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DYNAMIC REGULATION OF ERYTHROPOIESIS: A COMPUTER
MODEL OF GENERAL APPLICABILITY

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January 1979

(ASD)
APOLLO SYSTEMS DEPARTMENT

GENERAL ⟨ge⟩ ELECTRIC

HOUSTON, TEXAS	TECHNICAL INFORMATION RELEASE	TIR 741-LSP-9005

FROM		TO	
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DATE 2/2/79	WORK ORDER REF:	WORK STATEMENT PARA: NAS9-15487	REFERENCE:

SUBJECT	DYNAMIC REGULATION OF ERYTHROPOIESIS: A COMPUTER MODEL OF GENERAL APPLICABILITY

This report presents a detailed description of
the model of erythropoiesis regulation developed and
improved under previous contract (see TIR 741-MED-4012,
TIR 782-MED-6004, and TIR 782 LSP-7012). In addition
to the mathematical description, the study documents
several simulation studies of altitude hypoxia, infu-
sion polycythemia and hemolytic anemia, thereby demon-
strating validity of the model for general human
application in health and disease. A theoretical anal-
ysis of the overall control system is also presented
including: a) dynamic and steady-state responses,
b) sensitivity analysis to determine relative importance
of parameters and their influence on model behavior, and
c) properties of the model as a proportional controller,
including steady-state errors and feedback effectiveness.

J. I. Leonard, Ph.D.

Attachment
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ASD 4028

DYNAMIC REGULATION OF ERYTHROPOIESIS: A COMPUTER MODEL OF GENERAL APPLICABILITY

By

Joel I. Leonard

ABSTRACT

A mathematical model for the control of erythropoiesis has been developed based on the balance between oxygen supply and demand at a renal oxygen detector which controls erythropoietin release and red cell production. Feedback regulation of tissue oxygen tension is accomplished by adjustments of hemoglobin levels resulting from the output of a renal-bone marrow controller. Special consideration was given to the determinants of tissue oxygenation including evaluation of the influence of blood flow, capillary diffusivity, oxygen uptake and oxygen-hemoglobin affinity. A theoretical analysis of the overall control system is presented including: a) dynamic and steady-state responses, b) sensitivity analysis to determine relative importance of parameters and their influence on model behavior, c) properties of the model as a proportional controller, d) analysis of steady-state errors, and e) effectiveness of feedback regulation. Computer simulations of altitude hypoxia, red cell infusion hyperoxia, and hemolytic anemia demonstrate validity of the model for general human application in health and disease.

INTRODUCTION

Systems analysis has been shown to be a highly useful technique for understanding complex physiological processes, especially those under feedback control (Riggs, 1970). The systems analysis approach, as used here, involves integrating the primary physiological mechanisms, both those that are known and those postulated, into a single framework - a mathematical model - which represents the system under study. Computer simulations performed with these models often reveal theoretical inconsistencies, model refinements, new hypotheses, the design of new experiments or the format for reprocessing existing data.

The control of erythropoiesis is amenable to a modeling approach as demonstrated by a variety of investigators. These models have ranged from conceptual, qualitative feedback schemes (Fisher, et al, 1975; Erslev, 1975) to more detailed mathematical descriptions (Hodgson, 1970), some of which have led to computer simulation models (Mylrea & Abbrecht, 1971; Guyton, et al, 1972). Quantitative models have been developed for different aspects of erythropoiesis regulation including ferrokinetic models (Cavill & Ricketts, 1974; Berzuini, et al, 1978), and those describing the control of stem cell production (Mackey, 1978; Lajtha, 1962; Kretchmar, 1966).

A limited number of models are available which integrate the entire feedback circuit in sufficient detail to permit quantitative simulation of a diversity of hematological stresses directly affecting oxygen transport, tissue oxygenation, erythropoietin release, and red cell production. Hodgson (1970) has proposed such a model, but apparently has not implemented it for computer use nor performed the studies necessary for validation. An algorithm capable of predicting red cell mass changes by feedback processes was coupled to a much larger model of circulatory and fluid control (Guyton, et al, 1972), but it provided only a gross representation of the renal-bone marrow axis and failed to recognize renal oxygenation as a major control element. The most complete simulation model previously developed is that of Mylrea and Abbrecht (1971) which was validated for a single stress - altitude hypoxia in mice. No study presently exists of a fully documented model suitable for general human application.

The model proposed in this study has incorporated some of the best features of the three models discussed in the last paragraph and has extended them to include the following unique capabilities: a) a more realistic representation of renal tissue oxygenation, b) explicit representation of a large number of physiologically meaningful parameters to facilitate hypothesis testing and simulation of a large number of stress situations, c) an adjustable affinity of oxygen for hemoglobin, d) validated simulations of the human response, and e) computer software designed for non-expert user convenience including conversational mode of operation on remote terminals with graphic capability. While our original objective was to formulate a model to examine the loss of circulating red cell mass in astronauts returning from spaceflight (Kimzey, et al, 1976; Leonard, 1975), the present version has developed into a model of more general applicability. A model claiming to represent the overall control of erythropoiesis should be capable of simulating behavior to a wide variety of normal hematological stresses and pathological disorders. It is the purpose of this study to describe the model, review its limitations, demonstrate its diverse capability, and examine some of the control system characteristics of erythropoiesis regulation.

GENERAL MODEL DESCRIPTION

The model which forms the basis of this study was formulated to investigate the relative influence of the controlling factors of erythropoiesis on total red cell mass. Elements in the feedback regulation loop which have been incorporated into the model are shown schematically in Figure 1. The formulation was based on the generally accepted concept that the overall balance between oxygen supply and demand regulates the release of a hormone, erythropoietin, from renal tissues sensitive to oxygen tension levels and that this substance in turn controls bone marrow red cell production (Adamson & Finch, 1975; Fisher, et al, 1975; Jacobson, et al, 1957).

The amount of oxygen delivered to the tissue is accounted for in the model by the combined influence of several factors: hemoglobin concentration, lung oxygenation of hemoglobin, blood flow and oxygen-hemoglobin affinity (Finch & Lenfant, 1972). From this amount of oxygen, a certain fraction is extracted by the tissue depending on the oxygen demand parameter. Oxygen enters the cellular spaces by diffusion along an oxygen tension gradient between the venous capillaries and the cell (Hodgson, 1970). Decreasing the oxygen supply in relation to the demand reduces tissue oxygen tension which is, in effect, monitored by a local oxygen detector (Beutler, 1969) and results in increased rates of erythropoietin release (Krantz and Jacobson, 1970). Erythropoietin is released into the general circulation and its final plasma concentration is determined by its rate of release, volume of distribution and the rate at which it is metabolized (Reismann, et al, 1965), the latter being represented in the model by the hormone plasma half-life. The target organ for erythropoietin is the bone marrow. The production rate and release of red cells in the model is determined by the plasma erythropoietin concentration (Van Dyke & Pollycove, 1962). A time delay exists between marrow stimulation and red cell release (Harris & Kellermeyer, 1970). Splenic destruction of cells is represented in the model by a life-span parameter. Hemoglobin concentration in blood is based on the addition of new cells to existing cells and plasma.

In terms of control system theory (Milhorn, 1966) the controlled system includes the elements of redistribution of new cells, lung oxygenation, blood

transport and tissue oxygen extraction, while the controller system consists of erythropoietin release, marrow red cell production and splenic destruction. The hematocrit (or hemoglobin level) may be considered to be the primary feedback quantity and the level of tissue oxygenation can be taken as the directly controlled variable.

It is known that red cell production is modulated by factors other than those considered here. These include iron levels (Finch, et al, 1971), hormones other than erythropoietin (Peschle, et al, 1975), neural stimulation (Baciu, 1970), as well as inhibitors and activators of erythropoietin (Gordon & Zanjani, 1970). While it may be desirable to include these effects in future model applications, quantitative information regarding them is presently lacking or the need for their inclusion is not yet warranted. It is also important to note that overall oxygen transport is under the control of homeostatic mechanisms other than the erythropoiesis system. Thus, some of the fixed parameters of the model such as blood flow, capillary diffusivity, arterial oxygen tension, plasma volume and oxy-hemoglobin affinity can be considered variable elements of circulatory, ventilatory, biochemical and fluid regulatory feedback mechanisms which are beyond the scope of the present model's design objectives. Larger models which incorporate many of these features are available and these have been shown to be compatible with an erythropoiesis subsystem model (Guyton, et al, 1972). While these mechanisms are not included explicitly in the present model, their influence can be tested, in most cases, by known secondary effects on existing model elements.

MATHEMATICAL DESCRIPTION OF MODEL

Oxygenation of Blood

The oxygen concentration of arterial blood (neglecting oxygen dissolved in plasma) following passage through the lungs, can be expressed as the product of the carrying capacity of a gram of hemoglobin ($CHbO$; i.e. 4 moles O_2 per mole Hb), times the hemoglobin concentration (Hb), times the fractional degree of oxy-hemoglobin saturation (S_aO). We have found it convenient to use hematocrit rather than hemoglobin concentration as an index of red cell concentration in blood. These quantities are related by the mean corpuscular hemoglobin concentration, such that MCHC = Hb/Hct. Therefore, for arterial blood:

$$C_aO = S_aO \times Hb \times CHbO = S_aO \times Hct \times MCHC \times CHbO \qquad (1)*$$

At full hemoglobin saturation, $S_aO = 1.0$ and Equation (1) will then represent the maximum oxygen carrying capacity of blood at a given hematocrit. In most instances the parameters MCHC and CHbO will be invarient, so that the arterial oxygen concentration is influenced only by the hematocrit and hemoglobin saturation. In practice, the arterial oxygen tension (P_aO) is assigned a value* and a corresponding value of S_aO is determined from the oxy-hemoglobin equilibrium curve (OEC), an operation which can be expressed in functional form as:

$$S_aO = OEC(P_aO) \qquad (2)$$

Oxygen Delivery at Tissues

Oxygen transport at the tissue level is schematically represented in Figure 2. In the present model the tissue of concern is taken to be the erythropoietin producing cells known to be located primarily within the kidneys. It has been assumed that the oxygen sensor as well as sites of erythropoietin production are responsive to the mean oxygen tension of the

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* See Table I for symbol definition, units and normal values.

kidneys. This assumption permits tissue oxygen tension to be derived from an oxygen balance using blood flows, arterio-venous oxygen concentrations, oxygen consumption and transcapillary diffusion resistances common to the kidneys which are considered to be a homogenous tissue.

The elements of tissue oxygenation were determined using a two-phase model consisting of capillary blood and tissue fluid (Middleman, 1972). It is assumed that the blood compartment is well-mixed with an oxygen partial pressure ($P_v O$) equal to that in the venous outflow. Oxygen diffuses from blood to tissue along a gradient of oxygen partial pressure ($P_v O - P_t O$) where $P_t O$ is the oxygen tension of the homogenous tissue. The amount of oxygen unloaded from the blood is given by the difference in oxygen concentration between arterial and venous blood ($C_a O - C_v O$). At equilibrium the rate of oxygen transfer to the tissues is identical to the tissue oxygen consumption (V_m) as well as the unloading of blood oxygen as determined by the arterio-venous oxygen concentration, that is:

$$\underbrace{Q \times (C_a O - C_v O)}_{\substack{\text{rate of oxygen}\\\text{unloading}}} = \underbrace{K_d \times (P_v O - P_t O)}_{\substack{\text{rate of oxygen}\\\text{diffusion}}} = V_m \qquad (3)$$

where Q is the rate of regional blood flow and K_d is the diffusive transfer coefficient between blood and tissue.

