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A MATHEMATICAL MODEL OF ERYTHROPOIESIS SUGGESTS AN ALTERED PLASMA VOLUME CONTROL AS CAUSE FOR ANEMIA IN AGED MICE

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Abstract — In order to evaluate whether the anemia observed in aged C57Bl and B6D2F1 mice reflects a defect in the control mechanisms regulating erythropoiesis a mathematical model of erythropoietic control is employed, validated previously. In the model it is hypothesized that the most important mechanism for compensating an actual demand of red blood cells is an increase in the mitotic amplification (number of mitoses) of erythroid progenitors (CFU-E, erythroblasts). The same sigmoidal dose-response-relationship between mitotic amplification and hematocrit (Hct) is proposed for young and aged mice. It is mediated by erythropoietin (EPO). Using this relationship one can demonstrate that the expansion of the plasma volume (PV) observed in aged mice is appropriately compensated by an increase in the mitotic amplification of CFU-E and erythroblasts. This implies that aged mice operate in a stimulated state of erythropoietic amplification which is closer to the maximum of the dose-response-relationship than the steady state in young mice. This explains the finding of a reduced proliferative reserve in aged mice following further erythropoietic stimulation. An additional analysis regarding the response of aged mice to bleeding anemia is consistent with the view that young and aged mice share the same dose-response-relationship but start from different steady states. These findings suggest that the control mechanisms regulating erythropoiesis in young and aged mice are similar and that the anemia is due to alterations in the PV control.

Key Words: aging, mathematical model, erythropoiesis, anemia

INTRODUCTION

DEVELOPMENT OF mild anemia with age is a well-known fact for mice of different strains (e.g., Strong and Francis, 1940, in CBA; Ewing and Tauber, 1964, and Finch and Foster, 1973, in C57Bl/6; Silini and Andreozzi, 1974, in C3H × C57Bl; Tyan, 1982, in B6D2F1). Recently, the results in mice have been reviewed by Boggs and Patrene (1985a; 1985b). In additional experiments, they found an increase of plasma volume (PV), blood volume (BV), and total red cell volume (RCV) in 18-month-old B6D2F1 (C57Bl × DBA) mice. The changes of PV, BV,

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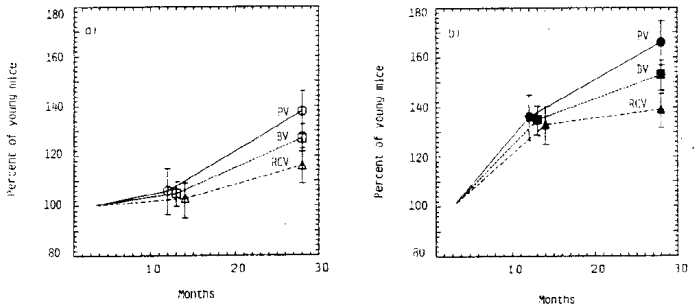

FIG. 1. Plasma volume (PV), blood volume (BV), and red cell volume (RCV) data recalculated and replotted from Boggs and Patrene (1985). a). The volumes per body weight as percentage of the young mice PV (○), BV (□), RCV (△) (100% represents: PV: 0.032; RCV: 0.032; BV: 0.064 ml/g body weight). b). The absolute volumes of PV (●), BV (■), V (▲) expressed as percentage of the young mice. (100% represents: PV: 0.75 ml; RCV: 0.76 ml; BV: 1.51 ml). The PV values were calculated from BV and HCT by using the formula PV = BV*(100-HCT).

and RCV with age are given in Figure 1. One can express these parameters either in absolute units (e.g., ml) or in % of body weight. Both representations are given. They differ somewhat because mice aged 13–28 months tend to have a 20–30% larger body weight compared to 3 month old animals. However, irrespective of the type of calculation, clear increases in PV and RCV can be noted, with the PV increasing more than the RCV. From these data Boggs and Patrene conjectured that a defect in PV control leads to a dilution anemia, which is supported by the fact that the mean corpuscular volume and red cell life span are identical in young and aged mice. This conclusion contrasts with findings in C57Bl/6 mice of a reduced proliferative capacity of marrow erythroblasts which was interpreted as a sign of hemopoietic senescence (Udupa and Lipschitz, 1984b). In addition, the pattern of erythropoietic recovery following bleeding seems to provide evidence that the control mechanisms regulating the production of red blood cells in 25- to 28-month-old B6D2F1 and C57Bl mice are somewhat impaired (Boggs and Patrene 1985a; Harrison, 1975b).

