AN ERYTHRON-DEPENDENT MODEL OF IRON KINETICS

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ABSTRACT The mathematical model here presented of steady-state iron kinetics in the human explicitly displays the influence of the maturative and proliferative behavior of erythrons (erythrocytes or their precursory cells). Based on a compartmented iron kinetics scheme, the model is in the form of a system of linear integrodifferential equations and describes the distribution of administered radioactive tracer as a function of time. Erythron behavior is characterized by three functions specifying iron uptake, proliferation, and survival. Simulative uses of the model are discussed and illustrated by an example.

INTRODUCTION

This paper presents a mathematical formulation of steady-state iron kinetics of the human blood and blood-forming system. The formulation or model describes the distribution in the body of administered tracer iron (Fe^{59}) so as to make evident the influence of maturation and proliferation of erythrocytes and their precursors, the erythropoietic cells. For both types of cells I use the collective term erythron.

These erythrons play a central role in iron metabolism and iron kinetics, but earlier mathematical models of iron kinetics ignore their detailed behavior (Huff and Judd, 1956; Pollycove and Mortimer, 1961; Sharney et al., 1963). A more recent paper (Garby et al., 1963) provides for very restricted consideration of the erythron. My model described here explicitly reflects the essential details of erythron maturative and proliferative behavior. The result is only a description of iron kinetics that is more accurate than previous ones, but a unified description as well, one which offers the opportunity to investigate the behavior of erythron itself. I have presented a special case of the new model, chosen and modified for use with certain radioiron tracer procedures (Nooney, 1965, referred to in the following as IK), and we have indicated the use of simulative computations in connection with both the special case and the general model; the general model and its specializations are parts of a more extensive theory of age-dependent cellular processes, also applicable, for instance, to neutrophil kinetics (Nooney, 1964).

In the paper presented here, I establish the general iron-kinetics model as a system of integrodifferential equations based on a compartmented iron-kinetics

system. This model is compatible with all observed erythropoietic and hemolytic mechanisms, as well as with most plausible conjectured mechanisms. The generality, accuracy of representation, and novelty of the model are provided by allowing the erythron to influence intercompartmental transfers explicitly and naturally.

I discuss application of the model and illustrate its use in an example.

DEFINITIONS AND ASSUMPTIONS

This section departs but slightly from the corresponding parts of IK, where more detail is provided. In accordance with previous models (especially that of Pollycove and Mortimer, 1961), I assign iron in the blood system to six mutually exclusive compartments. For convenience in reference, I shall use the term erythrocyte for both circulating reticulocytes and erythrocytes, reserving the term erythropoietic cells for the erythropoietic cells of the marrow. The six compartments are (*a*) iron in circulating erythrocytes, (*b*) iron in plasma, (*c*) iron in noncirculating erythropoietic cells, (*d*) bone-marrow iron, (*e*) iron in storage as ferritin, and (*f*) iron in storage as hemosiderin. The bone-marrow iron, which constitutes the labile marrow pool introduced by Pollycove and Mortimer (1956), may include iron compounds on the exterior membranes of erythropoietic cells or the ferritin of certain observed reticular cells (Bessis and Breton-Gorius, 1957). The ferritin and hemosiderin storage may be considered as short- and long-term storage, or as labile and reserve storage, respectively, according to evidence presented by Pollycove and Mortimer (1961). The definition of these six compartments may be made unique by defining them maximally and in the order given. I shall ignore other iron in the body, regarding the six compartments as being a closed system with regard to tracer, except for the introduction of tracer.

The following transfers between compartments are permitted. As we shall see, some of these transfers may be omitted, according to the demands of individual physiology or prejudice. Erythrons may enter the circulation with their iron. Upon the destruction of an erythrocyte or of an erythropoietic cell, its iron may go into ferritin storage, plasma, or bone marrow. Iron in bone marrow may go into plasma or erythropoietic cells; iron in plasma may go into ferritin storage, erythrocytes, or bone marrow. Iron in ferritin storage may go into plasma or hemosiderin storage; iron in hemosiderin storage may go only into ferritin storage. My system has the form shown in Fig. 1, where the arrows denote directed transfers. The number below each compartment will be used to identify that compartment.