The venous partial pressure may be obtained by solving Equation (3) for $C_v O$,

$$C_v O = C_a O - V_m/Q \qquad (4)$$

then computing venous hemoglobin saturation from a formulation analogous to Equation (1),

$$S_v O = C_v O/(\text{Hct} \times \text{MCHC} \times \text{CHbO}) \qquad (5)$$

and determining $P_v O$ from the OEC, expressed in functional form as:

$$P_v O = \text{OEC}(S_v O) \qquad (6)$$

Tissue oxygen tension can now be derived from Equation (3) as:

$$P_t O = P_v O - V_m / K_d \tag{7}$$

The assumption of steady-state in this formulation implies rapid equilibration of oxygen in the fluid phase and is not meant to suggest a constant tissue oxygen tension during the simulation of an erythropoietic disturbance. Since the erythropoietic process itself has been modeled dynamically (see below), the hematocrit will be time-varying until red cell production achieves its own steady-state. In this model, the hematocrit is, therefore, a major influence on alterations in tissue oxygen tension. In addition, other quantities in this algorithm (i.e. $P_a O$, V_m, K_d, P50, Q) are non-regulatory parameters and can also influence tissue oxygen tension if they are manually altered.

Erythropoietin Production and Distribution

Erythropoietin release is assumed to be governed by the tissue oxygen tension. A limited number of studies (Hodgson, 1970; Mylrea & Abbrecht, 1971; Adamson, 1968; Erslev, 1975) suggest a relationship of the form:

$$\bar{E}_p = E_o \cdot e^{-G_1 \overline{P_t O}} \tag{8}*$$

where $\bar{E}_p$ is the rate of erythropoietin production, $\overline{P_t O}$ is the tissue oxygen partial pressure, G_1 is the gain or slope of the function plotted linearly as $\ln \bar{E}_p$ vs. $\overline{P_t O}$, and E_o is the $\bar{E}_p$-intercept at $\overline{P_t O} = 0$. Setting $E_o = e^{G_1}$, ensures that Equation (8) will always pass through the normal operating point ($\bar{E}_p = 1.0$, $\overline{P_t O} = 1.0$) irrespective of values of G_1. In

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* The bar over the symbols represents normalized values. Thus, $\bar{X} = X/X(o)$, where $X(o)$ is the control or pre-treatment condition and X is a value during the post-control or treatment phase. The use of normalized values simplified comparison of model response with data from various laboratories.

certain cases, it may be desirable to postulate a shift in the normal operating point as well as gain, and in those cases E_o and G_1 may be adjusted separately. Figure 3 illustrates the semi-logarithmic relationship between tissue oxygen tension and erythropoietin production and shows the influence of G_1.

The concentration of erythropoietin in the plasma (E) is a function of the rate of production (E_p), the rate of clearance or destruction (E_d) and the volume of distribution (V_e). If it is assumed that the rate of disappearance is proportional to the plasma concentration (i.e. $E_d = K_e \times E$, where K_e = clearance constant = $\log_e 2$/plasma half-life), then the following first order differential equation can be written for the rate of change of erythropoietin concentration (Reissman, et al, 1965; Mylrea & Abbrecht, 1971):

$$\frac{dE}{dt} = \frac{E_p}{V_e} - K_e E \tag{9}$$

The steady-state concentration of E (at dE/dt = 0) is, therefore,

$$E(o) = E_p(o)/K_e V_e \tag{10}$$

Equation (9) can be normalized by letting $\bar{E} = E/E(o)$ and $\bar{E}_p = E_p/E_p(o)$ and substituting Equation (10) into Equation (9):

$$\frac{dE}{dt} = K_e(\bar{E}_p - \bar{E}) = \frac{\log_e 2}{TE_{\frac{1}{2}}} (\bar{E}_p - \bar{E}) \tag{11}$$

a form which has the advantage of being independent of distribution volume, and further, independent of erythropoietin half-life ($TE_{\frac{1}{2}}$) at steady-state, since $\bar{E}(o) = \bar{E}_p(o)$. The value of $TE_{\frac{1}{2}}$ = 12 hours was chosen for humans, but this does not appear to be well established for normal subjects (Waldman, 1962).

Red Blood Cell Production

An equation expressing the semi-logarithmic dose-response relationship between red cell production (RCP) and erythropoietin concentration (E) can be given as:

$$\overline{RCP} = G_2 \log_e \overline{E} + P_1 \tag{12}$$

As has been the convention, RCP and E have been normalized with respect to their steady-state control values. G_2 is the gain or slope of the response curve and P_1 is the value of $\overline{RCP}$ when $\overline{E} = 1.0$, and is normally taken as unity.

The accuracy of Equation (12) may diminish considerably at very low and very high values of erythropoietin levels. For example, at decreasing values of $\overline{E}$ approaching zero, the production rate tends toward minus infinity rather than zero, while at high $\overline{E}$ values the relationship does not exhibit a maximal production which is known to exist. Therefore, two additional equations were formulated and piecewise fitted to Equation (12) to account for suppressed and maximal erythropoiesis (see Figure 4). Their precise description is somewhat speculative, although this bone marrow function curve closely corresponds to the sigmoid shape of most biological dose-response relationships (Riggs, 1970) and to those observed by others for the bone marrow (Camiscoli & Gordon, 1970; Gurney, 1962; Dunn, et al, 1977).

In the present study it was assumed that there is no basal production of red cells unless erythropoietin is present (i.e. $P_o = 0$). Maximal red cell production is assumed to be six times normal (Mylrea & Abbrecht, 1971) (i.e. $P_m = 6$) and the upper limit of accuracy of Equation (12) was arbitrarily chosen at $\overline{RCP} = 5$.

Iron uptake studies of red cells indicates a bone marrow transit time for red cell production of 3.5 to 4.5 days (Harris & Kellerman, 1970). This effect was included in the model using a simple first-order time delay* with a time constant, T_{BM}. The inclusion of this transit delay clearly improved

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* If Y is the steady-state value predicted from a dose-response relationship, then the response delayed with a time constant, T, is obtained by the solution of the differential equation: $T \, dy/dt + y = Y$. In finite difference form, suitable for iterative computer solution, this becomes: $y_2 = y_1 + (Y - y_1)(H/T)$ where H = integration step size, y_1 = value of y at the ith iteration and y_2 = value of y at i+1th iteration.

the realism of the dynamic response of the model especially following
sudden changes in tissue oxygen tension.

Red Cell Destruction and Red Cell Mass

The life span of the red cell dictates the destruction rate of cells.
A model of red cell destruction was assumed in which cells are destroyed
randomly and none of the cells survive past a given life span (Berlin,
1964). In that case, the rate of destruction,(RCD),is simply proportional
to the amount of cells present at any time. If that amount is given as RCM
then the rate of RBC destruction will be:

$$RCD = K_r \cdot RCM = \log_e 2 \cdot RCM / TRC_{\frac{1}{2}} \tag{13}$$

where $TRC_{\frac{1}{2}}$ = red cell half-life and K_r = red cell clearance constant =
$\log_e 2 / TRC_{\frac{1}{2}}$. At normal values used in the model the rate of red cell
destruction is 1.1% of the total amount present or 22 ml packed cells/day.

The instantaneous change in total circulating red cell mass is the
net difference between red cell production and red cell destruction rates:

$$\frac{d(RCM)}{dt} = RCP - RCD \tag{14}$$

RCP is obtained from Equation (12) using the transformation $\overline{RCP} = RCP \times RCP(o)$
where $RCP(o) = RCD(o) = K_r \cdot RCM(o)$.

Finally, the current value of RCM, obtained by integration of Equation
(14), is combined with the plasma volume to obtain the whole-body hemato-
crit of the circulation:

$$Hct = \frac{RCV}{PV + RCM} \tag{15}$$

and the feedback loop is closed.

Model Operation

The system of Equations (1,2,4-8, 11-15) are solved by computer
simulation using an iterative procedure. Equations (11) and (14) are

integrated numerically using a simple Euler algorithm (Arden & Astill, 1970) and initial conditions $\bar{E}(o)$ and RCM(o), respectively. The program is currently implemented on a Univac 1110 and a PDP 11/40 using Fortran. Remote terminals including graphic display of the simulation responses (and experimental data simultaneously, when desired) have greatly facilitated user interaction, and enhanced convenience of model validation.

Perturbing the model away from its normal steady-state (initial conditions) is accomplished by altering one of the model parameters*. These quantities are normally constant in value, but can be altered during a run to simulate either independent stress stimuli or long term regulatory adjustments. Thus, hypoxia may be simulated by decreasing arterial PO_2 and hemolysis is simulated by decreasing the red cell life span. These and other physiological/clinical situations which the model is capable of simulating, and the major parameters which are involved are summarized in Table II. In some cases, alteration of more than one parameter may be desired in the simulation of altitude hypoxia which involves a primary change in arterial PO_2 and a compensatory shift in oxy-hemoglobin affinity (P50). Parameter values may be time-invariant with values fixed prior to a simulation run or they may be entered as a function which varies with time as the run progresses. Experimental data may be used to drive the model in this fashion. Thus, it is possible to simulate a wide variety of stresses and test a large number of hypotheses regarding regulating mechanisms with this model.

Parameter Estimation

Table I lists the values of the system parameters, chosen as representative of the human system. Also shown are the steady-state control values (i.e. initial conditions) of the major dependent (output) variables. The precise values of most of the quantities shown in Table I are not critical,

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* The term "parameter" is used to denote time-invariant quantities which are not altered by the dynamic properties of the model (i.e., see bullet ended arrows in Figure 1) as opposed to "dependent variables" which are time-varying and form the connecting links of the feedback circuit (i.e., P_tO, E, RCP, Hct, etc.).

however, to the general behavior of the model's response when expressed in percent deviation from control. An exception to this occurs for the highly nonlinear functions such as the oxygen equilibrium curves and the renal and bone marrow function curves. The location of the operating point on these curves can change the nature of the output response. Also, the shape of these curves, as defined by the gains and threshold parameters, are also critical to the magnitude of the response. These will be discussed next.

An equation for the oxygen equilibrium curve was obtained from Aberman, et al (1973). Their study included a computer algorithm that converts oxygen tension to saturation, and with iteration, oxygen saturation to tension. The agreement between measured and computed values is claimed to be better than 0.2%. In addition, the algorithm includes the capability of altering P50 values.

Analysis of Adamson's (1968) data, from which the erythropoietin release function was obtained, leads to an estimated value of G_1 = 2.8. In our simulation studies of bed rest and hypoxia, (Kimzey, et al, 1979; Leonard, et al, 1979) values of G_2 were determined by parameter estimation to range from 2 to 5. No data exists to confirm these estimates directly. It is, therefore, permissible to use the gain factors as adjustable parameters, within reasonable limits, in order to test hypotheses and possibly provide improved agreement between model and experimental data. In addition to the gains or sensitivities, the other parameters of these functions (i.e. E_o, P_o, P_1) which can be thought of as threshold indices are also not well known and are available for parameter estimation during a simulation. Changing these latter quantities implies a shift of the normal operating points (i.e. ($\overline{E_p}=1, \overline{P_tO}=1$), $\overline{RCP}=1, \overline{E}=1$)). The value of K_d was obtained from Equation (7) by dividing the oxygen uptake by the calculated ($P_vO - P_tO$). P_tO was arbitrarily assumed to be 20 mm Hg and P_vO was computed from Equations (1,2 and 4-6).

CONTROL SYSTEM PROPERTIES OF MODEL

Sensitivity Analysis

The effect of the model parameters on the overall behavior of the response can be demonstrated by sensitivity analysis techniques (Leonard, 1974; Miller, 1976). This is a systematic method of evaluating the relative importance of different parameters. Steady-state sensitivity coefficients were estimated by varying each of the most important parameters, one at a time, by small increments around the normal control state as defined by Table I. Table III lists the percent change in one dependent variable - red cell production rate - caused by a 1% decrease in the model parameters (shown in left column) and determined after a new steady-state condition was reached. Positive values of these coefficients indicates a response to al hypoxic condition and negative values indicates tissue hyperoxia. In each case the response is in a direction that agrees with the concepts of erythropoiesis regulation. The unusually high influence on erythropoiesis indicated for oxygen uptake and perhaps capillary diffusivity may not be representative of the real intact system (see Discussion). However, this analysis does support the claim that P50 shifts can dramatically augment tissue oxygenation (Brewer, 1974; Metcalfe and Dhindsa, 1972).

