IRON KINETICS AND ERYTHRON DEVELOPMENT

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ABSTRACT The mathematical model of steady-state iron kinetics in the human presented here extends the use of radioactive tracer observations in the determination of erythron maturative and proliferative behavior. Functions descriptive of that behavior appear explicitly in the model together with functions customarily measured in standard tracer procedures. The model is compartmental, with transfers compatible with all observed erythropoietic and hemolytic mechanisms as well as with most plausible conjunctured mechanisms. Obtainable from the model is quantitative information about iron uptake, intermitotic intervals, and maturation time of erythrons; about intra- and extramedullary hemolysis; and about certain standard exchange rates. The model also permits tests of competing conjectures about erythron behavior.

INTRODUCTION

This paper describes a mathematical model of steady-state iron kinetics and erythron development in the human. Although the general outline of iron metabolism and erythron behavior is known large and important areas of this outline remain to be precisely and quantitatively described. This paper indicates how portions of that description may be supplied.

The model discussed here is based on hematological concepts that have broad acceptance, and it provides for the inclusion of an array of commonly held opinions about the hematological mechanisms involved. One use of the model is to test conflicting opinions or hypotheses. The choice of a correct hypothesis will then permit use of the model to provide new quantitative information about iron kinetics and erythron development. Thus we may regard this model as the mathematical expression of a hypothesis or series of conjectures, and we realize that the model or hypothesis must be tested for conformance to biological reality. In addition to experimental data to be used directly in the model, a number of pertinent, independent observations are available for testing the compatibility of the model with the real world.

Erythroid cells play the central role in iron metabolism, and a vital explicative model must focus attention on those cells. Earlier models (Huff and Judd, 1956;

Pollycove and Mortimer, 1961; and Sharney *et al.*, 1963) ignore erythron behavior, and a single exception (Garby *et al.*, 1963) provides only for severely limited consideration of that behavior. In distinction, the model discussed here explicitly includes the maturative and proliferative behavior of the erythron, enabling the quantitative determination of that behavior under our assumptions. Our model is expected to provide quantitative information about iron uptake, intermitotic intervals, and maturation time for erythrons, and intra- and extramedullary hemolysis, as well as certain standard exchange rates.

In accord with earlier models (especially Pollycove's), we relegate all iron in the blood and blood-forming system to several mutually exclusive compartments; five for our model. Transfer between compartments is then described in terms completely compatible with observed erythropoietic and hemolytic mechanisms, as well as with most plausible conjectured mechanisms. These transfer descriptions contain mathematical functions relating to erythron behavior and yield relations between the compartments.

The relations are then subjected to formal mathematical manipulation to eliminate all compartments inaccessible to observation. The result is a fundamental equation containing only functions directly descriptive of erythron behavior and functions susceptible to measurement. Indeed, the latter functions are measured routinely as part of present radioactive tracer procedures.

The fundamental equation thus offers a possibility of computing the erythron behavior functions, and we show how this may be accomplished.

THE FERRO-KINETIC SYSTEM

We consider five types of fixed iron, defining five compartments of the blood-iron system. The five types are defined by location, kind of fixation, and function, and are as follows: (*a*) iron contained in circulating erythrocytes and reticulocytes; (*b*) iron contained in circulating blood plasma; (*c*) iron fixed in non-circulating (immature) erythrons; (*d*) iron contained in the bone marrow; and (*e*) iron contained in storage pools. The bone marrow iron constitutes the labile marrow pool introduced by Pollycove. We make the iron content of each compartment unique by requiring that the compartments be maximal and defined in the order given and that no compartment contain iron already allotted to a previously defined compartment. All iron not contained in those five compartments is assumed negligible in the rest of the paper, but in the last section we shall show how such iron may be considered.