It is the objective of the present study to demonstrate that these data are not necessarily in conflict but can be consistently explained within the framework of a recently proposed quantitative concept of erythropoietic control. The basic assumptions of the concept have previously been formalized as a mathematical model of murine erythropoiesis (Wichmann, 1983; Loeffler *et al.*, 1989).

THE MODEL

Model description

The mathematical model of erythropoiesis is used as described previously (Loeffler *et al.*, 1989). Briefly, the model consists of a series of compartments representing different maturation steps in the erythropoietic lineage (Fig. 2). Assuming a constant input of cells from early erythroid progenitors (BFU-E) the compartments for late erythropoietic progenitors (CFU-E, proliferating and nonproliferating erythroblasts (including marrow reticulocytes), blood reticulocytes, and erythrocytes are considered. The model describes the total erythroid cell production in the marrow and spleen. The mathematical description of the model compartments uses ordinary differential equations. A brief summary of the formulae used is given in the Appendix.

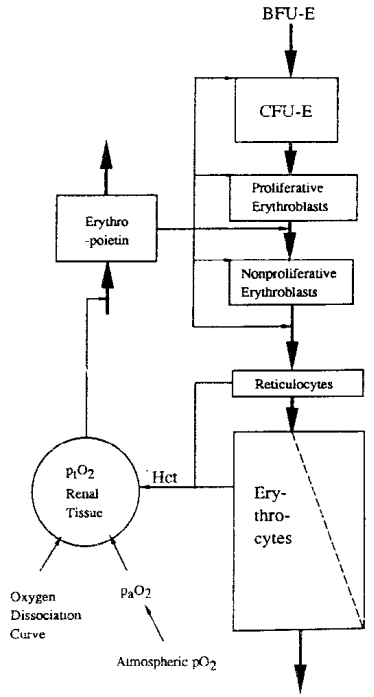

FIG. 2. Block diagram of a mathematical model of normal erythropoiesis. Thick arrows represent the cell flux between cell compartment or production and destruction of EPO. Small arrows indicate regulatory influences. The model has been described elsewhere in detail (Loeffler *et al.*, 1989).

The primary parameter of erythropoietic control is assumed to be the dose-relationship-response between the hematocrit (Hct) (or the partial tissue oxygen pressure p_tO_2) and the mitotic amplification factor f in the cell compartments CFU-E (f_{CFUE}) and proliferating erythroblasts (f_{PEP}). The cumulative dose-response-relationship ($f = f_{CFUE} * f_{PEP}$) is displayed in Figure 3. If the Hct is reduced below its normal value (of 0.5) additional mitoses take place which increase the amplification up to a certain maximum level that cannot be exceeded. The maximum is assumed to be six-fold higher than normal. This implies that per BFU-E cell in the course of erythroid amplification and maturation six times more erythrocytes are produced than under normal circumstances. In the normal steady state it is assumed that one BFU-E gives rise to 2048 erythrocytes (amplification of 2048-fold). With this in vivo dose-response-curve a comprehensive quantitative understanding of many experimental situations such as bleeding,

