STUDY REPORT

ON

Improvements and Validation of the Erythropoiesis Control Model

for Bed Rest Simulation

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Prepared by

J. I. Leonard, Ph.D.

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General Electric Company

Space Division

Houston, Texas

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1.0 INTRODUCTION

This report summarizes the results of a computer modeling study related to the regulation and control of erythropoiesis. The investigation is part of a continuing effort to apply systems analysis techniques to space flight hematology studies. In particular, the ultimate objective of the modeling effort is to better understand the mechanisms involved in the loss of circulating red cells observed in crewmen returning from space flight missions. Explanations for this phenomena have been proposed, but confirmatory evidence is still lacking. The opportunity to gather additional data and to test hypotheses in the weightless environment will not be available for several years when the Shuttle Spacelab flights are scheduled to begin. Until that time, ground-based studies have been proposed to search out and clarify mechanisms which may be operative during space flight. Bed rest is one type of study used in this experimental program because the hematological response is similar to space flight and it is believed that at least some of the same elements are involved in producing the space flight response. The objectives of this study are to utilize the systems analysis techniques developed during previous efforts, to improve them in several specific areas, and to apply them to the simulation of bed rest.

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. The function of this model will be to complement space flight and ground-based experiments. Computer simulations of these studies can reveal inconsistencies in the theoretical development and areas which require more intensive experimental examination.

The development of the model of the erythropoietic control system has proceeded carefully and systematically as indicated by our previous

reports. A thorough review of the regulation of erythropoiesis led to formulation of a conceptual model and eventually the design of a computer model (Leonard, 1974). Verification and validation of the model was accomplished by performing simulations of stresses related to space flight (Leonard, 1976). In the process, sensitivity analyses and parametric studies were used to identify candidate factors and develop hypotheses which may account for the erythrocyte response of space flight. Preliminary simulation studies of bed rest (Leonard, 1975) and of the Skylab flights (Kimzey, et al, 1976) were also accomplished.

The results obtained were encouraging, but it became clear that the model was limited in several respects. An element missing from the original formulation was an explicit representation of erythropoietin, the hormonal messenger that stimulates erythrocyte production. It was believed that including this factor would add a level of detail to the model necessary for incorporation of experimental data that are currently being furnished by other studies. Thus, the objective was established to include the erythropoietin factor in an improved model formulation prior to bed rest simulation studies.

The new formulation adopted was based on the concept originally proposed by Jacobson, et al (1957) that the overall balance between oxygen supply and demand regulates the release of erythropoietin from renal tissue and that this substance in turn controls bone marrow red cell production. More recently it has been proposed that formation of an erythropoietically active hormone involves the role of inhibitors and activators (Gordon & Zanjani, 1971; Peschle, et al, 1975a). In addition, it is known that red cell production is modulated by factors other than erythropoietin, including iron levels, other hormones, and the central nervous system (Baciu, 1970; Finch, et al, 1970;Peschle, et al, 1975b). However, 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.

Our continuing literature search has revealed additional evidence and support for one of the fundamental hypothesis upon which the model is constructed. The location of the renal sensing site for monitoring oxygen tension and releasing erythropoietin, has still not been accomplished, but we originally proposed : a) tissue oxygen tension (PO_2) rather than arterial PO_2 is monitored, b) it is located in an area where blood flow and oxygen consumption is held stable over a wide range of oxygen tensions, and c) erythropoietin release is highly sensitive to small changes in tissue PO_2. These characteristics have been indirectly confirmed by a number of investigators (Adamson, et al, 1969 ; Weil, et al 1968 ; Selkurt, 1963; Aperia, et al 1968, Metcalfe & Dhindsa , 1972). Under the circumstances of constant arterial oxygen tension and oxyhemoglobin affinity, the renal oxygen sensor is able to serve as a hemoglobinometer of the body (Beutler, 1969). This, as we have discovered from our simulation studies, is possibly the most essential factor in understanding the hemotologic response to bed rest.

2.0   RECENT IMPROVEMENTS TO ERYTHROPOIESIS MODEL

2.1   NEW FORMULATION OF RENAL-BONE MARROW RELATIONSHIPS

Previous Formulation of Renal Bone Marrow Relationship

The erythropoiesis model previously contained a formulation for red cell production based entirely on the level of PO_2 at a hypothetical renal sensing site. This was a "lumped" representation since erythro-poietin (the hormonal regulator of red cell production) was not explicitly considered and the functions of the kidney and bone-marrow were combined. The algebraic relationship describing red cell production rate (RCP) and tissue oxygen tension (PO_2) was given by[*]:

$$\overline{RCP} = G(1 - \overline{PO_2}) + P_1 \tag{1}$$

where G is the gain or sensitivity of the overall renal-bone marrow axis and P_1 is a constant. This is a straight line inverse relationship on a $\overline{RCP}$ vs. $\overline{PO_2}$ plot with slope $= -G$ and which goes through the normal operating point ($\overline{RCP} = 1.0$, $\overline{PO_2} = 1,0$) when $P_1 = 1$.
The upper portion of Figure 1 illustrates this relationship with the added restrictions such that: $0 \leq \overline{RCP} \leq 6$.   This general relationship can be inferred from several different studies (Eskuche & Hodgson, 1962; Van Dyke & Pollycove, 1962; Hodgson, 1970, Birkhill, et al, 1951).

New Formulation of Renal Bone Marrow Relationship

The goal of the present task is to include erythropoietin as an explicit element of the model. The approach used was to separate the erythro-poietin producing function of the kidney from the erythrocyte producing function of the bone marrow, as shown in Figure 1 (bottom).

[*] The bar over any term in this paper represents the normalized value with respect to control. If X_0 is the control value and X is the value during a stressed condition, then $\overline{X} = X/X_0$. The normalized form was used in the model to simplify comparison with data from various laboratories and for different subjects. See Appendix for glossary of symbols and abbreviations used in this report.
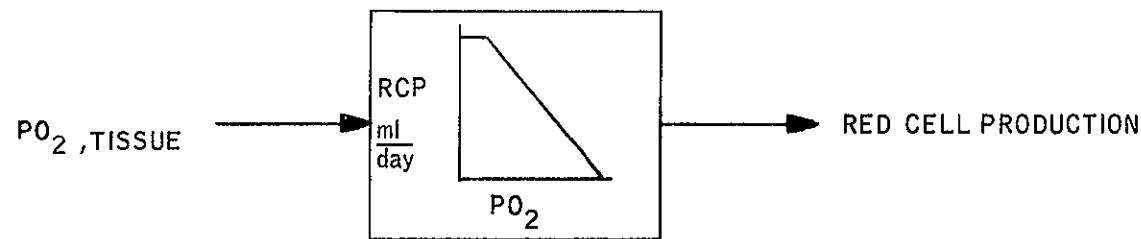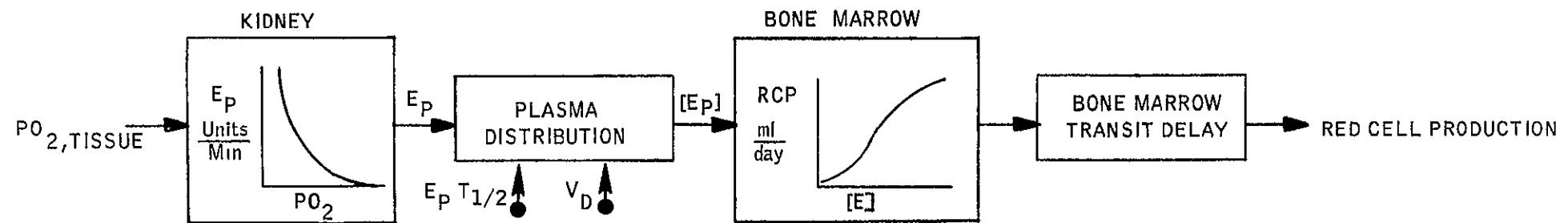
FIGURE 1

IMPROVEMENTS IN MODEL REPRESENTATION OF RENAL - BONE MARROW AXIS

Replacement of the original function (version I in the figure) with the improved representation (version II), if formulated properly, should yield similar response to changes in tissue PO_2. The similarity of the improved block response to the original function will be demonstrated later in this report. However, the addition of erythropoietin in production, erythropoietin clearance, a bone marrow transit delay, and non-linear function curves will be shown to increase the flexibility of the model and produce more realistic kinetic behavior than heretofore possible.

Renal Erythropoietin Production

Tissue PO_2 is computed in the model from a balance of oxygen delivery and oxygen demand with consideration for oxygen diffusion from blood and absorption into the tissue fluid. It is a widely accepted hypothesis that changes in the quantity of tension of oxygen in renal cells regulate the day-to-day production of erythropoietin (Fisher, et al, 1975; Gordon and Zanjani, 1970; A. J. Erslev, 1975). Therefore, it was desirable to formulate a relationship between oxygen tension at the renal sensing site and the rate of production or plasma concentration of erythropoietin. Unfortunately, the location of these oxygen receptors and measurement of renal cell oxygenation has continued to elude investigators in this field. In addition, measurement of plasma erythropoietin has, until recently, been restricted to levels above basal (Adamson & Finch, 1975). Therefore, there are not data available which explicitly relate tissue PO_2 and erythropoietin secretion rate. However, it is possible to postulate a functional relationship based on the single clinical study of Adamson (1968) who found a linear semi-logarithmic inverse relationship between daily urinary erythropoietin excretion and hematocrit in humans. By assuming a parallel between urinary and plasma erythropoietin (Krantz and Jacobson, 1970) as well as between hematocrit and tissue PO_2, (Thorling and Erslev, 1968),

the following logarithmic relationship has been derived to be compatible with Adamson's study:[*]

$$\ln \overline{E}_p = - G_1 \cdot (\overline{PO_2}) + E_o \qquad (2\ a)$$

or

$$\overline{E}_p = A \cdot e^{-G_1(\overline{PO_2})}$$

where $\qquad (2\ b)$

$$A = e^{E_o}$$

Erythropoietin production is given by $\overline{E}_p$ and tissue PO_2 at the sensing site by $\overline{PO_2}$. The gain or slope of the semi-logarithmic function is G_1, and E_o is a constant used to define the y-intercept at $PO_2 = O$. This curve, shown in Figure 2(A), (for various values of G_1) will always pass through the normal operating point $PO_2 = 1.0$, $\overline{E}_p = 1.0$ if $E_o = G_1$. Analysis of Adamson's data leads to a value of $G_1 = 2.8$, but until his study can be reconfirmed and the renal sensing site more precisely studied it is considered permissible to use the gain factor as an adjustable parameter within reasonable limits in simulating particular experiments. In certain cases, it may be desirable to postulate a shift in the normal operating point as well as gain (such as is thought to occur during clinical polycythemia; Hillman and Finch, 1974). In those situations E_o and G_1 may be separately adjusted.

Figure 2(B) illustrates the renal function curves shown in Figure 2(A), but for low release rates of erythropoietin (plotted on rectangular coordinates). There are no data to confirm this other than that of

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[*] A report was recently found which suggests, on theoretical grounds, that the relationship between PO_2 and hematocrit is semi-logarithmic and the relationship between PO_2 and erythropoietin is linear (Parer , 1970). We take issue with this analysis, but have not had time to evaluate it thoroughly.
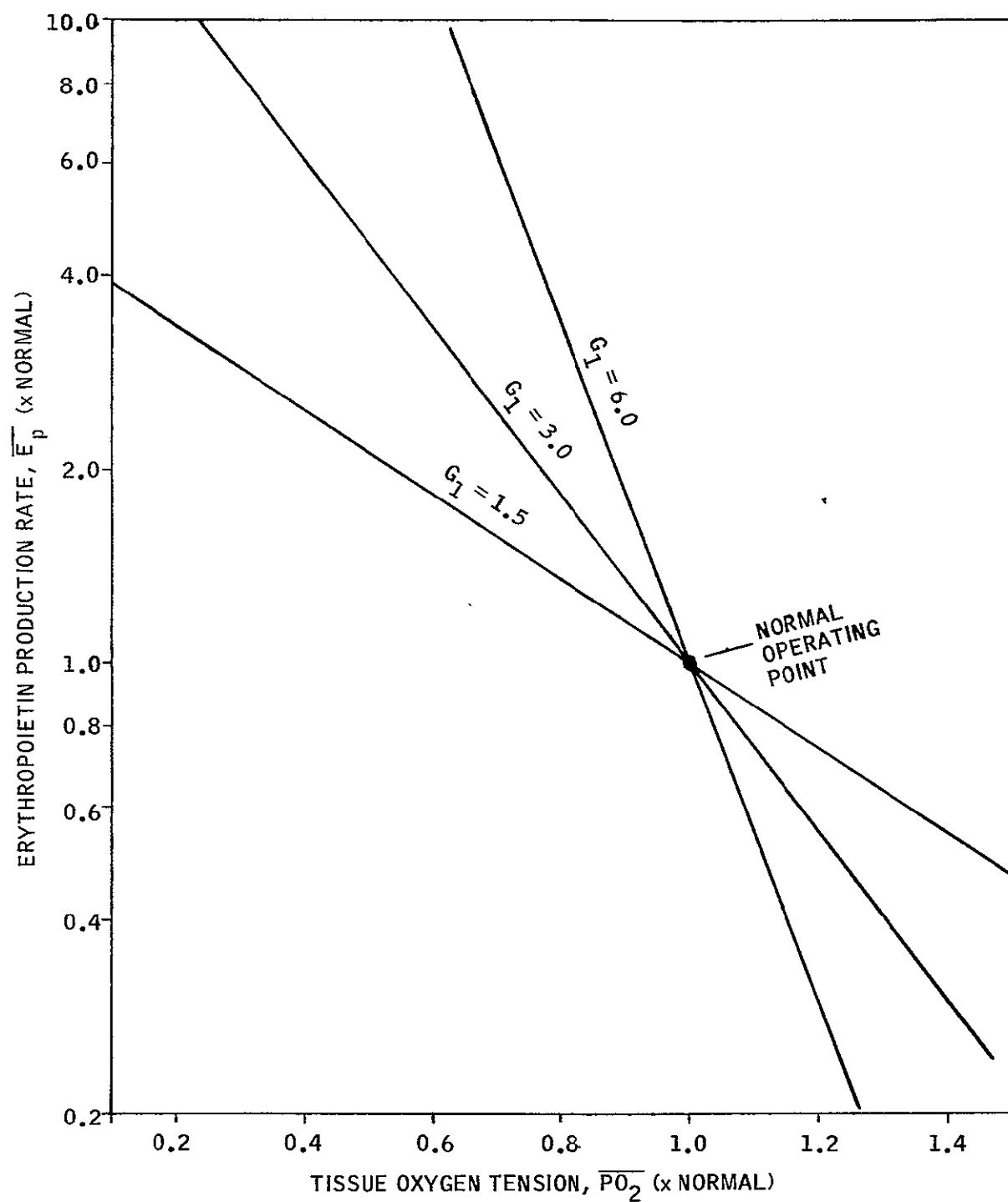
RENAL ERYTHROPOIETIN PRODUCTION RATE
FUNCTION CURVES

FIGURE 2(A)
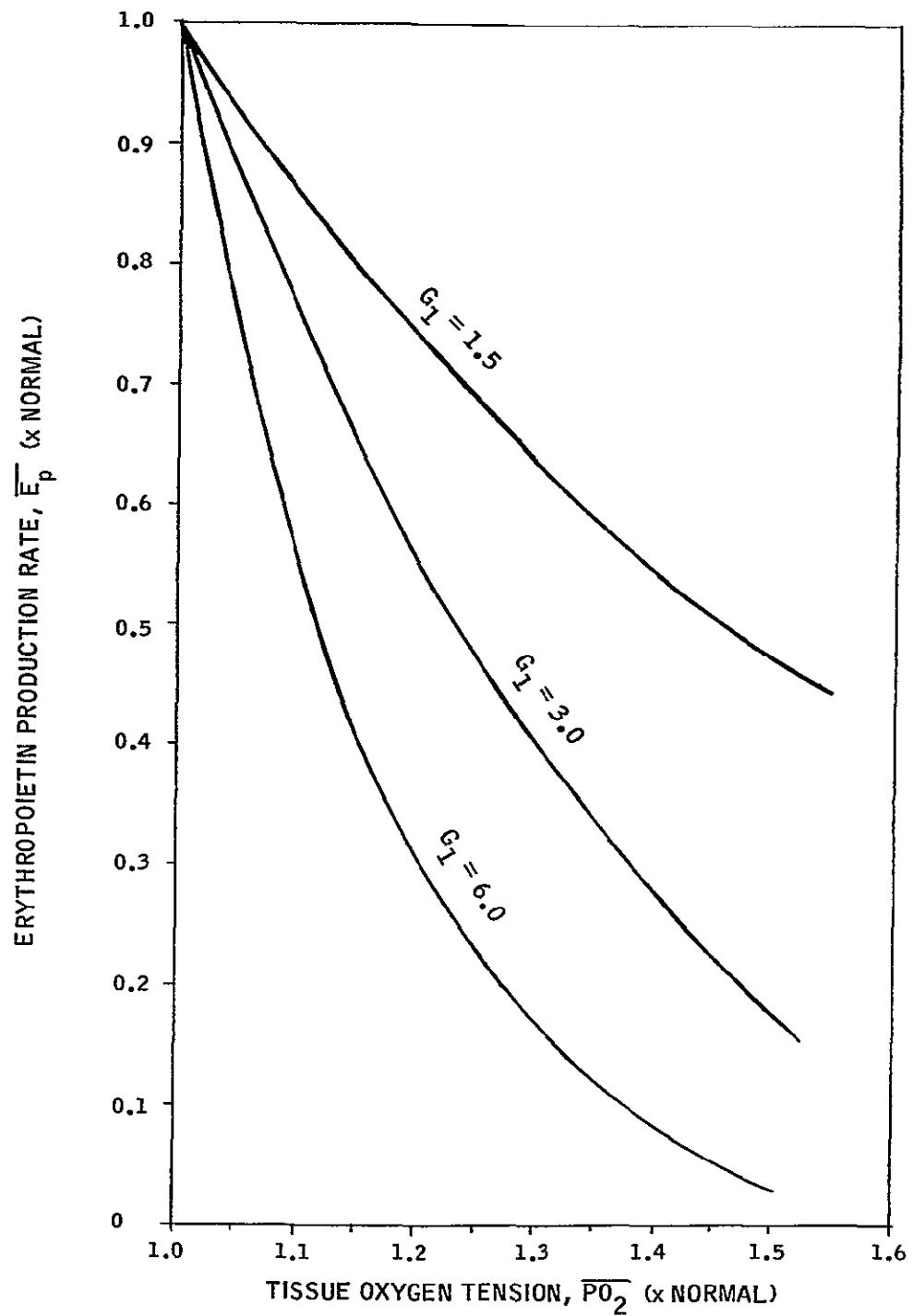
RENAL ERYTHROPOIETIN FUNCTION CURVE
FOR ABOVE NORMAL OXYGEN LEVELS

FIGURE 2(B)

Adamson's from which this was extrapolated by using Equation (2).
However, if bed rest and zero-g are accompanied by reduced levels
of erythropoietin, as is currently believed, (Dunn, et al, 1976), it is
crucial that the relationships shown in Figure 2(B) be verified.

Plasma Distribution and Concentration of Erythropoietin

The concentration of erythropoietin in the plasma is a function of
the rate of production, (E_p) the rate of clearance or destruction, (E_d)
and the volume of distribution (V). If it is assumed that the rate of dis-
appearance is proportional to the plasma concentration, then the first
order differential equation can be written for the rate of change of con-
centration ($[E]$) (Reissmann, et al, 1965; Mylrea, 1968):

$$\frac{V\,d\,[E]}{dt} = E_p - E_d \tag{3 a}$$

or

$$\frac{d\,[E]}{dt} = -\frac{E_p}{V} - k[E] \tag{3 b}$$

where k is the clearance constant denoting the fraction of plasma which
disappears per hour. Its numerical value equals one over the time con-
stant or log 2 divided by plasma half life. A normalized version of this
relationship can be obtained by letting

$$\bar{E}_p = E_p/E_{p,o} \quad \text{and} \quad \left[\bar{E}\right] = \left[E\right]\Big/\left[E\right]o \tag{4 a}$$

where

$$\left[E\right]_o = E_{p,o}\Big/kV = \text{control concentration} \tag{4 b}$$

(The control concentration is derived from Equation 3 b by letting $dE/dt = O$.)
Substituting Equations 4a and 4b, equation 3b becomes

$$\frac{d\,[\bar{E}]}{dt} = k\left(\bar{E}_p - [\bar{E}]\right) \tag{5}$$

which can be put into a form prepatory to numerical integration:

$$\left[\overline{E}\right] = \frac{0.693}{(T_E 1/2}\int\left(\overline{E}_p - \left[\overline{E}\right]\right)dt + \left[\overline{E}\right]_o \qquad (6)$$

where the clearance constant is expressed in terms of its half life $(T_E^1/2)$ and $\overline{E}_o$ is the initial normalized concentration defined as having a value of one. The steady-state plasma concentration is a function of the rate of production, the volume of distribution, and the clearance constant as shown by Equation 4 b. However, the _normalized_ steady-state plasma concentration (determined by setting the left side of Equation 5 to zero) is equal to the normalized rate of production and not dependent on dilution volume or clearance constant. That is,

$$\text{for steady-state,}\quad \left[\overline{E}\right] = \overline{E}_p \qquad (7)$$

On the other hand, non-steady-state normalized concentration, as shown by Equation 6, is inversely related to the clearance constant.

A value of the erythropoietin half-life does not appear to be well established for humans (Harris & Kellermeyer, 1970). Animal studies suggest that the half-life is larger for larger animals (1 - 4 hours in the rat (Reissman, et al, 1965) and 6 - 8 hours in the dog (Bozzini, 1966). In the few human studies reported, the subjects were patients with bone marrow defects and the measured half-life ranged from several hours to nearly two days. (Krantz and Jacobson, 1970). In this version of the model, the half-life of erythropoietin has been arbitrarily set at 12 hours, but can be changed prior to any simulation. Thus, if erythropoietin production is suddenly diminished as may occur during bed rest or zero-g, the plasma concentration will require at least one-half day to fall to half its initial value.

Red Blood Cell Production

There is an abundance of information to establish that there is a linear relationship between red cell production and the log of erythropoietin concentration over a wide range of supra-basal concentrations. This relationship is observed, for example, in obtaining the dose curves which relate erythropoietin and erythropoiesis in bioassay animals (i.e., Camiscoli and Gordon, 1970). Radioiron uptake over a period of several days is the parameter most often measured to represent erythropoietic activity. However, it has also been shown that if injected doses of erythropoietin into test animals are continued for up to four weeks, the large increases in red cell mass (a more direct measure of red cell production) can be related to the injected dose levels by a function nearly identical to the one described above (Gurney, 1962; Van Dyke and Pollycove, 1962). It is from these latter studies that estimates were obtained for equation parameters describing the mid and upper portion of the bone marrow function curves.

Figure 3 illustrates the generalized relationships and the empirical equations used to describe them in this version of the model. They are shown in two coordinate systems for convenience in relating them to curves appearing in the literature. As has been the convention in this report, the normal operating point is represented at the coordinates $\overline{RCP} = 1.0$, $\overline{E} = 1.0$. The nonlinear extension at the lower end of the erythropoietin scale is somewhat speculative, although it has been previously proposed (Caniscoli & Gordon, 1970), and is a reasonable shape for typical biological dose response curves (Riggs, 1970). As shown in Figure 3, the entire function curve is represented by piecewise fitting three empirical equations. For the purposes of this study, it was assumed that there is no basal production of red cells unless erythropoietin is present so that $P_o = 0$. The upper limit of red cell production

Erythropoiesis.