The following connections or transfers between compartments are assumed: upon the death of a circulating erythrocyte or reticulocyte, its iron may go into storage, plasma, or the marrow pool; upon the death of a non-circulating erythron, its iron may go into plasma or the marrow pool; iron in the marrow pool may go into plasma or maturing erythrons; iron in storage may go only into plasma. Of

course, we also permit the usual orderly progression from plasma to storage or the marrow pool, from marrow pool to maturing erythrons, and thence to erythrocytes.

Schematically then, our system has the form pictured in Fig. 1, where the arrows denote directed transfers. The number below each compartment will be used to identify that compartment: plasma is compartment 1; marrow, compartment 2; maturing erythrons, compartment 3; red blood cells, compartment 4; and storage, compartment 5.

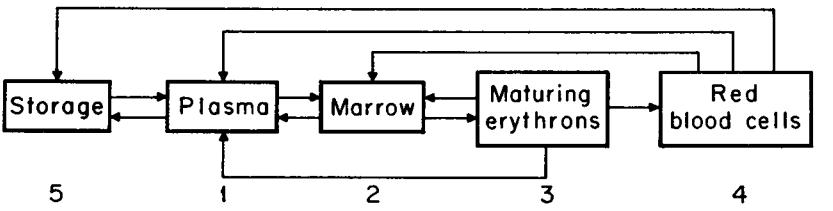

FIGURE 1 Iron compartmentation and kinetics.

We assume further that the system is in a steady state, that is, the iron content of each compartment and the transfers between compartments are constant during the period of interest. Of course the possibility is included that the system is in a steady diseased state. The physical requirements for the validity of the steady-state assumption have been discussed elsewhere (*e.g.*, Sharney *et al.*, 1963 and Sheppard, 1962). Since the non-steady state is presently beyond fruitful quantitative analysis, and since the steady state seems to offer significant results, we shall leave questions of validity and usefulness of our assumption for a pragmatic answer.

Note that we have excluded extramedullary erythropoiesis and iron incorporation by circulating erythrons. Note, further, that the system is assumed closed; that is, no iron enters or leaves the totality of our five compartments. Later, we shall show how the model may be extended to obviate these restrictions.

TRACER OBSERVATIONS

For the description of the mechanisms of our allowed transfers, let us assume that a serum injection of suitably bound radioactive iron, Fe^{59}, is made. The injection and, in particular, its iron content must be such as to leave sensibly unaltered the assumed steady state. Part of the distribution of Fe^{59} in the system may be ascertained at any time by determining the radioactive content of the plasma and of the red blood cells of a blood sample, as well as by external monitoring of certain organs, usually the sacrum, spleen, and liver. If one assumes the same mechanism in all erythropoietic marrow and no storage of iron in the sacrum, such observations of the sacrum yield a measure of the radioactivity contained in a certain proportion of compartments 2 and 3, as well as a certain proportion of the radioactivity in circulating blood. This relation of the sacrum observation to our compartments was first noted by Winchell

(1964) of Donner Laboratory. The liver and the spleen undoubtedly form part of the storage compartment of our system, but their role is imprecisely determined, so we shall attempt no quantitative use of those observations in our model.

Suppose the injection of Fe^{59} is made at time $t = 0$. We denote by $X_i(t)$ the amount of Fe^{59} in the ith compartment at time t, by $\dot{X}_{i,j}(t)$ the rate of transfer of Fe^{59} from the ith to the jth compartment at time t, and by $\dot{X}_i(t)$ the net rate of transfer into the ith compartment at time t. (Later we shall introduce a probability distribution and shall tacitly replace these rates by their expected values.) Analysis of blood samples yields values for $X_1(t)$ and $X_4(t)$ at various times, and the external monitoring of the sacrum yields values proportional to a function $X_m(t)$, the amount of Fe^{59} in the sacrum at time t. The function $X_m(t)$ satisfies the equation

$$X_m(t) = c[X_2(t) + X_3(t) + bX_4(t) + pX_1(t)],$$

where c is that proportion of the whole erythropoietic part of the skeleton which is the sacrum, b is the proportion of red blood cells, and p is the proportion of plasma in the erythropoietic part of the skeleton. We write the foregoing equation as