A dynamic sensitivity analysis is illustrated in Figure 5. In this case, the six most important parameters were changed by 10% in a direction which would initiate an hypoxic response. The dynamic behavior of four important dependent system variables during this constant load disturbance are shown over a period of 30 days. The controller gains used in the simulations of Table III and Figure 5 were the same: G_1=3 and G_2=4. It is apparent that the general ranking of parameter importance found in the steady-state is maintained for the dynamic state as well. Parameter influence on the steady-state response was found to be relatively insensitive to values of controller gain since doubling gains increases the sensitivity coefficients of Table III by less than 15%. However, sensitivity coefficients do vary more significantly with deviations from the operating point. If, for example, a new equilibrium state was simulated for a specific hypoxic condition and sensitivity coefficients were

obtained by small perturbations from that state, both the magnitude and ranking of the coefficients may be altered. This is an expected behavior of nonlinear control systems.

Figure 5 also illustrates the wide difference in dynamic properties of various elements in the model. This model may be viewed as having four sequential processes, each with a characteristic time constant that is correspondingly longer: alterations in tissue oxygenation (seconds to minutes), erythropoietin release (hours), red cell production (days) and red cell mass (days to months). An interesting prediction of these simulations, is that the dynamics of the hypoxia response is similar for a variety of constant load disturbances whether it be an increase in plasma volume or a decrease in renal flow rate. Unfortunately, the experiments required to confirm this conclusion are difficult to perform. These simulations should, therefore, be considered as model-to-model comparisons which demonstrate that the model responds appropriately in a gross sense. Model-to-data comparisons, a more challenging validation process, will be discussed in another section.

The Renal-Bone Marrow Axis as a Proportional Controller

A more visual understanding of the relationships for renal and bone marrow function can be obtained by determining the overall dose response curve of the combined kidney-bone marrow axis; that is, the relationship between tissue oxygen tension and red cell production. The results are shown below only for the mid-range of erythropoietin production and were obtained by mathematically combining the renal function (Equation (9)) with the steady-state plasma distribution function of erythropoietin (Equation (12); $\overline{E}=\overline{E}_p$)) and the bone marrow function (Equation (13)). In this way erythropoietin is eliminated as an explicit variable; i.e.,

$$RCP = G(1-\overline{P_t O}) \qquad \text{for } \overline{P_t O} < 1 \qquad (16)$$

$$\text{where} \qquad G = G_1 \times G_2$$

This is a simple inverse linear relationship which has previously been used in the models of Guyton, et al (1972) and Hodgson (1970). In this form, the gain of the renal-bone marrow (open-loop) system is seen to be the product of the two gain factors, G_1 and G_2. Similar (although non-linear) gain-product relationships were obtained for the extrema of hyper-oxia and maximal hypoxia. The results of this analysis have been plotted in Figure 6 for a range of values of G. This function represents the entire controller circuit of the erythropoiesis model. In general, hypoxic tissue is predicted to have a greater effect on red cell production than hyperoxic tissue as indicated by the relative slopes. However, at higher gain factors, the suppression of erythropoiesis can be considerable for relatively small increases in tissue oxygenation.

Equation (16) is a typical controller function for a linear propor-tional control system in which the actuating error signal is the deviation of $\overline{P_t O}$ from its control value (i.e. unity) and G is the constant of pro-portionality or controller gain. The control value of $\overline{P_t O}$ is taken as an arbitrary reference standard and is not meant to imply that there is an internal set point. It becomes clear from this control function that the primary controlled variable is tissue oxygen tension rather than red cell production, red cell mass or hematocrit which can be considered feedback variables. The control system always adjusts the feedback variables in a direction that returns the controlled variable toward normal after an initial load disturbance (see Figure 5).

The controller gain is a major determinate of the final feedback compensation following a disturbance and, within limits, the speed at which a disturbance is corrected. Although increasing the gain increases the feedback effect, it may be at the sacrifice of an oscillatory approach to the steady-state. Systems of higher order than this one will tend to become unstable as controller gain increases. Oscillations in the erythro-poiesis system are known to occur in special cases and analysis of these systems in terms of control system theory has proved to be rewarding (Mackey, 1978; King-Smith and Morley, 1970).

Steady-State Errors

It is an inherent property of most biological homeostatic mechanisms in general and proportional control systems in particular that there will be at least some residual steady-state deviation from the normal operating point when the system is disturbed by a constant load. This "steady-state error" will vary in size depending on the gain of the system and the magnitude of the load disturbance. The sensitivity coefficients of Table III, for example, indicate the steady-state errors of red cell production resulting from small changes in parameter disturbances.

A basis for understanding steady-state errors in the current model is the following: At any equilibrium state, the term dRCM/dt in Equation (14) must be identically zero. Therefore, Equations (13) and (14) imply that at steady-state, daily red cell production and destruction rates are equal. Furthermore, if red cell life span is constant, a steady-state alteration in red cell mass implies a proportionate change in red cell production. Since most load disturbances are accompanied by changes in circulating red cell mass (i.e. Figure 5) this implies that red cell production and one or more of the factors which effect red cell production (including tissue oxygen tension, erythropoietin, hematocrit, controller gain and set point) must have incurred a steady-state error, however small. It can be appreciated from Figure 5 that steady-state errors in tissue oxygen tension are reduced at the expense of larger errors in red cell mass and hematocrit.

Steady-state analysis may also provide insight into the independent determinants of the controlled variable (Guyton, et al, 1973). The upper diagram of Figure 7 shows the effect of tissue oxygen tension on red cell production (i.e. the controller function of Figure 6) and the balance between red cell production and destruction. Feedback control insures that the various elements of the model are adjusted until the rate of red cell mass change, dRCM/dt, becomes zero and that steady-state is defined by this condition. It is mathematically permissible to set dRCM/dt to equal zero and work backward from this point to visualize those factors that determine tissue oxygen tension (Figure 7, lower diagram). There

are only two such factors in our model: red cell destruction (which determines production rate) and the relationship between tissue oxygen tension and red cell production. Therefore, only these factors and those quantities that effect these factors will ultimately determine tissue oxygen tension. Experimental evidence is severely lacking on the determinates of the shape of the controller function curve, although it appears that it may be under the influence of neural and biochemical factors (see Discussion). The factors that are responsible for normal red cell destruction are also not apparent (Harris & Kellermeyer, 1970). Except for frank pathology, rates of destruction are generally considered to be a constant fraction of total circulating red cell mass.

Aside from these experimental shortcomings, it is important to note that the factors usually agreed to play a role in acute changes of tissue oxygenation (i.e. blood flow, capillary diffusivity, oxygen uptake, P50, hematocrit) are not represented between the zero point and the tissue oxygen point in Figure 7. Therefore, while they may be considered dependent variables in the system, none of them, from a mathematical point of view, are independent determinates of the final level at which the tissue oxygen tension will stabilize in the steady-state. While dRCM/dt will always return to its initial zero value, the tissue oxygen tension may exhibit a steady-state error due to the inherent properties of the control system in the face of a constant disturbance. However, based on the above analysis we see that even tissue oxygen tension will return to its initial value (i.e., zero steady-state error) when both of the following conditions are satisfied: a) a constant daily rate of red cell destruction, and b) a constant controller relationship between tissue oxygen tension and red cell production.

As an example of the last point, a simulation of hypoxia was performed (Figure 8) in which arterial oxygen tension was set at some low value for the entire run and red cell destruction was clamped at its control value of 22 ml packed cells/day. Tissue oxygen tension decreased and then began to return toward normal as red cell production and hematocrit rose, similar to the simulations with the intact system shown in Figure 8(A). However, since the

destruction rate was not permitted to increase, a greater net rate of red cells entered the circulation than would have occurred had destruction rate rose in accord with the mass action law of Equation (13). As a result tissue oxygen tension continued to rise and red cell production rates declined. When the system reached its new steady-state, red cell production and tissue oxygen tension returned exactly to the pre-hypoxic control conditions in accord with the concepts discussed in the previous paragraph. This was in spite of an arterial oxygen tension that was still significantly depressed and at the expense of an hematocrit and circulating red cell mass that was considerably above normal.

It is perhaps easy to visualize that a primary change in destruction rate, as in hemolytic anemia, leads to secondary changes in tissue oxygen tension. It is more difficult to conceive of destruction rate being a determining factor of tissue oxygenation in a stress like hypoxia in which it appears, at first, that the decreased oxygen loading of arterial hemoglobin is the primary stimulus for hypoxia. However, it is important to distinguish between the initial stimulus of the acute phase in which blood PO_2 is controlling and the ultimate stimulus of the steady-state condition in which destruction rate (and controller function) is controlling. These conclusions from a theoretical model may warrant further experimental examination.

The following simulation will illustrate the ability of the control system to minimize steady-state errors as well as demonstrate the use of the model to provide insight into a common hematological disorder.

Hemolytic Anemia: An Example of Steady-State Control

Hemolytic anemia is a disease characterized by abnormal shortening of the red cell life span and a tendency to significantly reduce red cell mass. Many such cases of this disease are "compensated"; that is, accompanied by increased red cell production and a near normal blood hemoglobin concentration (Crosby, 1977). It has been claimed that our present understanding of erythropoiesis regulation does not allow an adequate explanation of compensated hemolytic anemia since it is difficult to conceive of

an appropriate stimulus for red cell production in the face of a near normal hemoglobin level (Erslev, 1962). The simulations shown in Figure 9, on the other hand, indicate that compensated hemolytic anemia is quite explicable by normal feedback control mechanisms. Similar conclusions have been reached by Hodgson (1970).

In this study, the only load disturbance imposed on the model was a decrease in red cell life span. The model was allowed to achieve a new equilibrium state before the values shown in Figure 9 were obtained. In these simulations the limits of maximum production were removed since the extreme limits of bone marrow reserve may not be firmly established (Crosby, 1977). These results show that hemoglobin levels can be maintained quite close to normal even though life span has decreased significantly. In addition, this can be accomplished by taking advantage of only a fraction of the reserve capacity of the bone marrow to produce red cells. Maximal red cell production is not required until hemolysis causes life span to be reduced to less than 10-15 days. This prediction agrees well with clinical findings (Harris & Kellermeyer, 1970; p. 518). Compensation falls off sharply when life span is reduced to less than about 30% of normal.

The difference between a normal, unperturbed hemoglobin concentration (i.e. $\overline{Hb}=1$) and the hemolytic hemoglobin concentration is a steady-state error. As controller gain increases, the effectiveness of the feedback regulation in maintaining normal hemoglobin concentration improves. Doubling the controller gain, in the range of compensation, decreases the hemoglobin steady-state error by about 70% at the expense of a relatively small incremental increase (less than 10%) in red cell production rates. The dashed line in Figure 9 is the case of no feedback regulation or open loop control. In this case, it is assumed that red cell production is constant at its normal value and independent of the degree of hemolysis. When hemoglobin levels are compensated at 90% normal value, the steady-state hemoglobin error is about three (for $G=5$) to six (for $G=20$) times as large without feedback as it is with feedback. This is well within the regulating range of other physiological control systems (Riggs, 1970).

It is conceivable that the effective gain of the controller is much higher than normal in compensated hemolytic anemia due to the possibility that additional stimulus besides erythropoietin comes from breakdown products of red cells and also the observation that the size of the stem cell pool enlarges (Crosby, 1975; Erslev & Silver, 1975). Both of these factors would cause an effective increase in gain in the model and increase the degree of compensation more than shown here.

These simulations do not explain fully compensated anemia, but do suggest that levels of compensation approaching 100% can be reached by normal feedback regulation operating under high controller gain. It is interesting to note in this regard that when hemolytic anemia is induced in experimental animals over a period of many weeks, full compensation is never apparently reached (Erslev & Silver, 1975: discussion).

MODEL VALIDATION USING LABORATORY DATA

The sensitivity analyses and simulation of hemolytic anemia presented above indicates an appropriate behavior of the model in both equilibrium and dynamic states. However, ultimate credibility of any model depends on demonstrating a close correspondence with measurements obtained directly from the real system. Two examples of model validation are presented below to serve this purpose.

