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ABSTRACT

The author discusses the marurative and proliferative behavior of the erythroid series and presents a mathematical model describing that behavior in terms of iron kinetics. Computational experience with the model is summarized.

A discussion of the maturative and proliferative behavior and age distribution of the leukocyte series then is followed by the description of a new mathematical model of leukocyte kinetics. Simulation using the model and other means is suggested.

MODELS OF BLOOD CELL PROLIFERATION

This paper discusses two models of blood cell proliferation and kinetics in the human. The first model concerns the red blood cells or erythrocytes. For the benefit of the uninitiated, and to the possible amusement of the cognoscenti, I shall sketch my version of the physiological or biological processes involved in red blood cell kinetics. Then we shall have a glimpse of a mathematical model of those processes, followed by a discussion of the use of the model. As is customary with the mathematicians, a generalization is provided. The second model concerns certain of the white blood cells, the granulocytes. Here, my version of the pertinent physiological processes may be more contentious, but we proceed with a similar presentation and discussion of the model.

Our models of erythrocyte and granulocyte kinetics have a striking resemblance in their proliferation description, but diverge widely in other aspects. We shall indicate the reasons for the similarity and the difference.

I shall not give detailed reference citations for my assertions about the physiological foundations of the processes to be described, but rather cite in a general way [1, 2, 3]* for erythrocyte kinetics and [3, 4, 12] for granulocyte kinetics.

The components, circulation, and function of blood have long been objects of intense interest to medical workers, the blood being one of the most pervasive yet easily observed of bodily constituents. Many disorders are reflected in or caused by aberrations in blood composition and behavior, and it is to a better understanding of these aberrations that we address our considerations.

*Bracketed numbers in the text refer to the appended list of references.

Almost all cells of the body breathe, requiring oxygen for that respiratory function, and the task of oxygen transport to the tissues is fulfilled almost exclusively by the red blood cells. Indeed, these cells seem to have no other significant role. The transport mechanism employed depends mechanically on blood circulation through the lungs and tissues and chemically on the oxidation and reduction properties of hemoglobin, the red cell constituent which imparts the red color. Hemoglobin, a protein of modest molecular weight, contains heme, which in turn contains iron. It is by means of this iron that the oxidation and reduction process occurs.

We believe that every cell of the body contains iron; yet the total amount of iron outside the red blood cells and their production system is less than one per cent of all iron in the body. It appears, then, that the study of iron kinetics might be equivalent, in a sense, to the study of red blood cell kinetics. This, in fact, is the case, and our red blood cell model is an iron kinetics model.

Our main interest in this kinetic model will be to identify and quantitatively determine the influences due to the proliferation, maturation, and death of red blood cells and their precursors.

To this end, let us first examine the physiological distribution of iron in the blood and blood-forming system (Fig. 1). Iron occurs in the peripheral circulation in the hemoglobin of red blood cells and in the transferrin of plasma. There are also various iron storage depots outside the blood, such as in liver and spleen, where the iron is mostly bound in ferritin and hemosiderin. Finally, iron is present in significant amounts in the bone marrow, where the red blood cells are made. Marrow iron appears in various bound forms in a pool available for immediate incorporation into maturing red blood cells and appears also in hemoglobin after such incorporation. We divide the three main physiological iron locations into five compartments according to Pollycove and Mortimer [5], as shown in Fig. 2, where we have provided estimates for the

iron content of each compartment and have assigned a number to each compartment. Plasma is compartment 1; marrow production stores, 2; maturing red blood cells, 3; mature, circulating red blood cells, 4; and storage, 5. We shall refer to red blood cells, particularly the immature, as erythrons.

The body seems to take extreme care to conserve iron, and the iron released from hemoglobin is almost wholly reutilized. This process occurs as follows. The iron of plasma circulates through the bones and becomes part of the marrow production store, from where it is incorporated into maturing erythrons. After a maturation period of about five days, the erythron is released into the circulation as a red blood cell, carrying its incoporated iron. After living about four months, the red blood cell dies and its iron is released to be immediately fixed in a plasma-borne compound. The iron continues this cycle, indicated by the heavy arrows of Fig. 3. Other iron transfers occur. There is a constant exchange between plasma and ferritin storage, as well as between ferritin and hemosiderin storage. Plasma iron is thought to exchange continuously with the marrow production pool, and there may be some direct incorporation of plasma iron into erythrons. These transfers are shown in Fig. 3. The remaining transfers occur through the death of erythrons of various ages. Upon the death of an immature erythron, its iron is thought to go mainly back into the marrow production store, although some may return to plasma. Upon the death of a circulating red blood cell, its iron is thought to go mainly to plasma, but part may go into the marrow pool or into storage. Allowing for all these possible transfers results in all the arrows of Fig. 3.