$$X_2(t) + X_3(t) = \frac{1}{c} X_m(t) - bX_4(t) - pX_1(t). \tag{1}$$

ERYTHRON BEHAVIOR

In compartments 3 and 4, let us measure the age of each erythron from the time its earliest progenitor began iron accumulation. The operation of the system is defined for our purposes by three functions and several constants. The functions are: $P(s)$, the probability of survival to age, s, of an erythron and its descendants along a particular branch of their genealogical tree; $q(s)$, the number of erythrons of age s, if no erythron death were to occur; and $r(s)$, the rate of iron acquisition of each erythron at age s. If the erythron has divided only once before age s, then $P(s)$ is the probability of survival to age s of each daughter; if the erythron has divided precisely twice before age s, then $P(s)$ is the probability of survival to age s of each granddaughter. We allow the function r to assume negative values to account for conceivable iron loss by erythrons, but r is not to account for loss by mitosis, in which iron content is approximately halved. Thus, r describes the iron uptake of each erythron except at the (perhaps arbitrarily assigned) instant of mitosis.

Consider a fictitious erythron of age zero which matures without mitosis and which has the iron acquisition rate of $[q(s)/q(0)]\, r(s)$ at age s. At each age such a fictitious erythron has the same iron content as the total iron content of all possible descendants, of that age, of an actual erythron. These descendants are $q(s)/q(0)$ in number. Now let the function, P, give the survival probability of the fictitious erythron. It is clear that the expected iron content of each fictitious erythron of age s will be the same as the iron content of the expected number of descendants, surviving to age s of an actual erythron. Thus, in terms of expected iron delivery, we may consider the

fictitious erythron and ignore cell division. The foregoing remarks show also that only the product, $q(s)r(s)$, rather than the individual functions, will be of import in our formulation.

Let us derive an expression for $\dot{X}_{3,4}(t)$, under the assumption that all erythrons reaching age T are immediately transferred from compartment 3 to compartment 4 and that no other iron transfer occurs between those two compartments. An erythron reaching age T at time t is age s at time $t - T + s$. Thus, its rate of radioactive iron acquisition (all from compartment 2) at age s is $r(s)X_2(t - T + s)/I_2$, where I_2 is the total amount of iron in compartment 2. The total rate of all such erythrons at age s is $q(s)r(s)X_2(t - T + s)/I_2$. Therefore, if no erythron death were to occur, the total amount of Fe^{59} in erythrons reaching age T at time t would be

$$\frac{1}{I_2}\int_{s=0}^{T} q(s)r(s)\,X_2(t - T + s)\,ds.$$

Since $P(T)$ is the probability that any particular erythron will achieve age, T, we have

$$\dot{X}_{3,4}(t) = \frac{P(T)}{I_2}\int_{s=0}^{T} q(s)r(s)\,X_2(t - T + s)\,ds. \tag{2}$$

If we replace T by u, the right-hand side of equation (2) gives the expected iron content of all erythrons attaining age u at time t. Since the transfer of iron from compartment 3 to compartment 1 or 2 occurs only through the death of immature erythrons, we may immediately write

$$\dot{X}_{3,1}(t) + \dot{X}_{3,2}(t) = -\frac{1}{I_2}\int_{u=0}^{T}\int_{s=0}^{u} q(s)r(s)\,X_2(t - u + s)\,ds\,dP(u). \tag{3}$$

Transfer out of compartment 4 occurs only through the death of circulating erythrocytes, of age necessarily greater than T. Since we allow no acquisition of iron by erythrocytes, the total amount of iron contained in all of them aged $T + s$ at time t is $\dot{X}_{3,4}(t - s)$. Thus, for the transfer out of compartment 4, we find

$$\dot{X}_{4,1}(t) + \dot{X}_{4,2}(t) + \dot{X}_{4,5}(t) = -\frac{1}{P(T)}\int_{s=0}^{t-T} \dot{X}_{3,4}(t - s)\,dP(T + s).$$