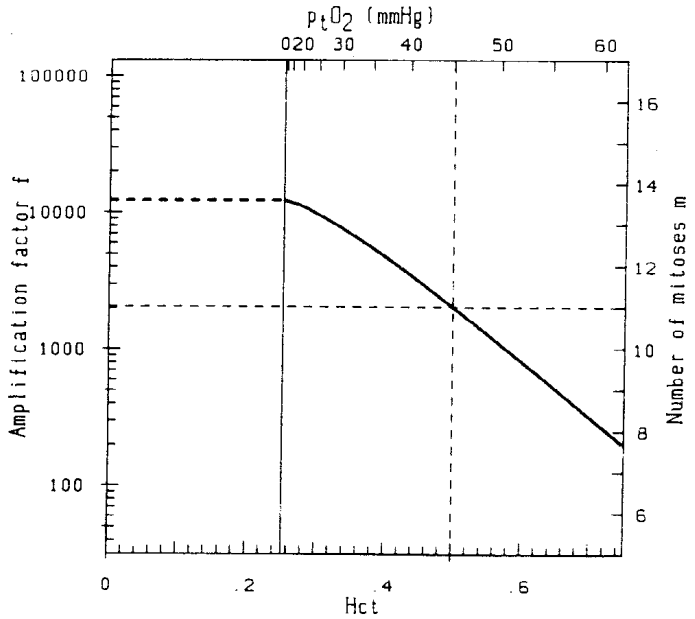

FIG. 3. Dose response relationship between the total erythropoietic amplification factor f and Hct (or partial tissue oxygen pressure p_tO_2) as derived from a previous analysis of erythropoietic control in mice (Loeffler *et al.*, 1989). The normal (young mouse) Hct value is assumed to be 0.50. A decrease in Hct leads to an increase in the amplification factor (full line) leveling off at a six-fold higher value. The amplification factor f and the number of mitoses m are related by the formula $f=2^m$.

hemolytic and dilution anemia, hypoxia, injection of EPO, hypertransfusion, hyperoxia, posthypoxia, and dehydration could be obtained (Wichmann *et al.*, 1989; Wulff *et al.*, 1989). It should be noted, that the model parameters used in this study are identical with those established in the quoted references and that they are not fitted to the particular mouse strains considered in the following.

MODEL SIMULATIONS

Steady state

The model is used to simulate the erythropoietic compensation of a permanent expansion of the plasma volume. Technically, the simulations start at the normal steady state values (i.e., Hct = 0.50) and then a change of the PV to a certain fixed value (e.g., 140%) is introduced. New steady states develop according to the model equations. These steady state values of Hct, RCV, etc. can be plotted against the PV used as input. This leads to nomograms predicting the steady state values for Hct or RCV for any given PV.

This exercise is performed for two different model scenarios:

1. Intact erythropoietic feedback with amplification regulated according to the dose-response-curve in Figure 3;
2. Absence of erythropoietic regulation with a constant erythropoietic amplification independent of Hct.

Proliferative reserve

The authors define proliferative reserve (PR) of mitotic amplification as the factor by which amplification can be increased from a given actual value to the maximum value. Given the maximum (f_{max}), normal (f_{norm}), and actual operating (f_{act}) values of the dose-response-curve one can calculate the normal PR as $PR_{norm} = (f_{max}-f_{norm})/f_{norm}$ and the actual PR as $PR_{act} = (f_{max}-f_{act})/f_{act}$. Consequently, the PR for a given situation compared to normal is given by the simple ratio:

$$PR = PR_{act}/PR_{norm}*100\%.$$

Recovery following bleeding

The assumptions for simulating recovery from bleeding anemia have been described previously (Wichmann *et al.*, 1989). Briefly, Hct is reduced to the experimental nadir observed initially after bleeding. The model equations then predict the temporal pattern of regeneration in all compartments.

Here three different regulatory scenarios are compared:

1. Intact erythropoietic feedback with a normal PV;
2. Intact erythropoietic feedback with a 40% larger PV;
3. Absence of erythropoietic regulation (constant amplification independent of Hct) with a 40% larger PV.

