ASD
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TIR 741-MED-4012

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| DATE | WORK ORDER REF: | WORK STATEMENT PARA: | REFERENCE: |
|---|---|---|---|
| 7/15/74 | MA-252T | NAS9-12932 | |

SUBJECT

Study Report
The Application of Systems Analysis and Mathematical Models to the Study of Erythropoiesis During Space Flight

(NASA-CR-160218) THE APPLICATION OF SYSTEMS ANALYSIS AND MATHEMATICAL MODELS TO THE STUDY OF ERYTHROPOIESIS DURING SPACE FLIGHT (General Electric Co.) 34 p HC A03/MF A01 CSCL 06P G3/52

N79-25739

Unclas 26965

This study report describes the application of systems analysis to the study of the erythropoietic control system, especially as it applies to space flight. Included are a review of erythropoietic mechanisms, an evaluation of existing models for the control of erythropoiesis, a description of a model proposed for further study, a computer simulation of the model's response to hypoxia, an hypothesis to explain observed decreases in red cell mass during weightlessness, suggestions for further research and an assessment of the role that systems analysis can play in the Skylab hematologic program.

Joel Leonard
J. I. Leonard, Ph.D.

Attachment
/db

CONCURRENCES

Counterpart:

Medical Projects L. C. Croston Engrg. & Advanced Programs
Unit Manager: R. C. Croston Subsection Mgr. C. W. Fulcher

DISTRIBUTION - NASA/JSC: Retha Shirkey/JM6 (1979 distribution) GE/TSS: D. Fitzjerrell

| | | | | |
|---|---|---|---|---|
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ASD 4028

# STUDY REPORT

# THE APPLICATION OF SYSTEMS ANALYSIS AND MATHEMATICAL MODELS TO THE STUDY OF ERYTHROPOIESIS DURING SPACE FLIGHT

By

J. I. Leonard

May 1974

## 1.0 INTRODUCTION

It has been demonstrated that individuals returning from space missions - from 4 to 85 days - have exhibited a significant loss of their preflight red blood cell mass. Some of the various factors that have been implicated in attempting to explain this loss include weightlessness, immobility of crew, high atmospheric oxygen partial pressure and lack of atmospheric nitrogen (1, 2, 3). A universally agreed upon explanation for this phenomena is still lacking.

This study is designed to be a preliminary systems analysis of the physiological systems that control red cell production. One of the purposes of this report is to review the physiological mechanisms that are presently believed to control erythropoiesis. A second objective is to evaluate existing mathematical models of erythropoiesis regulation. With this as a basis it was hoped to formulate a new model - either a composite of existing models or one embodying improved features - that would form the starting point for simulating the erythropoietic response to weightlessness. Finally, an assessment would be made regarding the role that systems analysis can play in the evaluation of the Skylab hematologic program.

Systems analysis has been shown to be a highly useful technique in helping to understand complex physiological processes, especially feedback control systems. This method usually consists of several phases of development: 1) the formulation of mathematical models of these processes, 2) a study of the behavior of these models using computer simulation techniques, and 3) the comparison of the behavior of the idealized model with the real system. The development of the model should be based, wherever possible, on accepted experimental evidence and physiological concepts. It is usually the case, however, that a complete understanding of the system does not exist. In those situations, systems analysis can be used to test various hypotheses quickly

and efficiently. This method finds its greatest utility when combined with a positive program of physiological research aimed at clarifying the hypothesized events.

