

CORRESPONDENCE

ERYTHROPOIETIN AND PLATELET PRODUCTION

To the Editor:

In a report entitled "Large, Chronic Doses of Erythropoietin Cause Thrombocytopenia in Mice," McDonald et al conclude that this thrombocytopenia may have been caused by competition among stem cells.¹ The reason for performing this study was that McDonald et al had found a similar thrombocytopenia in mice exposed to prolonged hypoxia. McDonald et al now find that prolonged administration of erythropoietin not only causes erythrocytosis but also a moderate thrombocytopenia. They apparently are unaware of a 1978 report showing that hypertransfusion of mice, with its associated suppression of erythropoietin production, also leads to thrombocytopenia.² One of the explanations given in that report is quite simple. The number of platelets, although one of the components of the coagulation system in plasma, is traditionally expressed per microliter of whole blood and not, as the other components, per microliter of plasma. If expressed per microliter of plasma in the hypertransfused mice, the platelet count was about the same as in normal mice.

In Table 1 in the report by McDonald et al, the mean platelet count and hematocrit in the control animals are given as $1.07 \times 10^6/\mu\text{L}$ whole blood and 44.4%, respectively, and in the experimental animals as $0.83 \times 10^6/\mu\text{L}$ whole blood and 56.9%. If the platelet

counts had been expressed per microliter of plasma, the count in the controls would have been $1.93 \times 10^6/\mu\text{L}$ and in the experimental mice as $1.89 \times 10^6/\mu\text{L}$. In their Table 2 on splenectomized mice, the platelet counts per microliter of plasma would have been 1.77×10^6 in the controls and 1.67×10^6 in the experimental group.

This may of course not be the correct reason for the thrombocytopenia and it does not explain why and how the platelets in plasma are kept at such stable concentrations. However, I doubt that the responsible mechanisms, operating at both low and high erythropoietin titers, involve stem cell competition.

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RESPONSE

I disagree with the notion that platelets are a part of plasma. I believe they should be treated as other formed elements in the blood and their values should be expressed in the same manner as red blood cells (RBCs) and white blood cells. Blood values such as hematocrits and platelet counts measure concentrations and do not allow for small, but important, changes in blood volumes. However, total circulating platelet counts (TCPC), unlike whole blood or plasma platelet counts, take into account changes in blood volume. In our study,¹ we found significant decreases in TCPC in mice after erythropoietin (EPO) injections, along with elevated erythropoiesis. Moreover, ^{35}S incorporation into platelets, a measure of platelet production, was significantly reduced after EPO injections, leading us to the conclusion that the thrombocytopenia was caused by reduced platelet production. These findings, along with several other previous studies showing that active erythropoiesis leads to decreased platelet production, led us to the conclusion that erythrocytes and megakaryocytes have a common precursor cell and its differentiation into one cell line does so at the expense of the other (stem cell competition hypothesis).

It should also be stated that both our work and that of Shaikh and Erslev² are in agreement with the stem cell competition hypothesis. Because the theory states that elevated erythropoiesis leads to reduced thrombocytopoiesis, and transfusing of RBCs into mice does not stimulate erythropoiesis, we would expect no change in thrombocytopoiesis. In fact, Shaikh and Erslev reported no change in TCPC in mice after polycythemia induced by RBC hypertransfusions.

In addition to this confirmation of our hypothesis, other work points to the stem cell competition hypothesis as the mechanism

for RBCs and platelets being inversely related. For example, it is well established that hypoxia, a stimulator of erythropoiesis, causes thrombocytopenia in laboratory animals. Thyroxine,³ a stimulator of erythropoiesis, and EPO, when administered in large, chronic doses,¹ elevates erythropoiesis and causes thrombocytopenia. Several biochemical similarities in megakaryocytes and erythrocytes have been found, and numerous clinical conditions (including cyanotic congenital heart disease, hypothyroidism in dogs, iron-deficiency anemia, and sickle cell anemia) point to an inverse relationship between RBCs and platelet production. We believe these *in vivo*, biochemical, and clinical data support the hypothesis that megakaryocytes and erythrocytes share a common precursor cell and that the two cell lines are in competition.

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3. Sullivan PS, McDonald TP: Thyroxine suppresses thrombocytopoiesis and stimulates erythropoiesis in mice. *Proc Soc Exp Biol Med* (in press)