RESULTS

Steady state analysis

The previously established mathematical model of erythropoietic control can be used to predict the steady state Hct that establishes during a permanent expansion of the plasma volume (PV). If erythropoietic feedback is active, the steady state Hct maintained is considerably higher than in an uncompensated case. Using the model the difference can be quantified. This is illustrated in Figure 4a. The full curves represent the model steady state Hct values that establish for a certain fixed increase of PV provided the erythropoietic regulation is intact. For example, for a PV increase to 160% a reduction of the Hct to almost 47% can be expected. In a second scenario the steady state Hct values are calculated that one would expect under the extreme assumption that no regulation of erythropoiesis takes place. In this case, the steady state Hct values are much lower and for a PV increase to 160% a reduction of the Hct to 39% can be expected (lower curve in Fig. 4a). The data obtained by Boggs and Patrene (1985a; 1985b) can be compared to these model predictions. It is apparent that the full symbols (derived from absolute values; see Fig. 1 are close to the model curves for compensated anemia, while the

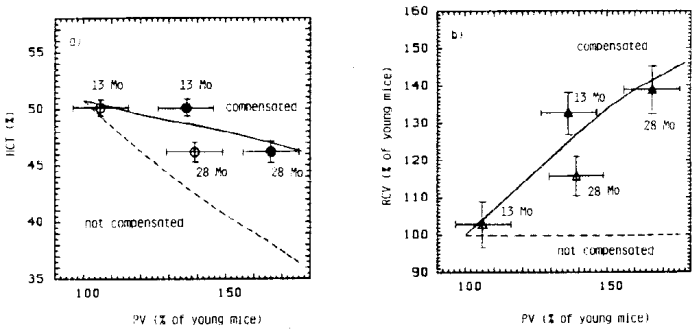

FIG. 4. a) Nomogram relating hematocrit (Hct) and plasma volume (PV) in steady state. Data deduced from Boggs and Patrene (1985a; 1985b) are plotted in the diagram: PV calculated from ratios of volume per g body weight (○) or as absolute volumes (ml) (●). In both cases, the data are expressed as percentage of the values obtained in young mice (see Fig. 1). The error bars represent the combined standard error for PV and Hct. The full upper curve represents a model calculation of compensated dilution anemia. The lower dashed curve represents the corresponding model curve if no erythropoietic compensation takes place (see constant dashed curve in Fig. 3). b) Nomogram relating red cell volume (RCV: △, ▲) and plasma volume in steady state.

open symbols (derived from values expressed as % body weight (see Fig. 1) indicate a slightly lower degree of erythropoietic compensation.

A similar result is obtained if one plots the corresponding nomogram for PV versus RCV (Figure 4b). The full curve is the model prediction for the steady state in case of active erythropoietic control. Plotting the corresponding data into the same diagram one finds that the full symbols are again very close to the model curve for compensated anemia while the open symbols suggest a slightly impaired compensation.

Proliferative reserve (PR)

The dose-response curve given in Figure 3 for the amplification factor f has implications for the proliferative reserve. Young mice are assumed to have a steady state Hct of 0.50. From this level erythroid amplification can be increased six-fold until the maximum of the dose-response curve is reached. Since aged mice exhibit a lower Hct than young mice their corresponding actual amplification factor is already increased under steady state conditions. Thus, their amplification is closer to the maximum than for young mice. In other terms, the proliferative reserve (PR) of aged mice is reduced compared with young mice. Table 1 gives the model predictions for the actual increase of the amplification factor at a given Hct and the respective proliferative reserve remaining. Lowering Hct gives higher amplification factors and lower PR: e.g., a Hct of 0.46 can be maintained by a 1.45-fold increase in amplification. But this goes parallel with a reduction of the PR to 63% of normal.

Recently, Udupa and Lipschitz (1984b) examined the proliferative reserve. The data revealed a moderate decrease in PR to 68% of normal for a Hct of 0.47 which is similar to the values predicted from our model calculation (see Table 1).

TABLE 1. AMPLIFICATION FACTOR AND PROLIFERATIVE RESERVE

	Hct	*Actual amplification Factor f*[a] *(Times normal)*	*Proliferative Reserve*[b] *(Percent of normal)*
Model	0.6 (normal)	1.00	100
	0.48	1.21	79
	0.46	1.45	63
	0.44	1.75	49
	0.42	2.10	37
	0.40	2.50	28
	0.30	5.28	3
	≤0.25	6.00	0
Data	0.47 ± 0.02[c]	not accessible	68 ± 8%[d]

[a]Values are obtained by calculating formula (7)–(12) with $f = f_{CFU} - E^* f_{PEB}$ from Loeffler *et al.* (1989). [b]Relative Proliferative Reserve =

$$PR = PR_{act}/PR_{norm} * 100\%.$$

[c]Values from Udupa & Lipschitz (1984a) Figure 1. [d]Values from Udupa & Lipschitz (1984b) Table 1.