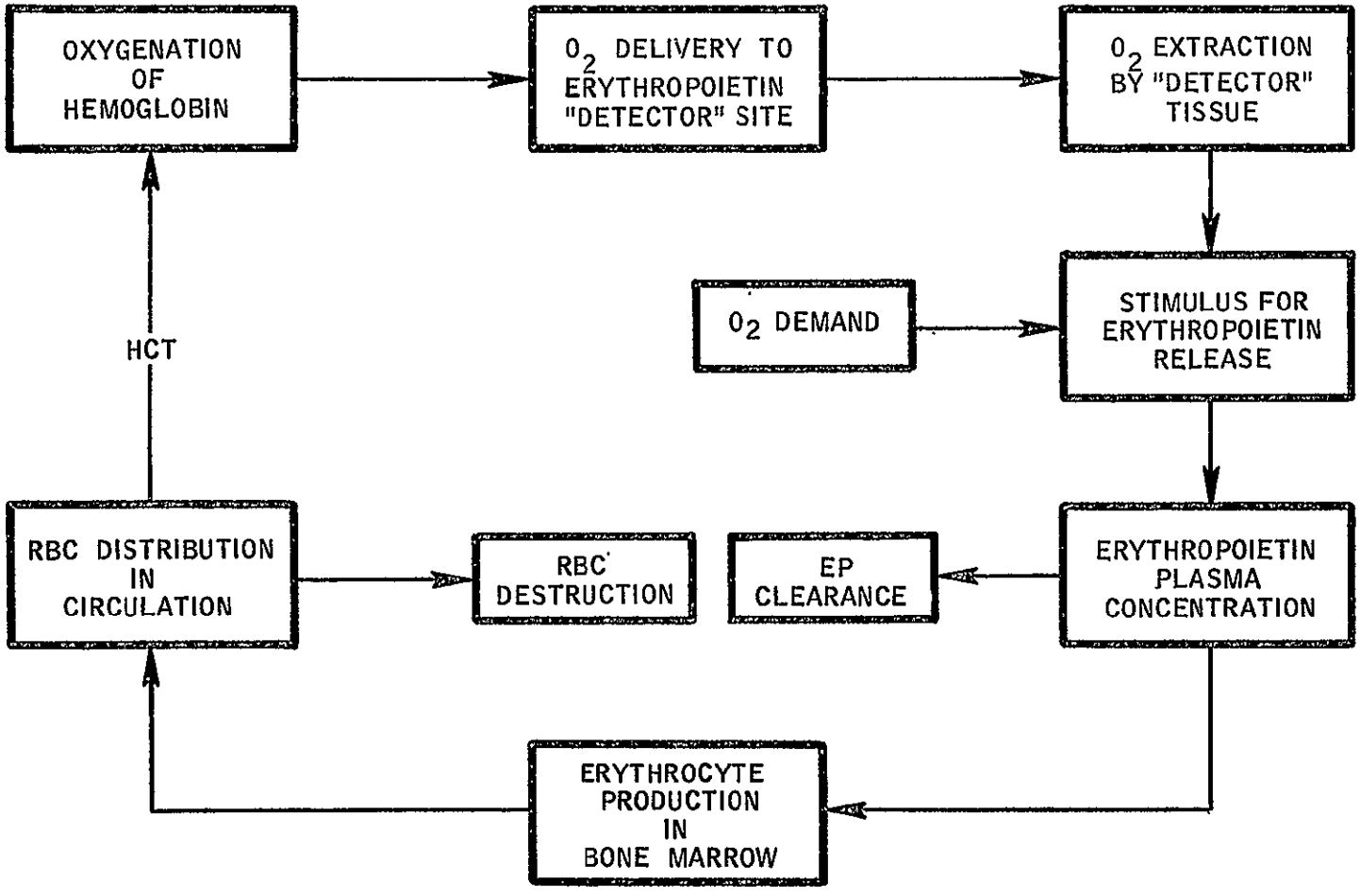
## 2.0 PHYSIOLOGY OF ERYTHROPOIESIS

### Factors that Control Erythropoiesis

Our present understanding of erythropoiesis, although far from complete, is sufficiently evolved to define a sequence of mechanisms that describe the regulation of red cell production (5, 6, 7, 8). It can be seen from Figure 1 that such a sequence forms a closed feedback loop in which red cell production is adjusted according to the balance of tissue oxygen supply and demand. There is general agreement that the direct stimulus for red cell production in the bone marrow is an erythropoietic stimulating factor known as ESF or erythropoietin. Release of erythropoietin, thought to take place primarily from some "oxygen detector" tissue in the kidney, is regulated by the balance between oxygen supply and oxygen demand. Decreasing the oxygen supply in relation to the demand results in increasing the rate of erythropoietin release and vice versa. Erythropoietin is released into the general circulation and its final plasma concentration is determined by its rate of release, volume of distribution and the rate at which it is metabolized. The target organ of erythropoietin is the bone marrow where it is believed the ESF plasma concentration determines the production rate and release of red cells. Although the mechanism of action has yet to be clarified, erythropoietin is thought to promote the mitotic activity of erythroid stem cells as well as stimulating hemoglobin production. Erythrocytes, once released and distributed into the circulation, become oxygenated in the lungs. The blood concentration of oxyhemoglobin and flow rates are the major determinants of the degree of tissue oxygenation which determines the rate of cell production. This oversimplified view accounts for the most important elements of the erythropoietic system. Some of the details of this system will be discussed below.