Finally, we write for the net transfer rate into compartment 4

$$\dot{X}_4(t) = \dot{X}_{3,4}(t) + \frac{1}{P(T)}\int_{s=0}^{t-T} \dot{X}_{3,4}(t - s)\,dP(T + s). \tag{4}$$

Assuming that net transfer out of compartments 3 and 4 occurs immediately and only upon death of erythrons, the steady-state conditions imply that each component of that net transfer is proportional to the total transfer out of the appropriate compartment due to erythron death. That is, there are constants, α_1, α_2, β_1, β_2, β_5, all between zero and unity, such that

$$\begin{aligned} \dot{X}_{3,i}(t) &= \alpha_i[\dot{X}_{3,1}(t) + \dot{X}_{3,2}(t)], && i = 1, 2 \\ \dot{X}_{4,j}(t) &= \beta_j[\dot{X}_{4,1}(t) + \dot{X}_{4,2}(t) + \dot{X}_{4,5}(t)], && j = 1, 2, 5. \end{aligned} \tag{5}$$

THE FUNDAMENTAL EQUATION

We proceed now to establish an equation relating the measured functions, X_1, X_4, X_m, and the functions, q, r, P.

For the net transfer rate into compartments 2 and 3, we have

$$\dot{X}_2(t) + \dot{X}_3(t) = \dot{X}_{1,2}(t) + \dot{X}_{4,2}(t) - \dot{X}_{2,1}(t) - \dot{X}_{3,4}(t) - \dot{X}_{3,1}(t). \tag{6}$$

If we assume each component of the exchange between compartments 1 and 2 to be governed by first order kinetics, then there are constants k_{12} and k_{21} such that $\dot{X}_{1,2}(t) = k_{12}X_1(t)$ and $\dot{X}_{2,1}(t) = k_{21}X_2(t)$.

These relations enable us to write for equation (6)

$$\dot{X}_2(t) + \dot{X}_3(t) = k_{12}X_1(t) + \dot{X}_{4,2}(t) - k_{21}X_2(t) - \dot{X}_{3,4}(t) - \dot{X}_{3,1}(t). \tag{7}$$

Elimination of $\dot{X}_2(t) + \dot{X}_3(t)$ between equation (7) and the differentiated form of equation (1) yields

$$k_{21}X_2(t) + \dot{X}_{3,1}(t) + \dot{X}_{3,4}(t) - \dot{X}_{4,2}(t) = k_{12}X_1(t) - \frac{1}{c}\dot{X}_m(t) + p\dot{X}_1(t) + b\dot{X}_4(t).$$

Making use of the relation

$$\dot{X}_4(t) = \dot{X}_{3,4}(t) - \frac{1}{\beta_2}\dot{X}_{4,2}(t),$$

obtained using equation (5), we find

$$k_{21}X_2(t) + \dot{X}_{3,1}(t) + (1 - \beta_2)\dot{X}_{3,4}(t) = f(t), \tag{8}$$

where

$$f(t) = k_{12}X_1(t) - \frac{1}{c}\dot{X}_m(t) + p\dot{X}_1(t) + (b - \beta_2)\dot{X}_4(t).$$

Note that $f(t)$ contains only measured functions and their derivatives, as well as some yet undetermined constants. Obtaining $\dot{X}_{3,1}(t)$ from equations (5) and (3) and $\dot{X}_{3,4}(t)$ from equation (2), we write equation (8) as

$$k_{21}X_2(t) - \frac{\alpha_1}{I_2}\int_{u=0}^{T}\int_{s=0}^{u} q(s)r(s)\,X_2(t - u + s)\,ds\,dP(u)$$
$$+ (1 - \beta_2)\frac{P(T)}{I_2}\int_{s=0}^{T} q(s)r(s)\,X_2(t - T + s)\,ds = f(t). \tag{9}$$