Recovery from bleeding

It was argued by Boggs and Patrene (1985a; 1985b), that a slower recovery from bleeding could indicate a defective erythropoietic regulation in old mice. Their Hct data are redrawn for 3-month and 28-month-old animals in Figure 5a. In Figure 5b corresponding model simulations are shown. Three model scenarios are shown, all starting with a Hct of 0.22 at day 0 (taken from the data):

1. The upper line indicates a recovery assuming that an erythropoietic feedback is active with the dose response curve given in Fig. 3. Here, a PV expansion is not assumed. This simulation is comparable to the data from young animals (Fig. 5a, upper curve).
2. In the middle curve, the same erythropoietic feedback is assumed as before. In addition, a permanent plasma expansion by 40% is taken into account. This model curve does not differ from the previous curve for the first two days. Subsequently, the recovery velocity slightly declines. Finally, a different steady state plateau is achieved. The shapes of both curves are similar. Indeed, data for young and old mice also exhibit a similar pattern but differ in plateau levels by the same amount as the model curves (compare Fig. 5a and 5b). Data by Harrison (1975a, 1975b) (not shown) also indicate an identical recovery for the first two days and completed recovery at different Hct levels after day 8.
3. The lower curve in Figure 5b indicates the recovery predicted after bleeding if erythropoietic regulation is assumed to be completely absent. In this case, red cell production continues at its normal rate resulting in a slow increase in Hct. It is evident that the data for old and young mice clearly contradict this simulation. Thus, the recovery after bleeding anemia does not provide evidence for a relevant defect of the erythropoietic control system.

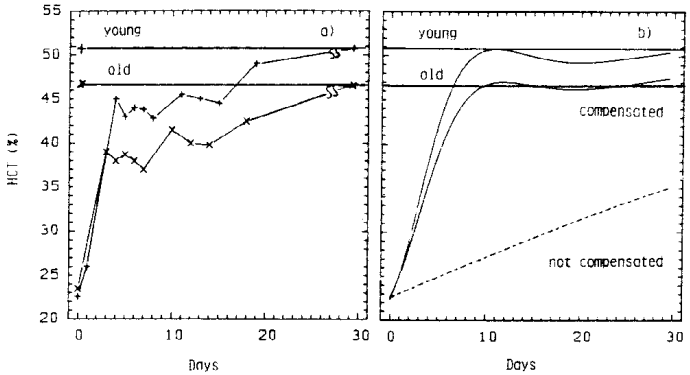

FIG. 5. Recovery from bleeding anemia: a) Data redrawn from Boggs and Patrene (1985a; 1985b) for 3-month-old (+) and 28-month-old mice (×) after severe bleeding anemia. b) Model calculations: The upper full line indicates the model curve for young mice assuming an intact erythropoietic feedback and no plasma expansion. The intermediate model curve is obtained by assuming an intact erythropoietic feedback and a 40% plasma volume expansion. The lower curve represents the model recovery for old mice (40% plasma volume expansion) after bleeding if no erythropoietic regulation takes place. This curve is not compatible with the data.

DISCUSSION

Based on a mathematical model of erythropoietic control validated previously (Loeffler *et al.*, 1989) it can be concluded that the control mechanisms regulating erythropoiesis in young and aged mice are similar and that the anemia in aged mice is more likely due to alterations in the PV control. Such PV changes seem to drive the erythropoietic system into different operational steady states which are located on a dose response curve for mitotic amplification of CFU-E and erythroblasts. Many observations on steady state and recovery behaviour in aged and young mice can apparently be explained by this concept of different steady states on a dose response curve which is identical for young and aged mice. This explanation is conceptually different from explanations of a defect erythropoietic control which would imply different dose response relationships for aged and young mice. This analysis shows that there is not enough evidence to conclude such a systematic regulatory difference.