Suppressed	Enhanced	Maximal
$0 < \bar{E} < 1$	$1 < \bar{E} < \bar{E}_s$	$\bar{E} > \bar{E}_s$

Semi-log Coordinates

$\overline{RCP}$

P_m P_s P_1 P_o

0.5 1.0 10 100 log scale

Rectangular Coordinates

$\overline{RCP}$

P_m P_1 Control E_s P_o

1.0 100 linear scale

Erythropoietin Plasma Concentration ($\bar{E}$)
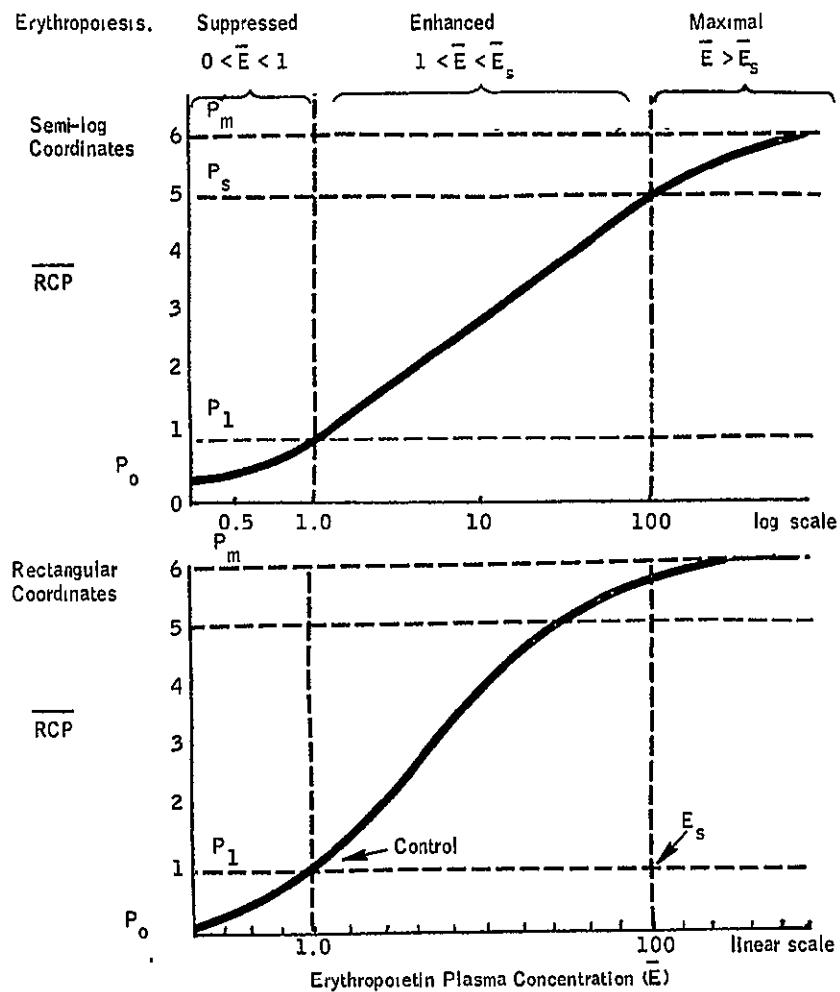
Range of Erythropoietin	Empirical Equation	
$0 < \bar{E} < 1$	$\overline{RCP} = P_o + (P_1 - P_o)\ \bar{E}^n$	(A)
	$n = G_2/(P_1 - P_o)$	
$1 < \bar{E} < \bar{E}_s$	$\overline{RCP} = G_2 \ln \bar{E} + P_1$	(B)
$\bar{E} > \bar{E}_s$	$\overline{RCP} = P_m + (p - P_m)\ e^{-k\bar{E}}$	(C)
	$k = G_2 \div \left[(P_m - P_s)\ e^{(P_s - P_1)/G_2} \right]$	
	$p = P_m - (P_m - P_s)/e^{-G_2/(P_m - P_s)}$	

Values Used In Present Study

$P_o = 0$
$P_1 = 1$
$P_s = 5$
$P_m = 6$

$n = G_2$

$k = G_2/e^{4/G_2}$

$p = 6 - e^{G_2}$

EMPIRICAL FIT OF DOSE RESPONSE RELATIONSHIP FOR ERYTHROPOIETIN PLASMA CONCENTRATION ($\bar{E}$) AND RED CELL PRODUCTION RATE ($\overline{RCP}$) (VALUES: X NORMAL)

FIGURE 3

has previously been suggested to be from five to seven times normal (Mylrea & Abbrecht, 1971) and, therefore, P_m was set to a value of 6. The normal operating point is set by letting $P_1 = 1.0$. Other values of P_1 will shift the curves in the y-axis direction and this parameter can be used to test hypothesis regarding threshold effects.

Figures 4(A) and 4(B) were drawn using these parameter values and several different choices for the gain constant, G_2 (slope of the mid-portion line). In addition, Figure 4(B) illustrates the effect of two different values of P_o (the basal level of red cell production over the entire range of suppressed erythropoiesis. The most important parameters in these relationships are P_o and G_2. The need for a separate empirical relationship for the low end of the erythropoietin scale becomes more obvious by considering the dashed line in Figure 4(B). This line, representing the extension of the mid-portion line (curvilinear on rectangular coordinates), has an unrealistic infinite slope for zero values of erythropoietin and red cell production is suppressed entirely for values of erythropoietin concentration that may not be much below normal.

It is unfortunate that data directly related to this bone marrow function curve are unavailable for the human system. Also, due to the difficulty of measuring subnormal levels of erythropoietin concentration, information on this range of the curve (which relates to the situation probably encountered during bed rest and weightlessness) is completely lacking for either humans or animals. Bioassay dose response calibration curves in animals can be used to estimate the gain or sensitivity parameter, G_2, (by assuming that 100% radioiron utilization is equivalent to about six times normal RBC production rates), but these studies are often highly variable even in the hands of a single investigator (Shore, et al, 1968). Similar studies performed on humans appear to be non-existent, presumably due to the large amount of erythropoietin required. Animal studies,
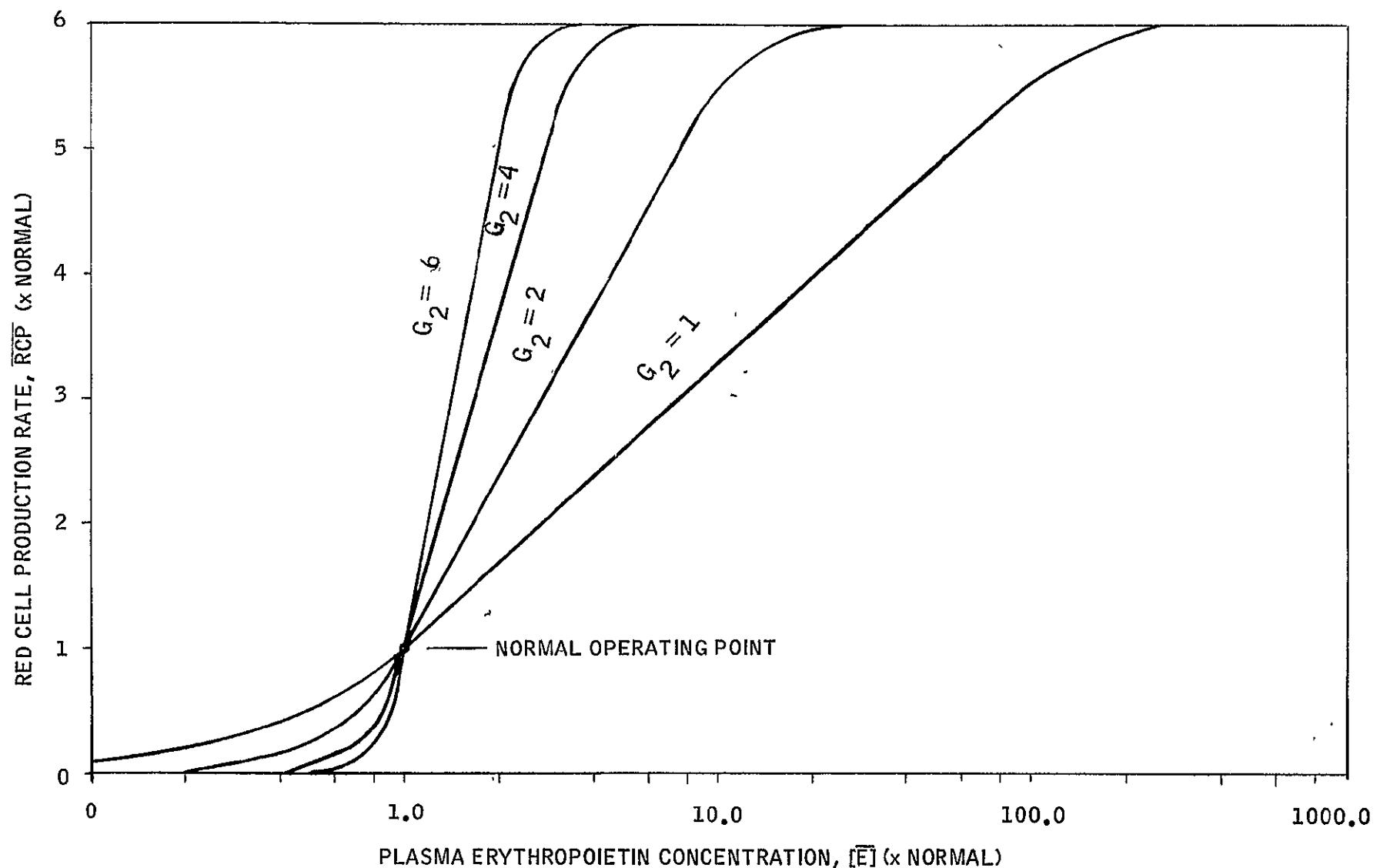
BONE MARROW RED CELL PRODUCTION FUNCTION CURVES

FIGURE 4(A)

DEPRESSED ERYTHROPOIESIS	ENHANCED ERYTHROPOIESIS
$RCP = P_0 + (1-P_0)\bar{E}^n$ $n = G_2/(1-P_0)$	$\overline{RCP} = G_2 \ln \bar{E} + 1$

RED CELL PRODUCTION RATE, $\overline{RCP}$ (x NORMAL)

$G_2 = 4.0$

$G_2 = 0.4$

NORMAL OPERATING POINT

$P_0 = .5$

$P_0 = 0$

$P_0 = .5$

$P_0 = 0$

PLASMA ERYTHROPOIETIN CONCENTRATION

(x NORMAL)
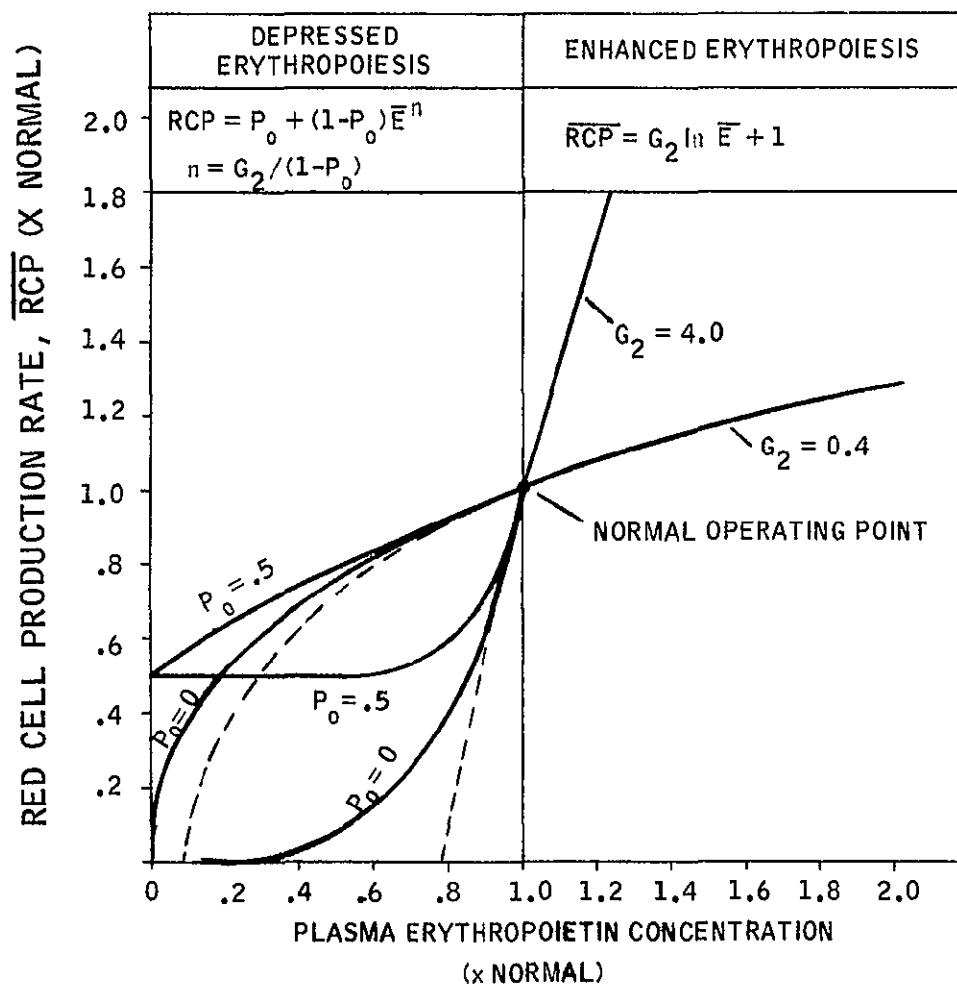
BONE MARROW RBC FUNCTION CURVE FOR LOW
CONCENTRATIONS OF ERYTHROPOIETIN

FIGURE 4(B)

in which red cell mass changes were measured as functions of the erythro-poietin dose injected, are not directly comparable inasmuch as plasma concentrations were not measured. However, Mylrea & Abbrecht (1971) have used data of this type in their computer model of erythropoiesis reg-ulation to successfully simulate hypoxic responses of mice. Following their example, we have reviewed several similar studies and derived values of G_2 for mice $G_2 = 0.4$;(Gurney, 1962) and rats $G_2 = 1.0$;(Van Dyke & Pollycove, 1962)). Preliminary analysis of more recent bioassay data in animals (Erslev, 1975) confirmed these findings.

It is possible to estimate values of the parameter G_2 for humans in a more indirect fashion. In the next section, it will be shown that the overall gain, G, of the renal-bone marrow axis (see Equation 1), is given by $G = G_1 \cdot G_2$. Values of G were employed in the previous version of the model and were determined for bed rest and hypoxia by parameter estimation techniques to fall in the range of 5 to 13 (Leonard, 1976). If the data of Adamson, previously presented, is used as an estimate of G_1 $(G_1 = 2.8)$, then it is possible to determine that G_2 is between about 2 and 5. Values in this range were used in the computer studies presented in later sections of this report with apparent success in simulating bed rest and hypoxia. If these results are confirmed by experiment, it would appear that the sensitivity of bone marrow production to erythropoietin increases with the size of the animal.

Overall Renal-Bone Marrow Function

A more visual understanding of the relationships discussed previously can be obtained by determining the overall dose response curve of the com-bined kidney-bone marrow axis; that is, the relationship between tissue oxygen tension and red cell production. The results are shown below for the low and mid-portion range of erythropoietin production. The proced-ure in both cases involved mathematically combining the renal function

curve $(\overline{PO}_2 \longrightarrow \overline{E}_p)$ with the steady-state normalized plasma distri-

bution function ($[\overline{E}] = \overline{E}_p$) and the bone marrow function curve

($[\overline{E}] \longrightarrow \overline{RCP}$) in such a way as to eliminate the erythropoietin factors.
The renal function curve is given by Equation (2 b) with $E_o = G_1$, and
the bone marrow function curves are shown in Figure 3 as Equation (A)
or (B) for the lower and mid-portion ranges of erythropoiesis, respec-
tively.   The results of these calculations are:

Mid-Range: Enhanced Erythropoiesis

$$\overline{RCP} = G\left[1 - \overline{PO}_2\right] + P_1 \qquad \text{for} \quad \overline{PO}_2 > 1 \qquad (8)$$

where $G = G_1 \cdot G_2$

Low Range: Suppressed Erythropoiesis

$$\overline{RCP} = P_1\, e^{-G/P_1(\overline{PO}_2 - 1)} \qquad \text{for} \quad \overline{PO}_2 < 1 \qquad (9)$$

It should be noted that Equation   (8) is an equation of a straight line and
is identical with Equation (1) which was used in the previous version of
this model.   This implies that the results obtained with both models will
be identical with regard to the overall hematological response in those
cases where an enhanced erythropoietic effect was simulated (i. e. , alti-
tude hypoxia).   However, due to the nonlinearity of Equation (9), con-
ditions involving suppressed erythropoiesis (i. e. , bed rest, red cell
infusions) will show a somewhat different and hopefully an improved
response.

It is important to observe from Equations (8) and (9) that for a
given level of tissue PO_2 (and assuming the normal control level, P_1,
is constant), the only parameter that determines RCP is the combined

gain constant, G. Thus, it is not the individual values of the renal gain
factor, G_1, or the bone marrow gain factor, G_2, which effect the overall
hematologic response (i.e., the change in red cell mass), but rather the
product of the two. Until more precise information regarding the renal
erythropoietin response becomes available it will only be possible to use
the model to predict the overall gain factor rather than its component
parts.

Equations (8) and (9) have been plotted in Figures 5(A) and (B) for
a range of values of G, and using the normal value of $P_1 = 1$. These
curves represent the entire feedback circuit of the erythropoiesis model,
and they were included in the previous model in linearized form. It is
believed that the nonlinearities which have been added during this study
will improve the basic model response. The function for suppressed
erythropoiesis (for values of PO_2 greater than 1.) has been plotted
separately in Figure 5(B) on semi-logarithmic coordinates. This illus-
tration relates directly to regulation of erythropoiesis during bed rest.
The bed rest simulations shown later in this report required a value of
G between 8 and 12 for optimum response. The steep slope of the curves
in this range may be suggestive of the mechanism which suppresses red
cell production during bed rest and weightlessness. If PO_2 changes are
related directly to hematocrit changes, as we had argued previously, then
an increase of only 5% in hematocrit could result in about a 40% decrease
in red blood cell production assuming a gain of 10. In their analysis of
the red cell mass changes during the 28-day JSC/Baylor bed rest study,
Johnson and Driscoll (1977) estimated that the production rate may have
decreased 25% for an average hematocrit change of +5%. (It will be shown
later that during actual simulation of this study, the mean decrease in red
cell production predicted by the model, with appropriate time delays and
nonlinearities superimposed on the curves of Figure 5(B), is closer to
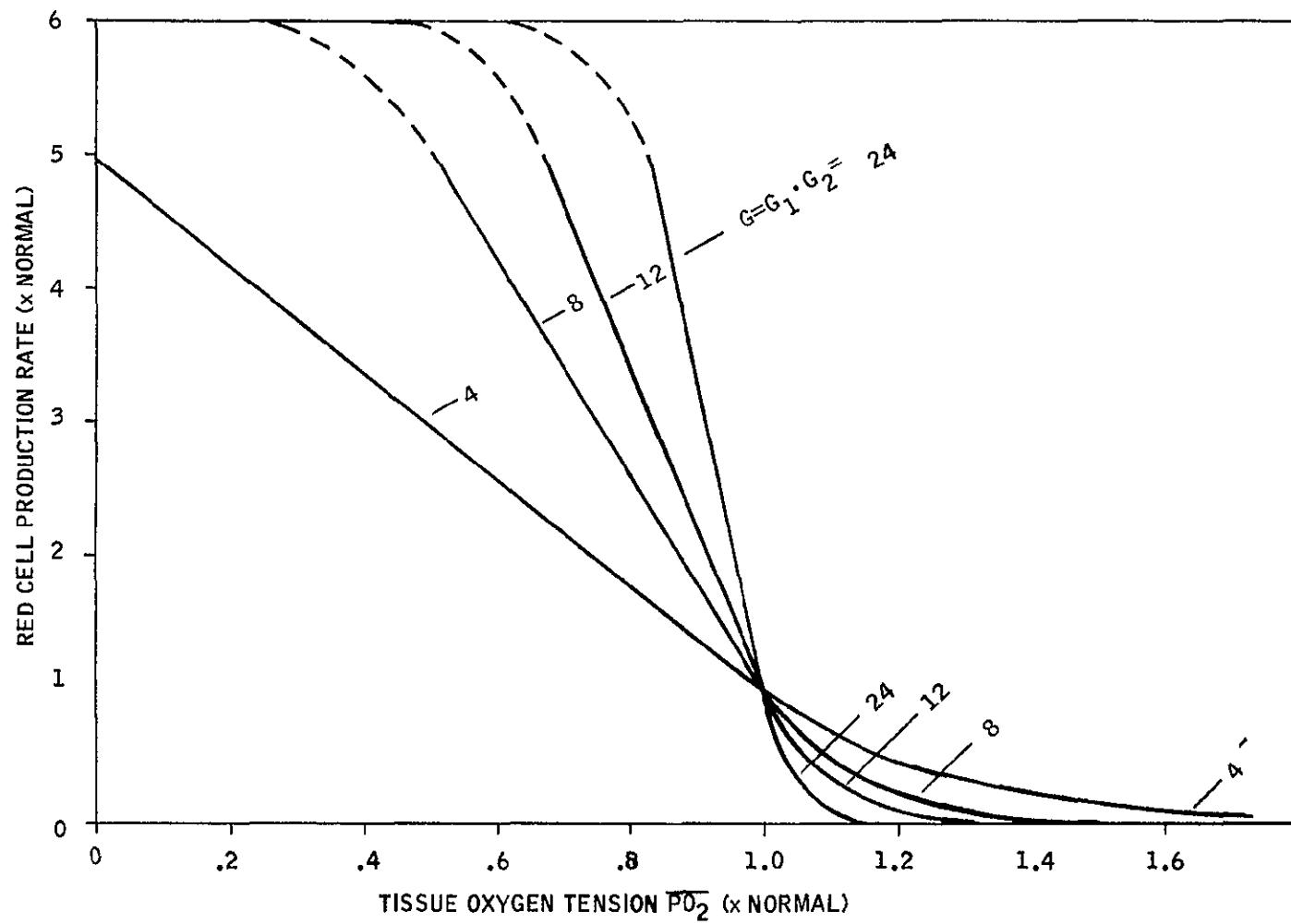
COMBINED RENAL-BONE MARROW FUNCTION CURVES
SHOWING EFFECT OF TISSUE OXYGEN ON ERYTHROPOIESIS

FIGURE 5(A)
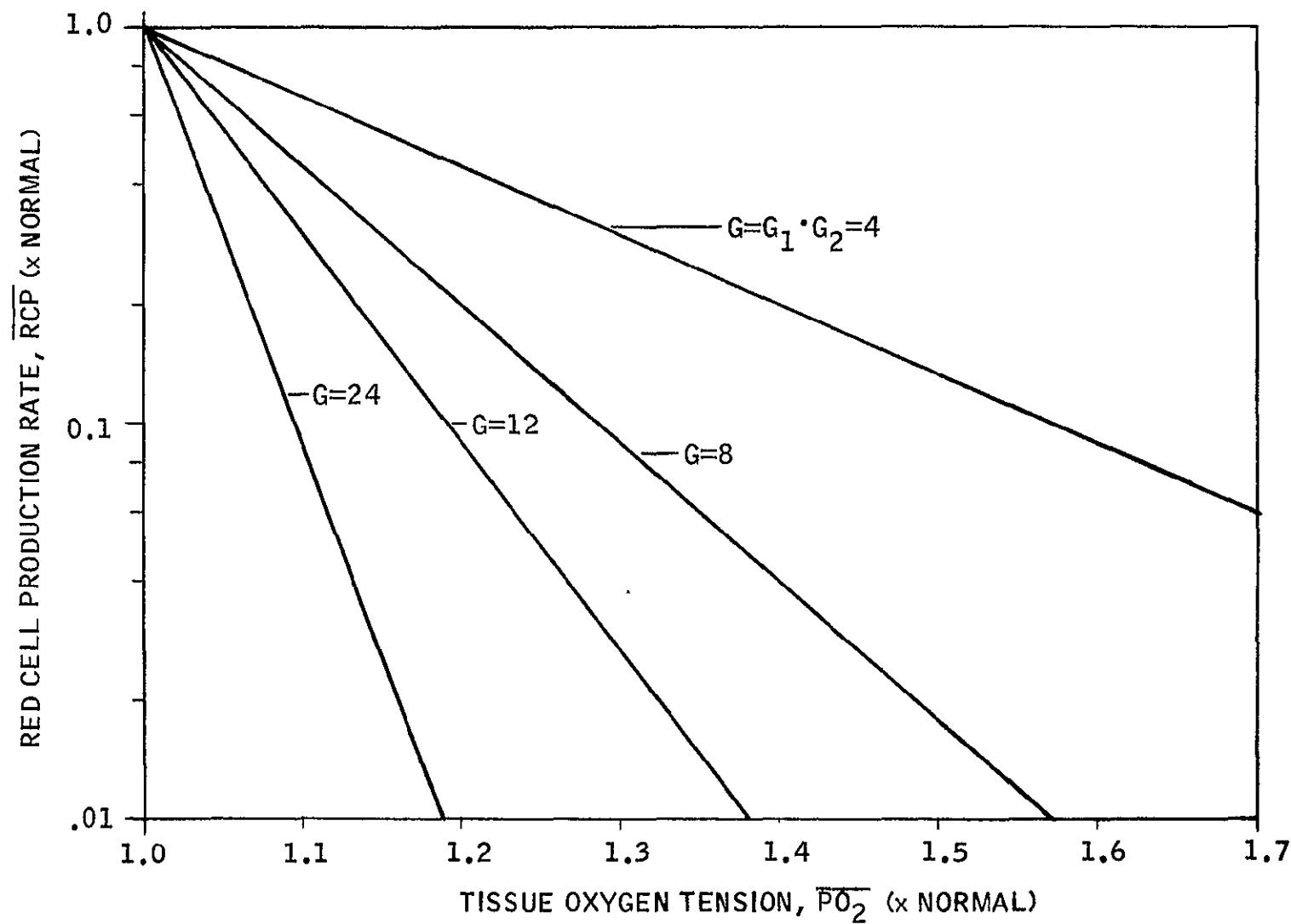
COMBINED RENAL-BONE MARROW FUNCTION CURVES
SHOWING DEPRESSED ERYTHROPOIESIS AT
HIGH OXYGEN TENSIONS

FIGURE 5(B)

27%). It should be noted that a finite basal production of red cells, given by P_o, would have the effect of decreasing the slope of each of the curves in Figure 5(B).

