filter and 1.0 mm. Al filter, target distance 54 cm. to center of cat, average rate
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Fig. 1.—A comparison of the red cell counts in irradiated and nonirradiated animals following hemorrhage.

Fig. 2.—A comparison of the production of new erythrocytes in irradiated and nonirradiated animals following hemorrhage.

of administration 32 to 38 r per minute, dosage calculated in air. Blood counts, hemoglobin determinations and blood volume determinations were done as previously described. It was found that changes in blood volume could be disregarded and the blood count used as a measure of regeneration.
The regeneration of erythrocytes in 13 irradiated and 11 nonirradiated animals is shown in figure 1. It can be seen that in both groups red cell counts reached a maximum at about forty-five days after hemorrhage and then fell somewhat. The irradiated animals did not do as well as the nonirradiated, but although they remained leukopenic for forty days after hemorrhage and irradiation, erythrocyte regeneration was not markedly impaired. In figure 2 the "birth rates" of the two groups are plotted as calculated from equation 3.

\[
\frac{dN}{dt} = Q \cdot N_0
\]

was derived by differentiating the curves in figure 1 by the method of successive differences.\(^{17}\) \(Q \cdot N_0\) is 60 per cent of the prehemorrhage baseline counts and \(t_m\) is approximately eighty days in the cat.\(^{18}\) It can be seen that the nonirradiated animals produce new cells at a rate about three and one-half times normal at first, but this rate of production falls off rapidly and actually goes below \(\frac{N_0}{t_m}\) which is the rate necessary to support a normal blood count. The irradiated cats do not produce cells at as high a rate as the nonirradiated and production falls below \(\frac{N_0}{t_m}\) in them too.

**Discussion**

The tendency of the red cell counts presented here to reach a maximum value above the baseline (100 per cent) and then to drop somewhat is, in the absence of significant blood volume changes, probably due to the "coupled" mechanism...
expressed in equation 10. In figure 3 the observed regeneration curve is compared with one derived from equation 10.

\( K_1 \) was calculated to be 0.0179 reciprocal days and \( K_2 \) was 0.0766 reciprocal days. It was assumed that \( b = D \). The slight disagreement between the predicted and observed curves after the fiftieth day is probably due to the assumption that all erythrocytes have a life span of exactly eighty days, rather than the actuality that eighty days is a mean expression. Because some of the erythrocytes generated after the hemorrhage will have disappeared by eighty days the observed fall-off is greater than that predicted.

The fact that in pernicious anemia the red cells left over from the pretreatment population disappear exponentially may account for the well documented observation that the erythrocyte counts after treatment rise to normal without overshooting. An alternative explanation is that the “precursors” are already increased before therapy and that therapy only allows them to produce mature erythrocytes without further proliferation of themselves. This would give a single compartment system and there would be no oscillation.

**Summary**

1. A method for the calculation of “birth rate” of erythrocytes is presented and the dynamics of erythrocyte regeneration are analyzed in terms of a two-compartment system.

2. The regeneration of erythrocytes after hemorrhage in irradiated and non-irradiated cats is compared to predicted values.

**REFERENCES**

2. **Isaacs, R., Bethell, F. H., Riddle, M. C., and Friedman, A.** Standards for red blood cell increase after liver and stomach therapy in pernicious anemia. J.A.M.A. 111: 2291, 1938.
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