Altitude Hypoxia and Descent

Buderer and Pace (1972) studied the dynamic changes in red cell mass, hematocrit and plasma volume in pig-tailed monkeys during six months at 3800 m altitude followed by descent to sea level for three months. Comparable data for human subjects were not available. The OEC for monkeys is similar to that of man (P50=30 mm Hg) and other elements of the model would not be expected to be fundamentally different, especially if responses were expressed as normalized values. The major driving function for the model was an arterial blood oxygen tension of 50 mm Hg and 95 mm Hg for the altitude and sea level phases, respectively (Rahn & Otis, 1949). The model's response was adjusted using the bone marrow controller gain, G_2, until a visual "best fit" was obtained. The comparison of model output and data are illustrated in Figure 10. The experimentally determined changes in plasma volume (bottom curve) was also used as a model driver, but its effect on the overall response was relatively small.

In addition to predicting the measured dynamic changes of red cell mass and hematocrit, the model was able to predict other system variables that were not measured such as plasma erythropoietin and red cell production-destruction rates. The simulation shows the general sequence of events, generally assumed to characterize the hypoxic response, including: tissue hypoxia (not shown), elevated erythropoietin and augmented red cell production levels which increase the mass of circulating blood cells (Abbrecht & Littell, 1972; Huff, et al, 1951; Faura, et al, 1969). The opposite scenario for the descent phase is also shown. The difference between

production and destruction rates provides a visual indication of the dynamic behavior of deviation from steady-state. The slow approach to equilibrium at altitude is also evident from the asymptotic nature of the measured quantities. Upon return to sea level, the increased hematocrit serves as a prolonged stimulus for tissue hyperoxia to the extent that red cell production may be totally inhibited for several weeks.

In order to obtain the agreement with observed results shown in Figure 10, two different values of overall controller gain were required for the different phases of the study (G(altitude)=2.2, G(descent)=12). This wide difference in effective gain may be more apparent than real, and may reflect other circulatory, ventilatory, and biochemical adjustments that are known to respond to changing oxygen transport disturbances (Finch & Lenfant, 1972) and which were not included in this simulation. These regulatory elements would also be expected to play a role in gradually reducing tissue hypoxia and thereby produce the dramatic return-toward-control behavior of erythropoietin, still not understood, typical of short term altitude exposure (Abbrecht & Littell, 1972; Dunn, et al, 1976). The model, in its present form, failed to generate this response. Other simulation studies, beyond the scope of this study, were performed in which increased fidelity of the hypoxic response was obtained by assuming changes in P50, capillary diffusivity, arterial oxygen tension due to ventilatory compensation, and increased sensitivity of erythroid producing tissues to erythropoietin (Mylrea & Abbrecht, 1973; Dunn, Leonard, & Kimzey, unpublished).

Red Cell Infusion

Polycythemia, induced by infusing red cells from a donor, has long been known to suppress erythropoietin and red cell production of the recipient (Gurney & Pan, 1958). Induction of the erythroid-suppressed state by this procedure in the mouse forms the basis of an erythropoietin bioassay. One of the few available studies of the long term effects of red cell infusion in humans was reported by Birkhill, et al (1951) who showed that the suppression of red cell production was directly related to the amount of red cells infused.

A simulation of this experiment is illustrated in Figure 11. At the start of the simulation 800 ml red cells were infused. The model was modified so that the infused red cell mass could be distinguished from the original circulating mass and could disappear at a linear rate over a period of 126 days. Analysis of the model's response showed that the increased hematocrit leads to tissue hyperoxia, decreased release of erythropoietin and suppression of red cell production. Loss of recipient's red cell mass continued until the hematocrit decreases to a point where erythropoiesis returns toward normal and is equal to the destruction of recipient cells. As production rates continue to rise slightly (due to an hematocrit which is just below normal) the recipient's red cell mass rises towards its control value. The results suggest that erythropoiesis is under the control of hematocrit levels and the renal oxygen sensor in this instance is behaving as the "hemoglobinometer" described by Beutler (1969).

The simulation results compare favorably with the experimental results, both with regard to magnitude and time course of the changes in hematocrit, disappearance of infused blood cells, and suppression and recovery of the recipients red cell mass. Allowance should be made for the fact that the experimental study used only two subjects, did not have the accuracy that radio-labeled cells would have afforded, and was performed at a time prior to the identification of erythropoietin.

The similarity between the descent phase from altitude of the previous simulation and the response to red cell infusion should be apparent. In both cases, the increased hematocrit contributed to tissue hyperoxia and erythro-suppression. The degree of suppression was much greater for the descent phase than for red cell infusion, primarily because of the initial higher hematocrit levels of the former case. In both simulations, a similar value of controller gain (G=12) was used to obtain the best fit with experimental data. This also compared favorably with the controller gain value obtained from mice data previously reported by Hodgson (1970).

DISCUSSION

Any conclusions from a study such as this must be tempered with the fact that a model is not the real system. The model should be judged, rather, by whether it serves the purpose of providing insight into the properties and characteristics of the real system. Since any model is only as good as the assumptions on which it is based, it is appropriate to review and justify the most important of these. For convenience, these remarks will be divided into two categories: the controlled system and the controller system.

Controlled System

A major assumption in the controlled system is the description of the renal oxygen detector. The evidence strongly indicates that the balance between oxygen supply and demand at intrarenal sites is the primary stimulus for erythropoietin release (Grant and Root, 1952; Krantz & Jacobson, 1970). Furthermore, these detector sites must monitor venous or tissue PO_2 rather than arterial PO_2 since anemia or increased oxygen-hemoglobin affinity lead to increased erythropoietin production without significantly altering arterial blood oxygen tension (Adamson, et al, 1969; Metcalfe and Dhindsa, 1972; Hodgson, 1970). The receptors sensitive to tissue PO_2 may be those cells which excrete erythropoietin or its precursor (Baciu, 1970). The present model is in accord with these concepts.

It has been suggested that the kidney has unique characteristics that enables it to function as a sensitive oxygen chemoreceptor and, in partic- ular, be responsive to changing hemoglobin levels. The peculiar renal microcirculation and the uniquely low arteriovenous oxygen difference pro- vides a gradient of tissue oxygen tension that amplifies changes in blood oxygen delivery (Metcalfe and Dhindsa, 1972; Gordon and Zanjani, 1970). In addition, the autoregulatory features of the kidney insures that blood flow and oxygen uptake are effectively stable over a wide range of oxygen tensions and blood pressures (Aperia, 1968; Selkurt, 1963). Moreover, if blood flows should be altered, the kidney, in contrast to other organs, will

exhibit proportionate changes in oxygen uptake (Pitts, 1960). This means that the ratio, V_m/Q, the only term in which blood flow appears in the model (Equation 4)), may be relatively constant and renal blood flow would not be expected to markedly influence tissue oxygenation.

The above discussion suggests that the powerful influence oxygen uptake, per se, was found to have in the model (Figure 5 and Table III) may be mitigated in the real system by concurrent changes in blood flow. Similarly, it is possible that an elevation of V_m, by whatever cause, promotes tissue hypoxia and results in local regulatory increases of K_d, the effective capillary diffusivity. This is now known to be true for skeletal muscle (Granger, et al, 1975), but has not been confirmed for the kidney. Such regulation would, however, further dampen the effect of oxygen uptake because K_d appears only in the ratio, V_m/K_d, in Equation (7). It may be desirable to add these local regulatory effects - between oxygen uptake, blood flow and capillary diffusivity - to the model. Our current alternate approach is to assume they are constant and to examine their influence, if the data so suggests, in improving the accuracy of simulation. Under these circumstances, and in accord with Equations (1) to (7), tissue PO_2 would be a function of the hemoglobin concentration of the blood, the arterial oxygen saturation of hemoglobin, and the shape and position of the OEC (Beutler, 1969).

It should be emphasized that the site of the intrarenal detector has not yet been confirmed and that the quantitative aspects of its oxygen supply-demand balance (including direct measurement of P_tO) remain unknown. Justification of this segment of the model is based on indirect evidence, gross characteristics of the kidney as a whole, and determinants of tissue oxygenation derived from other tissues.

The use of a steady-state formulation for tissue oxygenation (Equations 1 - 7) in a dynamic model is justified because, in the well perfused kidney, equilibrium of oxygen tension due to pure convection and diffusion may be achieved in the order of seconds to minutes following a load disturbance. This can be compared to the much slower changes of the erythropoietin distribution-bone marrow red cell production process. Estimates of true equilibration times were obtained from the non-steady state version of this

algorithm (Middleman, 1972; Duvellorory, et al, 1973) which was originally employed in our studies. The steady-state description permitted the use of a larger integration step size in the numerical algorithms and increased the speed of solution by several decades without decreasing the accuracy of the response for the long time periods in which we were interested.

Controller System

An accurate description of the relationship governing erythropoietin release is not yet available, presumably because of the difficulty in measuring intrarenal oxygen levels and the uncertainty surrounding the specific location of the receptor cells. The formulation used to relate tissue oxygen tension to erythropoietin release is in accord with the study of Adamson (1968) who found a semilogarithmic inverse relationship between daily urinary erythropoietin excretion and hematocrit in humans. A parallel between urinary and plasma erythropoietin (Krantz & Jacobson, 1970) as well as between hematocrit and tissue pO_2 (Thorling & Erslev, 1968) was assumed in deriving Equation (8). A similar relationship has been used by Hodgson (1970), while Parer (1970) has derived a linear relationship and Mylrea & Abbrecht (1971) have used arterial oxyhemoglobin concentration (i.e. Hb x $S_a O$) rather than tissue oxygen tension as the independent variable. At the present time there do not appear to be sufficient data to reveal the precise shape of this function.

Measurement of plasma erythropoietin has, until recently, been restricted to levels above basal (Adamson & Finch, 1975). Therefore, no data are available to confirm the relationship for reduced release rates of erythropoietin. This region is of particular interest because of the application of simulation to bed rest, spaceflight and related disturbances in which chronic elevation of hematocrit follows plasma volume shifts.

There is an abundance of information demonstrating that in experimental animals a linear relationship exists between red cell production and the log of erythropoietin concentration (Equation 12). This has been observed, for example, in bioassay animals in which doses of erythropoietin are injected either singularly with iron uptake used as the index of erythropoietic

activity (Camiscoli & Gordon, 1970; Dunn, et al, 1977) or administered at
frequent intervals for up to several weeks with production rate expressed
in terms of increased red cell mass (Gurney, 1962; Van Dyke & Pollycove,
1962). It is reasonable to assume that a similar dose-response relation-
ship exists for the human although confirmatory evidence is lacking.
In vivo estimates of the human function curve, especially for the suppressed
erythropoiesis range will be possible as erythropoietin becomes available
in large quantities and as more sensitive assay methods for this hormone
are developed.

The shape and position of the renal and bone marrow function curves
have been found to be crucial elements in the control of erythropoiesis in
general and the long term control of tissue oxygenation in particular.
Model parameters have been incorporated to allow for shifts in sensitivi-
ties and thresholds away from the normal operating points. Values of con-
troller sensitivities have not been well established in the human by direct
methods and only to a limited extent in experimental animals (Hodgson, 1970).
Several studies suggest that alterations in these parameters occur during cer-
tain physiological stresses such as dehydration and hypoxia (Dunn & Lange,1979;
Kretchmar, 1966), and pathological disturbances such as abnormal hemoglobin
(Adamson, et al, 1969), erythrocytosis (Adamson,1968) and hemolytic anemia
(Erslev & Silver,1975). It appears that the rate of red cell production is
determined not only by the concentration of erythropoietin, but also by the
size of the stem cell pool (Lajtha, et al, 1962). If this is true, the bone
marrow response to a given dose of erythropoietin should be greater than
normal (i.e. an effective increase in G_2). The availability of iron to
the erythron may also influence this function (Finch, et al, 1970). Certain
hormones, such as androgens, as well as neural stimuli, are assumed to exert
their effect on erythropoiesis by their modification of erythropoietin
release (i.e. an effective change in G_1; Peschle, et al, 1975; Baciu, 1970).
It is possible, using the present model, to predict these parameters within
narrow limits provided both the dynamic behavior of erythropoietin and red
cell production rates are measured simultaneously during a hematologic
stress. Unfortunately, such data are seldom available, especially for
humans.

