Brief Report

Periodicity during Recovery of Erythropoiesis following Irradiation

By Alec Morley and Frederick Stohlman, Jr.

There is now abundant evidence that erythropoiesis is controlled by a negative feedback circuit involving a plasma-hormone, erythropoietin. This hormone acts predominantly on erythropoietin-sensitive stem cells causing them to differentiate into erythroid precursors. Depletion experiments suggest that granulocyte and platelet production rates may also be controlled by feedback circuits acting at or near the stem cell stage. Any circuit causing differentiation out of the stem cell compartment must contain a substantial time-delay since cells of the erythroid, granulocytic and megakaryocytic lines take some days to mature inside the marrow before they are finally released into the blood. A negative feedback circuit containing a time-delay is notably prone to oscillation, but that periodicity may occur for this reason, however, has not been widely appreciated in hematology. Two periodic diseases, cyclical neutropenia and cyclical thrombocytopenia, have been recognized for many years. In 1923 Brown et al. reported that in several dogs with biliary fistulas the hemoglobin level and output of bile showed regular fluctuation with a period of about 2 weeks. More recently oscillation of the neutrophil count has been found in some normal individuals and this oscillation has been reproduced by an analog computer model in which granulopoiesis has been regarded essentially as a nonlinear negative feedback circuit containing a time-delay. Patients with chronic granulocytic leukemia have also been found to show oscillatory leukocytosis which suggests that normal homeostatic control is still partly retained in this disease.

Orr et al. recently reported that rabbits given thrice-weekly injections of hemolytic antibody developed oscillation of their hemoglobin and reticulocyte levels. Following this finding Kirk et al. proposed an analog computer model involving 2 feedback loops, one controlling stem cell number, the other stem cell differentiation under the influence of erythropoietin. Oscillation mimicking that found experimentally resulted from the interaction of these two loops. The model also reproduced the observation of Hulse who, among others, noted that the reticulocyte count of rats shows an overshoot above normal between 10-25 days after irradiation with 400 rad.

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PERIODICITY DURING RECOVERY OF ERYTHROPOIESIS

Hulse's finding, the abortive rise in blood elements after irradiation observed by many workers and the suggestion of periodicity during recovery of granulopoiesis observed by Langendorff and Papperitz all suggested to us that irradiation may affect hemopoiesis as a pulse-stimulus acting on an inherently oscillatory system. In order to detect any oscillation we therefore serially followed peripheral blood changes in mice given a small dose of total body irradiation.

MATERIALS AND METHODS

Twelve to sixteen week old female CF1 mice* were randomized into treated and control groups. Those in the treated group were irradiated with 200 rad of total body irradiation (dose rate 48 rad/min., 250 kV, 15 mA, 1.0 mm. Cu and 1.0 mm. Al filtration). Every 2 or 3 days thereafter 5 treated mice and 1 control were sacrificed and blood obtained by heart puncture. Red cell, reticulocyte and total and differential white cell counts were performed using standard methods.

RESULTS AND DISCUSSION

The serial changes in red cell count and in absolute reticulocyte and neutrophil counts are shown in Figure 1. The neutrophil count shows an early rise followed by a fall; subsequently there may be a suggestion of oscillation but this is not definite. However, the reticulocyte count clearly and the red cell count probably show damped oscillation which has a striking resemblance to Figure 6 (b) in the paper of Kirk et al. That figure illustrates the reticulocyte response of their mathematical model to a sudden reduction of stem cell number of 0.1 per cent of normal. During the first 6–8 days of our study the decrease in reticulocyte count was undoubtedly due to the decrease in stem cell number following irradiation. However, for the remainder of the experiment fluctuations in reticulocyte number followed about 5 days after fluctuations in red cell count. Conversely the fluctuations in red cell count appeared to follow changes in reticulocyte production. These findings suggest that the cause of oscillation was a single closed feedback loop containing a total time-delay of about 5 days. Since the production of erythropoietin is rapid, nearly all of this delay of 5 days can be attributed to the time taken for the erythropoietin-responsive stem cell to mature and become the blood reticulocyte.

Damping and disappearance of oscillation might have occurred owing to several possibilities. A damped oscillation might have been the true time-course of the reticulocyte count in individual mice. On the other hand the reticulocyte count in individual mice might have shown sustained oscillation but, if the periods in different mice differed slightly, the use of cohorts could have obscured oscillation towards the end of the study. Supporting this latter possibility are our preliminary observations in dogs which suggest that the normal steady-state of erythropoiesis is one of sustained oscillation.

Periodicity may be difficult to detect unless it is sought for specifically and prospectively. Since the phenomenon of compensated hemolysis in patients with hereditary spherocytosis has important implications for the control of erythropoiesis, we conjectured whether such patients might show oscillation.

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Fig. 1.—Changes in red cell, reticulocyte and neutrophil counts after irradiation with 200 rads. Results for control and treated mice are as means ± 1 S.E.

of their hemoglobin level; sampling of their blood at a time when the hemoglobin level was at a peak might then give a falsely high estimate of their mean hemoglobin level and mistakenly suggest that the hemolysis was compensated. Retrospective review of the records of one such patient failed to substantiate this possibility but we suggest that other patients should be studied prospectively to test this hypothesis.
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REFERENCES

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