Thus, even without implementing these changes in the simulation model, it is possible to predict a significant erythropoietic suppression effect during bed rest due to the changes in hematocrit alone. This conclusion is not different from that reached in previous systems analysis studies (Leonard, 1974, 1976).

Bone Marrow Transit Time Delay

The addition of the new erythropoietin and red cell production elements did not, by themselves, constitute a significant improvement in model response. As will be demonstrated later, the dynamic behavior of the erythropoietin response to stress was nearly identical to the red cell production response (see Figure 21). Since the latter effect was already included in the previous version of the model, no new information was obtained. It became apparent that not only was this duplicative response unrealistic, but that it could be easily remedied by including the well-known bone marrow transit time delay effect. Implementing this effect permitted the previous changes in the model to take on new significance, and the model at this stage became an obvious improvement over its predecessor.

A simple first-order time delay effect was accomplished with the formulation (in Fortran notation)·

$$RCPZ = RCPZ + (RCP - RCPZ)/Z$$

where RCP is the red cell production rate determined instantaneously from the function curves of Figure 4 at the current level of $[E]$, Z is the time constant for the delay, and RCPZ is the delayed production rate. In other words, if RCP should change value, RCPZ would approach the

value of RCP with a time constant of Z. The effect of varying the time

constant is shown in Figure 6 in which a simulated change in altitude was

initiated at T = 0, stimulating an increase in erythropoietin and red cell

production. (An open loop model was used in this simulation and the

time delay for erythropoietin production was eliminated; these changes

ensured that the increasing red cell mass would not have a feedback

effect on the response and that only a pure bone marrow effect would be

observed.) With no time delay (Z=0) there is an instantaneous rise in

red cell production. As the value of Z increases the rise toward equi-

librium requires more time.

It is possible to compare reticulocyte date (often taken as repre-

sentative of red cell production rates; Hillman & Finch, 1974) obtained

during altitude studies (e. g. , Faura, et al, 1969) with these theoretical

curves to ascertain their accuracy. However, an equivalent but more

precise reference would be the radioiron uptake curves obtained from

normal unstressed human subjects.[*] The shaded area of Figure 6 repre-

sents the normal range of these tracer responses derived from clinical

data. It is obvious that none of the first order delay curves are truly

representative of the more complex sigmoid shape found in the real

system. In the human, a stimulus for erythropoiesis does not produce

significant change in bone marrow release until after the first day while,

with a first-order delay, the greatest rate of change occurs at the outset.

As a compromise a time constant of 4 days was chosen for this study

(with the exception noted below) to simulate the bone marrow delay.

[*] It is possible to show on theoretical grounds that for a compartment
with delayed flow, the elution curves resulting from a step flow dis-
turbance at the inlet and that of a tracer material injected as a step
at the inlet during steady-state flow are identical. In the human the
transit time is shortened slightly when the bone marrow is acutely
and strongly stimulated so that this equivalency is not exact.
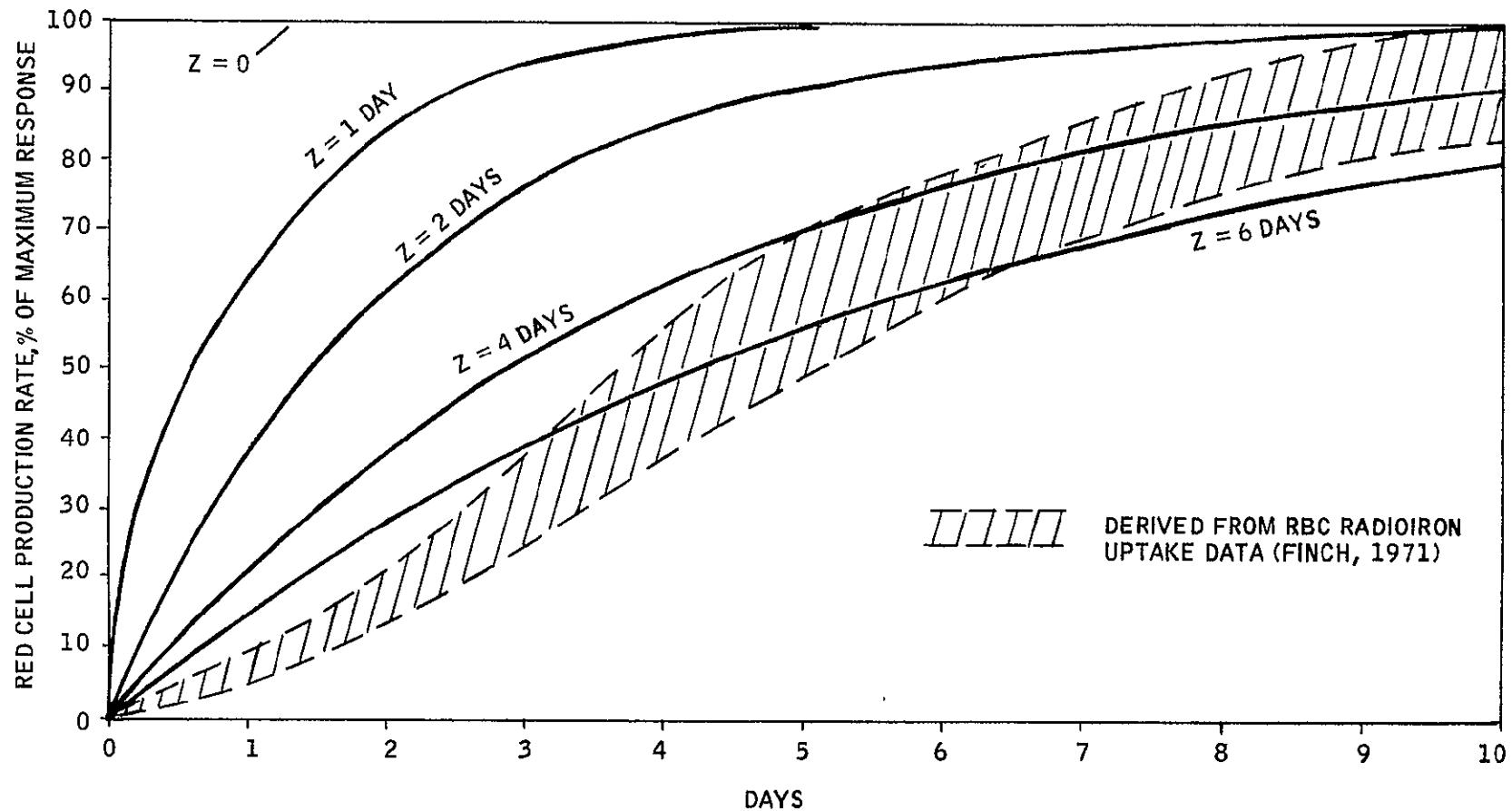
EFFECT OF FIRST-ORDER TIME DELAY CONSTANT ON RED CELL PRODUCTION RATE
FOLLOWING HYPOXIC STIMULUS

FIGURE 6

While results with a first-order delay were considered a marked improvement, simulations of certain experiments suggested that a second order delay or a simple transport lag would be even more realistic. Attempts to implement a second order delay were only partially successful. Figure 7 shows the hypoxic response of the model with a second order delay in red cell production showing the characteristic sigmoid shape.   This is compared to the response using the same first order delay of Figure 6. The effective time constant for both curves is approximately 4 days. Application of the second order delay was made in a single simulation study (shown later in this report) and resulted in increased fidelity. Unfortunately, it appears that the particular delay function used in this case does not have general applicability and time does not permit a thorough evaluation.   It is suggested that this effort be continued.

2.2   OTHER MODEL IMPROVEMENTS

P_{50} Shift of Oxy-Hemoglobin Dissociation

An improvement in the oxygen-hemoglobin dissociation curve function was made in order to test hypotheses regarding shifts in oxy-hemoglobin affinity during certain stress conditions.   The capability was added to the model to shift the position of the dissociation curve in accord with known effects of hydrogen ion, CO_2, temperature, or 2,3,-DPG (diphosphoglycerate) on the P_{50} value (the oxygen tension at which 50% of the hemoglobin is saturated).   Increasing amounts of all these quantities shift the curve to the right (increases P_{50}) thus decreasing the affinity of oxygen and hemoglobin.   The effects of 2,3-DPG, in particular, are of interest because of its unique role in regulating oxygen supply (Finch & Lenfant, 1972), and because of its possible contribution to erythrokinetic changes during bed rest or weightlessness (Johnson, et al, 1974).
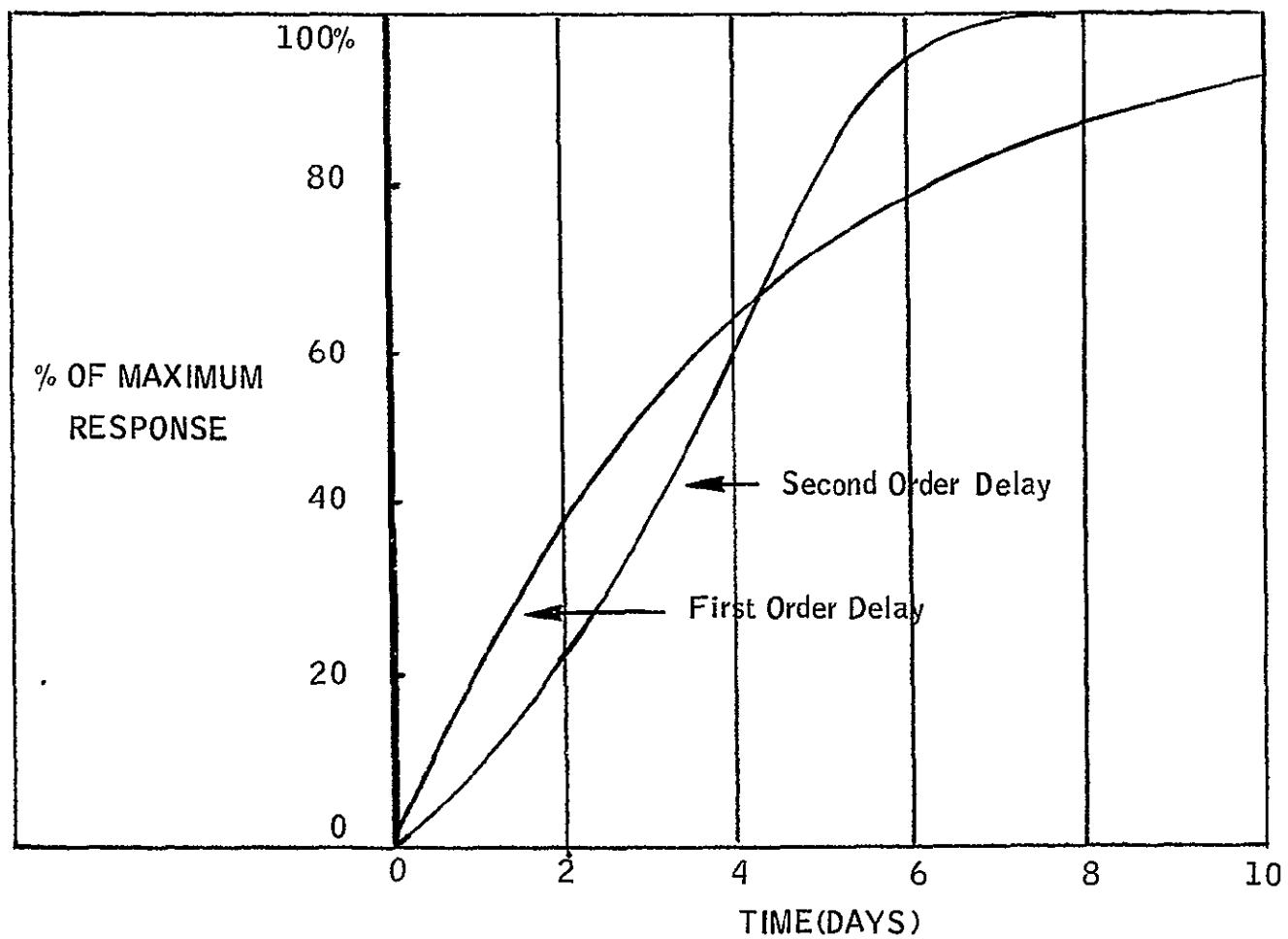
EFFECT OF FIRST AND SECOND ORDER DELAYS ON RED CELL
PRODUCTION RATE FOLLOWING HYPOXIC STIMULUS

FIGURE 7

The original formulation of the oxygen-hemoglobin dissociation curve used in this model contained the elements to perform shifts in P_{50} in response to changes in temperature, pH, and base excess, but not to DPG (Aberman, et al, 1973). This capability was not utilized at the time. The quantitative effect of DPG on the P_{50} value has been recently reported by a number of investigators for various conditions (i.e., Finch & Lenfant, 1972; Woodson, et al, 1970; Bellingham, et al, 1971) and can be added to the dissociation curve algorithm. However, until the levels of DPG during bed rest or weightlessness are known more accurately, it was decided to merely create a mechanism for adjusting the P_{50} as an input parameter to the model (i.e., oxygen-hemoglobin affinity is controlled by the user rather than being self-regulating in the model). The formulation adopted :(a P_{50} input change is converted to an effective blood temperature which shifts the curve) should be considered preliminary and should not be used outside the range $24 < P_{50_O} < .32$, where P_{50_O} is the normal value equal to 26.73 mm Hg. Figure 8 was prepared from computer generated graphs and shows the dissociation curve for the normal case and where P_{50} has been changed by $\pm$ 4 mm Hg. These curves agree well with data from the literature (Harris & Keller-meyer, 1970).

A schematic representation of the current model is shown in Figure 9 including all of the modifications discussed up to this point. The essential features of this model have been described in detail elsewhere (Leonard, 1974, 1976).

Input/Output Software Modifications

Several modifications, independent of model structure, were implemented to provide the user additional flexibility in simulating experimental, environmental and pathological stresses:
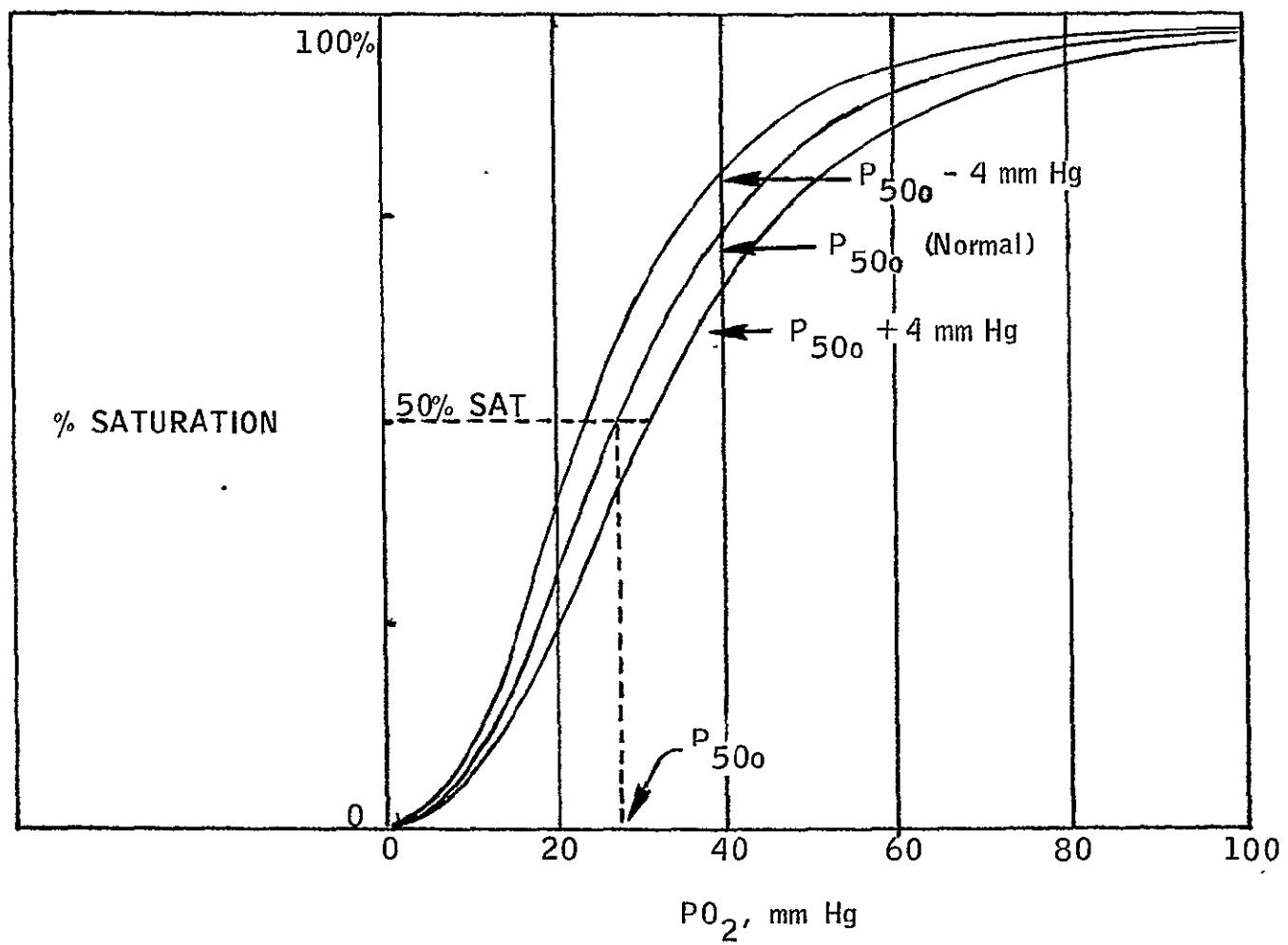
OXYHEMOGLOBIN DISSOCIATION CURVES USED IN MODEL
SHOWING EFFECT OF CHANGING P_{50} PARAMETER

FIGURE 8
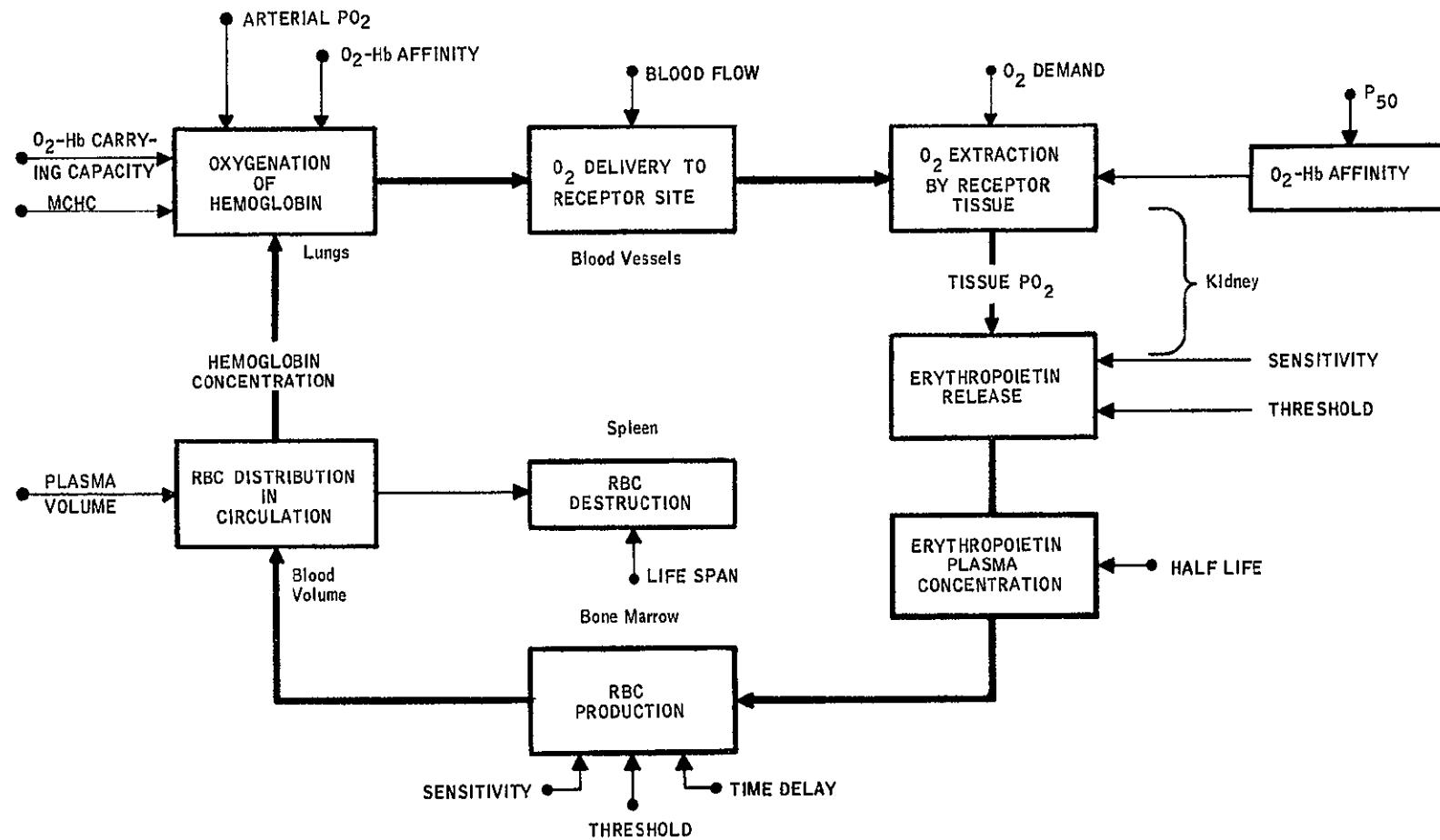
PHYSIOLOGICAL SYSTEMS DIAGRAM FOR CONTROL OF ERYTHROPOIESIS

FIGURE 9

a.   <u>Data Storage</u>

Experimental or idealized hematologic data (i.e., plasma volumes,
red cell mass, hematocrit, etc.) may be entered into a data block
associated with the model.   Each value is paired with a time value.
Either steady-state or kinetic data may be used.   It is convenient
to normalize the data with respect to the model's control values.
If discrete kinetic data are used an interpolation algorithm deter-
mines the values at any intermediate point in time.   This capability
has been used for two purposes thus far.   First, to display the data
on the associated CRT graphics unit and thereby visually comparing
it with the model's response.   In this way model parameters can be
more effectively adjusted (either manually or automatically) until
reasonable agreement between the two are obtained as suggested by
Figure 10.   Secondly, the input of kinetic data can be used as a
time-varying driving function for parameters which would otherwise
be fixed (see b.).

b.   <u>Hematocrit and Plasma Volume Data as Driving Functions</u>

The model, as first conceived, uses plasma volume as a fixed para-
meter.   More recently, the capability was added to allow plasma
volume to be added as a time-varying parameter to provide more
realistic results for altitude hypoxia and, in the case of a particular
bed rest study, as the only driving function for the simulation
(Leonard, 1976).   However, in preparation for Skylab simulations,
in which inflight hemoglobin (proportional to hematocrit) rather than
plasma volume measurements were obtained, an additional mode of
driving the model with hematocrit data was implemented.   In this
mode, the experimental change in hematocrit varies oxygen trans-
port, and eventually red cell mass, by feedback regulation; plasma
volumes are then determined from these two quantities.   This is
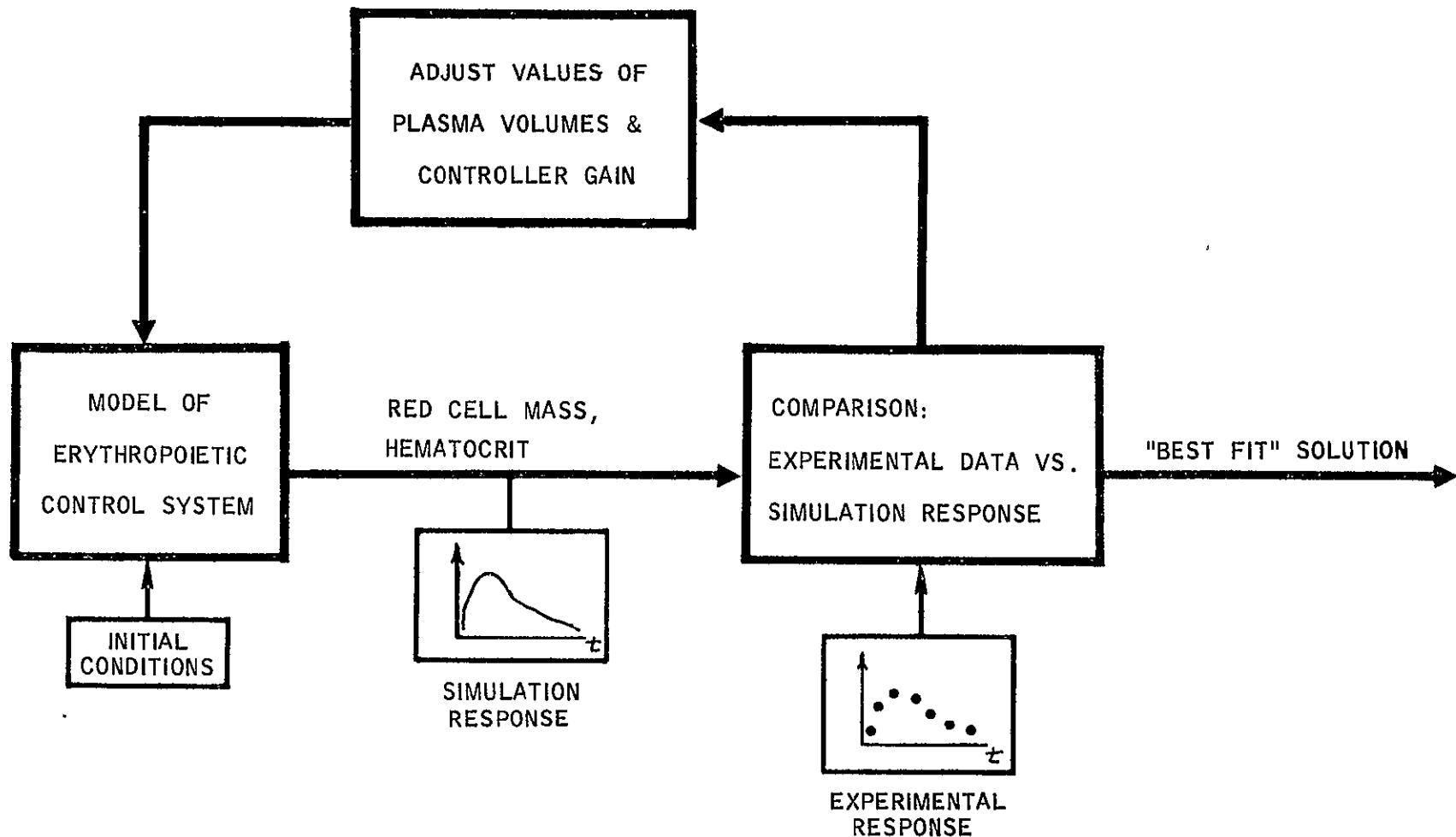
SIMULATION PROCEDURE FOR PARAMETER ESTIMATION

FIGURE 10

entirely equivalent to the previous method of directly using plasma volume changes to vary the hematocrit and thereby create a stimulus for red cell adjustment. Both of these driving modes were used in the present study. In using hematocrit data for driving the model or comparison with model response, the user should be aware that the hematocrit utilized or computed by the model refers to the whole-body hematocrit rather than peripheral hematocrit.

c. Simulated Infusions of Red Cells and Erythropoietin

The capability now exists to simulate impulse infusions of red cells and erythropoietin. These functions (RCVO and EINF, respectively) have been used to simulate laboratory studies involving red cell hyper-transfusion and fractionated/multiple injections of erythropoietin.

d. Removal of Variable Oxygen Diffusivity

The original model contained an element which permitted oxygen transport across the renal capillaries to increase exponentially with the degree of hypoxia present. This formulation was taken from Guyton's model, but there is little evidence in the literature to support the concept that renal capillaries respond to hypoxia in the same way as the extra-renal capillaries. Until more information is available regarding the renal sensing site for PO_2 or for renal oxygen transport in general, the extra degree of complexity was thought to be superfluous and this element was removed. This necessitated changing the overall gain of the model somewhat in order to obtain similar results. During an hypoxic response, the tissue PO_2 now varies over a wider range.