Conclusions

We have demonstrated the validity of a human model for the control of erythropoiesis based on the balance between oxygen supply and demand at the kidneys which serves as an oxygen receptor and erythropoietin producer. Validation studies included simulations of experimental hypoxia and hyperoxia and a pathological disorder. Feedback regulation of tissue oxygen tension is accomplished solely by adjustments of hemoglobin levels resulting from the output of a renal-bone marrow controller. Other parameters that are known to affect acute changes in tissue oxygenation are incorporated explicitly in the model, but are non-regulatory in nature, and can be altered manually to test various hypotheses. Similarly, the characteristics of the controller can also be adjusted to test their effect on long term control of tissue PO_2 and red cell mass. We have not found such parameter adjustment (other than for the primary disturbance) essential, in most cases, to simulate the basic behavior of the dynamic and steady-state response. However, fine tuning of parameters is required to scale the model output and achieve closer agreement with experimental values. In some cases, our studies indicate the need to propose additional regulatory elements to provide, for example, a more realistic simulation of the erythropoietin response to hypoxia. Other features of a general nature have also been identified that will increase the utility of the model even further including: a) the effect of blood volume and viscosity on oxygen transport, and b) a description of stem cell kinetics and reticulocytosis.

Obviously, in this limited study, we have been able only to examine a small fraction of the hematological conditions, experiments, and clinical syndromes which the model can theoretically simulate. It would not be realistic to claim, a priori, that the model is accurate for conditions for which it has not been tested. To the contrary, an important objective in developing this model was to provide an additional research tool that can achieve the required realism only by an iterative process between laboratory experimentation and model refinement. In this manner, the model can be quite useful in several ways: a) identification of important parameters and their sensitivity on the overall system, b) a method to test

hypotheses rapidly, c) identification of specific elements that must be experimentally quantified, and d) prediction of the behavior of certain unmeasured or difficult to measure quantities. This approach has already proven effective for such ground-based studies related to spaceflight as bed rest and dehydration (Kimzey, et al, 1979; Leonard, et al, 1979). The model, therefore, becomes a physical framework in which many kinds of diverse experimental and clinical findings may be incorporated resulting, hopefully, in a more consistent picture of erythropoietic control.

TABLE I

PARAMETERS AND INITIAL CONDITIONS

Parameters

Symbol	Definition	Value	Units
CHbO	Carrying capacity of hemoglobin	1.34	ml O_2/gm Hb
E_o	Intercept of erythropoietin function	20.09	x normal
G_1	Gain of erythropoietin function	3	non-dimensional
G_2	Gain of red cell production function	2	non-dimensional
K_d	Capillary diffusivity	0.567	ml O_2/min-mm Hg
MCHC	Mean corpuscular hemoglobin concentration	0.375	gm Hb/ml RBC
P_aO	Oxygen tension in arterial blood	95.0	mm Hg
PV	Plasma Volume	3.0	liters
P_m	Maximum production rate of red cells	6	x Normal
P_o	Minimum production rate of red cells	0	x Normal
P_1	Normal production rate of red cells	1	x Normal
P50	Oxygen tension of hemoglobin at 50% saturation	26.7	mm Hg
Q	Renal blood flow	1.2	liter/min
TBM	Bone marrow transit time	4	days
$TE_{\frac{1}{2}}$	Plasma half-life of erythropoietin	12	hours
$TRC_{\frac{1}{2}}$	Red cell half-life	63	days
V_m	Oxygen uptake of kidneys	20	mlO_2/min

Initial Conditions

Symbol	Definition	Value	Units
C_aO	Oxygen content of arterial blood	19.6	ml O_2/100 ml blood
C_vO	Oxygen content of venous blood	17.9	ml O_2/100 ml blood
$\overline{E}$	Erythropoietin concentration in plasma	1.0	x Normal

TABLE I (Continued)

Symbol	Definition	Value	Units
$\overline{E}_p$	Erythropoietin production rate	1.0	x Normal
Hct	Hematocrit	40	ml packed red cells/ 100 ml blood
P_tO	Oxygen tension in renal tissue fluid	20	mm Hg
P_vO	Oxygen tension in venous blood	55.3	mm Hg
RCM	Red cell mass	2.0	liters
RCP	Production rate of new red blood cells	22	ml packed cells/day
S_aO	Saturation of arterial hemoglobin with oxygen	97.6	percent
S_vO	Saturation of venous hemoglobin with oxygen	89.3	percent

Note: a) Units expressed here are not necessarily those used in model.

b) Bar over symbol denotes quantity normalized with respect to initial value.

c) Symbol followed by(o) as used in text denotes initial condition or steady-state value.

TABLE II

MODEL PARAMETERS AND EVENTS WHICH THEY INFLUENCE

PARAMETER	PHYSIOLOGICAL/CLINICAL EVENT INFLUENCING CHANGE IN PARAMETER
O_2 Demand	Hypo-/Hyper Thyroidism, Starvation, Metabolic Activity, Renal Blood Flow
O_2 Supply	
- MCHC	Abnormal Hb Synthesis, RC Membrane Disorders
- Hb-O_2 Affinity	Blood Temperature, pH, Base Excess, 2,3-DPG, abnormal Hb
- Hb-O_2 Carrying Capacity	Sickle Cell Anemia, Carbon Monoxide Poisoning
- Renal Blood Flow	Postural Change, Exercise, Hemorrhage
- Arterial PO_2	Hypoxia, Hyperoxia, Lung Obstruction
- Capillary Diffusivity	Hypoxia, Tissue autoregulation
- Plasma Volume	Bed Rest, Weightlessness, Dehydration, Hemorrhage, Infusions
Red Cell Life Span	Hemolytic Anemias, Hyperoxia, Abnormal Hemoglobin
Bone Marrow Time Delay	Hypoxia, Acute erythrogenic stresses
Controller Gain and Threshold	Renal and Bone Marrow Tumors and Insufficiencies, Iron Deficiency, Ineffective Erythropoiesis, Polycythemia Vera, Aplastic Anemia, Hemolytic Anemia
Initial Red Cell Mass	Transfusions, Hemorrhage

TABLE III

STEADY-STATE SENSITIVITY ANALYSIS*

PARAMETER	% RED CELL PRODUCTION
Oxygen Demand, V_m	- 4.55
O_2 - Hb Affinity, P50	+ 3.90
Capillary Diffusivity, K_d	+ 3.25
Blood Flow, Q	+ 1.45
Mean Corpuscular Hemoglobin Concentration, MCHC	+ 1.45
Hemoglobin O_2 Carrying Capacity, CHbO	+ 1.45
Arterial O_2 Tension, P_aO	+ 1.10
Plasma Volume, PV	- 0.90
Red Cell Half-Life, TRHL	+ 0.85
Controller Gain, G	- 0.03

* Values shown are % change in red cell production at steady-state due to a 1% decrease in parameter value.   (G=12)
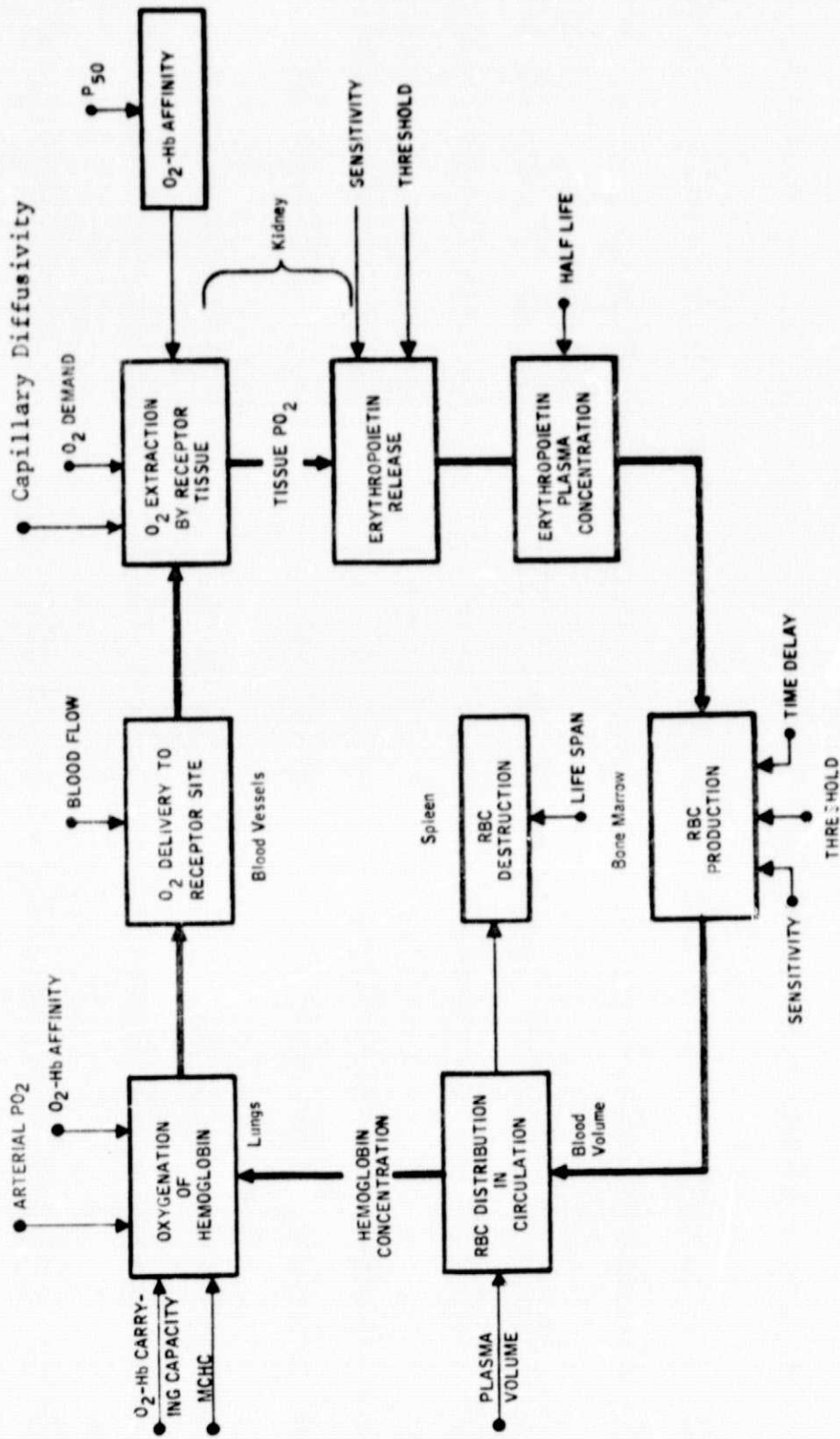
Figure 1. Schematic systems diagram of model for control of erythropoiesis.
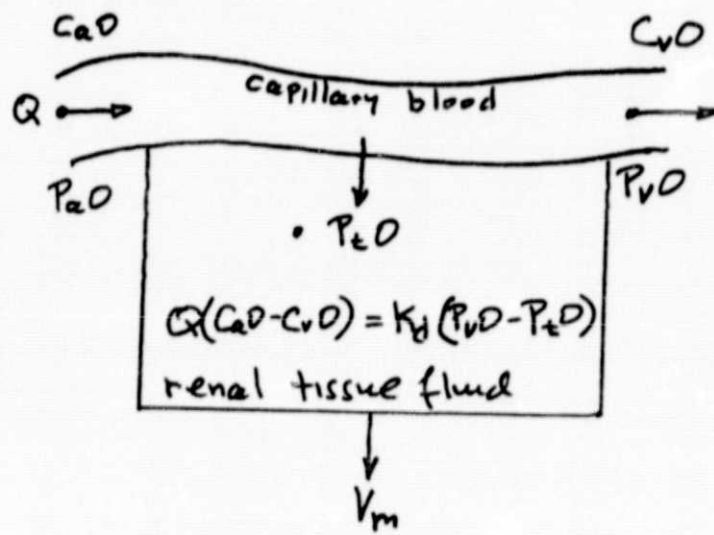
Figure 2. Two-compartment steady-state model of renal