FIGURE I

HYPOTHESIS FOR CONTROL OF ERYTHROPOIESIS



Physiology of Tissue Oxygenation

The amount of oxygen delivered to a tissue depends on a number of factors: oxygen tension of inspired air, pulmonary function, hemoglobin concentration, affinity of hemoglobin for oxygen, speed of dissociation of oxygen from hemoglobin, cardiac output, and the vascular distribution of circulation blood among the individual tissues. From this amount of oxygen, a certain fraction is extracted and consumed by the tissue. Oxygen enters the cellular spaces by diffusion along an oxygen tension gradient between the capillary and the cell. A change in any of the factors listed above or in the cellular metabolic rate will result in a change in tissue oxygenation.

Thus, there are many factors in addition to hemoglobin concentration that could cause a temporary imbalance between tissue oxygen supply and demand. Any small change in this balance is usually compensated for by rapid adjustments in the circulatory and respiratory systems. For example, changes in the number of active tissue capillaries and blood flow adjustments are the most common compensatory responses to minor local fluctuations in the degree of tissue oxygenation. Under these conditions the rate of red cell production and the circulating red cell mass are remarkably constant. However, in more extreme and chronic situations such as hemorrhage, altitude hypoxia, or pulmonary disorders, an increase in red cell production appears the preferred way by which the body compensates for the resulting insufficient oxygen transport to the tissues. In addition, conditions that lead to extreme levels of tissue hyperoxia such as breathing from an hyperoxic atmosphere or transfusion induced polycythemia or when the tissue demand for oxygen is decreased as in hypothyroidism, hypophysectomy, and starvation there is a significant decrease in erythropoiesis.

Available evidence strongly supports the presumption that changes in cell production and circulating red cell mass are triggered by changes in the tissue oxygen tension.

But, as we have discussed, the circulatory system is also capable of responding to a change in tissue oxygen tension. Hence, it is important to understand the delicate balance that may exist between the responses of the circulatory and erythropoietic systems. To say that the circulatory system responds to minor fluctuations in tissue oxygen tension and that the erythropoietic system responds to more extreme and prolonged changes is no longer adequate, especially if one is attempting to construct an integrated model describing overall circulatory function. It is quite possible, although not yet proven, that the erythropoietic system is temporarily activated by even minor imbalances between oxygen supply and demand. On the other hand, the characteristics of the still unknown tissue oxygen sensing sites may be such that a sufficient time delay exists before erythropoietin or its precursors are released. This could allow time for circulatory changes to take place that may fully compensate an imbalanced condition without stimulating the slowly responding erythropoietic system. A more complete understanding of this problem may have to await the identification and characterization of the special sites that are believed capable of responding to changes in tissue oxygenation.

A decrease in oxygen-hemoglobin affinity resulting in improved oxygen release can be considered comparable to increases in blood flow or hemoglobin concentration in promoting the supply of oxygen to tissues. Changes leading to this shift to the right of the oxyhemoglobin saturation curve have been observed in subjects exposed to hypoxic conditions at altitude, exercising individuals and anemic patients. A constituent of the red cells has recently been implicated in this phenomena when it was discovered that the concentration of 2,3-diphosphoglyceric acid (2,3-DPG) was abnormally high in these situations (8). The dissociation of oxygen appears to be facilitated by 2,3-DPG because it preferentially and reversibly binds deoxyhemoglobin. Conversely, conditions of relative hyperoxia, such as moving adapted individuals from altitude to sea level, has been observed to be accompanied by decreases in the levels of

2,3-DPG. It is understood that the blood analysis of the Skylab crewmembers includes an analysis of 2,3-DPG. This data might be useful in estimating the relative shifts of the oxyhemoglobin curves both during flight and upon recovery, and incorporating this information into an integrated model of the erythropoietic system.