A technique for the study of the system pictured in Fig. 3 is furnished by the use of radioactive tracers. If an injection is made of suitably bound Fe^{59} into plasma, parts of the subsequent Fe^{59} distribution may be observed. Blood samples may be taken at various times, the red blood cells and plasma separated, and their radioactive iron content determined. Bone marrow aspirations may be examined. External monitoring of the radioactivity of certain organs

may be conducted. Usually, one looks in this way at liver, spleen, and sacrum. These observations are shown in Fig. 4, where we have indicated also that the liver and spleen observations yield a measure of radioactivity of the storage pool together with a certain contribution from circulating blood. Likewise, the sacrum observation yields a measure of radioactivity in the marrow together with a contribution from circulating blood. This relation of the external monitoring observations to our compartments was first noted by H. S. Winchell of Donner Laboratory. Unfortunately, too little is known about the precise role of liver and spleen in our system, and we shall neglect their observations. Results of bone marrow examinations will likewise not be included.

Let us now assume the iron kinetics system described to be in a steady state, by which we mean that the iron content of each compartment is constant. Suppose an injection of Fe^{59} is made at time $t = 0$. Let $X_i(t)$ be the amount of Fe^{59} in compartment i at time t. Then our observations yield values for $X_1(t)$ and $X_4(t)$, as well as values for a function $X_s(t)$, related to our compartmental variables by the equation

$$X_s(t) = C[X_2(t) + X_3(t)] + C'[X_1(t) + X_4(t)],$$

where C and C' are constants. This, and the rest of the formal development of the model, will appear in detail [6].

Functions descriptive of erythron behavior may be defined, enabling us to translate the pertinent biological and chemical processes into the relations

$$X_2(t) + X_3(t) = \Phi_1(X_1, X_2, X_4; t) \qquad (1)$$

$$\frac{dX_4(t)}{dt} = \Omega[X_2(t)], \qquad (2)$$

where Φ_1 and Ω contain the erythron behavior functions. The function X_2 plays the central role in equations (1) and (2). The relation of X_s to the compartmental variables allows us to eliminate X_3 from (1), obtaining

$$X_s(t) = \Phi_2(X_1, X_2, X_4; t). \qquad (3)$$

The operator Ω may be regarded as an observation operator, transforming an inaccessible function into an observable one, or as a simulation operator, yielding system response (here, red blood cell radioactivity) for given input (marrow pool radioactivity). Applying the operator Ω to X_s as given by (3), we write

$$\Omega[X_s(t)] = \Omega[\phi_2(X_1, X_2, X_4; t)]. \quad (4)$$

Judicious definition of the erythron behavior functions results in a linear operator Ω and a ϕ_2 which is linear in X_1, X_2, and X_4. It follows that the relation (2) permits the elimination of X_2 from (4), and we obtain

$$\Omega[X_s(t)] = \phi_3(X_1, X_4; t), \quad (5)$$

which contains the erythron behavior functions and only the observed of our compartmental variables. We may write (5) somewhat more explicitly as

$$X_4(t) = \Phi(qr, P; X_1, X_4; t), \quad (6)$$

where q, r, and P are functions of erythron age describing erythron proliferation, iron acquisition, and survival, respectively. I rather pretentiously call (6) the fundamental equation of the system. Note that q and r appear only in the product qr. Their separate introduction occurred heuristically in my original derivation of the model.

As was evident during my description of the physiological and biological foundations of the model, there remain many important, unanswered questions about erythrons and their development. Some of these questions are: How long does an erythron mature? How many erythrons die prematurely, and when? How many mitoses has a mature erythron experienced? What is the rate of iron uptake by erythrons at various ages? Is there destruction of unsatisfactory mature erythrons soon after entry into the circulation? These questions are all basic to a precise understanding of erythron development, and I believe the present model and its extensions can furnish the answers. We expect data insufficiencies to limit the degree of determination of the functions involved,

but even in that event we expect the model to be useful in the choice between conflicting conjectures about erythron behavior. That is, the model will be used in the simulation of consequences of various conjectures.

The fundamental equation (6) relates to a general model. Fortunately, various specializations may be made which are easier to examine and which represent reasonable biological systems. The simplest form of (6) which still interests is obtained by considering the following special case of iron kinetics. We assume that no mature, circulating red blood cells containing radioactive iron will die during the period of observation. In view of the established, normal life span of about 120 days, such an assumption seems warranted for a normal patient observed for a period of, say, two weeks. We further assume that erythron maturation takes precisely T days, at which age the erythron is released into the circulation. The final simplifying assumption is that all radioactive iron released by the death of immature erythrons returns directly to the marrow pool. These assumptions result in the system shown in Fig. 5. The fundamental equation corresponding to this system is

$$X_4(t) = K\,P(T)\int_{s=0}^{T} r(s)q(s)\left\{\int_{u=0}^{t} X_1(u - T + s)\,du + A\left[X_s(t - T + s) - \frac{X_s(0)}{X_1(0)}X_1(t - T + s)\right] + B\,X_4(t - T + s)\right\} ds. \quad (7)$$

The constant K contains two constant transfer rates and the size of the marrow-iron pool; the constants A and B contain a constant transfer rate and two parameters depending on patient anatomy and observation geometry. The value P(T) is the probability of erythron survival to age T, and r(s)q(s) is the rate of iron uptake by all erythrons of age s.