tissue oxygenation.
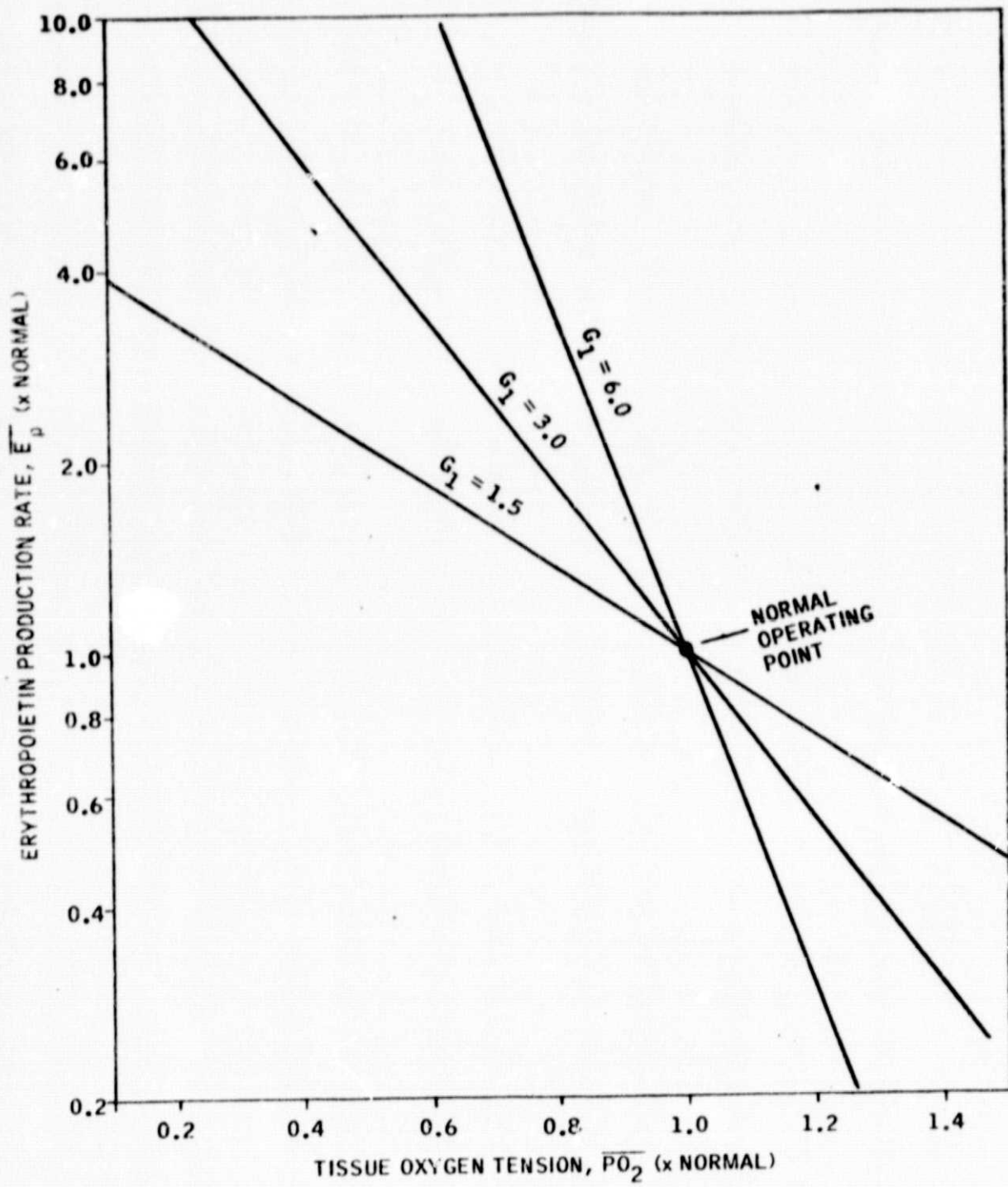
Figure 3. Renal controller function for erythropoietin
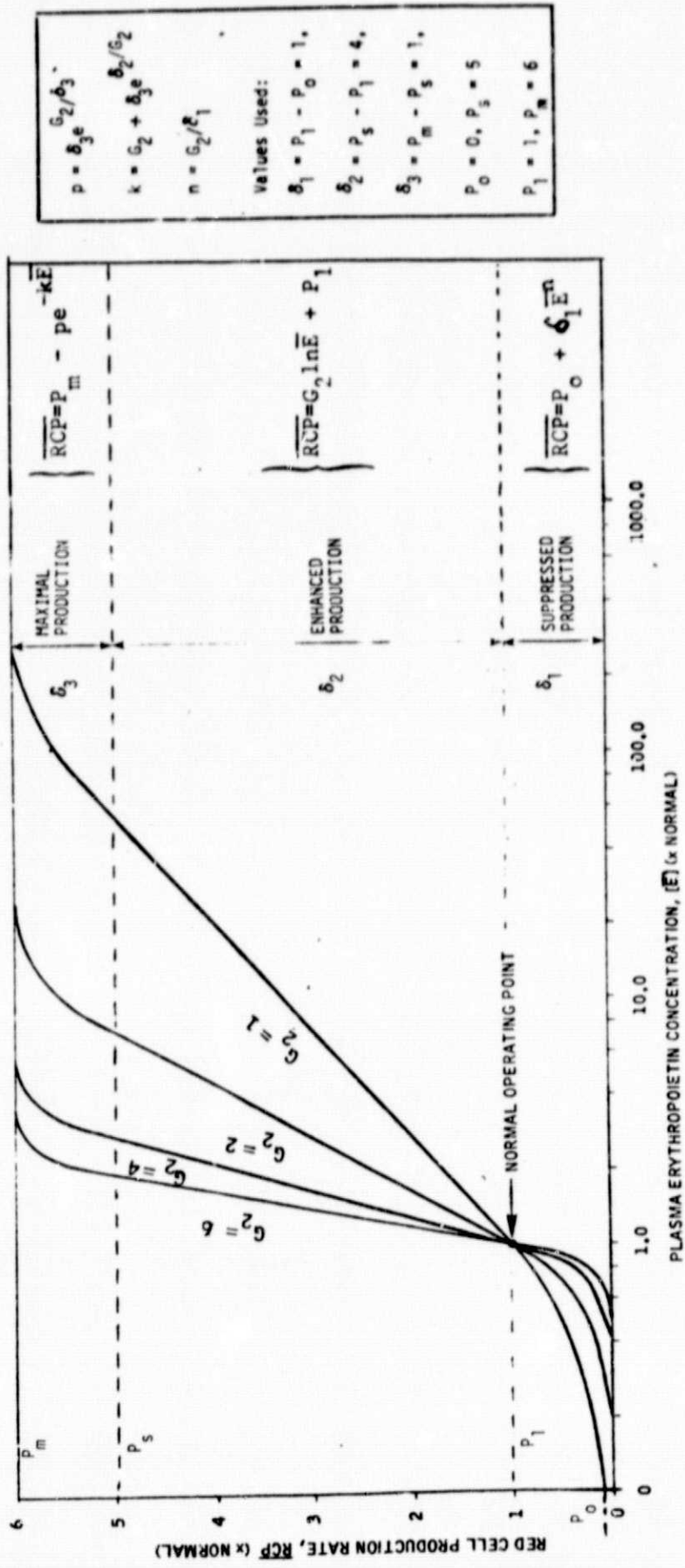production rate showing effect of gain, G_1.

Figure 4. Bone marrow controller function for red cell production rate showing equations used to piece-wise fit the dose response curve and demonstrating effect of gain, G_2.
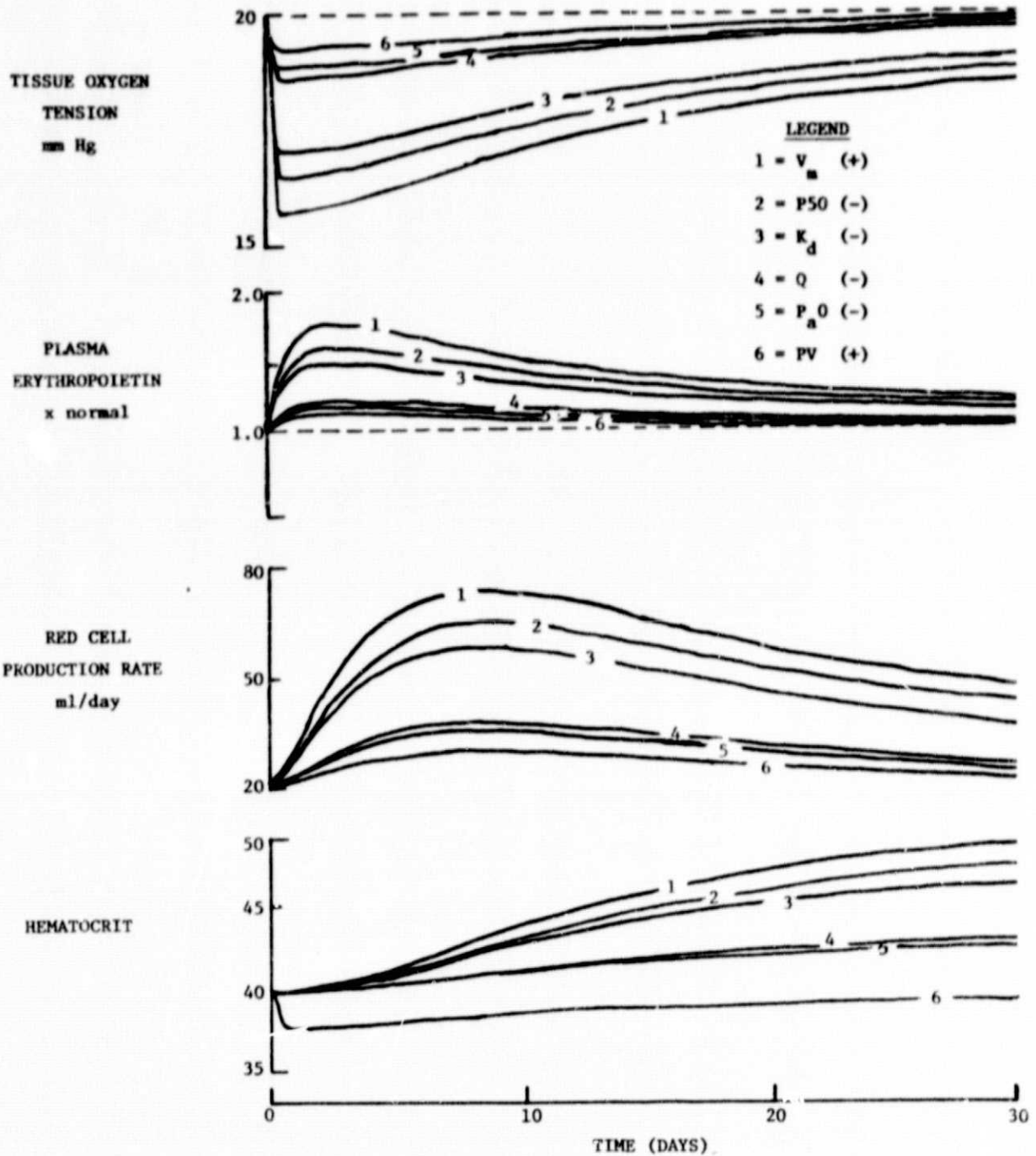
Text within figure:

$p = \delta_3 e^{G_2/\delta_3}$

$k = G_2 + \delta_3 e^{\delta_3/G_2}$

$n = G_2/\delta_1$

Values Used:

$\delta_1 = P_1 - P_o = 1.$

$\delta_2 = P_s - P_1 = 4.$

$\delta_3 = P_m - P_s = 1.$

$P_o = 0, P_s = 5$

$P_1 = 1, P_m = 6$

$RCP = P_m - pe^{-kE}$

$\overline{RCP = G_2 \ln E + P_1}$

$RCP = P_o + \delta_1 E^n$

MAXIMAL PRODUCTION

ENHANCED PRODUCTION

SUPPRESSED PRODUCTION

δ_3

δ_2

δ_1

NORMAL OPERATING POINT

$G_2 = 1$

$G_2 = 2$

$G_2 = 4$

$G_2 = 6$

PLASMA ERYTHROPOIETIN CONCENTRATION, [E] (x NORMAL)