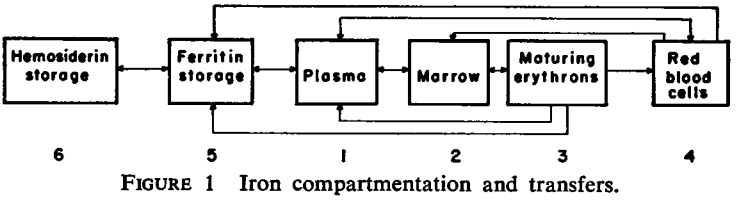

FIGURE 1 Iron compartmentation and transfers.

I shall assume the system to be in a steady state, in which the amount of iron in each compartment and the rate of each transfer are constant. Since I later introduce a probability distribution, a more precise and correct statement of the steady-state assumption is that the expected amount of iron in each compartment and the expected rate of each transfer remain constant. Note that this does not exclude certain disease states. The requirements for and the implications of the steady-state assumption have been discussed elsewhere (Sharney et al., 1963; and Sheppard, 1962).

Let us measure the age of an erythron from the time its earliest progenitor began iron accumulation, and let us assume for each steady state that the pertinent erythron behavior depends on age alone. Define $P(s)$ to be the probability of survival to age s of an erythron and its descendents along a particular branch of their genealogical tree. Thus, if an erythron has divided only once before age s, $P(s)$ is the probability of survival to age s of each daughter. Define $q(s)$ to be the number of erythrons of age s if no erythron death were to occur; define $r(s)$ to be the rate of iron acquisition by an erythron of age s. We allow r to assume negative values to account for conceivable iron loss, 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 instant of division. We set $R(s) = q(s)r(s)$. We further assume that erythrons pass into the circulation at the fixed age T.

Suppose administration of Fe^{59} into plasma is begun at time $t = 0$. We assume injection of isotope to occur instantaneously at $t = 0$, but our considerations are not restricted to this mode of isotope administration. Of course, the underlying steady state of the system is assumed to be undisturbed by the addition of isotope. Denote by I_j the constant amount of iron in compartment j. Denote by $x_i(t)$ the amount of radioactive iron in compartment i at time t, by $\dot{x}_i(t)$ the derivative of $\dot{x}_i(t)$ with respect to t, and by $\dot{x}_{i,j}(t)$ that portion of $\dot{x}_i(t)$ due to transfer from compartment i to compartment j. Some of these symbols will be used also to denote expected values of the corresponding quantities with respect to the probability function P. We assume six of the transfers to be of first order on the basis of chemical and tracer kinetics. That is, we assume the existence of constants k_{ij} such that

$$\dot{x}_{1,2}(t) = k_{12}x_1(t), \qquad \dot{x}_{5,1}(t) = k_{51}x_5(t),$$
$$\dot{x}_{2,1}(t) = k_{21}x_2(t), \qquad \dot{x}_{5,6}(t) = k_{56}x_5(t),$$
$$\dot{x}_{1,5}(t) = k_{15}x_1(t), \qquad \dot{x}_{6,5}(t) = k_{65}x_6(t).$$

Note that these transfers are physiologically independent of erythron behavior.

A prime requirement for the validity of the assumed first-order relations is the homogeneity of tracer iron relative to total iron in each compartment appearing on the right sides of those relations. This requirement is probably satisfied for compartments 1 and 2, but its satisfaction may be doubtful for the storage compartments 5 and 6. Thus the foregoing first-order transfers from storage compartments

must be regarded only as approximations to the true form of those transfers. More precise formulations of these transfers must take into account the specific mechanisms of storage and retrieval and will depend on the history as well as the amount of stored material. Since our present concern is with the influence of the details of erythron behavior on iron kinetics, we postpone consideration of storage details.