Steady state values for Hct clearly indicate the presence of capable erythropoietic compensation mechanisms. Although the PV increase is substantial the Hct is only slightly reduced, much less than what one would expect in an uncompensated circumstance.

Previous reports using C57Bl mice showed a reduced proliferative reserve if stimulated by erythropoietin (Udupa and Lipschitz, 1984a; 1984b). This was interpreted as a defect in erythropoietic control. However, these findings can consistently be explained on the basis of an intact feedback regulation. Since Hct is decreased in aged mice, the corresponding mitotic amplification is already increased under steady state conditions. Consequently, the remaining reserve of mitotic amplification from this operational steady state to its maximum is reduced compared to that of young (nonanemic) mice. Indeed, the degree of the reduction predicted by the model as a consequence of the dilution anemia observed is similar to the reduction measured in mice by Udupa and Lipschitz (1984b).

On the same basis, one can explain the response of aged mice to bleeding by an intact erythropoietic regulation. The different recovery pattern as compared to that of young mice can be understood quantitatively by the expanded PV. Likewise the model predicts that a response to continued hypoxia should result in a slightly slower increase of Hct in old mice compared to young reaching also different plateau levels. This has actually been found by Udupa and Lipschitz (1984a) although one has to be cautious due to the large variance in their data.

Although the model curves approximated the data well the fit was not always perfect. The model curves after bleeding show a faster recovery (day 6–16) than is actually found in the data (see Fig. 4a, b). This discrepancy is most likely due to the oversimplified model assumption that the total blood volume after bleeding and during the recovery is constant. This may not be entirely justified but the error should affect both the upper and the middle model curves in a similar way. Thus, their relation to one another will change if this assumption is corrected. Therefore, the differences observed should be comparable to the differences predicted by the model.

It should be noted that the model was designed as an average mouse model to represent general patterns of erythropoietic regulation. This implies that the parameters are not adapted to a particular mouse strain such as B6D2F1 or C57Bl mice. This might also account for some differences between the model and the data. Thus, this analysis is not sensitive enough to exclude subtle differences in the dose-response curves of young and old mice.

It should also be noted that several studies could not show a significant difference in the steady state number of CFU-E, erythroblast, or incorporation of ^{59}Fe between young and old B6D2Fl or C57Bl mice (Boggs and Patrene, 1985b; 1986; Udupa and Lipschitz, 1984a). However, this might not contradict the results presented here. The increase in the mitotic amplification predicted for the steady state conditions in old mice is only small. The corresponding increase in absolute numbers of CFU-E and erythroblasts in the total animal might be too small (about 20% each) to be detectable, particularly as aged mice tend to be larger (20–30% heavier) and correction procedures to estimate the total cell numbers from femur measurements are difficult.

Recent results showed that spleens removed from 28-month-old WCB6Fl and WBB6Fl donors and transplanted into constitutionally anemic SL/SL^{D} recipients were less effective in correcting their anemia than spleens from 5- to 10-month-old-donors. This might indicate a decrease in the hematopoietic function of the spleen in aging mice (Harrison *et al.*, 1988). Since the spleen has been shown to contribute to the erythropoietic recovery following bleeding anemia in mice (Loeffler and Wichmann, 1985), the modified recovery observed in 25- to 28-month-old mice may result from a decrease in the erythropoesis-supporting function of the spleen. Separate modeling of marrow and spleen conditions is underway to examine this point.