1.0   10.0   100.0   1000.0

RED CELL PRODUCTION RATE, RCP (x NORMAL)

P_m P_s P_1 P_o

0   2   4   5   6

Figure 5. Response of erythropoietic elements to a 10% constant
load disturbance of various parameters. Algebraic
sign in legend refers to direction of change in each
parameter.
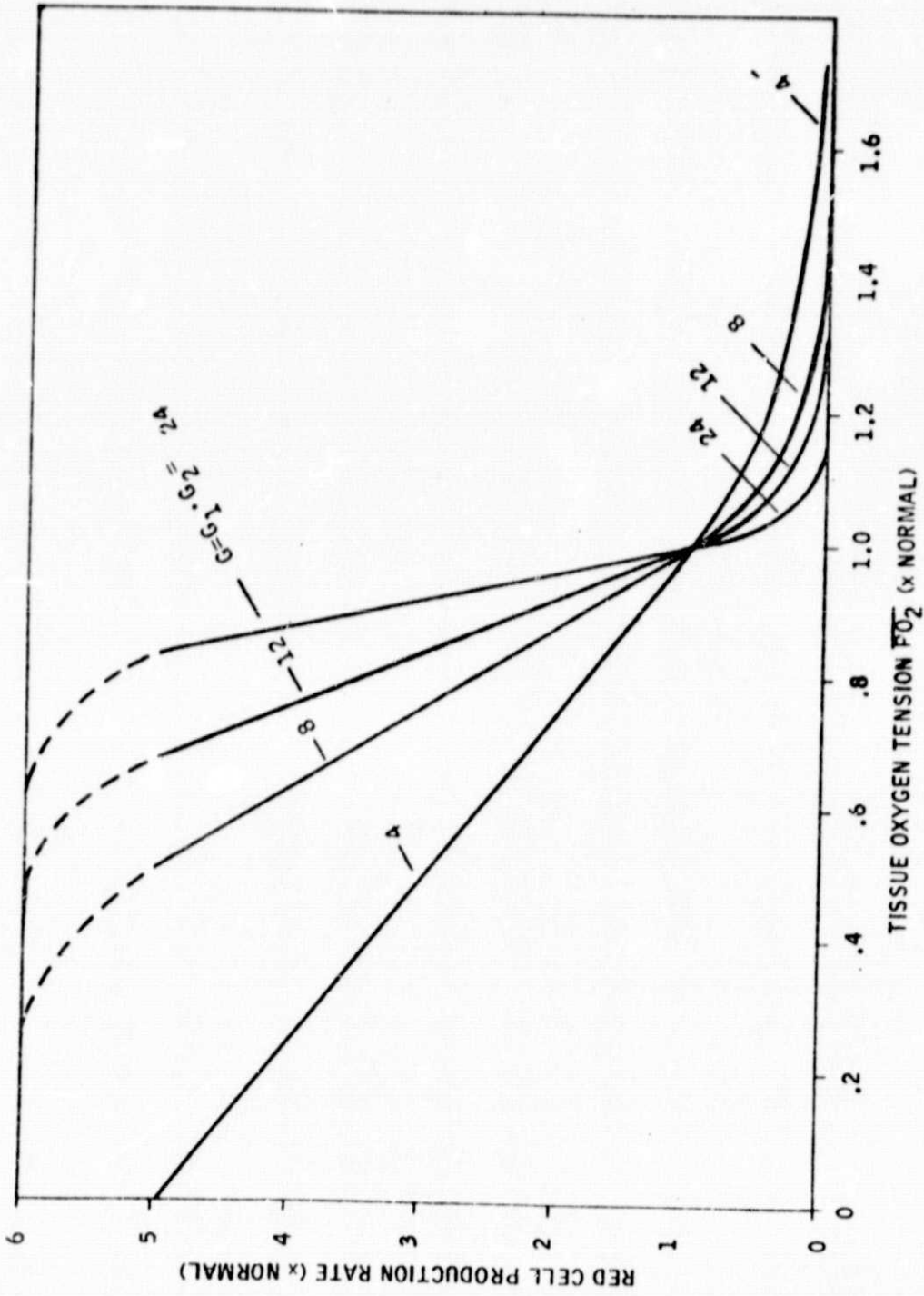
Figure 6. Combined renal-bone marrow controller function showing effect of tissue oxygen tension on erythropoiesis for various values of overall gain, G.
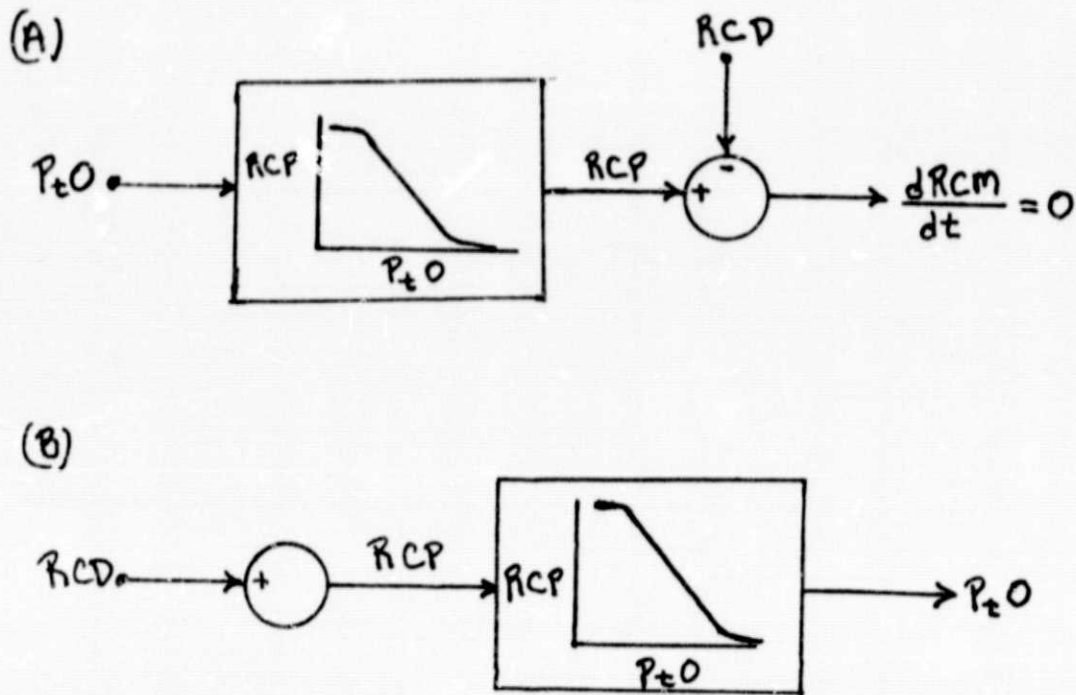
Figure 7. Steady-state analysis of long term determinants of tissue oxygen tension. (A) Segment of feedback circuit that results in the term dRCM/dt becoming zero at steady-state when destruction and production rates are equal. (B) Reversal of top diagram starting from the zero point and showing mathematically equivalent influences on tissue oxygen tension.
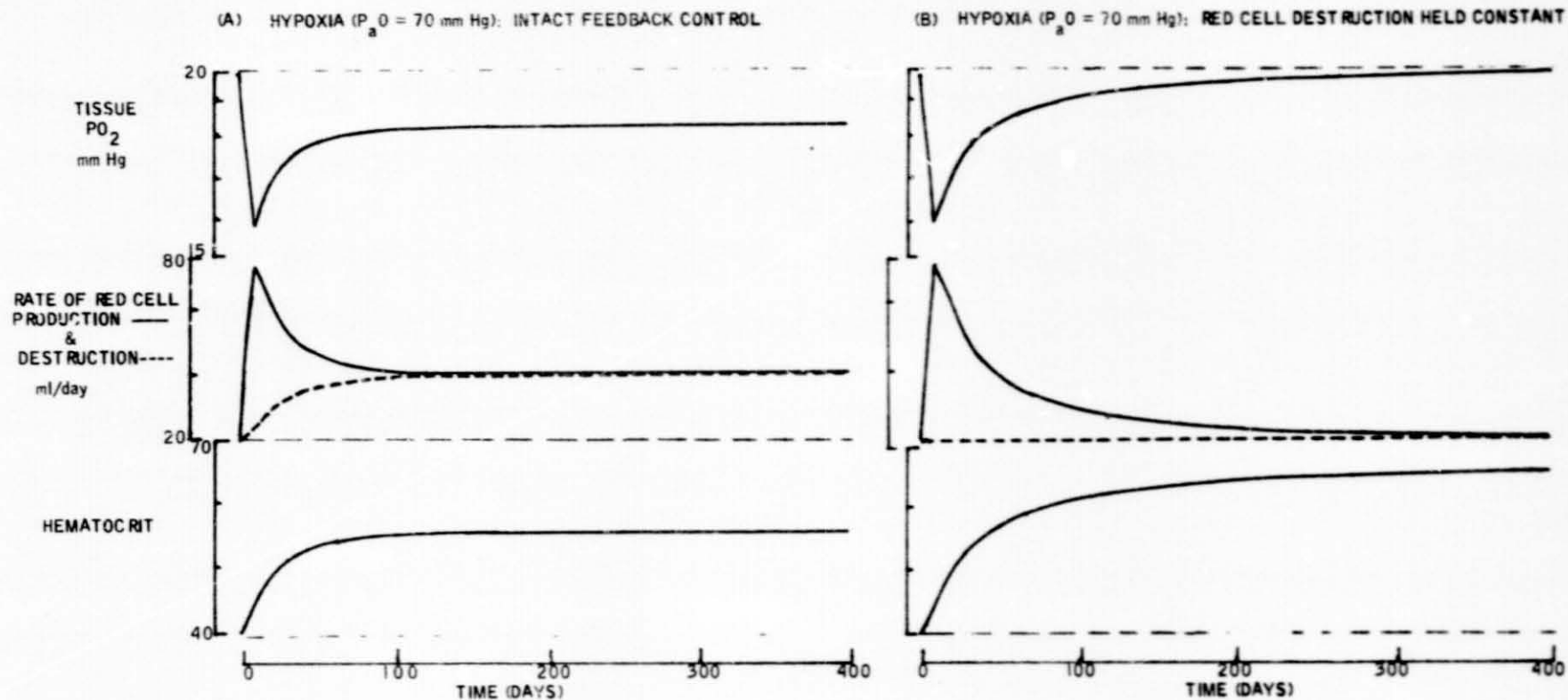
Figure 8.   Effect of destruction rate on long term control of tissue oxygen tension.
(A) Normal simulation response to hypoxic stress. (B) Hypoxic simulation
with destruction rate clamped at control value and showing regulation of
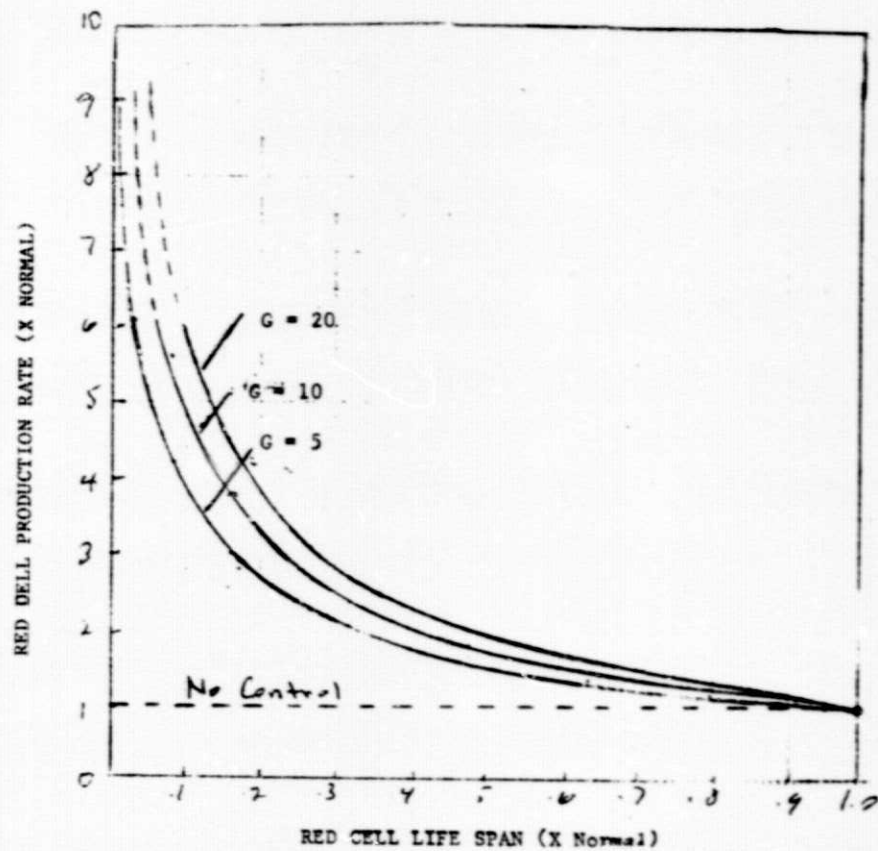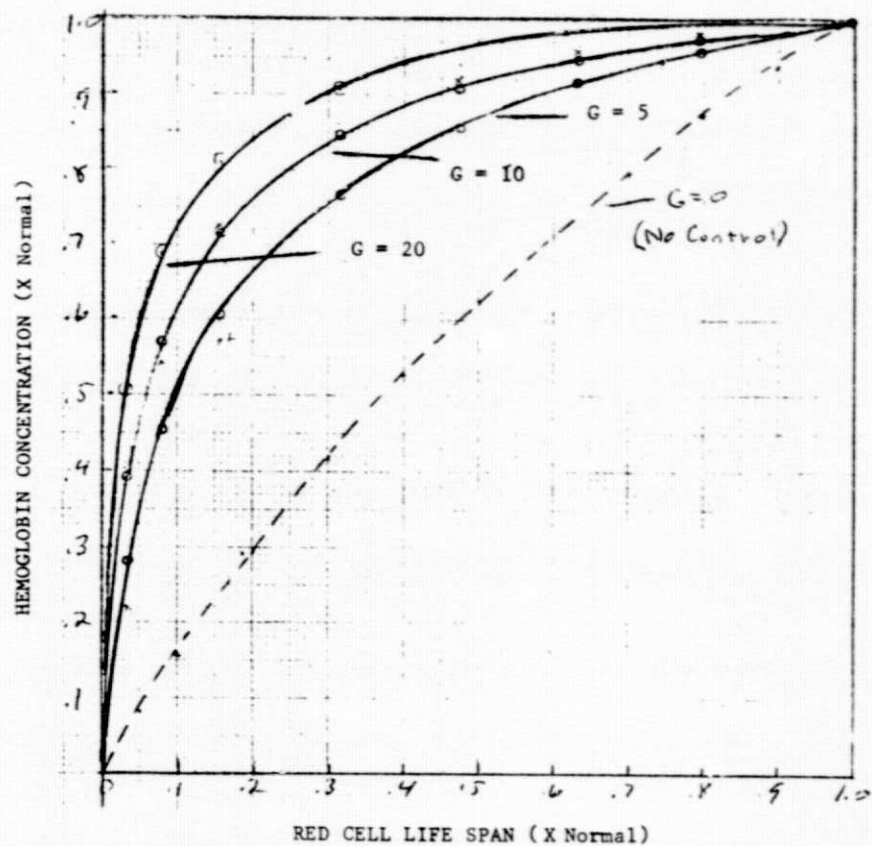tissue pO$_2$ back to normal in spite of reduced P$_a$O.