For convenience of notation, let us now define three operators, Ω_1, Ω_2, and Ω, by the relations

$$\Omega_1[g(t)] = \frac{P(T)}{I_2}\int_{s=0}^{T} q(s)r(s)g(t - T + s)\,ds$$

$$\Omega_2[h(t)] = h(t) + \frac{1}{P(T)}\int_{u=0}^{t-T} h(t - u)\,dP(T + u)$$

$$\Omega[g(t)] = \Omega_2\{\Omega_1[g(t)]\}.$$

By virtue of equation (2), we may write

$$\dot{X}_{3,4}(t) = \Omega_1[X_2(t)],$$

and by virtue of equation (4), we may write

$$\dot{X}_4(t) = \Omega_2[\dot{X}_{3,4}(t)] = \Omega[X_2(t)].$$

Applying the operator, Ω, to equation (9) and changing the order of integration yields

$$k_{21}\dot{X}_4(t) - \frac{\alpha_1}{I_2}\int_{u=0}^{T}\int_{s=0}^{u} q(s)r(s)\dot{X}_4(t - u + s)\,ds\,dP(u)$$

$$+ (1 - \beta_2)\frac{P(T)}{I_2}\int_{s=0}^{T} q(s)r(s)\dot{X}_4(t - T + s)\,ds = \Omega[f(t)]. \qquad (10)$$

This is the fundamental equation, relating X_1, X_4, X_m to q, r, P, and the constants k_{21}, k_{12}, α_1, β_2, c, b, p, and I_2.

The measured functions appear in equation (10) in differentiated form, undesirable for numerical work, but the derivatives may be eliminated by integrating by parts a portion of $\Omega[f(t)]$ and then integrating equation (10) with respect to t.

SPECIAL FORMS

Various specializations may be made of equation (10), corresponding to various conjectures about the process described. If $P(s)$ is constant for $T \leq s \leq T_1$ (that is, no extramedullary hemolysis involving Fe^{59} occurs in the system before time T_1), then $\Omega[X_2(t)] = \Omega_1[X_2(t)]$, for $t < T_1$, so that the right-hand side of equation (10) involves only a linear combination of integrals of $r(s)q(s)$ against known (measured) functions. Of course, in this case, we may set $\beta_2 = 0$.

If α_1 is taken to be zero (that is, all iron released by intramedullary hemolysis goes into compartment 2), a significant simplification results. In fact, this with the foregoing specialization removes the function, P, from consideration except for the one value, $P(T)$.

If β_2 is taken to be unity (all iron released by extramedullary hemolysis goes into compartment 2), then some simplification results, the last term on the left-hand side of equation (10) vanishing.

The simplest form of our model occurs when we assume no extramedullary hemolysis involving Fe^{59} during the period of interest, and $\alpha_1 = \beta_2 = 0$. These assumptions lead to the equation

$$k_{21}\dot{X}_4(t) + \frac{P(T)}{I_2}\int_{s=0}^{T} q(s)r(s)\dot{X}_4(t - T + s)\,ds = \Omega_1[f(t)], \qquad (11)$$

where

$$\Omega_1[f(t)] = \frac{P(T)}{I_2}\int_{s=0}^{T} q(s)r(s)[k_{12}X_1(t - T + s) - \frac{1}{c}\dot{X}_m(t - T + s)$$

$$+ p\dot{X}_1(t - T + s) + b\dot{X}_4(t - T + s)]\,ds.$$

An alternate form of equation (11) is obtained by integration with respect to t, change of order of integration, and slight rearrangement:

$$X_4(t) = \frac{P(T)}{I_2 k_{21}} \int_{s=T-t}^{T} q(s)r(s)\Big\{k_{12} \int_{u=0}^{t} X_1(u - T + s)\, du - \frac{1}{c}[X_m(t - T + s) - X_m(0)] + p[X_1(t - T + s) - X_1(0)] + (b - 1)X_4(t - T + s)\Big\}\, ds.$$