If the functions X_1, X_4, and X_s are sufficiently well-measured, the fundamental equation (7) for the special case offers the possibility of computing a function proportional to rq, under rather weak restrictions on that function. Combining this with other data not directly included in our model permits the calculation of the important function r itself. Mr. J. Borges of the Lawrence Radiation Laboratory has undertaken such calculations and has obtained good results. The procedure is to determine the various constants and the function rq, of a particular form, so as to best satisfy (7) at the times of observation, in the least-squares sense. The particular form for rq is derived from the assumption of a fixed number of doubling mitoses experienced by each erythron and a function r which is constant over each intermitotic interval.

Preliminary calculations with data from each of five normal patients yield results which are in good agreement both among themselves and with independent experiments.

Detailed quantitative results together with associated independent data will appear in the future. We are able now to offer the following tentative conclusions with regard to normal subjects. Erythron maturation takes five days, apparently via three mitoses about one day apart, the last occurring at three days. The iron uptake rates over the intermitotic intervals and over the final, non-dividing phase are about in the ratio of 100:37:19:6. We are now trying to evaluate P(T), which gives the probability that an erythron reaches maturity.

Our next task will be to find observed subjects with certain erythroid disorders not violating the assumptions of our special case, then to derive the corresponding numbers for comparison.

As I have hinted, data insufficiencies limit the resolving power of the model. However, these difficulties may be alleviated simply by making more intense observations of X_1, X_4, and X_s over longer periods, and this offers little technical difficulty. Already, we have been able to define periods of exceptional interest, and expect the corresponding observational emphasis to be made in the near future.

You will have noticed that the fundamental equation (6) does not include the storage compartment or compartments. Several blood disorders are reflected in the storage function and pools. It is for this reason that the full kinetic model is considered [7]. This full model contains too many parameters to determine with presently available data unless, perhaps, more precise liver and spleen functions can be identified. Thus, now it is regarded primarily as a simulation tool, by means of which the consequences of specified erythron behavior and iron transfers may be examined. Our full kinetic model has the form of a system of integro-differential equations,

$$\dot{X}_1 = L_1(X) + \alpha G + \beta H, \qquad \dot{X}_4 = -H + M,$$

$$\dot{X}_2 = L_2(X) + \gamma G + \delta H, \qquad \dot{X}_5 = L_5(X) + \epsilon H,$$

$$\dot{X}_3 = L_3(X) - G + M, \qquad \dot{X}_6 = L_6(X),$$

$$M(t) = \frac{P(T)}{I} \int_{s=0}^{T} q(s)r(s)\, X_2\,(t - T + s)\, ds,$$

$$H(t) = -\int_{s=0}^{t-T} M(t - s)\, dP(T + s),$$

$$G(t) = \frac{1}{I} \int_{u=0}^{T} P(u) \int_{s=0}^{u} q(s)r(s)\, X_2(t - u + s)\, ds\, dP(u).$$

Initial conditions on the X_i are $X_i(t) = 0$ for $t \leq 0$, but $X_1(0) = 1$. We have included a compartment 6 for long-term (hemosiderin) storage. The subscripted L represent linear homogeneous forms in the X_i with constant coefficients. It is clear that with all constants specified and the functions q, r, and P given in some reasonable way, the full kinetic model is a computable

system. Its use as a simulator is thus possible. Moreover, it is the only complete, mathematical model of iron kinetics explicitly including erythron behavior. Comparison may be made, for instance, with the models of [5, 8-11].