Figure 9. Simulated steady-state response to chronic hemolytic anemia. Red cell life span and controller gain, G, were varied in this simulation. Dashed line indicates no feedback control. Results suggest that hemoglobin levels can be maintained near normal for large range of reduced cell survival times provided controller gain is high.
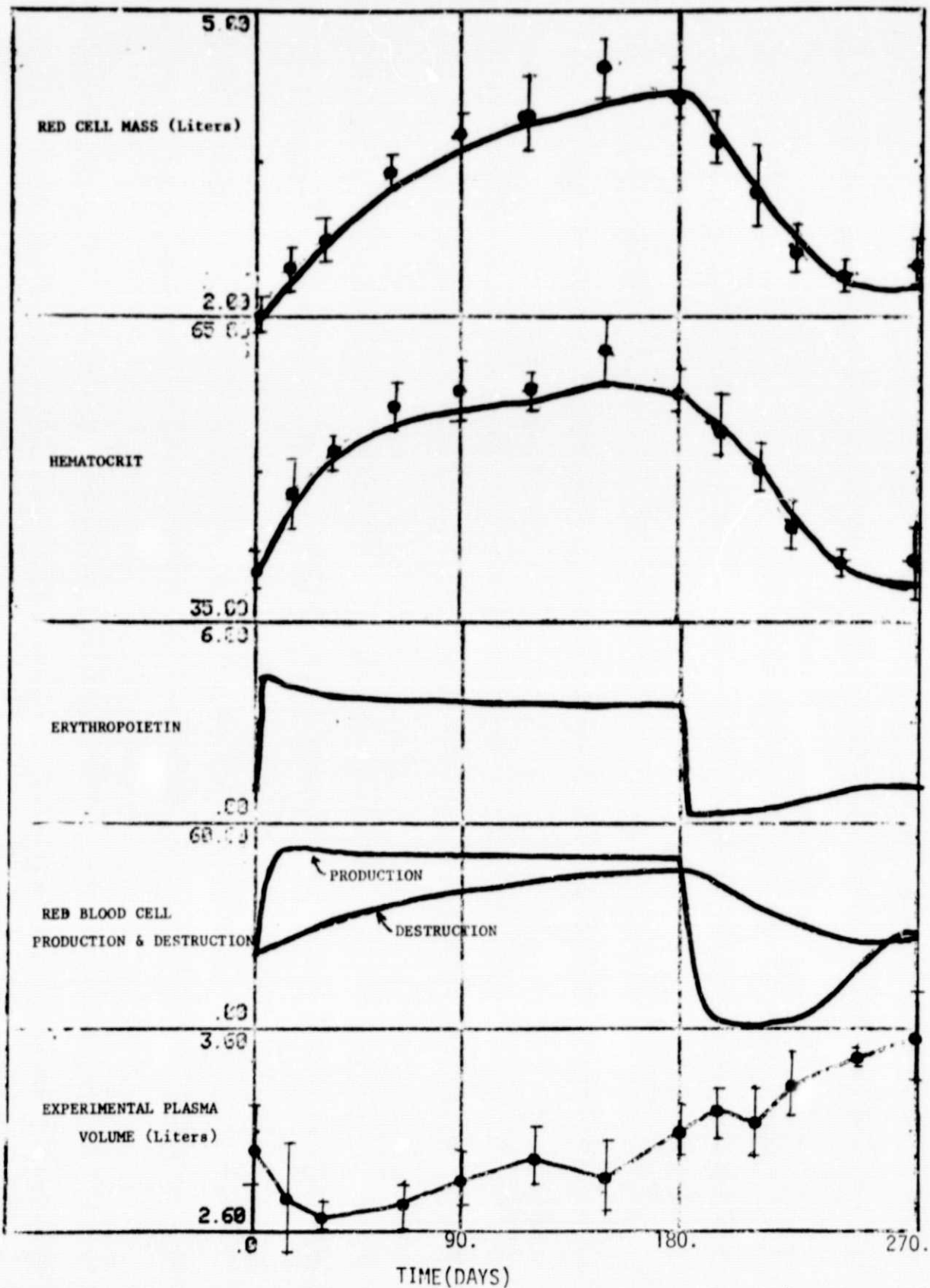
Figure 10. Simulation of altitude hypoxia and descent to sea level (solid lines). Experimental data from pig-tailed monkeys is shown as filled circles and SE intervals (Buderer & Pace, 1971). Hypoxia was simulated by reducing P_aO to 50 mm Hg. Experimental plasma volumes (bottom curve) were also used to drive model.
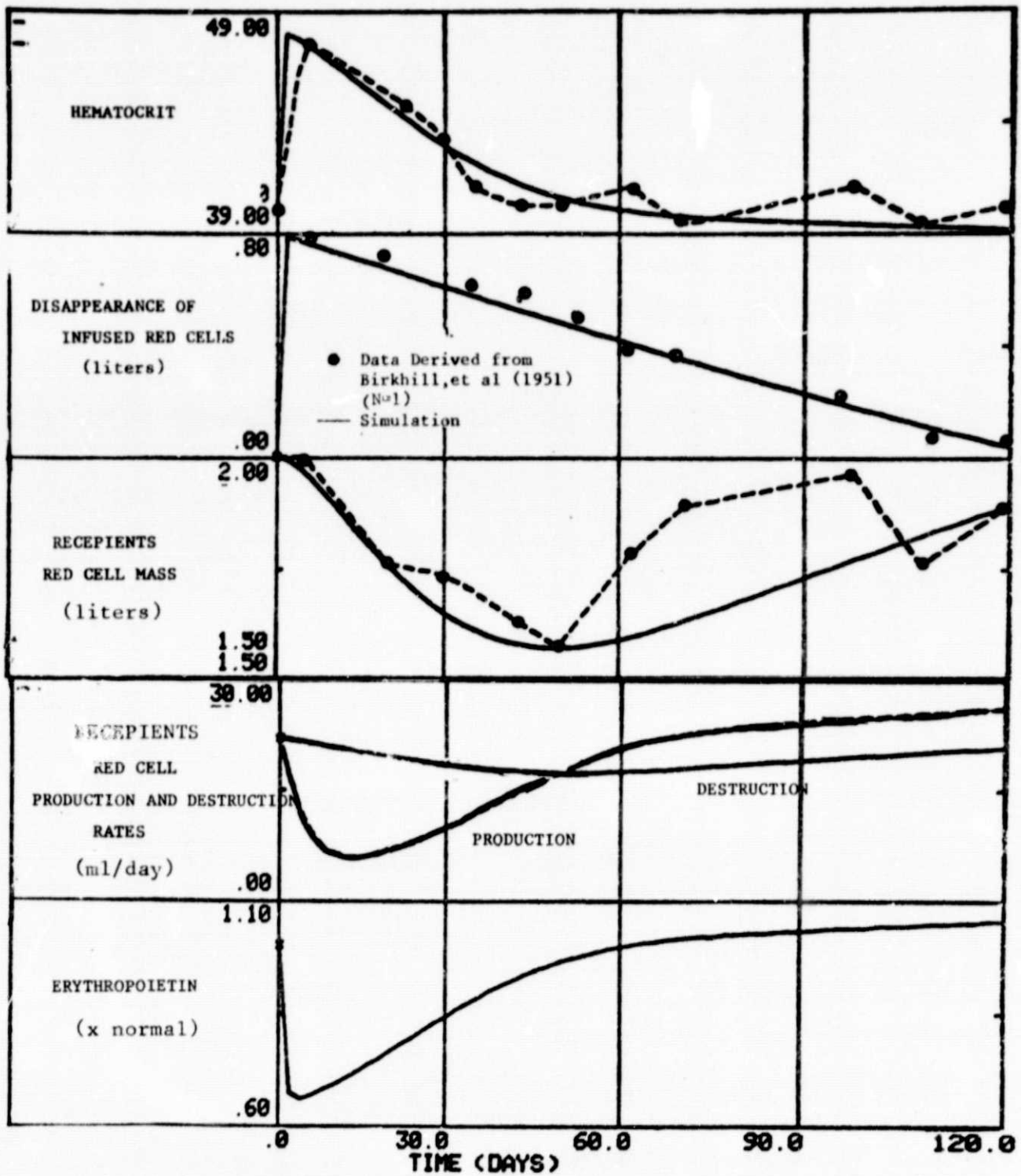
Figure 11. Simulated response to sudden infusion of 800 ml red blood cells
(solid lines). Experimental data from a single subject are
shown as filled circles and dashed lines. Infused cells disappear
completely at constant rate while recipients red cell mass
decreases to a minimum value as erythropoiesis is temporarily
inhibited.

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