Regarding hemopoietic stem cells several studies showed that the number of erythroid myeloid stem cells CFU-S in the bone marrow remains constant with age (Chertkov and Gurevitch, 1981, in C57Bl × CBA/H mice) or even increases (Silini and Andreozzi, 1973, in C3H × C57Bl mice; Yuhan and Storer, 1967, in C57Bl/6 mice; Ciggle *et al.*, 1975, in SAS/4 mice; Tyan, 1982, C57Bl). Only in the RFM/Un mouse strain Davic *et al.* (1971) found a decline in CFU-S number after 12 months of age. Albright and Makinodan (1976) reported a reduced growth capacity of stem cells. However, the majority of the data suggests that the age related anemia is not caused by a change on the stem cell level. This conclusion is supported by the fact that bone marrow taken from 29- to 39-month-old donor mice functioned as well as that from young mice (1–12 month) in establishing hematopoiesis in lethally irradiated recipients (Harrison, 1975a). In particular, injection of bone marrow from young mice into old

mice could neither cure their anemia nor modify the response to bleeding (Harrison, 1975b). Recently Harrison *et al.* (1989) examined whether the primitive stem cells (PCS) change with age. These are more primitive than CFU-S and give rise to lymphoid cells as well. It could be shown that PSC are about two times more frequent in old mice compared to young mice and that they can be effectively transplanted to give long lasting clonal growth in recipients. Thus, these studies do not provide conclusive evidence that the erythropoietic changes in old mice are caused by changes at the hemopoietic stem cell level. This justifies our model assumption to consider the input of cells into erythropoiesis as constant. On this basis, a separate modeling of CFU-S and BFU-E stages for young and old mice did not appear necessary.

Finally, it should be stated that anemia in aged mice is not found in all mouse strains (e.g., not in C57Bl × CBA mice, Chertkov and Gurevitch, 1981) nor in all individuals of an affected strain (Udupa and Lipschitz, 1984b). According to the authors' concept, these animals may not have the expansion of PV seen in others, indicating that their PV-regulator may be more efficient than that in other strains or individuals. In this context, it should be noted that the reason for the expansion of PV in aged mice remains unclear. One possible mechanism might be a decrease in the renal or cardial function with increasing age, leading to an increase in water retention.

Although the above model analysis suggests that young and aged mice have the same response, direct experimental proof would be desirable. How could it be obtained? At present, there is no reliable technique available to measure the in vivo dose-response relationship directly. A possible approximation might be an experiment involving continuous long-term application of recombinant EPO at various dose levels. One could inject r EPO over two weeks to drive the erythropoietic amplification system into a new steady state (new operation point on the dose-response curve). One should then try to quantify parameters of red cell production, e.g., by determining how many reticulocytes are produced per time unit during the steady state (using possibly techniques of cohort labelling). Accompanying measurements should quantify the total erythroblasts cell counts in marrow and spleen. This sort of experiment could be undertaken for various dose levels of r EPO achieving up to 100-times normal serum levels. Plotting steady state EPO-levels versus steady state cell production for young and old mice separately should give very similar dose-response curves. This procedure however requires a certain precision because one wants to demonstrate equivalence and not difference. Another indirect test of equivalence would be to bring young and old mice to similar hematocrits by infusion of plasma expander into young mice or by dehydration of old mice and to carry out similar erythropoietic manipulations like bleeding anemia, or short term application of r EPO.

In conclusion, this analysis suggests that the anemia in aged B6D2Fl and C57Bl mice is caused by a yet unexplained plasma volume expansion and that the feedback control regulating the proliferative response of CFU-E and erythroblasts in young and old mice is fairly similar providing no clear evidence for a defect of the erythropoietic control process.

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APPENDIX

A brief summary of the essential model equations is given (for details and choice of parameters see Loeffler *et al.* 1989):
The following notation is used for the model compartments:

Y = number of cells in a compartment
f = amplification factor ($f = 2^m$, m = number of mitoses)
τ = average transit time

Model equations of the compartments

The compartment of the late erythropoietic progenitors (CFU-E) is described by the differential equation:

$$\dot{Y}_{CFU\text{-}E} = f_{CFU\text{-}E} \cdot I - Y_{CFU\text{-}E}/\tau_{CFU\text{-}E}. \quad (1)$$

I is the influx from the early erythropoietic progenitors (BFU-E) which are not explicitly considered in the model. While I is constant, the amplification of this influx, $f_{CFU\text{-}E}$, depends on EPO. $\tau_{CFU\text{-}E}$ is assumed as constant.
The cells enter the second compartment of proliferative erythropoietic precursors (PEP):

$$\dot{Y}_{PEP} = f_{PEP} \cdot Y_{CFU\text{-}E}/\tau_{CFU\text{-}E} - Y_{PEP}/\tau_{PEP}. \quad (2)$$