Renal Release of Erythropoietin

The majority of experimental evidence reviewed in recent years (7, 8, 9, 10) supports the hypothesis that oxygen supply (as measured by tissue $PO_2$) to a renal "detector" site in relation to the oxygen demand of that region is the primary stimulus for erythrocyte production via the release of a renal erythropoietic factor (ESF). However, the renal site of origin or activation of the ESF has not yet been found. It has been suggested (7, 10) that the kidney tissue has developed a specialization that enables it to function as a sensitive oxygen chemoreceptor. While most organs in the body exhibit a blood distribution pattern that results in an even release of blood oxygen, the kidney has a peculiar microcirculation: a) the sharp angles between arterioles and arteries leads to plasma-skimming where the blood in some of the smaller vessels have a reduced hematocrit; b) efferent arterioles from the cortex dip deep into the medulla and then return as capillaries, resulting in a steep gradient of tissue oxygen tension along this axis. Thus, a relative hypoxia is present which may act as a continual stimulus for daily erythropoietin production. Any small change in blood oxygen delivery should have a marked effect on this area of low tissue $PO_2$.

Although a large number of experiments have shown that changes in red cell production are accompanied by corresponding changes in plasma ESF, this has not always been observed. In order to explain some of these "unexpected" results it has been speculated that there are agents formed in the plasma that act to accelerate or inhibit erythropoiesis independently of ESF. However,

others (7) seem to feel that many of the apparent discrepancies appear to result from the low level of resolution of various bioassays for erythropoietin and the indirect means of estimating total oxygen supply. They do not believe that existing data call for the postulation of additional chemical factors. Thus, it would seem that the theory of oxygen supply and demand is the best explanation we have for the existing data.

Even if an additional system of erythropoietic regulation besides ESF does not exist, there is a growing body of evidence to suggest that ESF is not formed in the kidney, but that the kidney produces a renal erythropoietic factor (REF) which can be activated to ESF by unknown constituents in normal serum. If this precursor to ESF does exist, the dynamics of the erythropoietic system could follow the laws of second order, rather than first order, kinetics, mathematical simulation of this system might be improved by including this effect.

Renal blood flow could markedly affect the amount of oxygen delivered to the special sensing sites. Moreover, in contrast with all other body organs and tissues, the oxygen demand or consumption in the kidney is more or less proportional to blood flow rather than remaining constant (11). Thus, while increasing blood flow may increase oxygen supply there is a proportional increase in oxygen demand. In addition, renal blood flow is known to be under a high degree of autoregulatory control. These considerations suggest that the balance between tissue oxygen supply and demand is not markedly influenced by blood flow in the kidney. Whether the renal oxygen detector sites exhibit these same characteristics that may exist for the kidney as a whole is not known. Several experimental studies have shown that reduction in renal artery blood flow resulted in significant increases in plasma levels of erythropoietin (e.g. 12). However, in summarizing the total body of evidence for the effects of renal blood flow on erythropoiesis, several reviewers have appeared to reach opposite conclusions (7, 10).

## 3.0 COMPARISON OF MODELS FOR THE CONTROL OF ERYTHROPOIESIS

A review of the published literature reveals only three models useful for mathematical simulation of the erythropoietic control system (5, 6, 13, 14). The following section is a review of these models discussing their similarities and differences. Comparison will be facilitated by breaking each model into component parts as suggested in Figure 1. Figures 2, 3, and 4 are flow charts of the models of Mylrea and Abbrecht, Hodgson, and Guyton*. An explanation of symbol definitions used in Figure 4 appears in Table 1. Figure 5 is a summation of the discussion to follow.

### Oxygenation of Hemoglobin (2/1&2; 3/4; 4/3)**

The degree of oxyhemoglobin saturation in arterial blood is simply an input term in the Hodgson model. Mylrea and Abbrecht account for changes in blood $PO_2$ in response to acute and acclimatized hypoxia using an empirical relationship and then compute hemoglobin saturation from an experimental oxyhemoglobin saturation curve. The percent hemoglobin saturation is computed by Guyton from a pulmonary dynamics section of his model and appears as an input term in the red cell production block of Figure 4.