3. 0   VALIDATION STUDIES USING THE IMPROVED ERYTHROPOIESIS
       MODEL

An important phase of model development is to assure that each
element contained in the model responds appropriately to known stresses.
Version I of the model has been previously subjected to this testing pro-
cedure.   The additional capability of Version II of the model requires
verification of such new elements as the erythropoietin response, time
delays effects, bone marrow response, DPG effect, etc.   In this section,
we will document three studies which indicate that these elements respond
appropriately and in so doing will demonstrate the increased flexibility of
the model.

3. 1   EFFECT OF SINGLE AND MULTIPLE DOSES OF ERYTHROPOIETIN

The effect of single, multiple, and fractioned doses of erythropoietin
in mice were studied by Gurney, et al (1961).   They found that a single
dose of erythropoietin will initiate a wave of bone marrow erythropoiesis
activity as indicated by the reticulocyte response.   This event was simu-
lated by an impulse change in erythropoietin concentration and is shown in
Figure 11(A).   A second simulation was performed by fractionating the
single dose into four equal doses and administering them one day apart
(Figure 11(B)).   This experiment was also performed by Gurney who
unexpectedly found a greater response to repeated doses of erythropoietin.
While this effect can also be noted in our simulations, it is due to the
effect that erythropoietin (with a half-time clearance of 12 hours for
humans) does not disappear completely from the plasma before the next
dose is administered.   In the mouse the half life of erythropoietin is
considerably shorter and other mechanisms must be postulated to explain
the effect.   One such mechanism involves postulating an increased poten-
tiating effect of erythropoietin based on its concentration history (Schooley,
1965)   In terms of the model, this involves a shift in gain of the bone
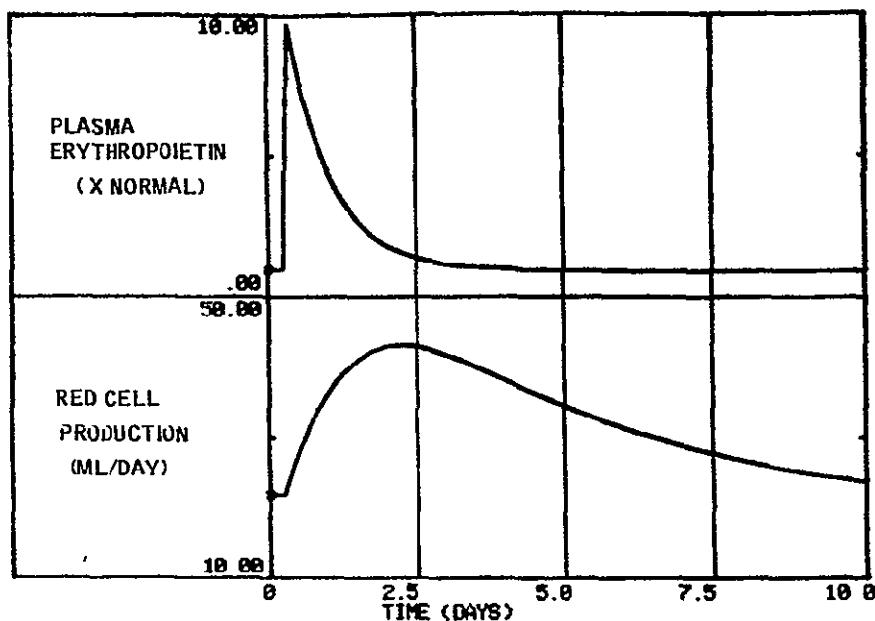
(A) BONE MARROW RESPONSE TO SINGLE DOSE OF ERYTHROPOIETIN
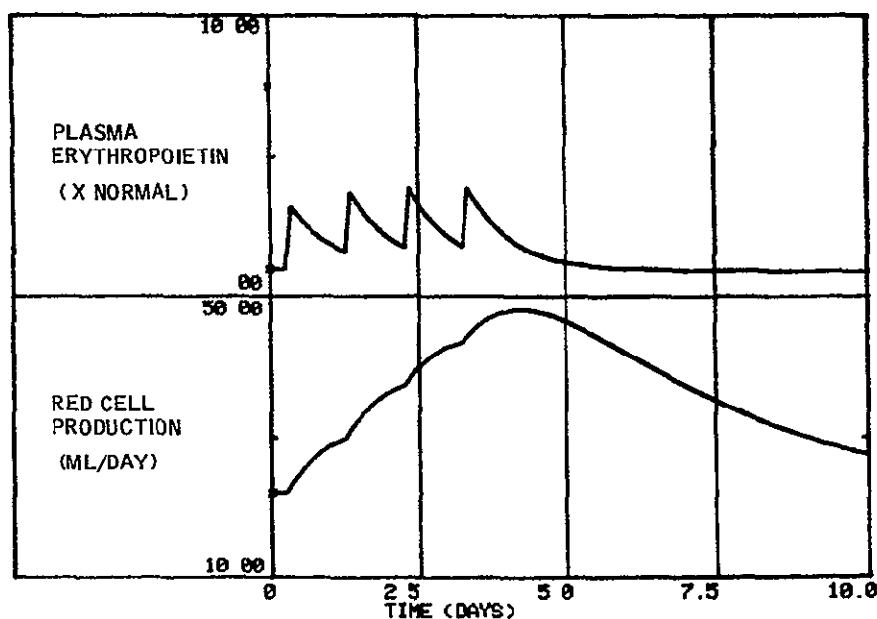
(B) BONE MARROW RESPONSE TO MULTIPLE DOSES OF ERYTHROPOIETIN

RESPONSES TO ERYTHROPOIETIN INJECTIONS:
SINGLE DOSE VS. EQUIVALENT FRACTIONATED DOSE

FIGURES 11(A) & (B)

marrow function curve. It is mentioned here because this mechanism
has been found useful for explaining certain responses in polycythemic
animals and has been successfully employed in computer models by
Kretchmar (1966) and Mylrea & Abbrecht (1973). It might prove fruitful
to consider this effect for incorporation into the present model.

The erythropoietic response curves of Figure 11(A) and (B) are much
broader in appearance than shown by Gurney, et al, in mice. There are
no comparable data available for humans. While this may be a species
difference, we decided to test the possibility that a more realistic bone
marrow transit delay effect would improve the response. In Figure 11(C),
the effect of using the second order delay function, previously shown in
Figure 7, is compared to the simulation of Figure 11(A) in which a simple
first-order delay was used. The impulse function of erythropoietin was
identical in both cases, but the response with the second order effect has
a greater resemblance to Gurney's data. In both cases, however, the
wave of erythropoiesis realistically continues to completion despite the
rapid disappearance from plasma of erythropoietin (Finch, et al, 1970).

3.2   RESPONSE TO ALTITUDE HYPOXIA

A previous study of altitude hypoxia showed excellent agreement
with data from monkeys during a nine month ascent-descent study (Leonard,
1976). The model used in that case, however, did not include erythro-
poietin. The short term erythropoietin response to acute altitude stress
has been well described but is not completely understood (Abbrecht &
Littell, 1972). Acute hypoxia results in an increase in erythropoietin
which reaches a maximum on the first or second day and then falls to
levels close to normal. The transient nature of the erythropoietin
response has been postulated by various authors to be the effect of:
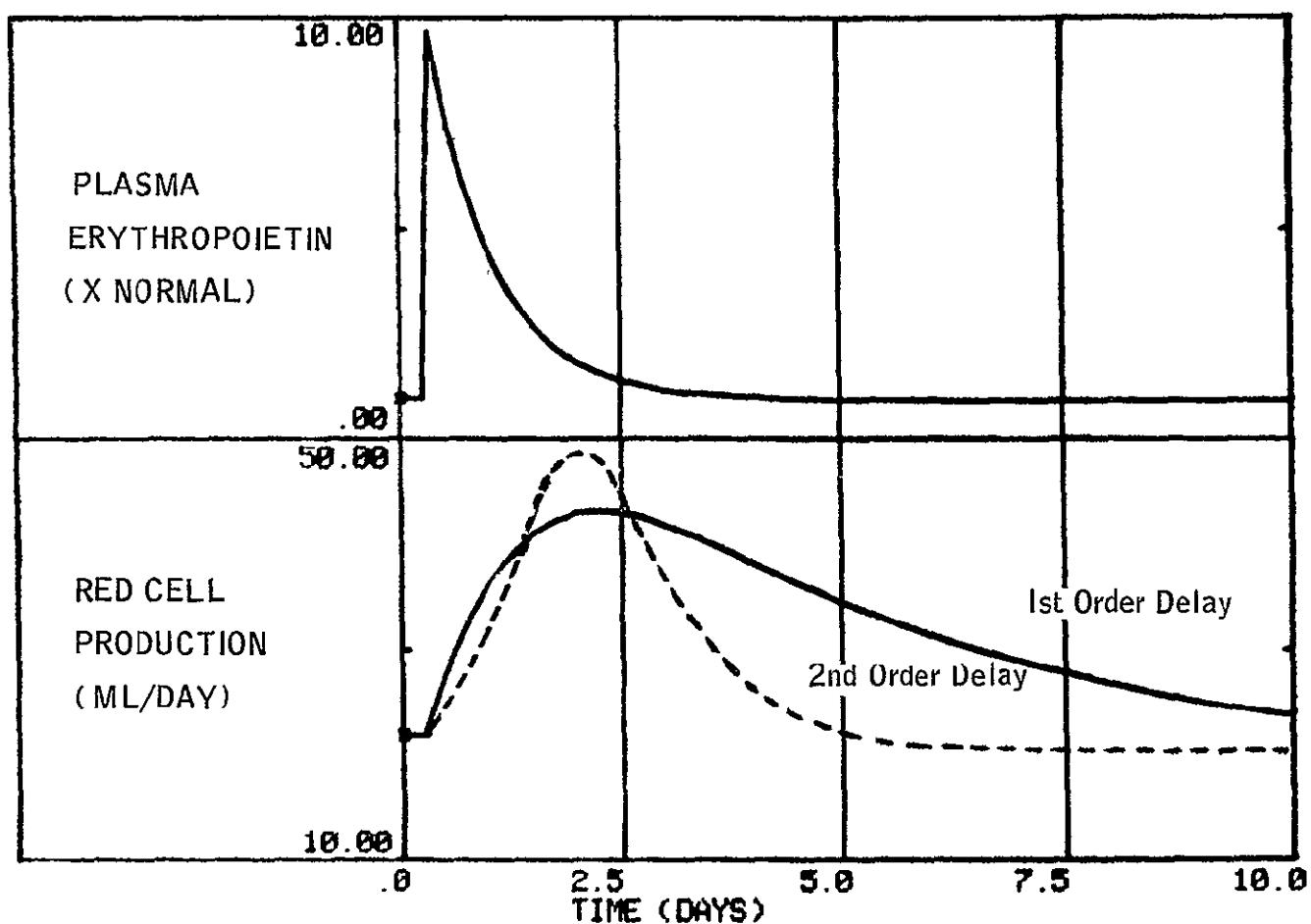
EFFECT OF FIRST AND SECOND ORDER BONE MARROW TIME DELAYS
ON RESPONSE TO ERYTHROPOIETIN DOSE

FIGURE 11(C)

a)   adaptation processes in oxygen transport,   b)   release of performed erythropoietin, and c)   increase marrow utilization of the hormone (Mylrea and Abbrecht, 1971, 1973; Krantz and Jacobson, 1970).   We have performed a preliminary study of altitude hypoxia including the adaptation effects.

In Figure 12(A), the results of simple altitude exposure (simulated by reducing arterial PO_2) are presented with no adaptation.   The fall in tissue PO_2 results in increases in erythropoietin, red cell production and red cell mass, all with widely varying dynamic behavior.   As the red cell mass and hematocrit increases there is a slight feedback effect and erythro-poietin concentration gradually declines.   In Figure 12(B), we have applied three adaptive mechanisms which are known to occur within the first several days at altitude.   Each was initiated five days apart to provide a visual indication of their relative influence.   In Figure 12(C), they were applied at the same time (on Day 4) to show their combined effect.   In the real system, of course, they would exert their effects gradually.   The adaptive mechanisms which we have used include: a) an increase in arterial PO_2 arising from greater ventilation efficiency (Lenfant & Sullivan, 1971), b) a decrease in plasma volume (Buderer & Pace, 1972), and c) an increase in P_{50} due to elevated DPG levels (Lenfant, et al, 1971).   The magnitude of all these changes are physiologically plausible and the effect of these on erythropoietin production and concentration, as well as red cell production and mass is realistic (Faura, et al, 1969; Van Dyke, 1960).

3. 3   SECONDARY ANEMIA - A CLINICAL APPLICATION

The new capability to predict erythropoietin levels allows the model to be directed towards a variety of applications that previously were not possible.   One of these is in the simulation of a number of hematological disease states which have known physiological etiology.   In particular,
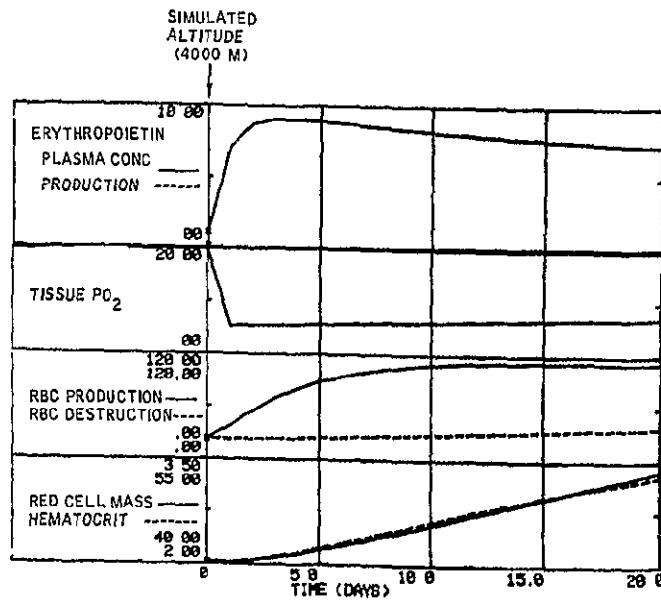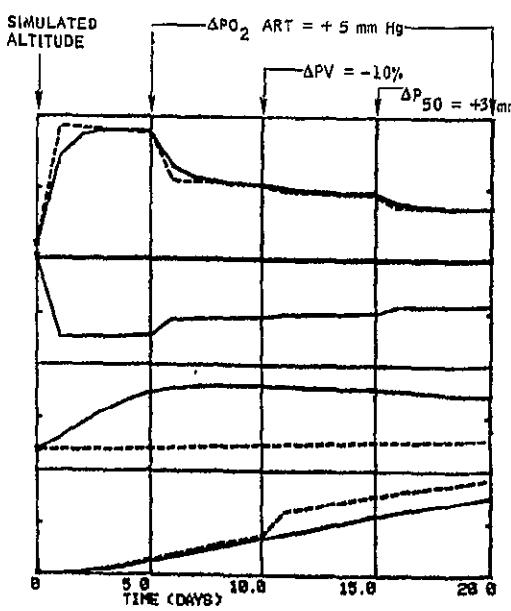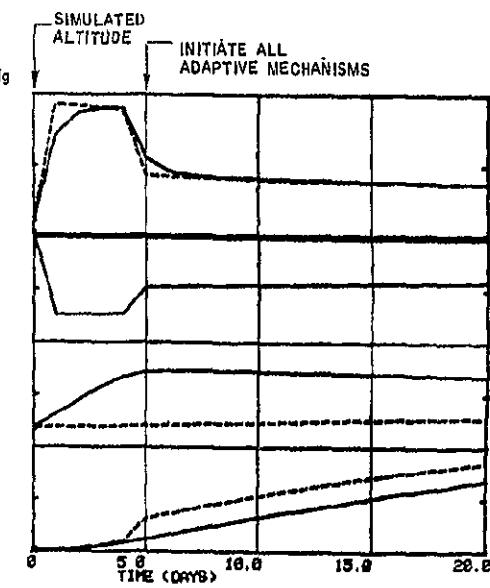
SIMULATION OF ALTITUDE HYPOXIA SHOWING EFFECT OF
ADAPTIVE MECHANISMS

FIGURE 12

there are various types of polycythemias and anemias which arise from disorders in oxygen uptake or transport, renal production of erythro- poietin, bone marrow production of red cells, or in the hemolytic process. One such case was chosen to illustrate the model's ability to simulate the onset, diagnosis, and treatment of hematologic disorders.

Onset of Disease

The inability of the kidney to produce an appropriate erythropoietin response is an example of secondary anemia. This disease was simulated by reducing the slope and set point of the renal function curve $($G_1 = 0.8$, $E_o = 1$) as suggested by the data shown by Erslev (1975). This change impairs, but does not completely inhibit basal erythropoietin pro- duction; it also will suppress normal release in the face of an hypoxic challenge.

Figure 13(A) shows the onset of the disease. Renal impairment was applied suddenly at Day 0, but a new stable state was not reached until the eighth month. At this time the reduced red blood cell production had equilibrated with destruction rates and red cell mass and hematocrit were depressed to less than half their normal values.

Diagnosis of Disease

A diagnosis could be made on the basis of symptoms given the new steady-state values shown in Figure 13(A). However, reduced levels of erythropoietin are difficult to determine with routine clinical assays. Therefore, further testing may be warranted to determine if either impaired bone marrow or renal function is responsible for the anemic con- dition. Two such tests are suggested in Figure 13(B) in which: a) an hypoxic stimulus fails to elicit a normal renal erythropoietin response or an appropriate bone marrow response, in spite of the fact that, b) a pulse infusion of erythropoietin indicates that the marrow's ability to produce red cells is normal when an exdogenous erythropoietin stimulus is presented.
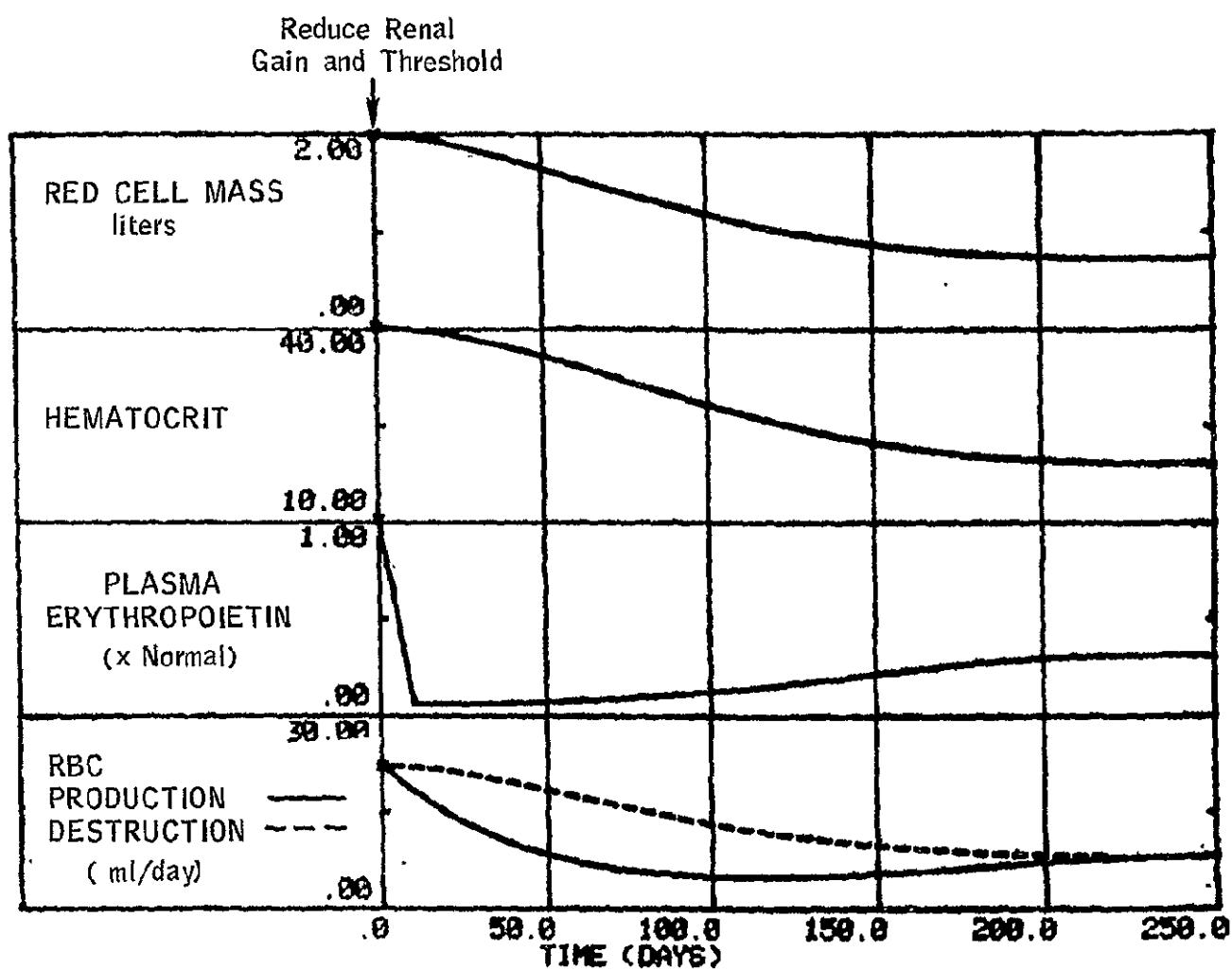
ANEMIA OF CHRONIC RENAL INSUFFICIENCY:
SIMULATION OF ONSET