Both the amplification factor f_{PEP} and the transit time τ_{PEP} depend on EPO.
The erythroblasts loose their ability to proliferate and enter the compartment of the nonproliferative erythropoietic precursors (NPEP = erythroblasts and bone marrow reticulocytes) described by:

$$\dot{Y}_{NPEP} = Y_{PEP}/\tau_{PEP} - Y_{NPEP}/\tau_{NPEP}, \quad (3)$$

with the transit time τ_{NPEP} depending on EPO.
The blood reticulocytes (RETI) are described by:

$$\dot{Y}_{RETI} = Y_{NPEP}/\tau_{NPEP} - Y_{RETI}/\tau_{RETI}. \quad (4)$$

The compartment of erythrocytes (ERY) is divided into two parallel parts. The first one, Y_{ERYA}, obeys an almost age dependent destruction law (rectangular age structure) and represents the majority of cells produced at normal proliferation. The second part, Y_{ERYR}, has an exponential age structure, suggesting a random destruction process. The distribution of the influx into the subcompartments Y_{ERYA} and Y_{ERYR} is governed by a function alpha ($h(t)$). Hence,

$$\dot{Y}_{ERYA} = \text{alpha}(h(t)) \cdot h(t) - \text{alpha}(h(t-\tau_{ERYA})) \cdot h(t-\tau_{ERYA}), \quad (5)$$

with $h(t) = Y_{RETI}(t)/\tau_{RETI}$.

$$\dot{Y}_{ERYR} = (1\text{-alpha}(h(t))) \cdot h(t) - Y_{ERYR}/\tau_{ERYR} \quad (5')$$

with $\text{alpha}(h(t)) = \exp(-0.1 \cdot (h(t)/h\text{norm})^2)$.
Finally, compartment EPO describes the feedback hormone erythropoietin. The model equation is:

$$\dot{Y}_{EPO} = p_{EPO} - Y_{EPO}/\tau_{EPO}, \quad (6)$$

with p_{EPO} as the production rate depending on the oxygen-supply and τ_{EPO} as the constant turnover time.

Feedback influences of erythropoietin

In the model it is assumed that EPO influences directly the amplification factor $f_{CFU\,E}$ and f_{PEP} as well as the transit times τ_{PEP} and τ_{NPEP}.
For these regulatory functions a sigmoid form is assumed:

$$f(Y_{EPO}/Y_{EPO}^{norm}) = A - B \cdot \exp(-C \cdot (Y_{EPO}/Y_{EPO}^{norm})^{BR}), \quad (7a)$$

and

$$\tau(Y_{EPO}/Y_{EPO}^{norm}) = A' + B' \cdot \exp(-C' \cdot (Y_{EPO}/Y_{EPO}^{norm})^{BR}). \quad (7b)$$

The constants A, B, C, and A′, B′, C′ are positive and can be determined from measurements of the minimum, maximum, and normal values of the proliferation rates and transit times (Loeffler *et al.*, 1989).

Feedback influences on erythropoietin production

It is assumed that the production rate of erythropoietin p_{EPO} depends exponentially on the tissue oxygen pressure p_tO_2:

$$p_{EPO}(p_tO_2/p_tO_2^{norm}) = D \cdot \exp(-E \cdot p_tO_2/p_tO_2^{norm}). \quad (8)$$

p_tO_2 is determined by the tissue oxygen saturation (S_tO_2) according to the Hill equation:

$$p_tO_2 = p50 \cdot (S_tO_2/(100\text{-}S_tO_2))^{1/n}. \quad (9)$$

The parameters p50 and n characterize the oxyhemoglobin dissociation curve. S_tO_2 depends on the arterial saturation and the oxygen desaturation which is related to the hematocrit:

$$S_tO_2 = S_aO_2 - F \cdot (1/Hct - 1). \quad (10)$$

Readers interested to have a review of other models of erythropoiesis are referred to Wichmann (1983).