### Oxygen Delivery to Kidney (3/2; 4/1)

Mylrea and Abbrecht consider blood flow to the kidney to be constant and do not include a blood flow term in their model. Hodgson utilizes renal blood flow as an input variable, but also states that "it is not kidney blood flow that is the significant factor, but the flow to the (renal) tissue in which the (renal tissue partial pressure) detector is located". Guyton considered the site of erythropoietic stimulation to be located in "non-muscle, non-renal tissue". Consequently, the blood flow term that is used in his model (computed from a circulatory model) is non-renal blood flow which appears as an input variable in Figure 4.

* Figure 4 is a portion of the complete Guyton model (13, 14) concerned only with the control of red cell production. This model will become the basis for a proposed model for future study. There are some minor differences between Guyton's section for red cell control and the representation in Figure 4. These will be explained more fully in the text.

** This notation refers the reader to the appropriate flowchart and block number. In this example, oxygenation of hemoglobin is described in Figure 2, Blocks 1 and 2; Figure 3, Block 4; and Figure 4, Block 3.

FIGURE 2

MODEL FOR CONTROL OF ERYTHROPOIESIS

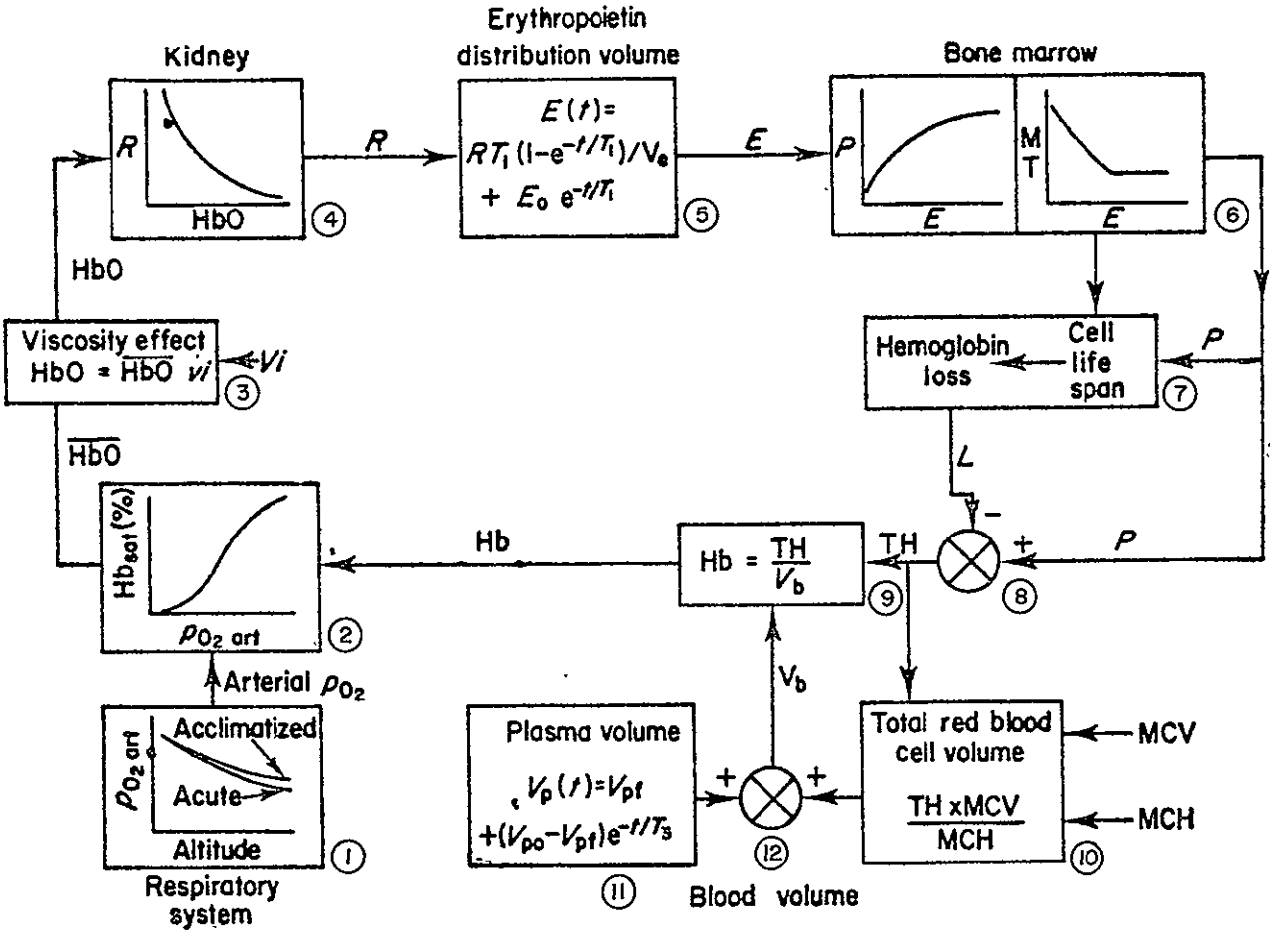


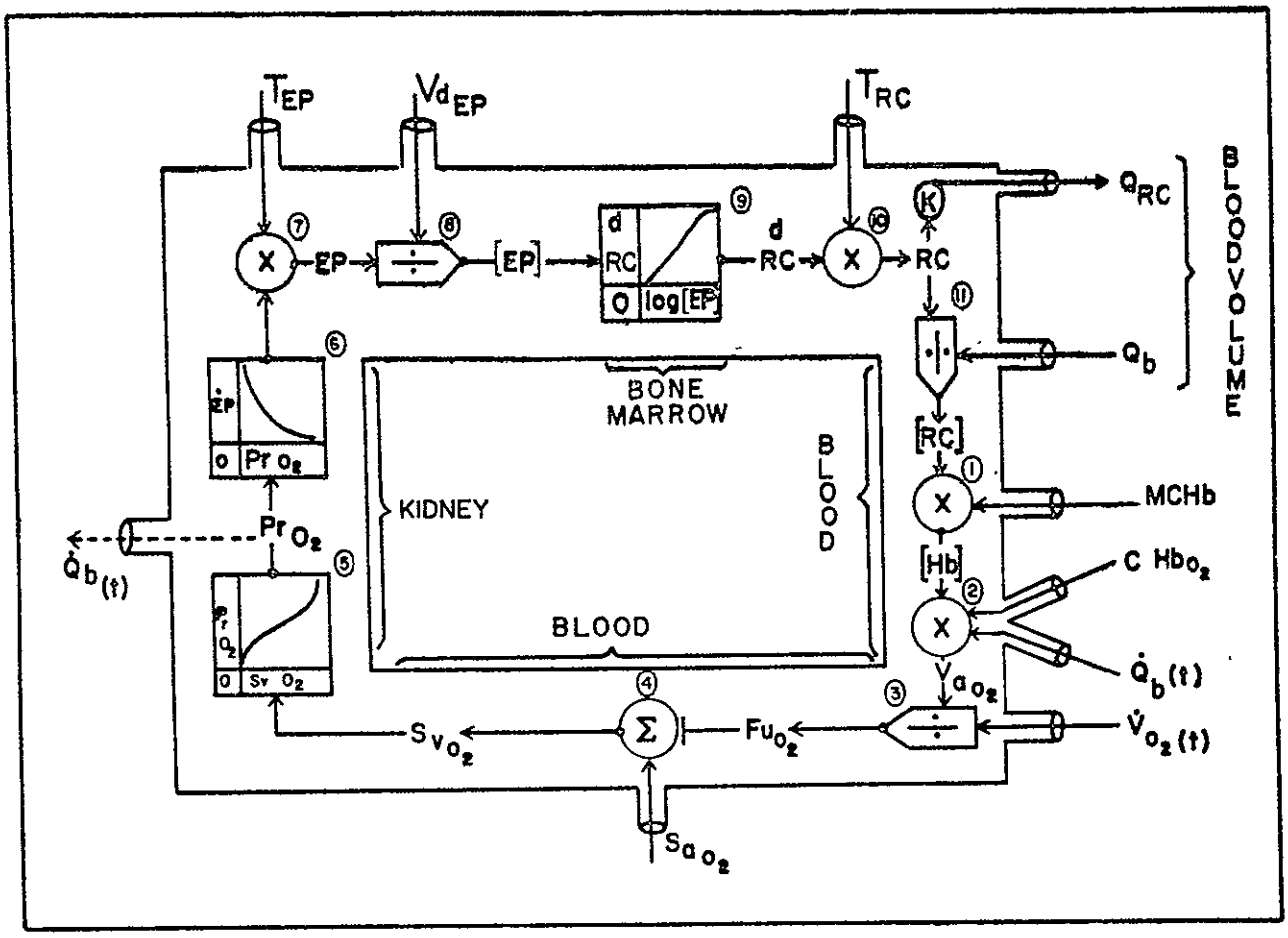

FIG. 1. Block diagram of a model for the control of erythropoiesis. $\overline{HbO}$ = oxyhemoglobin concentration, $Vi$ = viscosity factor, HbO = effective oxyhemoglobin concentration, $R$ = rate of erythropoietin release, $E$ = plasma erythropoietin concentration, $E_0$ = normal plasma erythropoietin concentration, $V_e$ = distribution volume for erythropoietin, $P$ = rate of hemoglobin production, MT = erythrocyte maturation time, $L$ = rate of hemoglobin loss, TH = total circulating hemoglobin, [Hb] = blood hemoglobin concentration, $V_b$ = blood volume, $V_p$ = plasma volume, $V_{po}$ = normal plasma volume, $V_{pf}$ = steady state hypoxic plasma volume, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, $k$ = constant.

(MYLREA & ABBRECHT, 1971)

FIGURE 3

MODEL FOR THE CONTROL OF ERYTHROPOIESIS

(HODGSON, 1970)




$CHbO_2$ = oxygen capacity of Hb, EP = total erythropoietin, ( EP) = plasma erythropoietin concentration, $FuO_2$ = fraction of maximum oxygen flow delivered to renal tissues, (Hb) = hemoglobin concentration, MCHb = mean corpuscular hemoglobin, $P_rO_2$ = oxygen tension of renal tissue, $Q_b$ = blood volume, $\dot{Q}_b(t)$ = blood flow rate, $Q_{RC}$ = red cell volume, $R^dC$ = red cells produced daily, RC = red cell count, $S_aO_2$ = oxygen saturation of art. blood, $S_vO_2$ = oxygen saturation of ven. blood, $T_{EP}$ = mean life span of erythropoietin, $T_{RC}$ = mean life span of red cells, $V_aO_2$ = maximum oxygen flow rate in arterial blood, $\dot{V}O_2$ = tissue oxygen consumption rate.

FIGURE 4

GE MODEL FOR CONTROL OF ERYTHROPOIESIS
(DERIVED FROM GUYTON)