Some further comments are necessary, relative to the ferritin and hemosiderin compartments and their transfers. We shall treat those compartments as labile and reserve storage, respectively, although such correspondence has not been rigorously established. It is natural then to require that reserve iron pass through the labile stage before further participation in the system. That hemosiderin is physiologically associated with ferritin and the iron of ferritin is more readily available for the synthesis of hemoglobin (Bell et al., 1961) supports such treatment. Our use of the ferritin-hemosiderin nomenclature is an attempt to specify the composition of the storage compartments, which otherwise are identified only functionally. The considerations that follow are not influenced by that nomenclature.

DERIVATION OF THE EQUATIONS

The steady-state condition implies that a constant fraction of the iron made available through the death of erythrons is transferred to each compartment. Thus, there are constants α_i and β_i, all between zero and unity, such that

$$\begin{aligned} \dot{x}_{3,i}(t) &= \alpha_i[\dot{x}_{3,1}(t) + \dot{x}_{3,2}(t) + \dot{x}_{3,5}(t)], \\ \dot{x}_{4,i}(t) &= \beta_i[\dot{x}_{4,1}(t) + \dot{x}_{4,2}(t) + \dot{x}_{4,5}(t)], \end{aligned} \quad \text{for} \quad i = 1, 2, 5.$$

It follows, of course, that $\alpha_1 + \alpha_2 + \alpha_5 = \beta_1 + \beta_2 + \beta_5 = 1$.

At any time, the rate of transfer of iron from compartment 2 to erythropoietic cells in compartment 3 is

$$k_{23}(T) = \int_{s=0}^{T} P(s)R(s)\, ds.$$

Therefore

$$\dot{x}_{2,3}(t) = \frac{k_{23}(T)}{I_2}\, x_2(t).$$

Similarly,

$$\dot{x}_{1,4}(t) = \frac{k_{14}(T)}{I_1}\, x_1(t),$$

where

$$k_{14}(T) = \int_{s=T}^{\infty} P(s)R(s)\, ds.$$

An erythropoietic cell in compartment 3 reaching age u at time t was age s at

time $t - u + s$. Therefore, if no death were to occur, the amount of radioactive iron in all such cells of age u at time t would be

$$C_2(u, t) = \frac{1}{I_2} \int_{s=0}^{u} R(s)x_2(t - u + s)\, ds.$$

Taking into account the probability of death, we write

$$\dot{x}_{3,4}(t) = P(T)C_2(T, t),$$

$$\dot{x}_{3,i}(t) = -\alpha_i \int_{u=0}^{T} C_2(u, t)\, dP(u), \quad \text{for} \quad i = 1, 2, 5.$$

An erythrocyte of age u at time t entered the circulation at time $t - u + T$ and was age s at time $t - u + s$. Therefore, if no death of erythrocytes were to occur, the amount of radioactive iron in all erythrocytes of age u at time t would be $C_2(T, t - u + T) + C_1(u, t)$, where the term

$$C_1(u, t) = \frac{1}{I_1} \int_{s=T}^{u} R(s)x_1(t - u + s)\, ds$$

represents radioactive-iron acquisition in the circulation. Again taking into account the probability of death, we write

$$\dot{x}_{4,i}(t) = -\beta_i \int_{u=T}^{\infty} [C_2(t, t - u + T) + C_1(u, t)]\, dP(u), \quad \text{for} \quad i = 1, 2, 5.$$

We have now furnished expressions for all nonzero transfer components.

For initial injection of Fe^{59} into plasma, the sought system of integrodifferential equations is

$$\dot{x}_i(t) = \sum_j \dot{x}_{j,i}(t) - \sum_j \dot{x}_{i,j}(t), \quad \text{for} \quad i, j = 1, 2, \cdots, 6. \tag{1}$$