Let us now consider a model of white blood cell or leukocyte kinetics. We shall confine attention to the granulocyte series within the leukocyte classification and, strictly speaking, we consider only neutrophils among the granulocytes. The granulocyte proliferates and matures in the bone marrow, whence the mature granulocyte enters the blood, dispersing throughout the body in the performance of its functions. There is disagreement as to these functions, but the phage or scavenger function seems well established. Fig. 6 gives a closer look at the travels of the granulocyte. The words of Fig. 6 joined by arrows are compartment names; the arrows represent transfer of granulocytes. The cells in question remain in the marrow after maturation in a reserve whence they enter the blood apparently without regard to age. The blood is viewed principally as a transport mechanism, by which granulocytes reach the tissues of the body. There is probably a continuous exchange between granulocyte populations in the blood, on one hand, and in the reserve or tissues on the other hand. We have divided the extramedullary parts of the body, other than the blood, into three types: tissue, where granulocytes perform their major functions; storage, where granulocytes simply await the call to function; and the lung, where both tissue and storage behavior is evidenced. The lung further acts as an excretory mechanism for whole, apparently viable granulocytes, which is indicated by the horizontal arrow leaving the lung of Fig. 6. A granulocyte may reside temporarily in each compartment and ultimately may have occupied all compartments. Whether granulocytes tend to die at a particular age is an open question, as is whether they have a definite life span in any compartment except marrow. Upon the death of a granulocyte anywhere in the body except in marrow, the components are broken down chemically and diluted in the comparatively vast material reservoirs of the body.

Details of granulocyte growth are hinted in Fig. 7. These cells proliferate in the marrow by the usual process of cell division, undergo there a maturation period during which no cell division occurs, and finally go into the reserve pool of the marrow, presumably remaining until required elsewhere. We must admit the possibility of granulocyte death at any point in the marrow. Death in the marrow may be followed by reutilization of fairly large and complex sub-units of the cell, such as certain genetic material, DNA (deoxyribonucleic acid), or purine.

Also shown in Fig. 7 is the mechanism of transfer into tissue. Such transfer from the blood seems to occur as a result of granulocytes' adhering to capillary walls and then finding their way through those walls. All transfers involving blood are thought to employ the same mechanism.

A means for investigating the kinetics of the granulocyte processes sketched is again the use of radioactive tracers. The favored tracers are P^{32} in $DP^{32}F$ (diisopropylfluorophosphate) or H^3 in tritiated thymidine. Both of these radioactive substances are incorporated in DNA within the granulocyte during each of its premitotic phases. DNA synthesis apparently ceases in the cell just prior to its last division, and there seems to be no DNA loss in the mature cell. Thus, if the granulocyte is properly exposed to these radioactive compunds during its proliferative phase, it will acquire a constant, life-time label. The foregoing remarks suggest that granulocyte kinetics may be equivalent, in sense, to granulocyte DNA kinetics, and we shall actually consider a model of DNA tracer kinetics.

Observation of process dynamics here is more difficult than in the case of erythrocytes. Since both erythrocytes and platelets, as well as granulocytes, have acquired tracer by DNA synthesis, a complete separation of cells must be accomplished for meaningful observation. This restricts consideration at present to marrow samples and blood samples, giving a measure of DNA radioactivity in a mixture of unknown proportions of the three marrow compartments

and a measure of DNA radioactivity in blood granulocytes.

At this point, we might consider what sort of questions might be asked of a mathematical model based on the physiological processes described. Those questions include significant ones about proliferation: How long does a cell reside in the proliferation compartment? How many mitoses are undergone by cells? How many cells die in the proliferation compartment? How many cells are delivered to the maturation compartment? None of the answers are known with acceptable accuracy and precision. Similar obvious questions might be posed in reference to the other marrow compartments and, particularly if the appropriate transfer rates are age-dependent, similar questions might be posed in reference to all other compartments. Here, answers occur less frequently and usually appear as qualitative conjectures.

The important disease called leukemia emphasizes some of these questions. Granulocytic leukemia [13] is usually characterized as a disorder in the proliferation or elimination of granulocytes, resulting in excessive concentration of those cells in the blood, with consequent massive cellular infiltration of organs and impairment of function. However, some variants of granulocytic leukemia display no increase of granulocytes in the blood, but rather a more or less subtle change in age distribution. I think these variants indicate not only proliferative disorder, but also distributional or transfer disorder other than elimination. Transfer disorders and strange age distributions may be characteristic of all granulocytic leukemias. For that reason, I believe it of interest and perhaps of use that a mathematical model of granulocyte kinetics explicitly contain granulocyte age dependencies. The model must, of course, include the proliferative behavior of the granulocyte.

Let us assume the described granulocyte system to be in a steady state, by which we mean that the total amount of DNA contained in granuloytes of each age is to be constant in each compartment. That is, the total amount of DNA held by granulocytes of a particular age in a particular compartment may depend

on that age and compartment, but does not depend on time. It does not necessarily follow that the number of granulocytes of each age be constant in each compartment, but we shall include such constant age distribution as part of our steady-state definition. It may be suggested that the leukemic state is not a steady state. We hope that the steady-state description will suffice for short periods, especially for the slowly developing, chronic leukemias. For the purpose of convenience in presentation, let us assume also that there is no significant reutilization of the labelling isotope.