FIGURE 13(A)
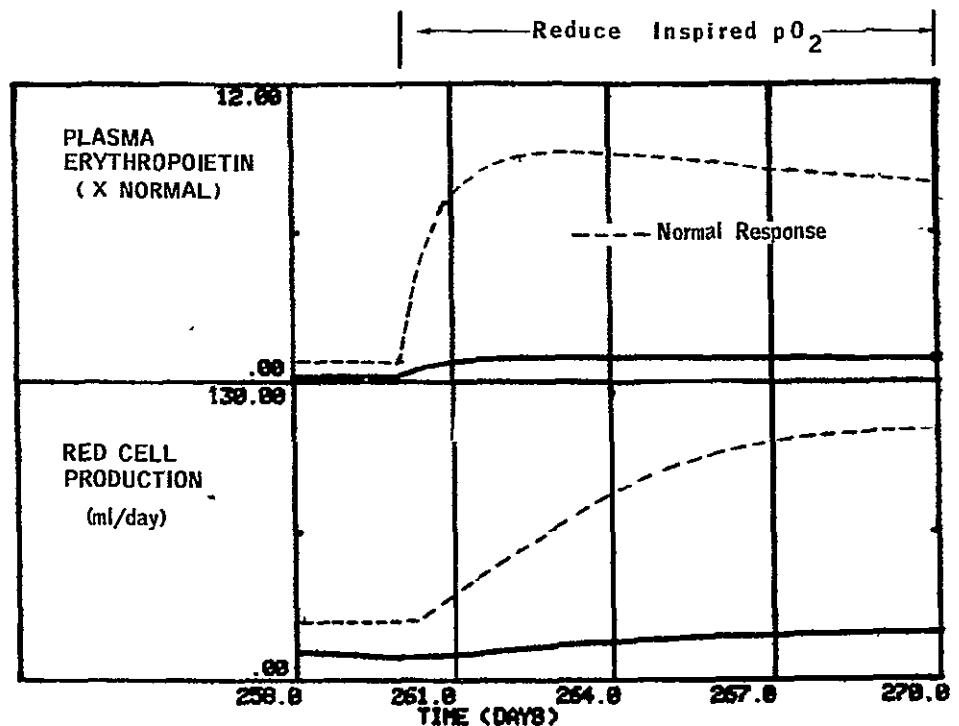
ERYTHROPOIETIC RESPONSE TO HYPOXIA
SHOWING ABNORMAL RENAL RESPONSE
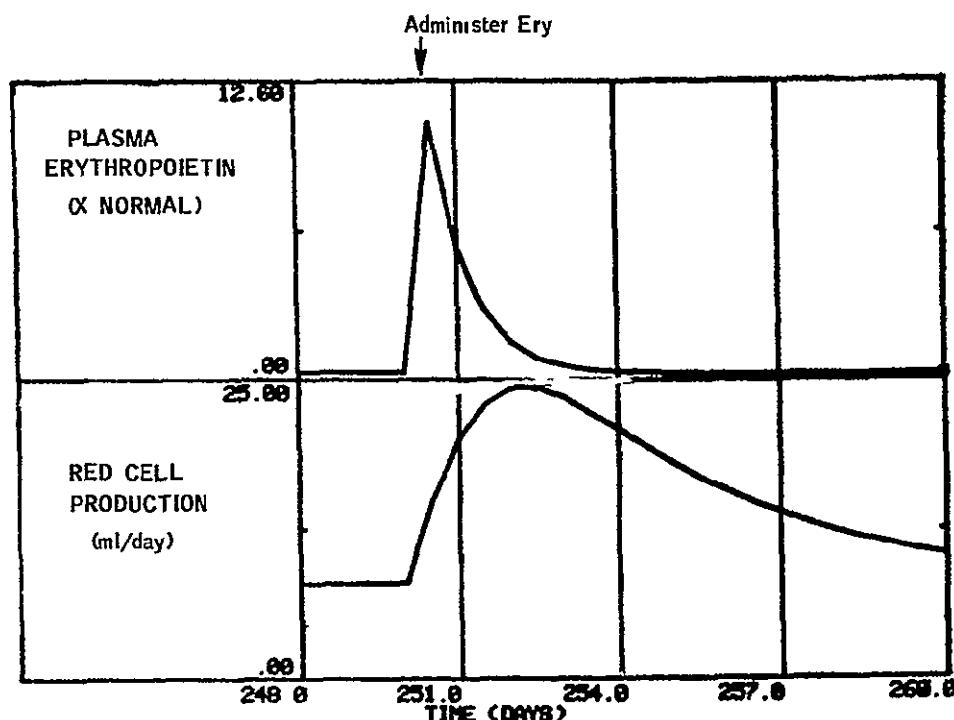
RETICULOCYTE RESPONSE TO INFUSE DOSE OF ERYTHROPOIETIN
SHOWING NORMAL BONE MARROW RESPONSE

ANEMIA OF CHRONIC RENAL INSUFFICIENCY:
SIMULATION OF DIAGNOSTIC STRESS TESTS

FIGURE 13(B)

Treatment of Disease

Treatment (see Figure 13(C)) was simulated by first restoring the red cells to normal levels with an infusion of 1.1 liters of packed red cells followed by a maintenance dose of erythropoietin given every five days. * This dose was found by a previous trial-and-error procedure to produce a normal mean daily level of red cell production.   It would be possible to design a computer algorithm that would automatically calculate the optimum dose under a variety of circumstances.

*
It is recognized that this method of hormonal treatment is far from routine and awaits greater availability of erythropoietin.
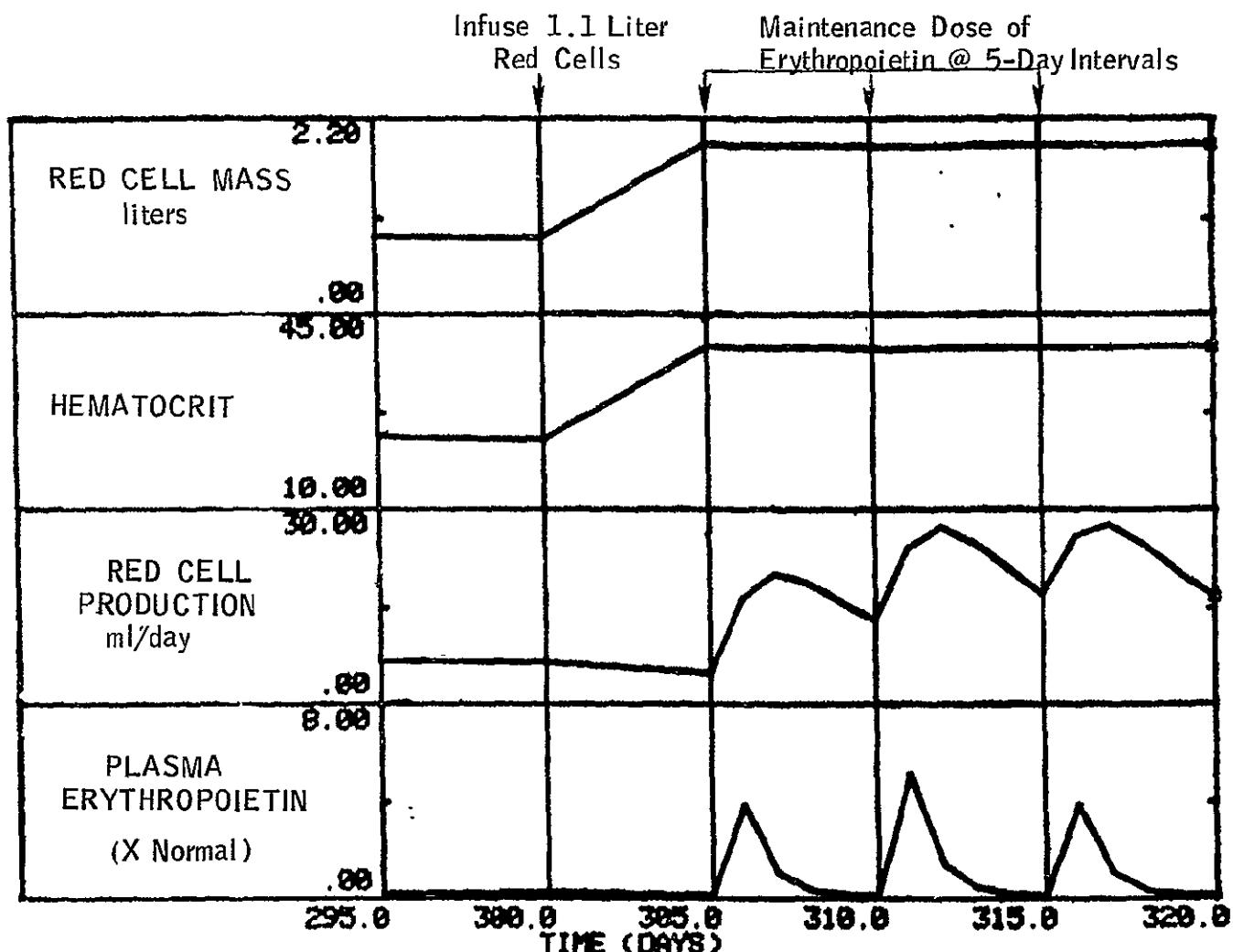
ANEMIA OF CHRONIC RENAL INSUFFICIENCY:
SIMULATION OF TREATMENT

FIGURE 13(C)

4.0   SIMULATION OF BED REST WITH THE ERYTHROPOIESIS MODEL

4.1   OBJECTIVES

The improvements and validations of the erythropoiesis model pre-
sented thus far were preparatory to the primary goal of this effort, which
is to simulate the recent Baylor Medical College's (BMC) 14-day and
28-day bed rest studies (Johnson & Driscoll, 1975, 1977).   As in prev-
ious studies of this type, a small but significant decline of red cell mass
was observed (Figure 14).   The 28-day BMC study is particularly worthy
of close scrutiny because it was of the same length as one of the Skylab
missions.   In addition, the procedures used were nearly identical to those
for the Skylab hematologic experiments and were performed under the same
principal investigator.   Furthermore, the time course was obtained for
several important hematologic measurements which were not obtained
during space flight.   This data is crucial for maximum utilization of
the erythropoiesis model.

A simulation of bed rest was made earlier with the original model
(Leonard, 1976) and reasonable agreement was obtained with Morse's (1967)
35-day study.   However, the data analyzed since that time, including the
recent BMC studies, revealed several facets of the red cell loss which
previously were not fully appreciated.   First, the combined results from
a number of bed rest studies demonstrate that the red cell loss is a linear
function with time for at least 28 days (Johnson & Driscoll, 1977).   A
predictive equation describing this phenomena was given as: % decrease
= 0.90 + 0.24 x days of bed rest.   Previous simulations have predicted
an exponential decline.   Secondly, the earlier observation by some inves-
tigators that red cell mass continues to decline following bed rest was
confirmed during both the BMC studies.   It appears that in many instances
this "refractory" period lasts for up to two weeks of recovery (Miller, et al,
1964; Morse, 1967; Taylor, et al, 1945;Hyatt, et al, 1970).   Eventually,
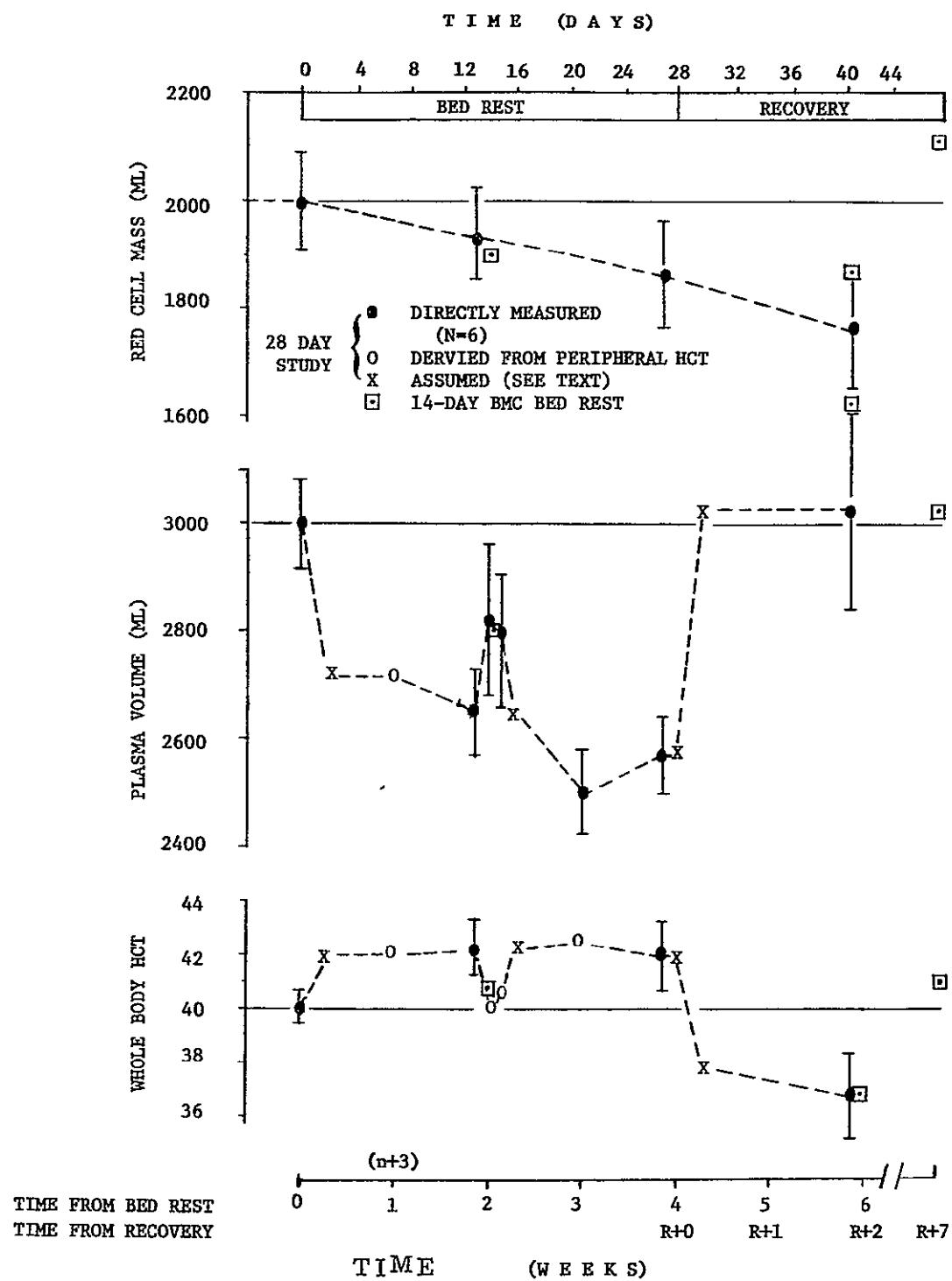
BLOOD VOLUME MEASUREMENTS (NORMALIZED)
FROM BMC 14 & 28-DAY BED REST STUDIES

FIGURE 14

red cell mass returns to normal during the recovery phase, but the dynamics of this event are not yet clear due to sparsity in the data. The ability to simulate both of these phenomena, operative during the "treatment" phase or the recovery phase, was singled out as a particular goal of the simulation study.

4.2   APPROACH

The general approach for bed rest simulation was to test various hypotheses (including those formulated by other investigators) which would lead to a simulation response similar to those found in bed rest. A model of any system whose function is not clearly understood, including the present erythropoiesis simulation model, is, in itself, an hypothesis. Therefore, if the model were perfectly formulated, it would, given the appropriate initial stress, respond very much like the real system with respect to dynamic and steady-state behavior, limited only by the restricted number of quantities it can compute. Thus, one aspect of our approach was to determine if there is a single stress or multiple set of physiologically plausible stresses which, when activated, would set in motion the representation of the natural feedback regulating system so as to produce the appropriate response. The results of this effort were largely successful, especially during the treatment phase of bed rest. However, during simulation of recovery, it was apparent that certain mechanisms were not accounted for in the model. Some of these could be introduced, however, in a reasonable way so as to suggest how the model would respond if the mechanism were integrated into the regulation system more completely. For example, the P_{50} parameter of the model will shift the dissociation curve in a realistic fashion only if activated by the user; it is not yet a self-regulating feature. Thus, another aspect of our approach was to test the effects of various parameters which are normally held constant.

This method resulted in a more realistic simulation, but time did not permit a thorough evaluation of the model's parameters which have become large in number.

Simulations were performed using either the bed rest hematocrit data as a driving function or an idealized plasma volume function as a driver. In the first case the simulation response (for red cell mass and plasma volume) was compared directly with the experimental data. In the second case, the purpose of the simulations was to investigate certain model characteristics and so the model's response was compared with previous simulations during various parameter perturbations.

4.3 DATA USED FOR BED REST SIMULATION

Only the 28-day study was considered during these simulations. The 14-day study did not include intermediate measurements of the important hematologic indices, and the few measurements that were made during recovery were consistent with those of the longer bed rest (see Figure 14). Several comments must be made with regard to the manner in which the 28-day data were processed prior to its use in the model. First, all the data were normalized with respect to the model's control values (RCM_o = 2 liters, PV_o = 3 liters, HCT_o = 40). Secondly, the hematocrit data that were used to drive the model (see Figure 14) was a combination of: a) direct whole-body hematocrit data, b) indirect hematocrit data obtained from peripheral hematocrit data using the mean F_{cell} value of 0.908 that was obtained for these subjects and c) assumed data. In the latter case, the following assumptions were made: a) the value at Day 2 was the same as that measured on Day 7, b) the value on Day 16 (following the saline ingestions) was the same as measured on Day 13 (immediately prior to the saline ingestions), c) the value at Day 28 (last bed rest day) was identical to that measured the day before, and d) the value on Day 30

(R+2) was obtained by assuming the plasma volume on that day was identical to the value obtained on Day R+13 while the red cell mass on Day 30 was found by linear interpolation between the last two measurements. The resulting functions (dashed line in Figure 14) hopefully represent a more realistic time-varying driving function.

These assumptions were necessary since prior experience with the model has shown it to be sensitive to small shifts in plasma volume and data were missing during those periods when it is generally agreed that large changes may have occurred. For example, Johnson, et al (1971) have shown from composite data that the largest shifts in plasma volume after the start of bed rest occur during the first several days. The recovery of plasma volume during the first several days is surprisingly not well documented, but in view of the fact that plasma volume changes can occur very rapidly and be of large magnitude, the assumed recovery value shown in Figure 14 seems reasonable. Nevertheless, this particular value was subjected to further examination during our study.

During the simulation study, several major hypotheses were tested including the effects on the erythropoietic response during bed rest or recovery due to: a) plasma volume or hematocrit shifts, b) shifts in oxy-hemoglobin affinity, c) mechanical hemolysis of red cells due to activity, d) non-linearities of renal and bone marrow functions, and e) combined renal-bone marrow time-delays. The results will be discussed in this order.

4.4   RESULTS OF THE 28-DAY BMC BED REST STUDY SIMULATION

Effect of Plasma Volume and Hematocrit Shifts

The results shown in Figure 15 were obtained with the current version of the model as shown in Figures 1 and 9 and using the hematocrit data as the only driving function. In this simulation the overall gain, G, was adjusted until the red cell mass at Day 28 was in agreement with the data
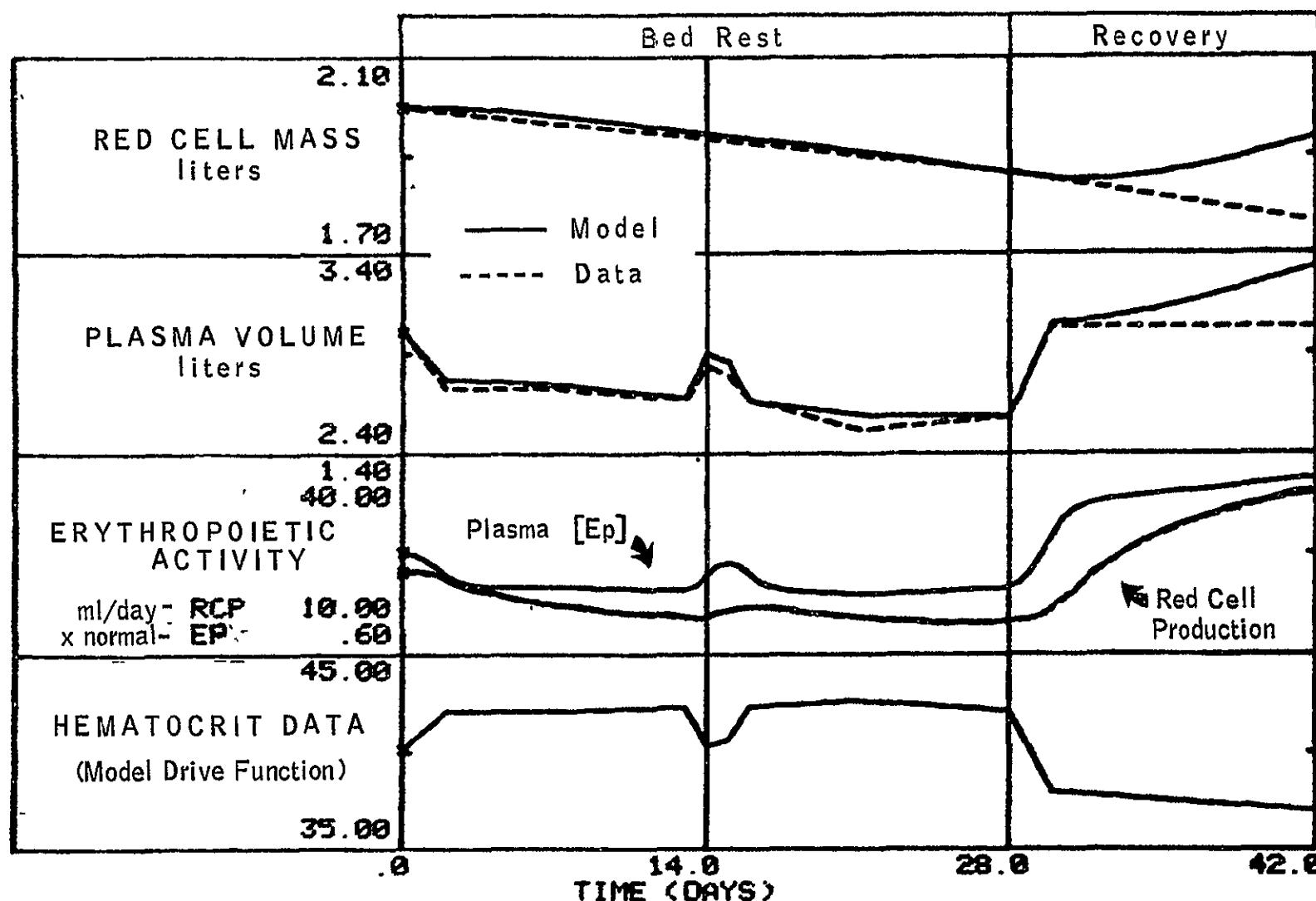
ERYTHROPOIESIS MODEL SIMULATION OF BMC 28-DAY BED REST STUDY

Improved Model With EP and RBC Time Delays Added

FIGURE 15

on that day. A value of G = 10 was used here as well as for simulations shown in subsequent Figures 16 through 19. Agreement with the linear red cell mass and with the plasma volume responses observed during the bed rest phase are considered very good, with little further improvement necessary. (It should be recalled that only three red cell mass measurements are available during this period which were taken on Days 0, 13, and 27; therefore, slight deviations exist during periods when there were no measurements).

The model predicts a fall in plasma erythropoietin levels of about 15% and in red cell production rate of about 27%. During recovery, these two indices of erythropoietic activity reversed direction and the absolute magnitude of the increase was greater than the preceding decrease. These model predictions are consistent with the bed rest studies of Shcherba, et al (1975) and Morse (see Lancaster, 1971) with respect to direction, magnitude, and time course of change. (We have assumed that experimental reticulocyte index is a measure of red cell production). They are also in accord with the suggestion of Johnson & Driscoll (1977) that a decrease in red cell production of about 25% could account for the results of the 28-Day BMC study. Serum erythropoietin during the 28-day BMC study was measured, and, while reduced levels were expected during bed rest, no significant changes were observed (Dunn, et al, 1977). However, a strong post bed rest reticulocyte and erythropoietin response were reported, again consistent with the model results. The only major disappointing result of this simulation was the failure of the model to predict a continued decline in red cell mass during recovery. This was examined further and will be discussed in the next sections following a discussion of the findings in the literature.