We used the fact that $X_4(0) = 0$. It is also true that $X_2(0) = X_3(0) = 0$. Hence, from equation (1), $[1/c]X_m(0) = pX_1(0)$. Using this, factoring k_{12}, and setting $q(s)r(s) = R(s)$, we finally obtain

$$X_4(t) = \frac{P(T)k_{12}}{I_2 k_{21}} \int_{s=T-t}^{T} R(s)\Big\{\int_{u=0}^{t} X_1(u - T + s)\, du - \frac{1}{ck_{12}}\Big[X_m(t - T + s) - \frac{X_m(0)}{X_1(0)} X_1(t - T + s)\Big] + \frac{b - 1}{k_{12}} X_4(t - T + s)\Big\}\, ds. \tag{12}$$

It is clear we cannot obtain directly from equation (12) the individual constants k_{12}, k_{21}, etc., or the function $R(s)$. Rather, only certain combinations may be determined, such as

$$\frac{P(T)k_{12}}{I_2 k_{21}} R(s), \quad \frac{b - 1}{k_{12}} \quad \text{and} \quad \frac{1}{ck_{12}}$$

(or, what is the equivalent, p/k_{12}). However, results of other biological experiments may be used to advantage in resolving the individual parameters. For instance, if the sacral hematocrit is known, from equation (12) we may expect to determine p, b, k_{12}, c and $P(T)R(s)/k_{21}I_2$. Further, since erythrocyte life-span and the total iron in circulating hemoglobin may be found independently, we may normalize that ratio, obtaining $P(T)R(s)$ itself. Similarly, independent observations of the iron content of single erythrocytes and iron uptake rates may be used in determining or verifying individual parameters of the model. These procedures will be discussed in a future report of computational experience with the model.

THE FUNCTIONS q AND r

Turn now to specification of a parametric form for $R(s)$, with the expectation of determining the parameters from equation (12). Assume that each erythron of given age has proceeded along a single path of development. Also, assume the existence of certain distinguished erythron ages, $\tau_1, \tau_2, \cdots, \tau_{m-1}$ with $\tau_1 < \tau_2 < \cdots < \tau_{m-1}$, when and only when cell division occurs. We take $\tau_0 = 0$ and $\tau_m = T$. This permits the specification of the proliferation function, q, as

$$q(s) = q(0)2^j, \qquad \tau_j \leq s < \tau_{j+1}, \qquad j = 0, 1, 2, \cdots, m - 1.$$

Little is known of the function, r, describing the rate of iron uptake, except for rough estimates of average behavior. Most information about r comes from radioautographic studies in which, of course, it is impossible to follow a cohort of erythrons, although that is precisely the kind of information we require. It is natural, in this state of ignorance, to seek shelter in simplicity and assume r constant over each intermitotic interval, with each mitosis occurring instantaneously. More complicated assumptions on r may become appropriate in later computations as knowledge of the uptake rates increases, but for the present we make use of the simple form of r as a first approximation, recognizing that this approximation may not be biologically exact.

With that approximation, there are constants r_j, such that

$$r(s) = r_j, \qquad \tau_j \leq s < \tau_{j+1},$$

and consequently,

$$R(s) = q(0)2^j r_j, \qquad \tau_j \leq s < \tau_{j+1}, \qquad j = 0, 1, 2, \cdots, m - 1.$$

For fixed τ_j, this specification of R, results in equation (12) containing $m + 2$ independent parameters:

$$\frac{P(T)k_{12}q(0)}{I_2k_{21}} r_j, \frac{b - 1}{k_{12}}, \text{ and } \frac{p}{k_{12}}.$$

As is evident, these parameters appear in a quadratic rather than a linear way. However, if the functions, X_1, X_4, X_m, are sufficiently well determined by measurements, a straightforward application of minimization techniques allows the determination of all those parameters. Such computations are presently in progress, with definite prognosis of success, and will be reported in the future with a discussion of expected error and the sufficiency of available data. Of course, the biological significance of the parameters so determined depends on the validity of our assumptions.