We may then construct a model along the following lines to describe the tracer kinetics after an intravenous injection of $DP^{32}F$. Define a plasma compartment, and call the plasma, proliferation, and maturation compartments 1, 2, and 3, respectively. The isotopic compound enters plasma and is incorporated into the DNA of the proliferation compartment. The labelled DNA then is transferred to the maturation compartment. We assume that a granulocyte spends a fixed time in each of compartments 1 and 2. If $X_i(t)$ again denotes the amount of tracer in compartment i at time t, then we may write, in strict analogy to the erythrocyte model,

$$\begin{aligned} &\dot{X}_1(t) = -k\, X_1(t), \\ &\dot{X}_2(t) = k\, X_1(t) - \dot{X}_{23}(t), \\ \text{and} \quad &\dot{X}_3(t) = \dot{X}_{23}(t) - P(T_2)\, \dot{X}_{23}(t + T_1 - T_2), \\ \text{where} \quad &\dot{X}_{23}(t) = P(T_1) \int_{s=0}^{T_1} r(s) q(s)\, X_1(t - T_1 + s)\, ds. \end{aligned} \tag{8}$$

The quantity k is a transfer rate, constant by virtue of our steady-state assumption. We have used again the designations P, q, and r to reinforce the similarity with the erythrocyte model. Naturally, P, q, and r now refer to granulocytes and r to the acquisition of P^{32} instead of Fe^{59}. The similarity between our models, expressed in $\dot{X}_{23}$, is, of course, shared by all systems involving the transfer of material gradually collected from a compartment by elements at an age-dependent rate.

Our models must now diverge one from the other, for although erythrocyte age distribution was completely determined by the function P, this is no longer true for the granulocytes. Simple survival is not the single governing factor, since age-selective transfers may occur from elsewhere than the proliferation and maturation compartments.

Define compartment 4 to be the marrow reserve and compartment 5 to be the blood. Let $X_i(t, s)$ be the amount of P^{32} in cells of age $s + T_1 + T_2$ in compartment i at time t. Then we may write for compartment 4 the equations

$$\frac{\partial X_4(t,s)}{\partial t} = - \frac{\partial X_4(t,s)}{\partial s} - [p(s) + a(s)]\, X_4(t,s) + b(s)\, X_5(t,s), \quad (9)$$

$$\frac{\partial X_4(t,0)}{\partial t} = P(T_2)\, \dot{X}_{23}(t - T_2 + T_1) - [p(0) + a(0)]\, X_4(t,0) + b(0)\, X_5(t,0), \quad (10)$$

$$X_4(t,0) = 0, \text{ for } t \leq T_1 + T_2. \quad (11)$$

Here $a(s)$ is the rate of transfer of a cell of age $s + T_1 + T_2$ from compartment 4 to compartment 5; $b(s)$ is the similar transfer rate from 5 to 4; and $p(s)$ is the rate of death of cells of age $s + T_1 + T_2$ in compartment 4. Equation (9) holds for $s > 0$ and gives the rate of change with time of $X_4(t,s)$ as the contributions of aging in compartment 4, death in 4, loss to 5, and gain from 5. Equation (10) is the same as equation (9) for $s = 0$, except that aging is replaced by the influx from compartment 3.

Note that the relations (10) and (11) define an ordinary differential-difference equation for the function $X_4(t,0)$ with given initial conditions. The solution of that differential-difference equation then provides initial values for the solution $X_4(t,s)$ of the partial differential equation (9). Of course, equations similar to (9), (10), and (11) are to be written for each extramedullary compartment. This yields a system of equations for all the $X_i(t)$ and $X_i(t,s)$.

Any talk of solution of the system of equations presumes that all constants and functions other than the X_i are known, whereas those constants and functions and the X_i represent precisely the information we wish to derive from the model. With data from only the tracer observations I have mentioned, it would be futile to try to calculate the desired information directly from the model. However, there remains the possibility of simulation, in which the model would yield a calculated response to specified rate functions. This calculation of system response to assumed values for parametric functions I call indirect simulation. It is the kind of simulation mentioned in reference to our full erythron kinetics model, and seems to furnish the only fruitful approach with our granulocyte age-distribution model.

Another type of simulation is possible, however, and I unimaginatively call it direct simulation. Direct simulation involves a more or less idealized imitation of the process simulated, usually with particular attention to process effects on individual elements. In view of the complex form of the granulocyte model suggested in equations (8), (9), (10), and (11), I propose complementing the use of that model in indirect simulation by a direct simulation of granulocyte kinetics. The direct simulation will involve following the travels of individual granulocytes (or their DNA) through the various compartments of our system, individual behavior in each instance being determined by some set of random variables. The distributions of those random variables are, of course, determined by the specification of the process parameters we have mentioned. Following a large number of cells in this way yields information about system behavior as a whole. Questions of sufficient statistics arise, but their importance is minimal, since any indications of system behavior furnished by the direct simulation may be subjected to detailed scrutiny by our indirect simulation. Thus, the direct simulation will be used as a guide for the indirect simulation.