This simulation suggests very strongly that hematocrit changes alone can account for the magnitude and time course of red cell mass
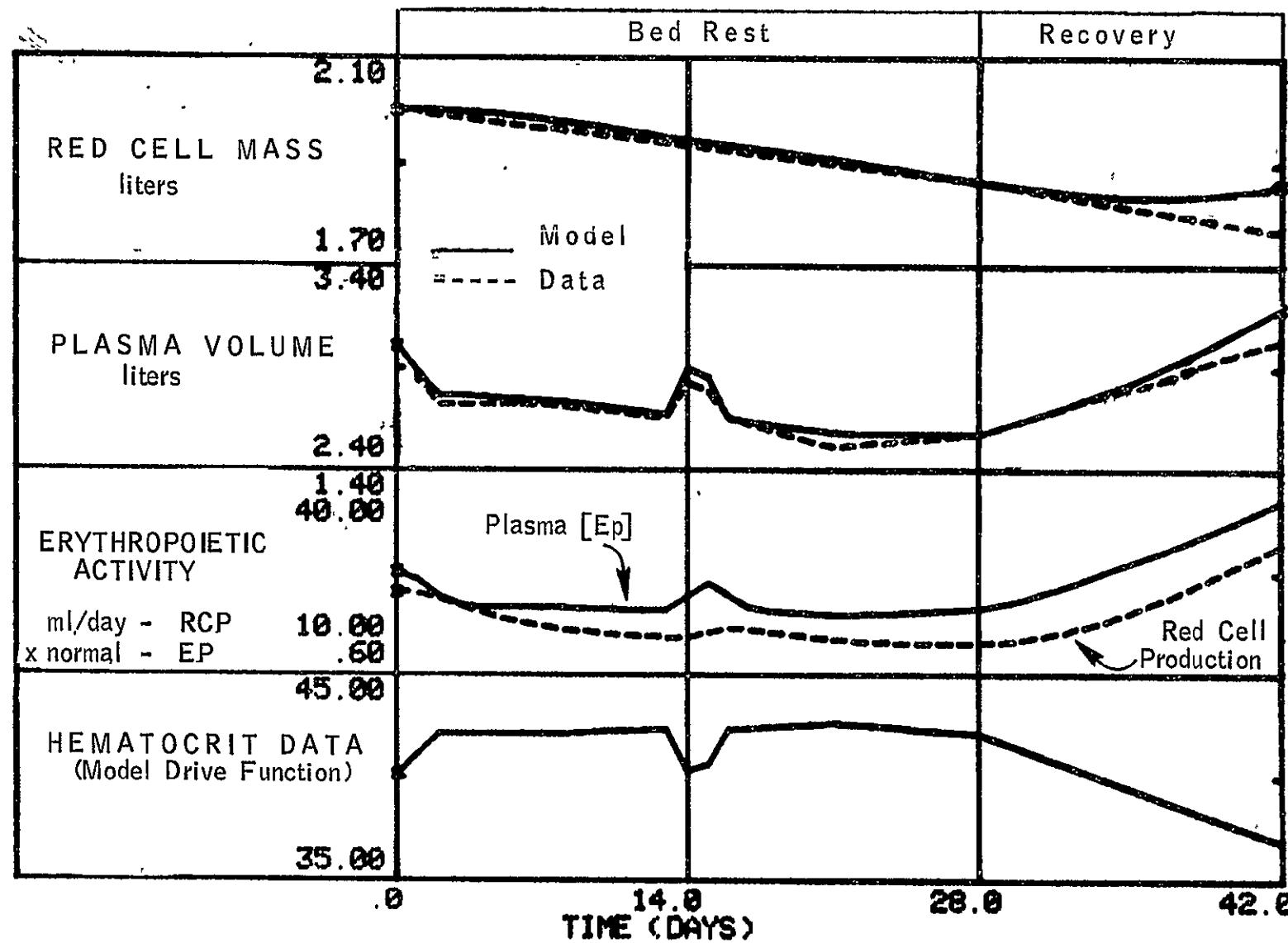
ERYTHROPOIESIS MODEL SIMULATION OF BMC 28-DAY BED REST STUDY

With Linear Post Bed Rest Hematocrit and Plasma Volume

FIGURE 16
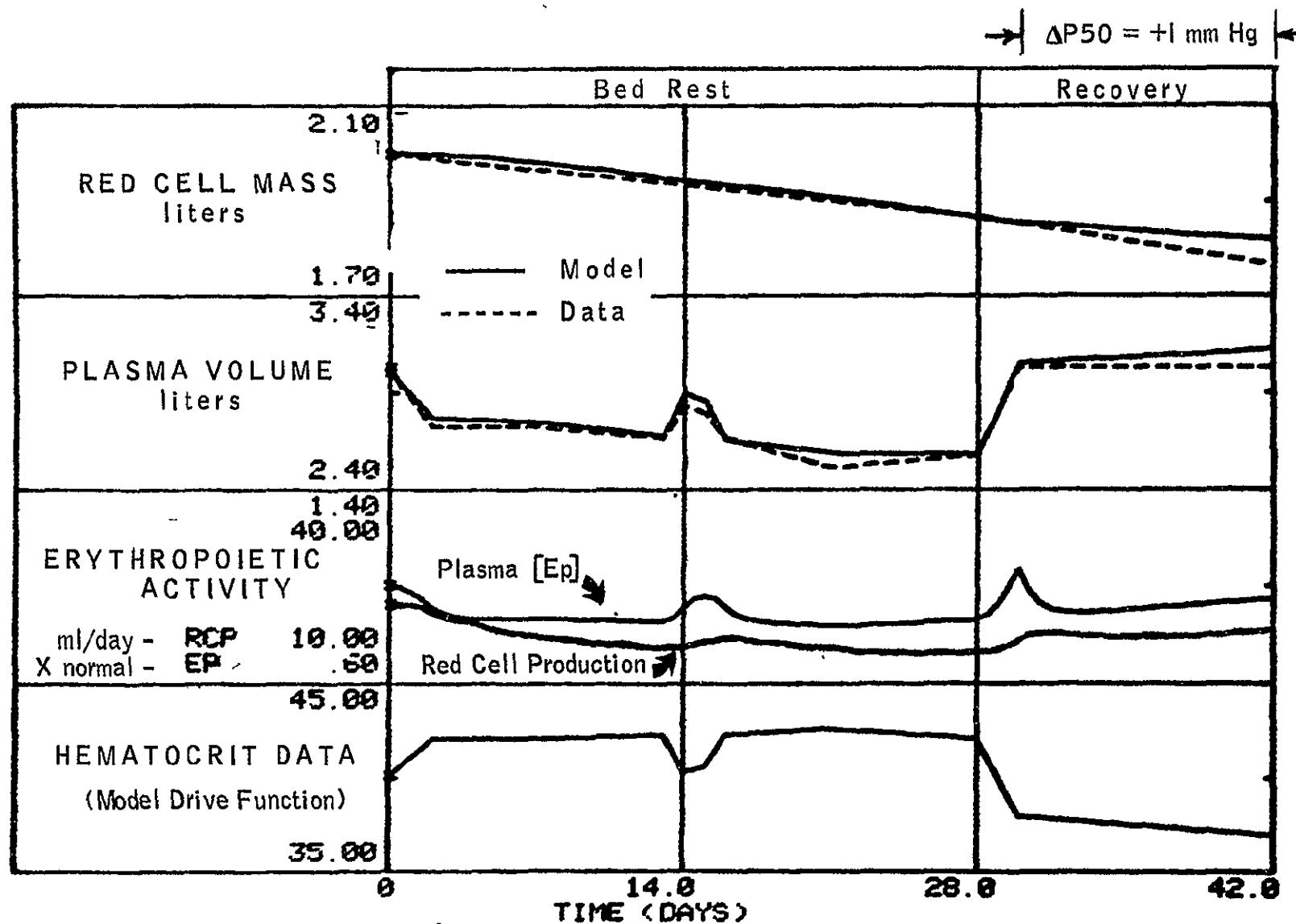
ERYTHROPOIESIS MODEL SIMULATION OF BMC 28 DAY-BED REST STUDY

Improved Time Delayed Model with Post Bed Rest P_{50} Shift Hypothesis

FIGURE 17
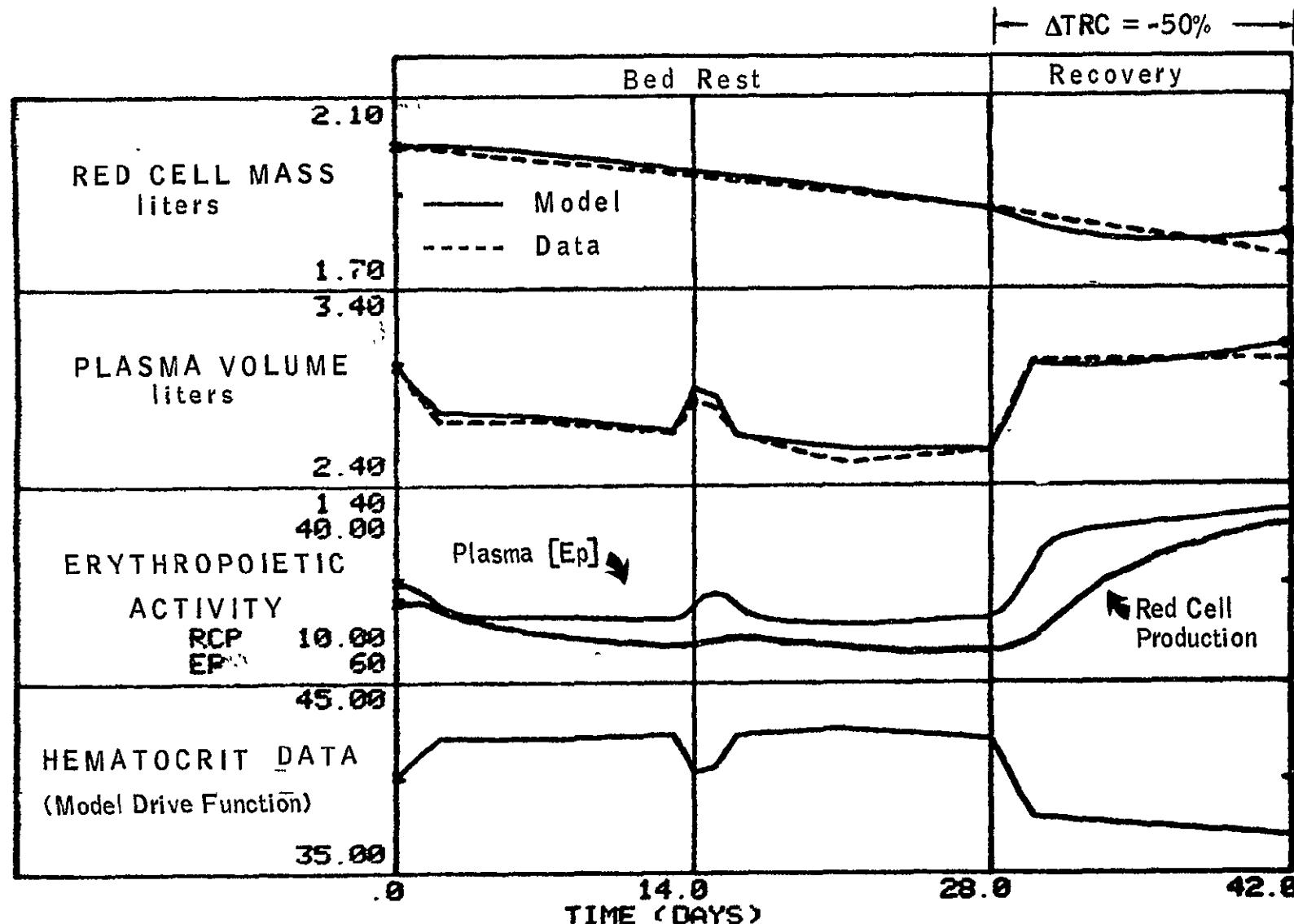
ERYTHROPOIESIS MODEL SIMULATION OF BMC 28-DAY BED REST STUDY

Improved Time Delayed Model With Post Bed Rest Hemolysis Hypothesis

FIGURE 18
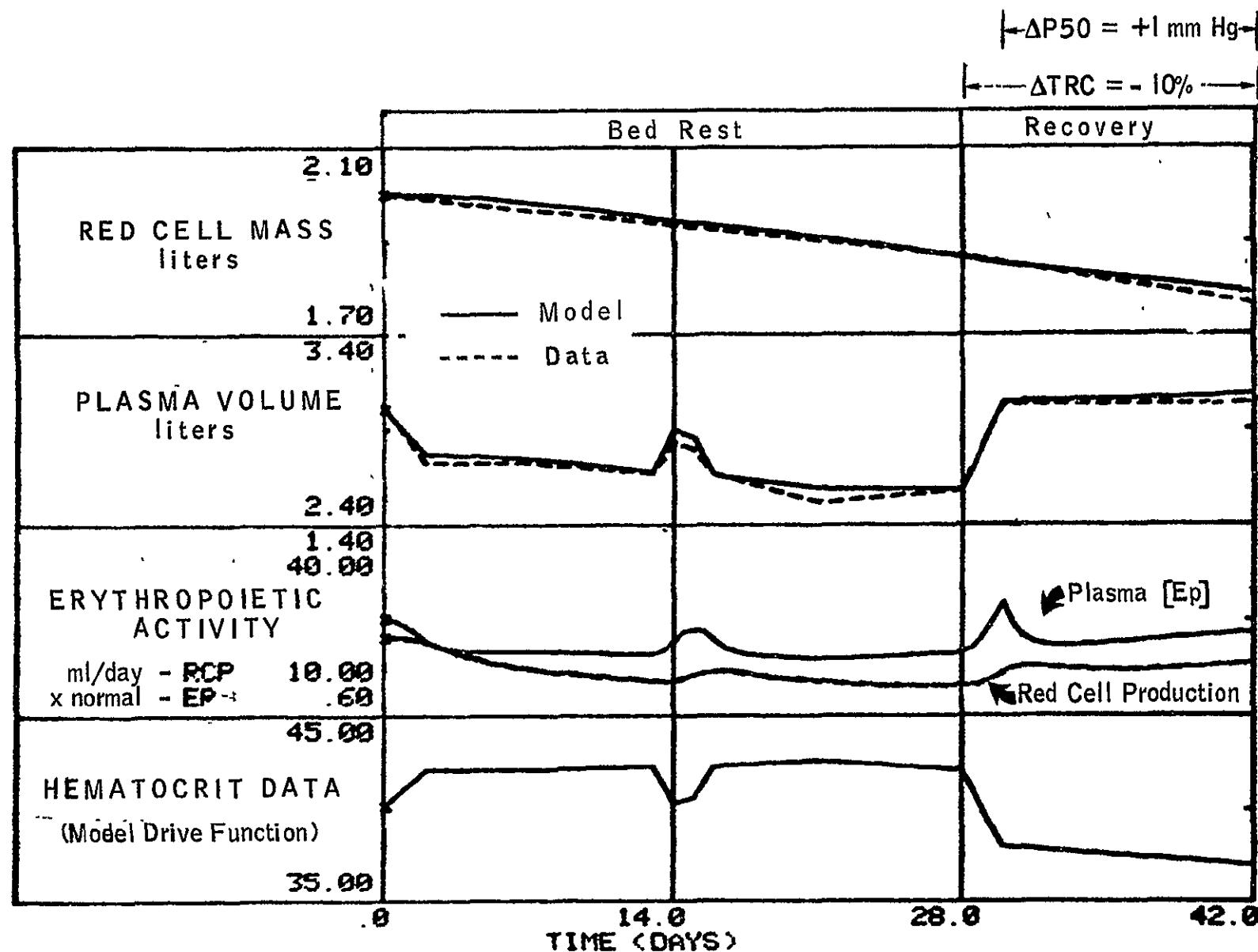
ERYTHROPOIESIS MODEL SIMULATION OF BMC 28 DAY BED REST STUDY

Improved Time Delayed Model With Post Bed Rest Hemolysis and P_{50} Shift Hypotheses

FIGURE 19

decrements observed during the BMC bed rest study. While not univer-
sally accepted, this idea has received consideration from other investi-
gators of bed rest (Morse, 1967; Jensen, 1972; Dunn, et al, 1977). Other
than bed rest there is a sparsity of information relating to the long term
effects of decreased plasma volume on erythropoiesis. However, there
is considerable evidence to suggest that the erythropoietic system is very
sensitive to hematocrit changes in either direction. Significant reduc-
tions in erythropoietic activity have been observed following the increases
in hematocrit induced by red cell infusion in humans (Birkhill, et al, 1951);
and animals (Gurney & Pan, 1958), thirst dehydration (Kilbridge, et al,
1969), and altitude hypoxia preceding descent to sea level (Buderer & Pace,
1972; Huff, et al, 1951). All except one of the above studies were con-
cerned with long term changes lasting many days or weeks. As for
decreased hematocrit changes, the enhanced erythropoietic response of
many types of acute and chronic anemia are well known (Adamson, 1968;
Erslev, 1975).

There are also a number of studies (mostly acute) in which trans-
fusion-induced changes in hematocrit in either direction are not consistent
with the reports cited above. However, these seemingly paradoxical
results appear to be explained by known effects of hematocrit (and viscosity)
and total blood volume on blood flow (Castle & Jandl, 1966; Thorling and
Erslev, 1968; Murray, et al, 1963; Murphy, et al, 1966). However,
Kilbridge, et al (1968) suggest that blood volume or red cell mass changes
by themselves have much less influence on erythropoietin and erythropoiesis
than do moderate changes in hematocrit. This, in fact, is one of the basic
premises of our model of erythropoiesis. On the other hand, the complete
independence of blood volume and erythropoietic activity in the model is
also unrealistic and it is suggested that this is an appropriate area for
further analysis.

Effect of Plasma Volume Changes During Recovery

There have been other hypotheses proposed to account for the behavior of the erythropoietic system both during bed rest and space flight, including: a) changes in oxygen requirements (Shcherba, et al, 1975; Shvets & Portugalov, 1976), b) age-dependent loss of red cells (Kimzey, 1975), c) changes in plasma phosphates (Johnson, et al, 1974), d) increased renal blood flow (Leonard, 1974; Fuller, et al, 1970; Shcherba, et al, 1975) and e) changes in gain and thresholds of the kidney-bone marrow axis (Kimzey, et al, 1976). Time does not permit a thorough evaluation of these mechanisms and we are not discounting that they may be operative to some extent. However, our model simulations suggest they are of relatively minor influence compared to the plasma volume shift hypothesis, at least during the treatment phase of the 28-day BMC bed rest study.

The remainder of the study was devoted to examining hypotheses that could produce a more faithful recovery response. As was emphasized earlier, there is some question with regard to the dynamic behavior of the post bed rest plasma volume and hematocrit responses. Since we have shown that red cell production is sensitive to hematocrit shifts, it was reasonable to test the hypothesis that plasma volumes at recovery do not return towards normal as rapidly as we had assumed. If this is true, then the model should predict a slower repletion of red cell mass. The results of Figure 16 were obtained after the assumed data values at Day 30 (for plasma volume and hematocrit) were removed; this resulted in using only actual bed rest measurements for recovery and a linear driving function for this phase as shown in the bottom curve. As expected, the RCM recovery response was significantly improved during the first recovery week. This emphasizes the importance of collecting data early in the recovery period. The remaining simulations included the assumed values at Day 30.

Shift in Oxyhemoglobin Affinity Due to DPG

The importance of 2,3-DPG in displacing the oxyhemoglobin curve
to the right and thus enhancing "unloading" of oxygen to hypoxic tissues
has only been recently appreciated (Brewer, 1974). Higher levels of
DPG accompanied by proportional changes in the P_{50} have been observed
almost consistently in circumstances which impair oxygen supply to the
tissues such as acute and chronic high altitude hypoxia, chronic cardio-
pulmonary disease, and anemias of various origins (Harris & Kellermeyer,
1970). It is assumed that such an effect is the result of tissue hypoxia.
Any change in position of the oxygen dissociation curve profoundly affects
the amount of oxygen available at normal tissue oxygen tensions, whereas
oxygen uptake by hemoglobin is little affected (Finch and Lenfant, 1972).

There is no conclusive evidence that changes in DPG can account
for the loss of red cell mass during space flight or bed rest. Skylab
measurements showed no significant change in inflight 2,3-DPG (Mengel,
1974) and no measurements from bed rest studies have been reported.
To our knowledge, measurements of P_{50} have not been measured in these
instances. Therefore, this area is still fruitful for further investigation
and hypothesis testing with the erythropoiesis model.

Both bed rest and space flight result in small rapid increases in
hematocrit which could result in a slight enhancement of tissue oxygena-
tion if other parameters involved in this process (such as O_2 demand,
arterial PO_2 and blood flow) do not change. Changes in DPG and P_{50}
during hyperoxic states are less frequently reported but these quantities
are known to decrease in some instances (Harris & Kellermeyer, 1970).
The decrease in hematocrit following bed rest is slightly more severe
than the initial increase (Johnson & Driscoll, 1975, 1977), and the data
suggesting an increase in DPG as a compensatory mechanism during this
temporary "anemic" state is more abundant. Thus, it is tempting to

speculate that if DPG and P_{50} shifts occurred during bed rest or zero-g, they would decrease during the "treatment" phase and increase during recovery.

The results of this hypothesis were tested with the model. It was not necessary to account for shifts in P_{50} to explain the decreased red cell mass during bed rest itself; the hematocrit effect alone was sufficient. However, it was determined that only very small increases in P_{50} ($\Delta = +1$ mm Hg) were necessary to account for a large part of the decreased red cell mass during the two weeks of recovery as shown in Figure 17. The effect of P_{50} shifts in this situation is similar to that of an increase in blood flow, arterial oxygen tension or other parameters which increase tissue oxygen. Erythropoietin release is suppressed along with red cell production. The transient increase in erythropoietin concentration shown in Figure 17, at the time the P_{50} shift was activated, corresponds to a similar event reported during the 28-day bed rest study (Dunn, et al, 1977).

The profound influence that small changes of P_{50} had on the response was surprising although suppressed erythropoietin is not an entirely unexpected result (Hillman & Finch, 1974). This phenomena should be investigated further. Evidence is available which apparently shows that the position of the dissociation curve significantly influences the steady-state level of the hemoglobin concentration of the blood via the normal erythropoietic control mechanisms (Beutler, 1969). A pathologically or experimentally induced shift of the dissociation curve could conceivably result in anemic or polycythemic conditions which otherwise appear inappropriate.

Effect of Exercise and Confinement on Red Cell Destruction

The effects of daily exercise on erythropoietic activity and circulating red cell mass are complex and poorly understood. This is unfortunate in that the complete absence of exercise and elevated metabolic

activity is a major characteristic of bed rest and may have an effect in modifying the observed decrements in red cell mass. No clear picture emerges, regarding this effect, from a review of recent studies. On the one hand, bed rest accompanied by supine exercise was found to enhance the loss of red cells compared to simple bed rest (Miller, et al, 1965). On the other hand, the Skylab experience has shown that in space flight (thought by some to be analogous to bed rest in this respect) increasing levels of exercise were accompanied by smaller decreases of red cell mass. In addition, while most investigators find an increase in blood volume during simple exercise conditioning, there is as yet no clear agreement on whether this is accompanied by an increase or decrease in red cell mass (Sjostrand, 1962; Rocker, et al, 1976; Holmgren, et al, 1960). However, exercise conditioning is known to have major long and short term effects on the oxygen transport system. Therefore, it is certainly conceivable that exercise or the lack of it would affect the erythropoietic process and modify the red cell mass response to both bed rest and space flight and perhaps the recovery process as well.

It seems that exercise may have several different opposing effects on the circulating red cell mass. Broun (1923) found that the red cell mass in dogs decreased after a single day of exercise and that this effect was exaggerated when dogs were exercised daily after prlonged confine-ment. It was suggested that exercise induced blood destruction due to mechanical hemolysis. On the other hand, exercise may act as a bone marrow stimulant and increase production of red cells. The cause of this enhanced production is not well understood, but it certainly could result from the stimulus of blood loss (Broun, 1923).

Tests with the erythropoiesis model have shown that increased . destruction of cells will reduce the hematocrit and this slight anemic con-dition can result in large increases in red cell production. The net result,

however, is a slightly reduced hematocrit; that is, over-compensation and net increases in red cell mass do not occur as implied by Broun. We have confirmed the analysis of Hodgson (1970) who showed on theoretical grounds that large increases in destruction rate (life span reduced by 60%) will result in decreases in hematocrit of only 10% at steady-state due to an effective and sensitive controller of bone marrow production.

Other factors are present during exercise which could conceivably create a hemopoietic response. Among these are increased oxygen demand, release of chemical substances from muscle, increased oxygen requirement of the kidneys which must rid the body of more waste material, decreased renal blood flow (Astrand & Rodahl, 1970),etc. However, the influence of such factors has not been studied and will not be considered here. Our present interest is to determine if exercise could have a depressant, rather than a stimulating, effect on red cell mass during bed rest recovery.

Recovery from bed rest appears to be somewhat, but not totally, different from space flight recovery. On the one hand, the 14-day BMC bed rest study showed that a return to normal red cell mass occurred before 7 weeks after bed rest which is not significantly out of the 3 - 6 week range for repletion of the three Skylab crews. However, the "refractory" phenomena of bed rest, which now appears to be nearly a consistent finding, was not observed in Skylab except perhaps for the SL-2 crew. This difference does not appear to be the result of the degree of ambulatory activity during recovery which was similar for both bed rest subjects and for space crewmen. (Whether or not the stress of re-entry was a contributing factor is not known.) However, it is possible that the history of exercise during space flight compared to the history of inactivity during bed rest may be partly responsible for changes in red cell mass during recovery. As Johnson & Driscoll (1977) have

postulated "the lack of exercise during bed rest conserves fragile red cells which are more vulnerable to destruction during the early ambulation period." During Skylab, however, the "exercise during flight (may have been) great enough to destroy vulnerable cells" prior to the first recovery measurements of red cell mass.