WEAKENING THE RESTRICTIONS

The most fundamental restriction on our model is expressed in the assumption of a steady state. Eliminating this restriction would necessitate dependence of most of the quantities we have defined on the iron content of each compartment. Of course, we can construct such a model. Unfortunately, almost nothing is known about how the iron content of the various compartments would influence the system, and, therefore, it seems that the analysis of such a system is presently impossible. We shall retain the steady-state restriction in the following.

The restriction to a closed system is unnecessary, provided that any entrance or exit of iron occurs only through the plasma or storage compartments. A review of our derivations will reveal that neither derivation nor result is affected by loss or gain of iron through compartments 1 or 5. This means, in particular, that a hypothesis of an instantaneous injection of radioactive iron is too restrictive. The present model

is valid also; *e.g.*, for constant infusion of radioactive iron. The same remark shows that the model is valid for arbitrary exchange between compartments 1 and 5 and other, unspecified compartments, such as extracellular, extravascular fluid space.

We have also excluded any acquisition of iron by circulating erythrons, whether or not mature. Presumably, such acquisition would occur directly from plasma. To accommodate it, we extend the range of definition of the uptake rate function, r, and the proliferation function, q, beyond erythron age, T, so as to include the age of the longest surviving erythrocyte, say to age, T'. Then the net rate of increase of Fe^{59} in compartment 4 will include the term $\dot{X}_{1,4}(t)$ where

$$\dot{X}_{1,4}(t) = \frac{X_1(t)}{I_1} \int_T^{T'} r(s)P(s)q(s)\, ds. \tag{13}$$

Since $X_1(t)$ is known (measured), the inclusion of $\dot{X}_{1,4}(t)$ and the subsequent application to it of the operator, Ω, offers no additional difficulty. In practice, one would replace the constant factor of $X_1(t)$ by a single constant, say, k_{14}, to be determined from the measurements.

Direct acquisition by maturing erythrons from plasma also may be included, simply by adding the term $\dot{X}_{1,3} = X_1/I_1 \int_0^T r(s)P(s)q(s)\, ds$. The remarks concerning $\dot{X}_{1,4}$ also apply here. The inclusion of $\dot{X}_{1,3}$ results only in replacing the k_{12} of our fundamental equation by $k_{12} + k_{13}$, where

$$k_{13} = 1/I_1 \int_0^T r(s)P(s)q(s)\, ds.$$

Extramedullary erythropoiesis may be included in our model by adding another compartment, 6, with transfer into compartment 4 and transfer out of compartment 1. The inclusion of these two extra transfers and their rates, $\dot{X}_{1,6}(t)$ and $\dot{X}_{6,4}(t)$, offers no new difficulty, but rather more of the old difficulties. Namely, functions q, r, and P relating to the process in compartment 6 would be required, and the integral expressions corresponding to those for compartment 3 would be introduced. Note that in these new expressions, $X_1(t)$ plays the role of $X_2(t)$. Thus, the application of the operator, Ω, is straightforward. It follows that the fundamental equation would reflect the additional process simply by the inclusion of appropriate terms, depending on the additional q, r, and P. Several different types of extramedullary erythropoiesis could be included in a similar way. We note that if a new compartment between compartments 1 and 6 were required to play a role like that of compartment 2, then the kind of derivation we used to obtain the fumdamental equation would no longer be applicable.

Finally, we deal with the assumption that erythrons pass into circulation only at age, T. Let us assume, rather, that the entry of erythrons into the circulation is governed by some distribution, say $\tilde{P}$, where $\tilde{P}(s)$ is the probability that an erythron passes into the circulation before age, s. We then accommodate this assumption in our model by using, instead of expressions involving T, the expected value of those

expressions with respect to the distribution, $\tilde{P}$. Such expected values greatly complicate the model, and if both P and $\tilde{P}$ are unknown and to be determined from the model, even the most sanguine analyst might be dismayed.

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