One hopes to point out in this way probably fertile areas of medical experiment. Eventually, such experiments may lead to sufficient observational data to permit determination of system parameters through our model.

# # # # # # # #

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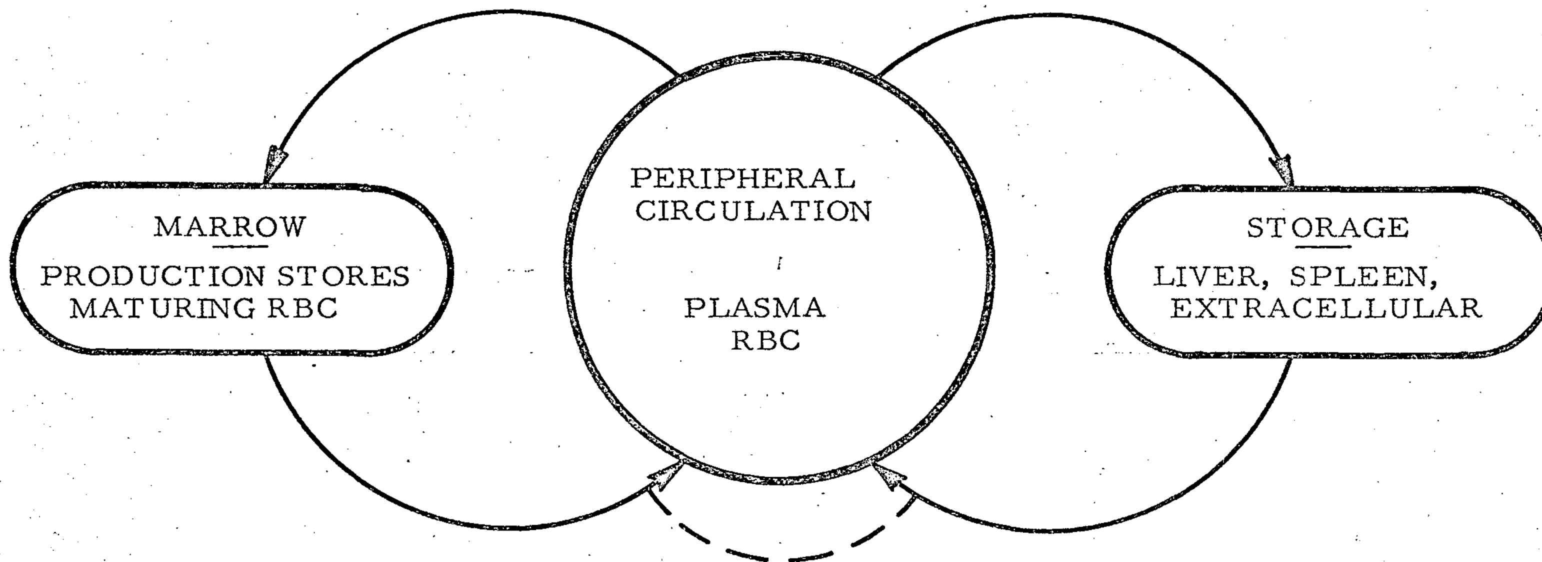

Fig. 1. Physiological iron distribution.

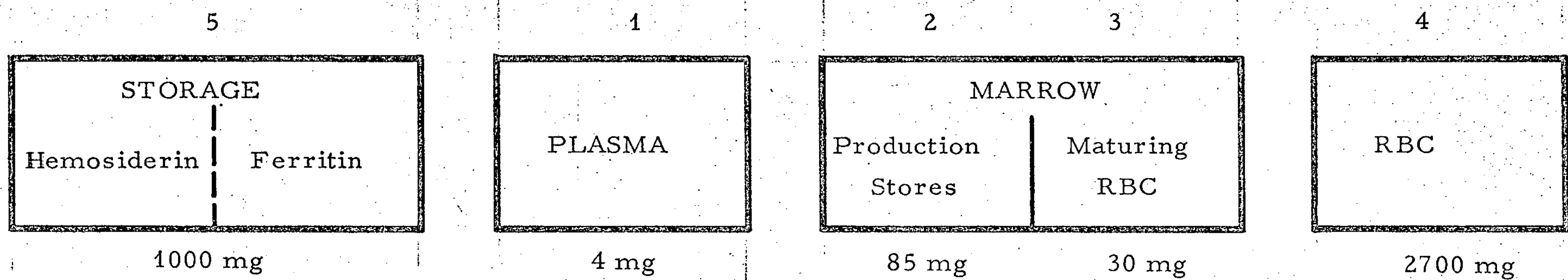

Fig. 2. Iron compartmentation.