Owing to the conservation of isotope, these equations contain only five independent x_i. For example, the first of these equations is

$$\begin{aligned}\dot{x}_1(t) = {} & -(k_{12} + k_{15} + k_{14}(T)/I_1)x_1(t) + k_{21}x_2(t) + k_{51}x_5(t), \\ & - \frac{\alpha_1}{I_2} \int_{u=0}^{T} \int_{s=0}^{u} R(s)x_2(t - u + s)\, ds\, dP(u) \\ & - \frac{\beta_1}{I_2} \int_{u=T}^{\infty} \int_{s=0}^{T} R(s)x_2(t - u + s)\, ds\, dP(u) \\ & - \frac{\beta_1}{I_1} \int_{u=T}^{\infty} \int_{s=T}^{u} R(s)x_1(t - u + s)\, ds\, dP(u). \end{aligned} \tag{2}$$

Since these equations are linear in the x_i, we may assume the normalized initial conditions $x_1(0) = 1, x_i(0) = 0$, where $i = 2, 3, \ldots 6$.

If another mode of isotope introduction is used (e.g., infusion), with the rate of

introduction given by $f(t)$, then we must add $f(t)$ to the right-hand side of the equation for $\dot{x}_1$ and change the corresponding initial condition to $x_1(0) = 0$.

DISCUSSION

Equations (1) uniquely define functions x_i if the rate parameters and erythron-behavior functions are given and physiologically acceptable (finite erythrocyte life span and piecewise continuous R and P, for instance). The proof may be made as a slight extension of the classical Picard-Lindelöff proof for ordinary differential equations; that proof shows that the solution of equations (1) may be obtained by successive approximations or by stepwise integration (Bieberbach, 1926). Thus, these equations may be used in the simulating of iron kinetics or, what is perhaps more important, in the testing of conjectures about erythron behavior. The conjectures must specify the erythron-behavior functions used in the model, but some parameters might be determined in the usual way, by fitting the model to experimental data. In a previous paper (IK) I have described a method for the calculation of the erythron-behavior functions from such data. The present model verifies the calculation by allowing reproduction of the data if the calculated erythron-behavior functions are correct.

Extensions of the model are immediately obvious. For instance, acquisition of iron from plasma by noncirculating erythrons could be accommodated by defining an extra iron-uptake function. The restriction to a fixed erythron-maturation time could be relaxed by introducing a stochastic maturation time; this would require replacement of all expressions involving T by their expected values, and would require also, as a referee has observed, the extension of my steady-state assumption to imply steady expected state of the system with respect to this additional stochastic variable. Such extensions complicate, but do not prohibit, calculation and simulation with the model.

For those who, like myself, are unsatisfied with storage participation in this model, an alternative approach is available. The function x_1 has been measured for many subjects with various hematological disorders (e.g., Pollycove and Mortimer, 1956, 1961; Sharney et al., 1963; Gevirtz et al., 1965). If x_1 is taken as known from these measurements, then a review of equations (1) reveals that the explicit appearance of x_5 and x_6 may be suppressed and that attention may be confined to x_2, x_3, x_4, and the known x_1. Such a procedure reduces the dimensions of the problem from 5 to 3.

EXAMPLE

Equations (1) have been implemented by a general and efficient computing machine program, SBLOOD, written by Thomas Mahan (1966) of the Lawrence Radiation Laboratory. The results given in the following example were obtained with that program.

To illustrate application of the model, we have used equations (1) to calculate some effects of differences in severity and timing of intramedullary hemolysis. For this purpose we chose a system with $k_{15} = 0$, $\alpha_1 = 1$, and for $s > T$, $R(s) = 0$ and $P(s) =$ constant, so that storage plays no role in isotope distribution, all isotope released by intramedullary hemolysis is transferred to plasma, and erythrocytes neither acquire isotope nor release it by death in the time period considered. We set $T = 5$ (days), a plausible maturation period (Harris, 1963), and specified $k_{12} = 9.21$, $k_{21} = 0.131$ (days^{-1}), and $I_2 = 84.9$ (mg). The last three values, apparently hematologically acceptable, are mean values for 13 normal subjects as obtained by Pollycove and Mortimer (1961). The mean daily delivery of 21.4 mg of iron to compartment 4 was taken from the same source. The iron uptake rate R was taken as linearly decreasing to zero at 5 days and was adjusted for each hemolytic situation to yield that same daily delivery. The four cases considered were then distinguished by the following hemolytic behavior: a 10% (case I) and a 50% (case II) hemolysis of erythropoietic cells midway in their maturation period, and a 10% (case III) and a 50% (case IV) hemolysis of erythropoietic cells at the end of their maturation period. More precisely, $P(s)$ was specified as continuous and composed of three linear segments for each case:

$$\text{Case I.} \qquad P(s) = \begin{cases} 1 & s < 2.5 \\ 0.9 & s > 2.6 \end{cases}$$

$$\text{Case II.} \qquad P(s) = \begin{cases} 1 & s < 2.5 \\ 0.5 & s > 2.6 \end{cases}$$

$$\text{Case III.} \qquad P(s) = \begin{cases} 1 & s < 4.9 \\ 0.9 & s > 5 \end{cases}$$

$$\text{Case IV.} \qquad P(s) = \begin{cases} 1 & s < 4.9 \\ 0.5 & s > 5 \; . \end{cases}$$

It should be emphasized that none of the values used is known to be physiologically correct. Indeed, some were obtained with models that I have implied are faulty. I use these values only in an illustrative sense.

The calculated proportion in plasma of injected isotope as a function of time after injection is displayed for each case in Fig. 2 or Fig. 3. The most striking feature of the curves shown is the obvious departure from convexity (the appearance of bumps) in Fig. 3. Gevirtz and coworkers (1965) showed that such aberrations occur in the plasma curves of normal subjects; they attributed this to ineffective erythropoiesis and hemolysis. Our simple example suggests that if this phenomenon is due to the hemolysis of erythropoietic cells, then that hemolysis probably occurs late in the maturation period. A comparison of Fig. 3 with the data of Gevirtz further

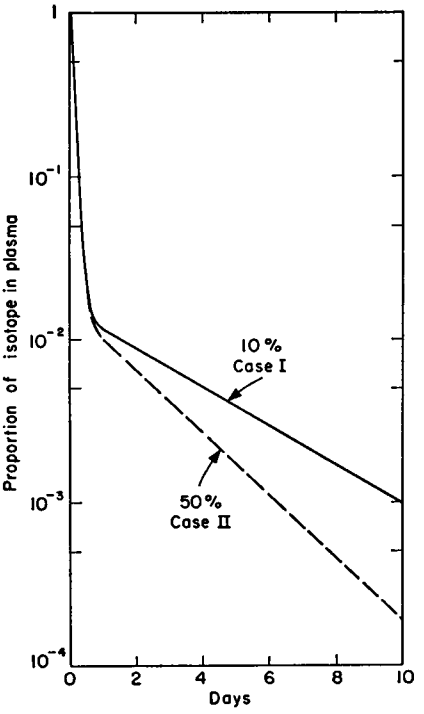

FIGURE 2 Proportion of isotope in plasma; hemolysis of 10% and 50% at erythrone age 2.5 days.

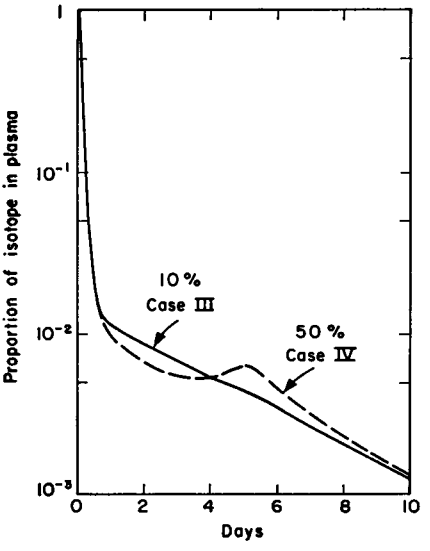

FIGURE 3 Proportion of isotope in plasma; hemolysis of 10% and 50% at erythrone age 4.9 days.

suggests that such hemolysis results in the death of 10 to 50% of the erythropoietic cells that would otherwise reach maturation.

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