A preliminary test of this hypothesis was carried out during the bed rest simulation effort. The mean life span of the red cell is a parameter in the model which can be reduced in value to represent the more rapid destruction of fragile cells during recovery. Our objective was to determine the amount of increased destruction necessary to maintain the linear nature of the red cell decrement during the two weeks of recovery. The results showed that the best approximation of the data were obtained by a reduction in life span of 50% over the entire two week recovery period (Figure 18). This appears unrealistically large, but changes in red cell survival throughout the recovery period are not well documented. While Morse (1967) reported a significant 25% decrease in the Cr^{51} red cell half survival value, but this was apparently corrected in a later publication to a -7% change (Lancaster, 1971).

One of the peculiarities of Morse's study and the 28-Day BMC study was a sharp increase in reticulocyte index after bed rest in the face of continued decline of red cell mass. Morse speculated that this paradox could be accounted for by "a compensated hemolytic syndrome in which the rate of production balances the rate of hemolysis." As previously discussed, this is consistent with the studies of Broun and our own theoretical analysis. It is also in accord with the recovery simulation shown in Figure 18 if one accepts large value of red cell destruction. The model prediction that red cell production decreases during bed rest to a lesser extent than it increases during recovery is also a finding observed during bed rest (Morse, 1967; Dunn, et al, 1977).

We considered the possibility that more than one mechanism may be operative during the recovery process. For example, reductions in red cell life span and increases in P_{50} could have occurred which were small enough to be experimentally undetectable, but could produce measurable effects on red cell mass over a long enough period. This hypothesis was used in the simulation shown in Figure 19 where the life span was decreased 10% in combination with a +1 mm Hg shift in P_{50}. This resulted in improved agreement with red cell mass response although red cell production levels failed to rise above control levels, contrary to the reticulocyte data of Dunn, et al (1977) and Morse (1967). Ineffective erythropoiesis, a mechanism not included in the model, will produce reticulocytosis while circulating red cell mass is reduced. However, this effect was apparently ruled out during bed rest (Johnson & Driscoll, (1977). If this observation is correct, the model can explain increases in red cell production accompanied by a decreasing red cell mass during recovery only if significant cell destruction is occurring, a conclusion also reached by Johnson & Driscoll. However, the evidence for a strong post bed rest hemolysis effect has not been forthcoming.

A possibility that should be examined further is that the erythrocytes and precursors emanating from the bone marrow during a strong erythropoietic stimulus do not have the same characteristics as normal cells. There is evidence that under these conditions some of the erythrocytes skip their terminal division, have a shorter maturation time, and a markedly decreased life span (Mylrea & Abbrecht, 1971). Reticulocytes also appear much earlier than usual and are not a reliable index of red cell production (Harris & Kellermeyer, 1970). These effects are not accounted for in the model and might lead to a resolution of the recovery enigma discussed above.

4.5   RESULTS OF A HYPOTHETICAL BED REST STUDY SIMULATION

The following simulation study was performed to better understand some of the elements in the model which produced the appropriate bed rest response seen in Figures 15 - 19.

Effect of Nonlinear Renal-Bone Marrow Functions

Version I of the model predicted an exponential decline of red cell mass, rather than a linear decline, as we have previously reported (Leonard, 1976), and as shown in Figure 20. The driving function for this simulation as well as for those shown in the two subsequent figures was a simple step decrease in plasma volume of 300 ml while recovery was initiated by an identical increase (bottom curve of Figure 20). These idealized plasma volume changes were derived from Morse's (1967) bed rest study which has been frequently cited for comparison purposes. While production rate declines and hematocrit increases initially, they subsequently return towards normal at a faster rate than observed in Morse's study. The simulated recovery is characterized by a sudden exponential rise; i. e. , there is no indication of a refractory period.

Figure 21 shows the identical simulation performed with Version II of the model except that the time delays for erythropoietin decay and bone marrow transit have been eliminated. Aside from the fact that erythropoietin is represented in the newer model, the basic difference between the two models is in the nature of the function curve relating tissue PO_2 and red cell production. The curve for Version II has been shown in Figure 5(A); the curve for Version I is a linearized representation of this and in particular does not include the nonlinearities in the suppressed erythropoiesis range (RCP 1.0). There is little difference between Figures 20 and 21. The dynamic behavior of erythropoietin concentration (Figure 21) is identical to that of red cell production. And while the decline in red cell mass during bed rest is still exponential in nature, closer inspection reveals that it is slightly more linear than the Version I response. (See also Figure 25(A)).
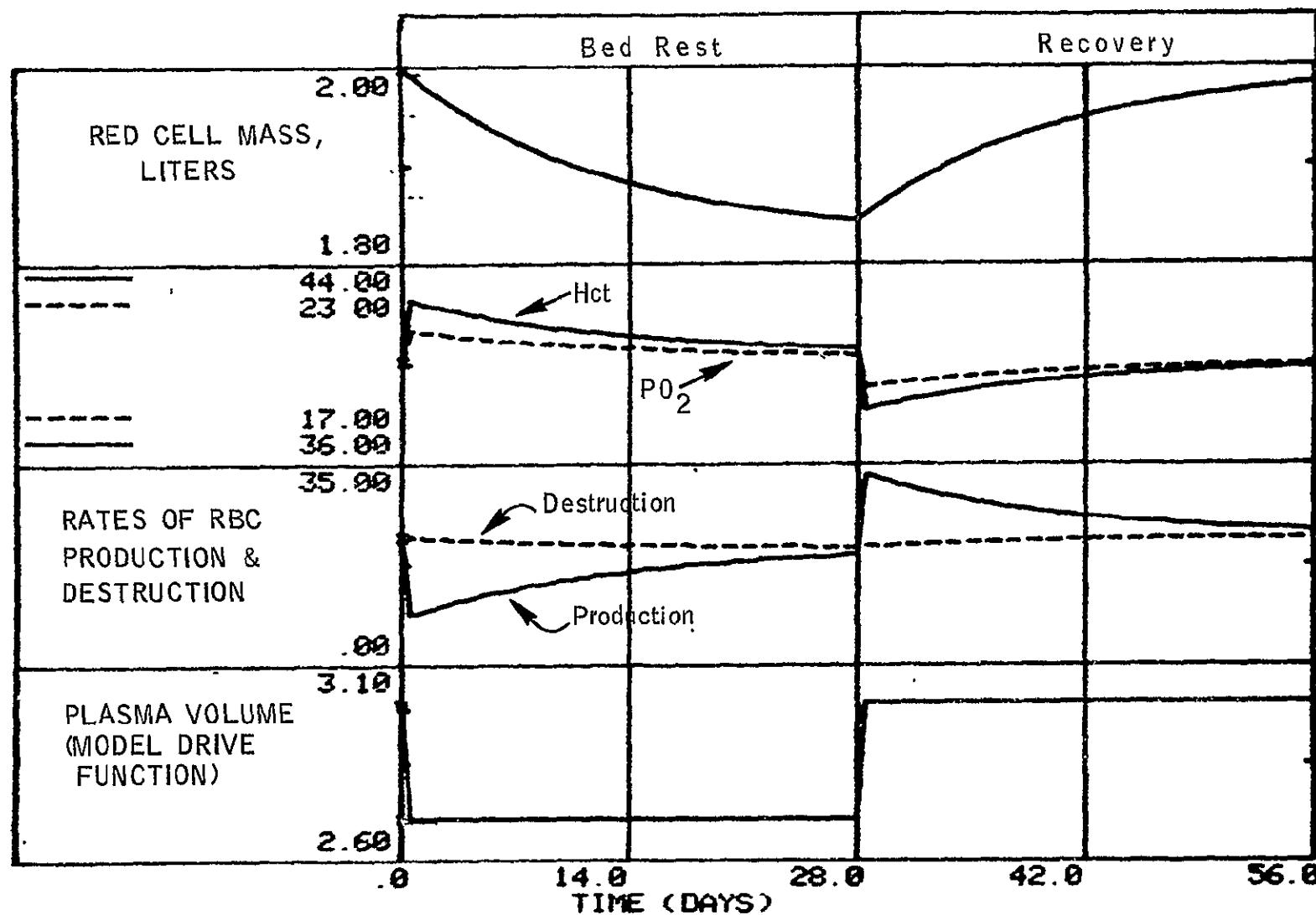
SIMULATION OF HYPOTHETICAL BED REST STUDY: VERSION I MODEL

(USING PLASMA VOLUME STEP FUNCTION   300 ML)

FIGURE 20
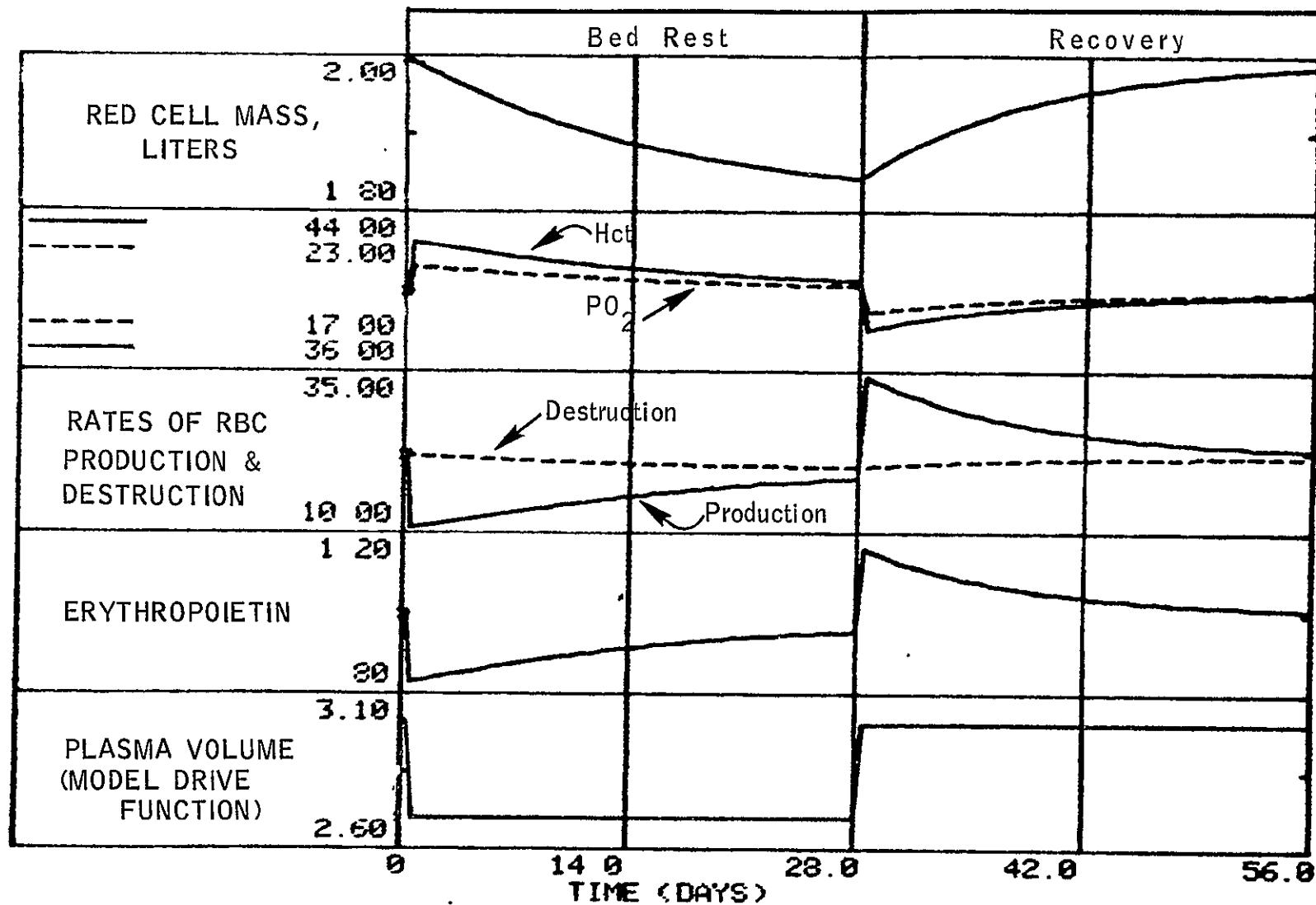
SIMULATION OF HYPOTHETICAL BED REST STUDY: VERSION II MODEL WITH NO TIME DELAYS
(USING PLASMA VOLUME STEP FUNCTION' 300 ML)

FIGURE 21

Effect of Renal-Bone Marrow Time Delays

With the time delays for erythropoietin clearance (half-time = 12 hours) and bone marrow transit (half-time = 4 days) included in the Version II model, the simulation of the hypothetical bed rest is significantly improved (Figure 22). First, red cell mass shows little change for the first day or so and then declines in a manner similar to that of the 28-day BMC study. Secondly, a delay in red cell recovery is now evident. Thirdly, the hematocrit stays elevated during bed rest and depressed during recovery for a longer period than before. These more realistic changes are brought about because of an erythropoietin response which is not as acute; but more importantly, because the production of red cells does not reach its minimum or maximum until nearly a week after the initial stress of bed rest or recovery.

Effect of Nonlinear Plasma Volume Driving Function

The previous simulations demonstrate that the model responds reasonably well to an idealized fluid stress suggested by a single bed rest study. We also created an idealized plasma volume function which is perhaps more representative of the general case based on Johnson and Driscoll's (1977) description of plasma volume shifts during bed rest. In this function, plasma volume declines in an exponential manner, losing 10% of its original volume by the end of two days and an additional 6% (for a total of 500 ml out of 3000 ml at control) by the end of four weeks. This more realistic driving function was tested in the model with the results shown in Figure 23.

Significant changes were noted during the first 28 days in all of the model responses: a) red cell mass decline was nearly linear after the first two days, b) the hematocrit rose more gradually and significantly, and stayed elevated (this is the result of a plasma volume that continued
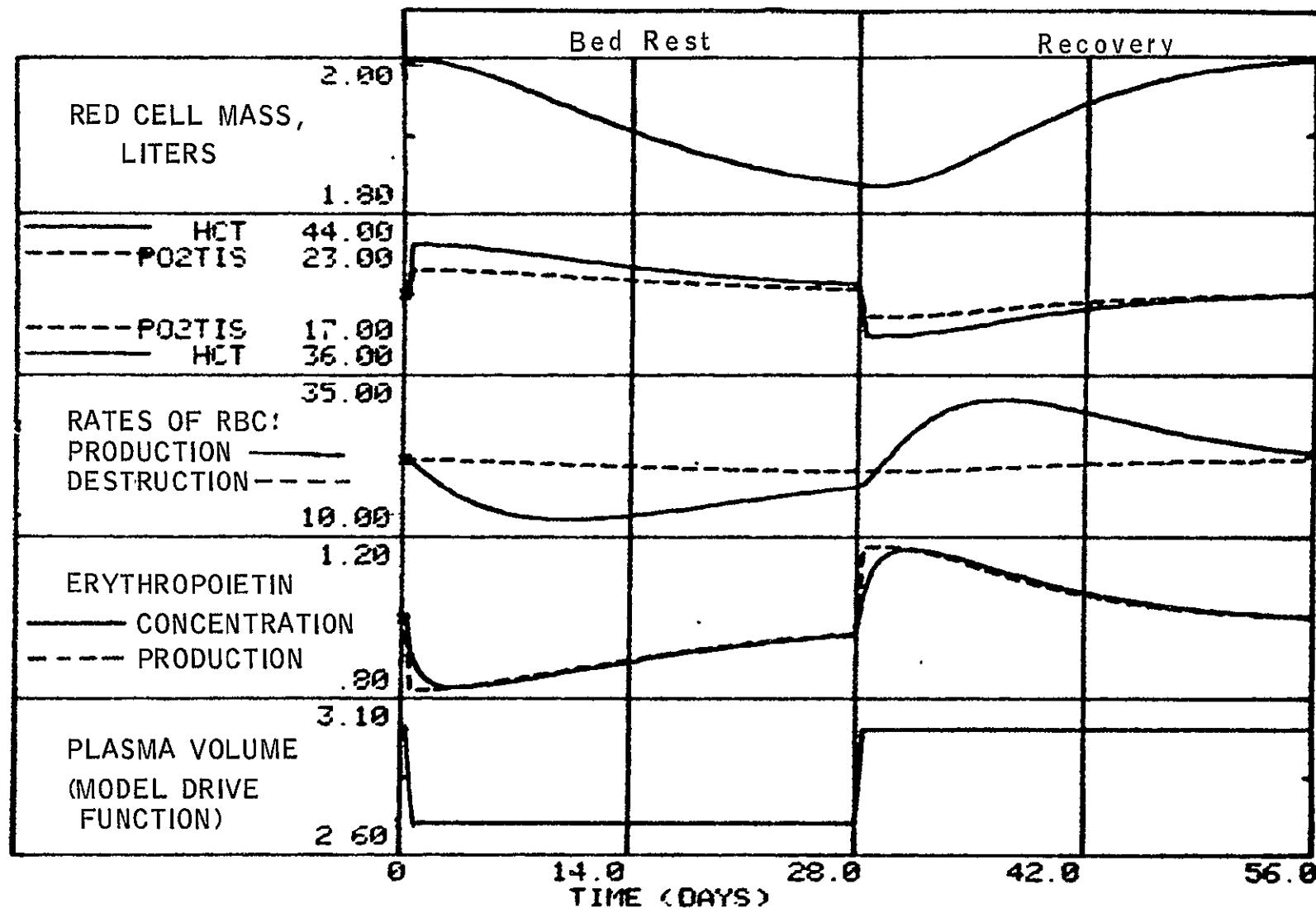
SIMULATION OF HYPOTHETICAL BED REST STUDY: VERSION II MODEL
WITH E_p AND RBC TIME DELAYS

(USING PLASMA VOLUME STEP FUNCTION $\pm$ 300 ML)

FIGURE 22
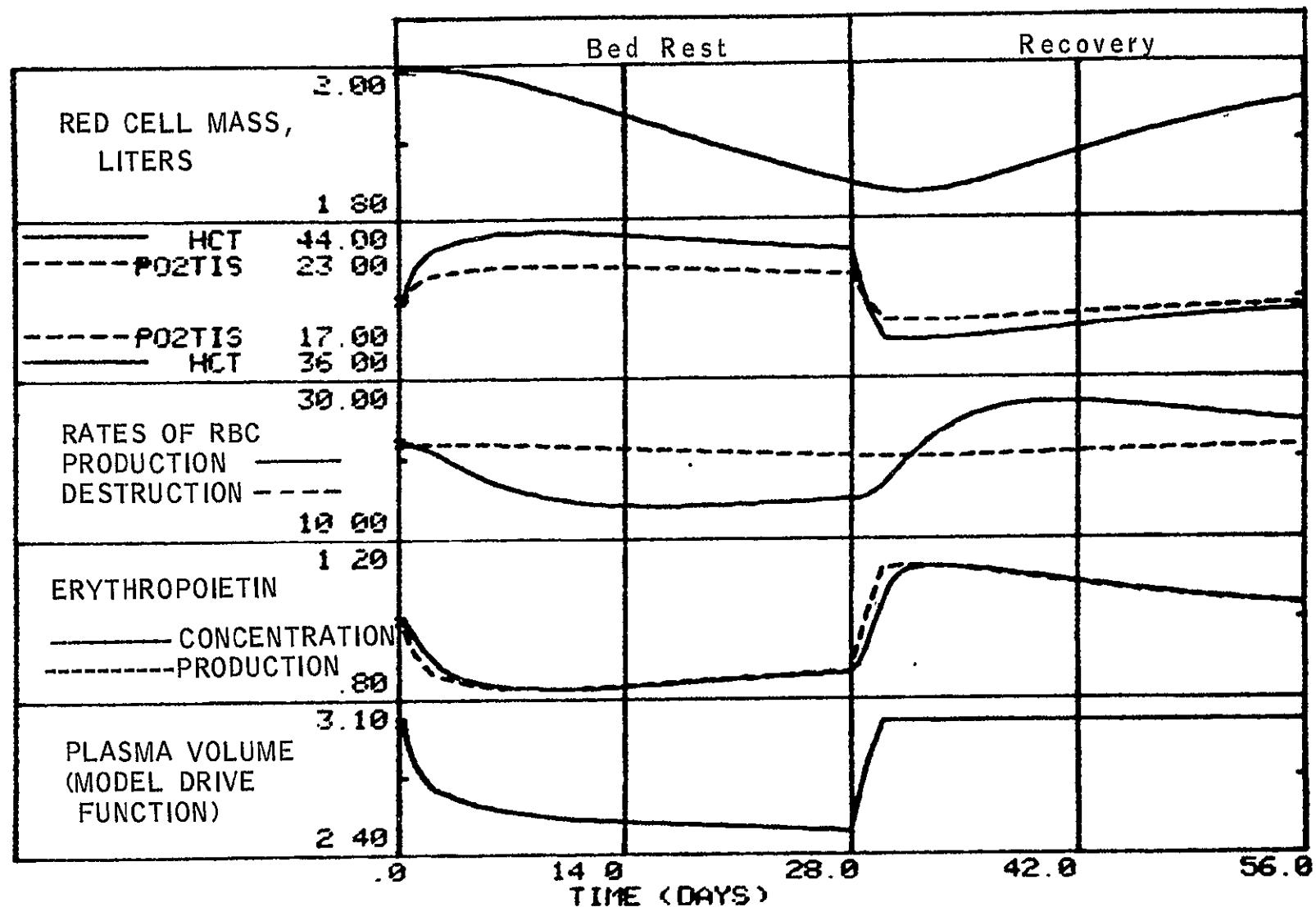
SIMULATION OF HYPOTHETICAL BED REST STUDY: VERSION II MODEL WITH TIME DELAYS
(USING NONLINEAR PLASMA VOLUME FUNCTION AS SHOWN)

FIGURE 23

to decline), c) both erythropoietin and red cell production declined even less rapidly than was seen previously and remained depressed. Plasma volume behavior during recovery is not as well understood as during bed rest. Time did not permit a thorough evaluation of this recovery function and in this simulation it was assumed that plasma volume increased linearly to normal levels two days after bed rest ended. Comparing this case to the previous one in which plasma volume rose nearly instantaneously, there was a notable increase in the refractory phase; i.e., red cell mass did not begin to recover until about four days following bed rest. Also there are significant differences in the dynamics of the other responses.

Figure 24 is derived from the same simulation run as that of Figure 23, but the recovery period was allowed to continue for 72 days instead of 28 days. This simulation was included to emphasize that recovery of red cell mass is rather slow. The model predicts, in this instance, that 95% red cell repletion takes 7 - 8 weeks, not significantly different from that observed on the 14-Day BMC Bed Rest Study.