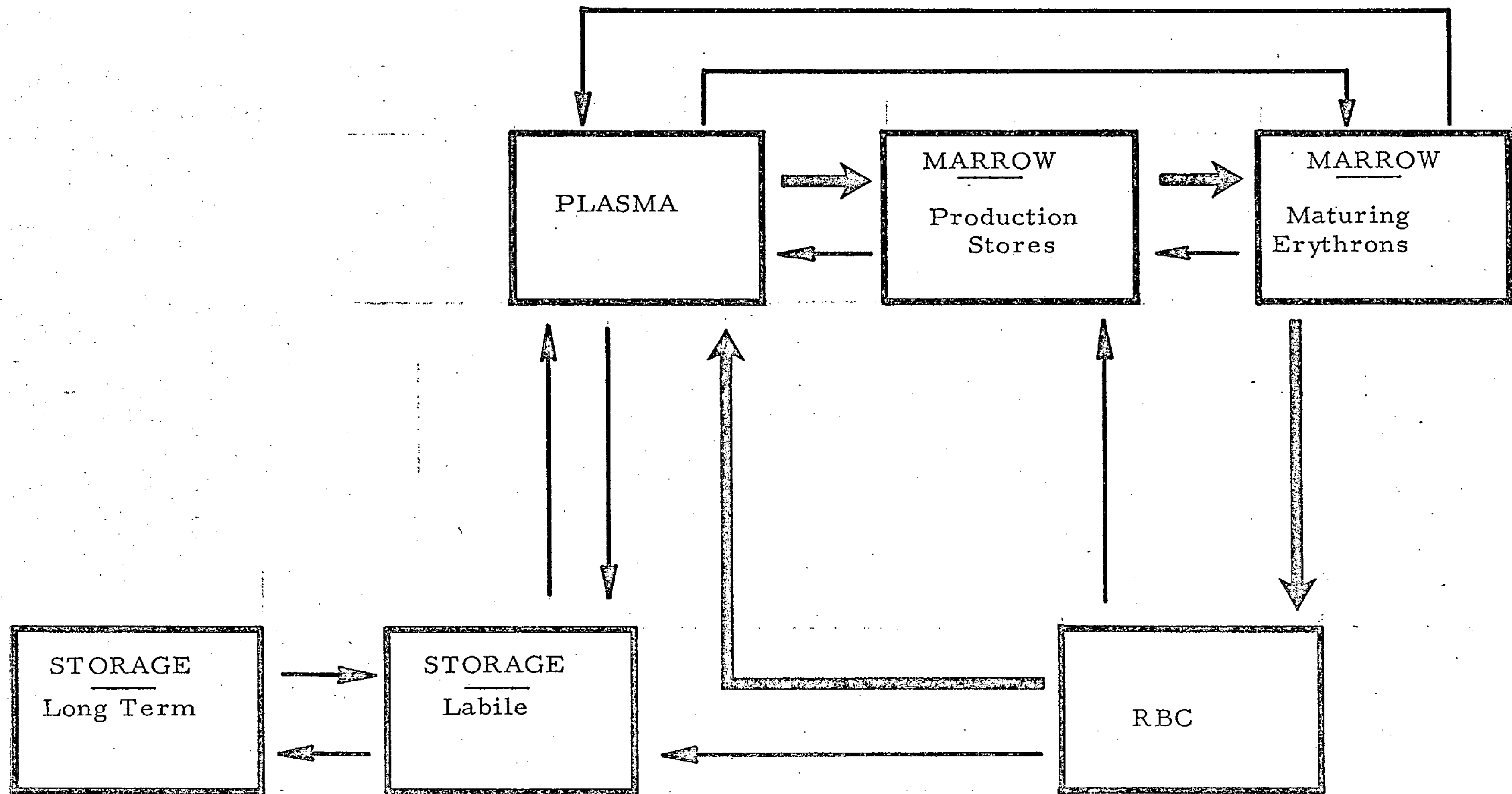

Fig. 3. Iron transfers.

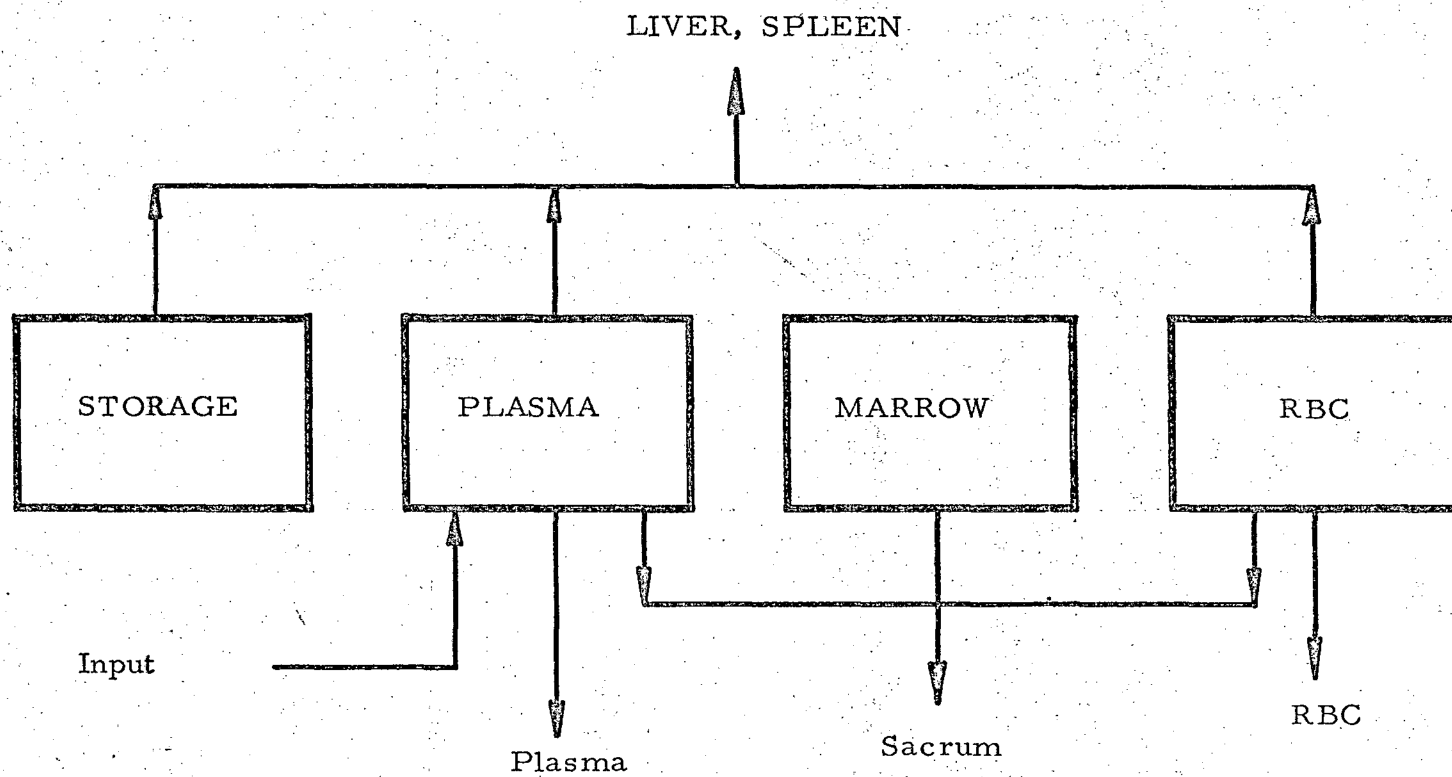

Fig. 4. Tracer observations.

Fig. 4

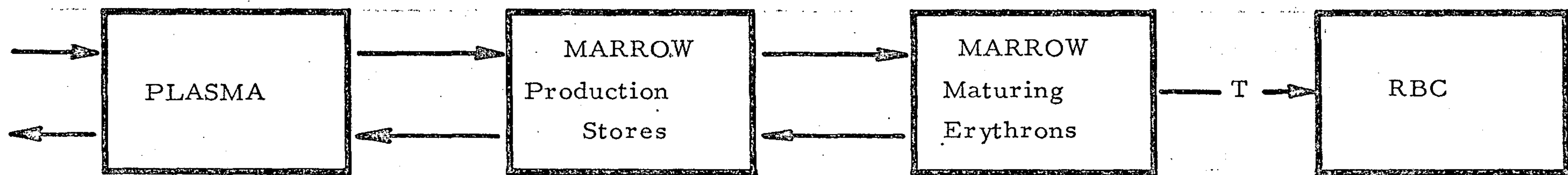

Fig. 5. A special case.

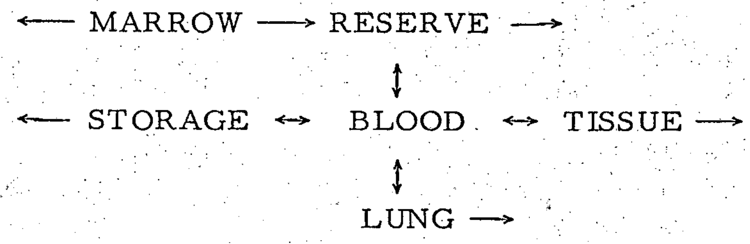

Fig. 6. Granulocyte kinetics.

MARROW

PROLIFERATION → MATURATION → RESERVE ↔ BLOOD

BLOOD ↔ CAPILLARIES ↔ TISSUE

Fig. 7. Kinetic details.