The red cell mass and hematocrit responses during the first 28 days of bed rest, for the four simulations shown in Figures 20 - 24, are summarized in Figure 25(A) and (B), respectively. This overlayed plot shows more clearly the realistic trend toward linearization of the red cell response which occurs as each improvement was added to the model. The dramatic difference in the hematocrit response between curves (C) and (D) should also be noted. The red cell mass at Day 28 is nearly the same for all cases — approximately a 7.6% decrease which is consistent with Johnson & Driscoll's predictive equation. This was accomplished by adjusting the overall gain, G. The values of G used for curves A, B, C, and D were 13, 15, 15, and 7.5, respectfully in this identical bed rest simulation. The value of G used for the 28-Day BMC study was 10 which is well within this range.
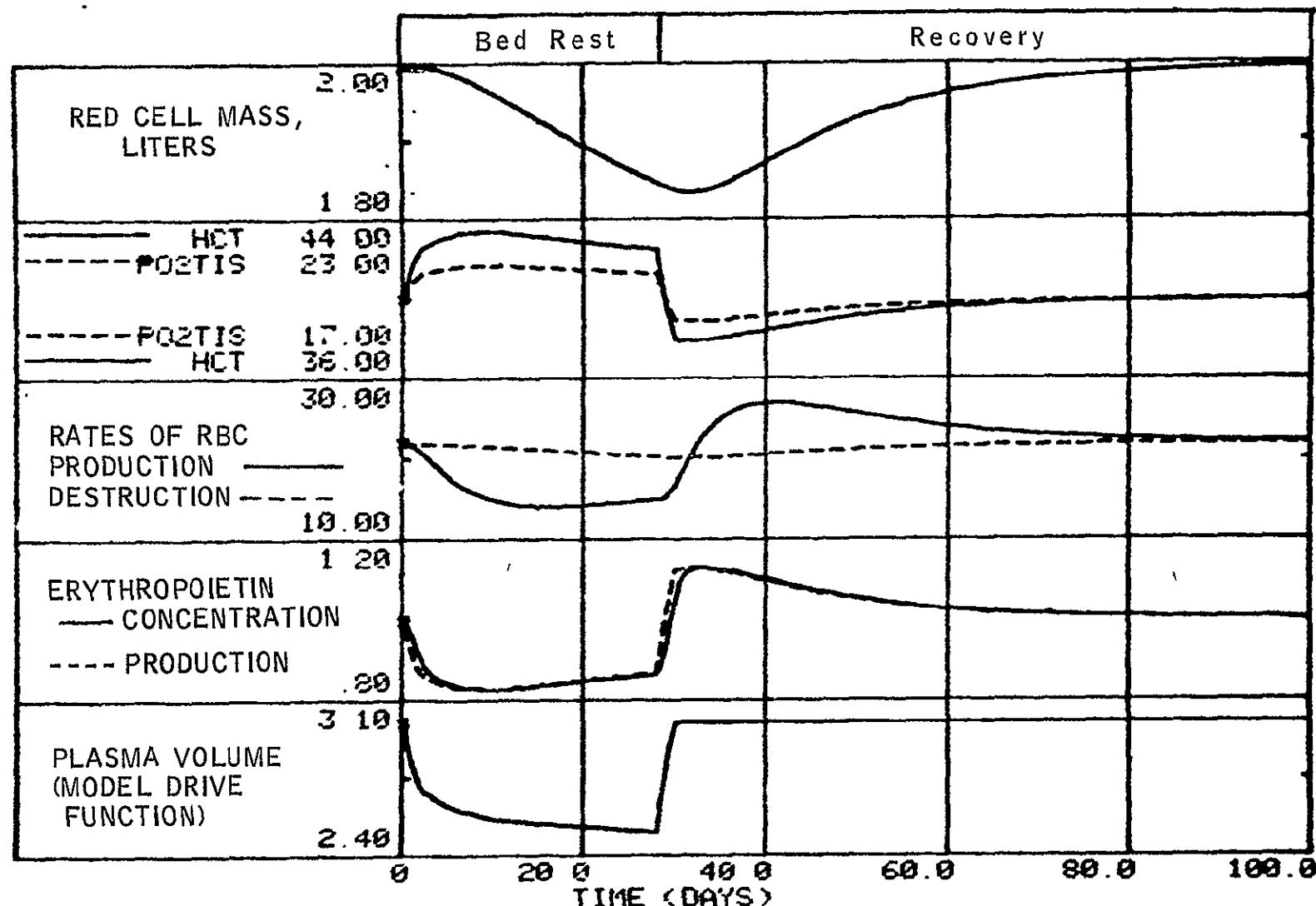
SIMULATION OF HYPOTHETICAL BED REST STUDY: VERSION II MODEL
WITH TIME DELAYS ADDED

(SAME AS FIGURE 23 BUT SHOWING LONGER RECOVERY PERIOD)
FIGURE 24

RED CELL MASS (LITERS)

KEY:

(A) Version I Model

(B) Version II Model No Time Delays

(C) Same as (B) With E_p and RCP Time Delays

(D) Same as (C) With Non-Linear Plasma Volume Function*

* PV = Step Function in (A),(B), & (C)

2.00

1.30

TIME (DAYS)

HEMATOCRIT

43.00

40.00

TIME (DAYS)
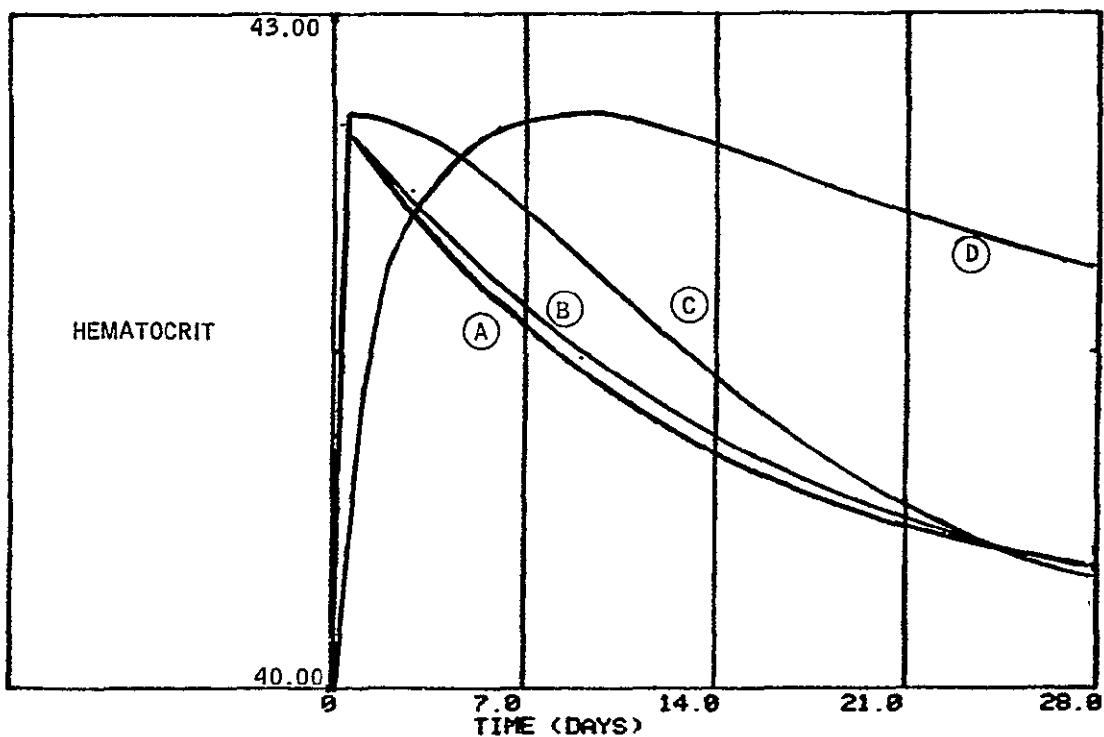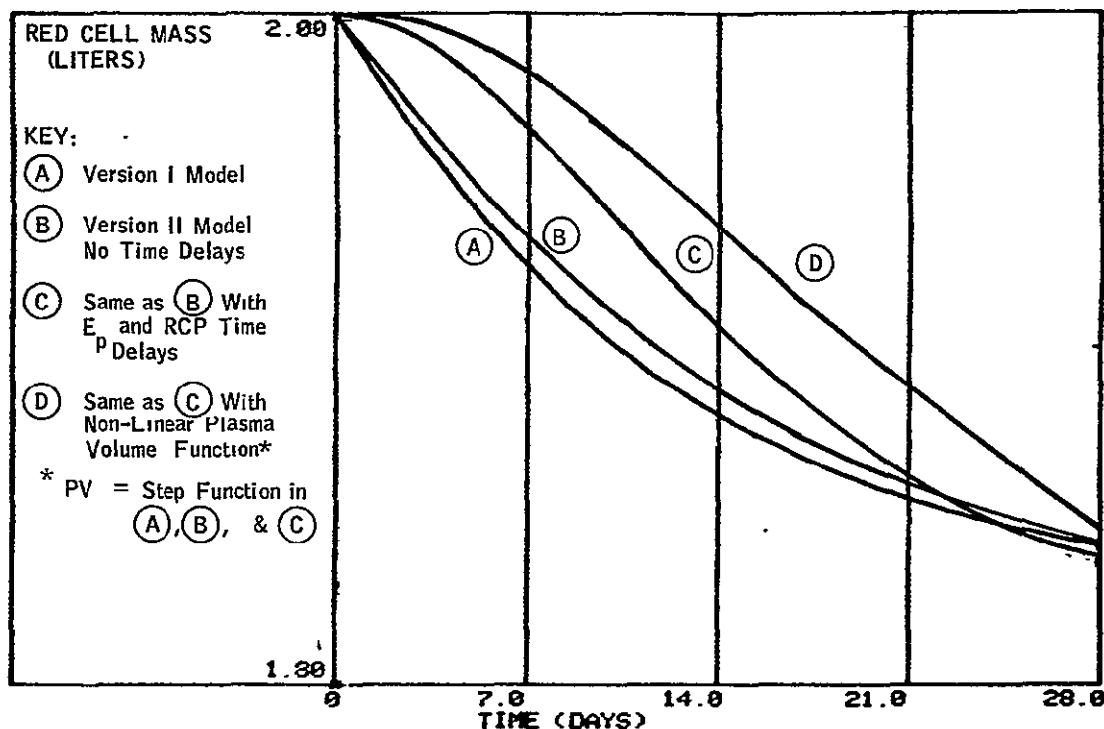
COMBINED RESULTS OF HYPOTHETICAL BED REST SIMULATIONS

FIGURE 25

One important point to be obtained from this series of simulations is that the dynamic behavior of the plasma volume (or more importantly, hematocrit) shifts which accompany bed rest and recovery appear to be crucial to an understanding of the red cell mass response. Bed rest studies to date have shown that red cell mass decreases linearly without apparent limit. These simulations have replicated this phenomenon and, in the process, have revealed that this is true only as long as plasma volume continues to decline. As soon as the plasma volume stabilizes at a reduced level, the hematocrit will fall with continued red cell loss and the depressant effect on erythropoiesis will be diminished. This process will continue until red cell production rises toward the now slightly reduced destruction rate and a new equilibrium level will be established at which time red cell mass will be reduced, but it will neither increase or decrease and hematocrit will be normal.

5. 0   SUMMARY AND CONCLUSIONS

The improvements to the erythropoietin model accomplished during this study have added a greater degree of realism to the simulation responses. In particular, the addition of an explicit representation of erythropoietin increases the usefulness of the model and permits it to be employed for a greater variety of applications. The model presently contains three time-delay constants of widely varying magnitudes (i. e., erythropoietin clearance (12 hours), red cell production delay (4 days), red cell destruction (60 days)) as well as nonlinear functions in the renal and bone marrow compartments. This, together with the new capabilities for shifting the nonlinear oxyhemoglobin affinity relationship and for introducing time-varying experimental data for driving functions, has created a model response that is beyond simple intuition. But as a model becomes more complex, it is also more difficult to validate. Therefore, it was gratifying to find that as each new formulation and element was added the model responded with greater realism and accuracy to a diversity of stresses. One of these included an example of simulating onset, diagnosis, and treatment of disease — an application which opens up new areas of model development. The enhanced capability and flexibility of the model was largely responsible for gaining new insights into bed rest simulation — a major objective of this effort. The study suggested that bed rest and bed rest recovery involve different processes and the results of this investigation are summarized below.

It is currently believed that during bed rest the red cell mass decreases due to a reduction in red blood cell production rather than increased destruction. A reduced erythropoietic state can be caused by a decrease in oxygen demand and/or an increase in oxygen supply. Both of these factors are present during bed rest. The model predicts that the small changes in hematocrit that occurred during the 28-day Baylor

(BMC) Bed Rest Study was sufficient by itself to account for the dynamic behavior of several hematologic indices which were measured, including red cell mass. The linear fall in red cell mass shown by the BMC investigators was confirmed by our simulation study in which no additional effect to the basic model was required other than the experimentally determined hematocrit-time profile. Further examination of the model showed that improved renal-bone marrow function curves and realistic time delays contributed to achieving this result. However, the nonlinear plasma volume shift that is observed during bed rest turned out to be an even more powerful influence on the response, especially during the later periods of bed rest. A slow prolonged decline in plasma volume following the initial rapid reduction is responsible for maintaining elevated hematocrits in the face of diminishing red cell mass. The model predicts that small changes in hematocrits, if unopposed by other factors, will proportionately increase oxygen supply to a renal sensing site and exert a sensitive suppressant effect on erythropoietin and red cell production. Furthermore, red cell mass will continue to decline as long as does plasma volume. If plasma volume stabilizes, the model predicts that hematocrit will decline to normal levels and a new equilibrium level will be established whereby the reduced red cell mass will neither increase or decrease. This regulation of red cell mass represents a normal physiological feedback process.

The basic model responded with a rise in red cell mass during recovery that was more rapid than observed in human subjects. In fact, bed rest recovery appears to be characterized by a continuing decline in red cell mass for at least the first two weeks. The improved model was able to predict such an effect for about the first 4 days by including a known bone marrow delay factor. Better agreement was obtained by testing various hypothesis including: a delayed recovery of plasma volume, a decrease in oxyhemoglobin affinity and increased hemolysis. While changes

in red cell mass during bed rest mass during bed rest may be entirely accounted for by hematocrit effects, the recovery process may involve more than the mechanism, each involving effects that may be too small to measure experimentally. The profound influence that small shifts in oxyhemoglobin affinity had on erythropoietic activity was unexpected and deserves further analysis. The simulations also suggested that a better experimental description of the time course of plasma volume recovery might aid in explaining the post bed rest response. The model fails to predict the proper combination of red cell mass and red cell production responses during recovery unless a large degree of red cell destruction occurs as well. Alternative explanations were offered to explain the data, such as shifts in bone marrow transit time and early release of reticulocytes, but these remain to be tested in the model.

These simulation studies will continue to raise more questions than they can answer. Many specific suggestions for additional data resulted from this study. This is, in fact, one primary function of the modeling process — to quantitatively evalute the effects of experimental data within an integrated theory of how the system under study is supposed to function and in so doing provide insights for new experimental design. The process of iterating between experimental and model testing is outlined in the flow diagram of Figure 27.
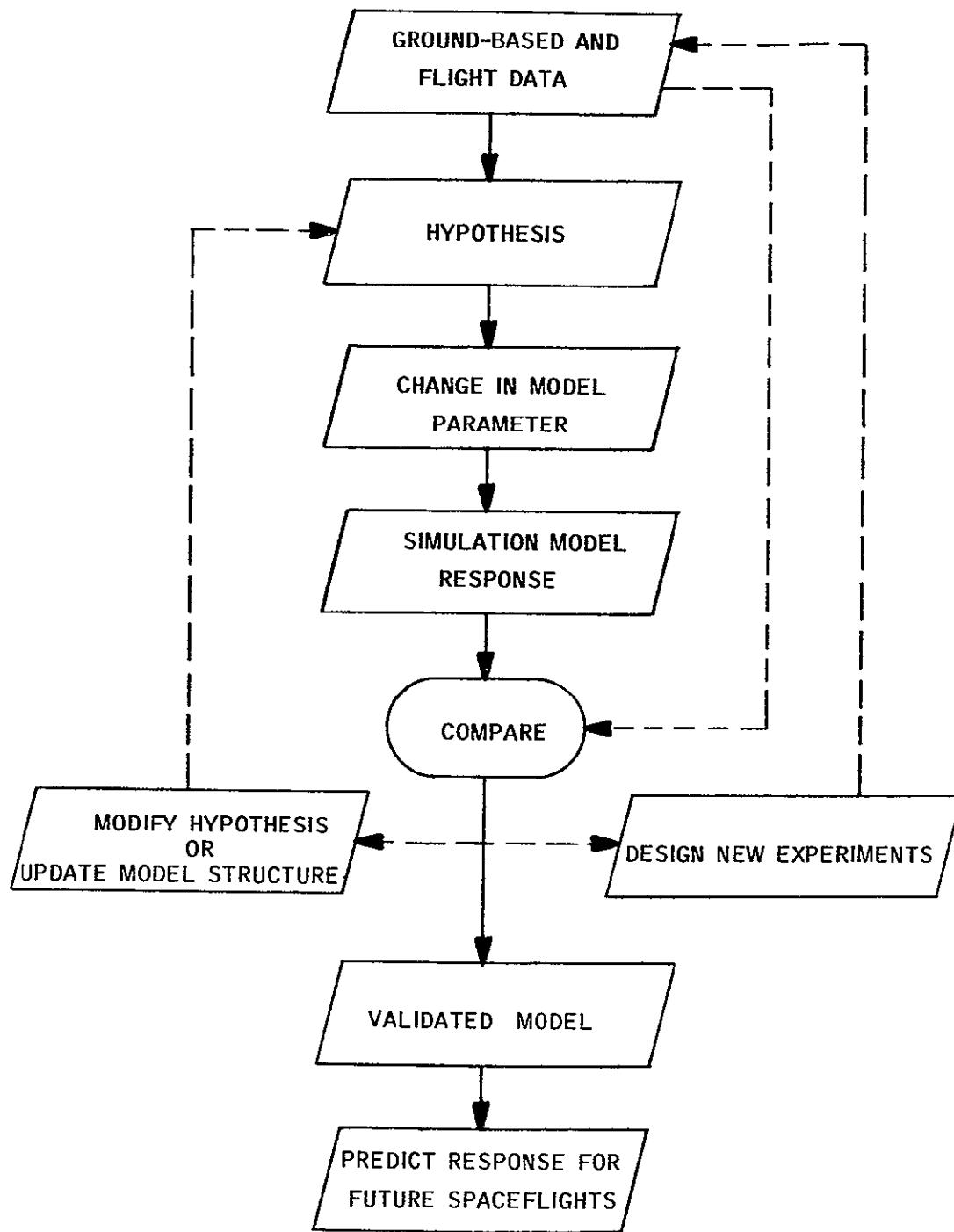
USE OF ERYTHROPOIESIS SIMULATION MODEL IN
NASA HEMATOLOGY PROGRAM

FIGURE 26

6.0   RECOMMENDATIONS

The performance of this study has resulted in several specific recommendations for improvements in the model and suggestions for collecting additional experimental data necessary for creating a more realistic model. These recommendations are identified and discussed in the report in the appropriate subject related sections. A list of these specific recommendations is provided here as a summary and to focus attention on candidate areas for future studies. The section in which the detailed discussion can be found is provided for convenience. The arrangement of this list is not intended to indicate order of importance or ease of implementation, but rather as a logical grouping of ideas. Figure 27 provides a systems overview of an earlier concept for improving the model which identifies those improvements which have been included as a result of creating Version I and II.

Improvements in Model Design

The following factors should be evaluated for their suitability for inclusion in a quantitative model.

- effect of blood volume on flow changes to the renal sensing site (p. 55, 56)
- effect of hematocrit and viscosity on blood flow and oxygen transport (p. 55)
- DPG effect on oxygemoglobin affinity;consider implementing a self-regulating mechanism perhaps based on levels of tissue oxygenation (p. 25-27, 57-58)
- improved characteristics of bone marrow transit delay (p. 22-25, 35)
- effect of decreased hematocrit, decreased maturation time and shortened life span on erythrocyte and reticulocyte production;distinguish between reticulocyte and erythrocyte release (p. 62)
- erythropoietin potentiation effect on red cell production (p. 33-35)
- alternative mechanisms for erythropoietin formation;higher order kinetics introduced due to "pro-Ep - plasma factor" and Ep Inhibitor" theories (p. 2-3)
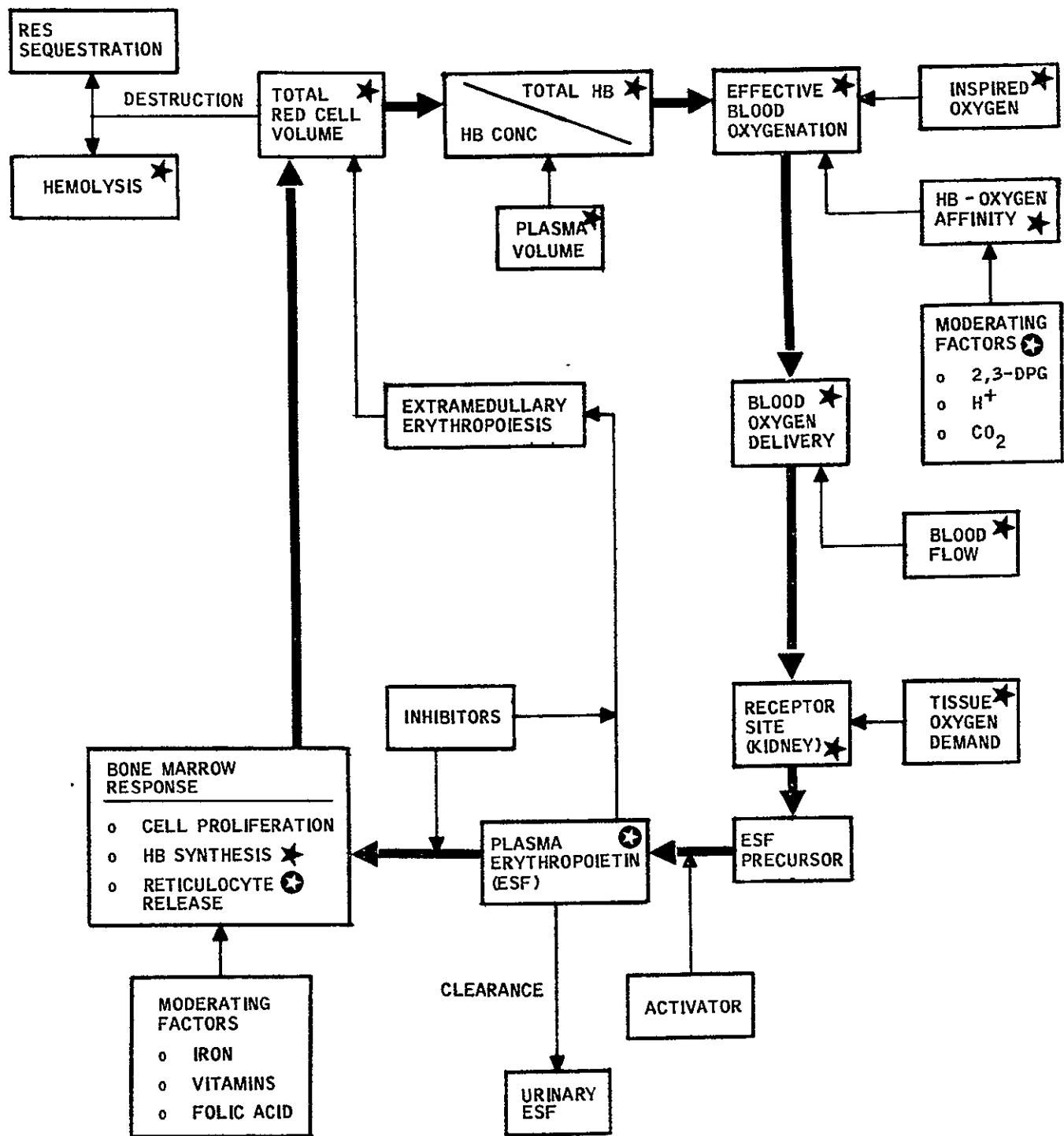
CONCEPT FOR AN IMPROVED ERYTHROPOIESIS MODEL

FIGURE 27

Simulation Studies with Current Model

- sensitivity analysis and parametric variation study of improved model
- characterization of bed rest response as a function of different plasma volume time profiles and red cell destruction rates (p. 48-62, 66-72)
- re-examination of Skylab data in light of model improvements and bed rest validation study

Design of Related Models

- teaching model for hematological abnormalities (p. 37-43)
- species specific animal models for predicting results and integrating data for ground-based and Shuttle animal experiments
- ferrokinetic models for iron uptake studies

Experimental Data Required for Model

In some cases there are data available for animals, but not for human subjects; in some cases data exists, but are not sufficient for inclusion in a quantitative model.

- dynamic response of erythropoietin for hyperoxic stimuli (p. 7-10)
- erythropoietin concentration effects on red cell production rates including basal production rates (p. 12-17)
- erythropoietin clearance rates (p. 11)
- plasma volume behavior during first week of bed rest recovery (p. 56, 66-69, 75)
- P_{50} measurements during bed rest and recovery (p. 57-58, 75)
- renal blood flow measurements during bed rest and recovery (p. 56)

APPENDIX

GLOSSARY OF SYMBOLS, NOTATIONS, AND ABBREVIATIONS

BMC = Baylor Medical College

DPG = Diphosphoglycerate

E_p = Rate of erythropoietin production and release, units/hr

E_d = Rate of erythropoietin disappearance from plasma, units/hr

$[E]$ = Concentration of plasma erythropoietin, units/ml

E_o = Constant used to define threshold of renal function curve

F_{cell} = Ratio of peripheral to whole-body hematocrit

G = Overall gain or sensitivity of renal-bone marrow axis relating tissue oxygen tension to red cell production

G_1 = Gain or sensitivity of renal function curve relating tissue oxygen tension to erythropoietin production

G_2 = Gain or sensitivity of bone marrow function curve relating erythropoietin concentration to red cell production

P_o = Parameter of bone marrow function curve representing basal level of red cell production

P_1 = Parameter of bone marrow function curve representing normal level of red cell production

P_m = Parameter of bone marrow function curve represnting maximum level of red cell production

P_s = Parameter of bone marrow function curve representing transition point between two empirical equations

P_{50} = Parameter of oxygen hemoglobin dissociation curve representing value of oxygen tension at which 50% of hemoglobin is saturated with oxygen.

APPENDIX (Continued)

PO_2 = tissue oxygen tension, mm Hg

RCM = Red cell mass, liters

RCP = Red cell production rate

$T_E^{\frac{1}{2}}$ = half-life of erythropoietin

$\bar{\bar{X}}$ = bar over any variable represents normalized value (dimensionless); ratio with respect to normal

X_o = subscript "o" attached to any variable represents its normal steady-state control value

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