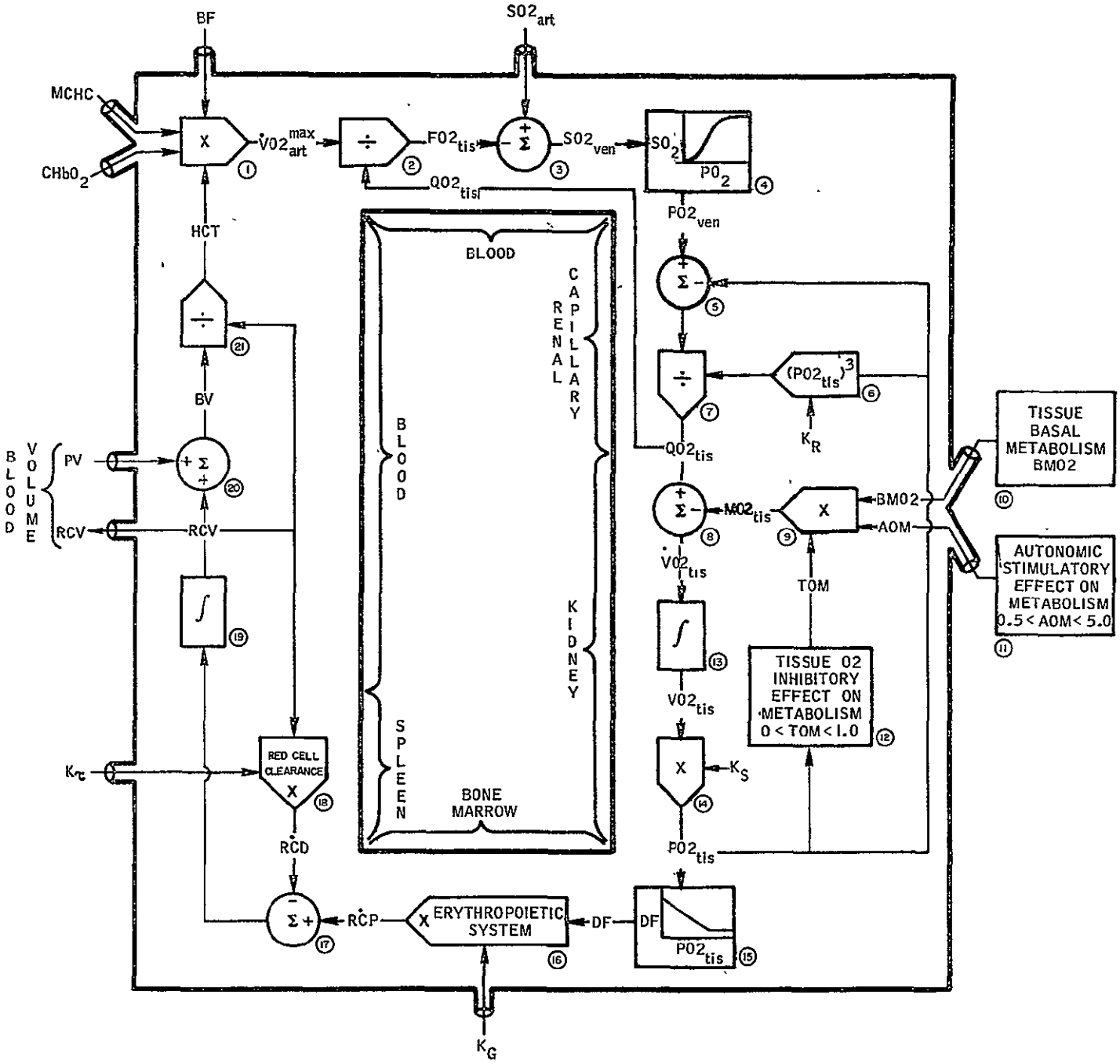


TABLE I

SYMBOLS AND DEFINITIONS OF TERMS USED IN FIGURE 4

| GUYTON NOTATION | THIS REPORT | DEFINITION | UNITS |
|---|---|---|---|
| AOM | AOM | Autonomic stimulatory effect on tissue oxygen utilization | ND |
| *BFN | BF | Renal blood flow | l/min |
| VB | BV | Blood volume | liters(l) |
| *02M | BM02 | Basal oxygen utilization in renal tissue | ml/min |
| ** | $CHb0_2$ | Oxygen carrying capacity of hemoglobin | ml/gm |
| OVA | $CO2_{art}$ | Volume concentration of oxygen in arterial blood | ml/l |
| P02 | DF | Drive factor causing red cell production | mm Hg |
| - | $F02_{tis}$ | Fraction of maximum oxygen flow delivered to tissues | ND |
| HM | HCT | Hematocrit | ml/100 ml |
| POY | $K_G$ | Sensitivity of red cell production | l/min-mm Hg |
| ** | $K_R$ | Resistance coefficient for $0_2$ diffusion | min/ml-mm $Hg^2$ |
| ** | KS | Solubility coefficient for oxygen | mm Hg/ml |
| RKC | $K_T$ | Rate constant for red cell destruction | $hr^{-1}$ |
| ** | MCHC | Mean corpuscular hemoglobin concentration | gm/10 ml |

| GUYTON NOTATION | THIS REPORT | DEFINITION | UNITS |
|---|---|---|---|
| *M02 | $M02_{tis}$ | Rate of oxygen utilization of renal cells | ml/min |
| ** | $P02_{art}$ | Oxygen tension in arterial blood | mm Hg |
| POT | $P02_{tis}$ | Oxygen tension in renal tissue | mm Hg |
| POV | $P02_{ven}$ | Oxygen tension in venous blood | mm Hg |
| VP | PV | Plasma volume | l |
| ** | $Q02_{art}$ | Oxygen flow rate in arterial blood | ml/min |
| *DOB | $Q02_{tis}$ | Oxygen delivery rate to renal tissue | ml/min |
| ** | $Q02_{ven}$ | Oxygen flow rate in renal veins | ml/min |
| RC2 | $\dot{RCD}$ | Red cell destruction rate | 1/min |
| RC1 | $\dot{RCP}$ | Red cell production rate | 1/min |
| VRC | RCV | Red cell volume | l |
| OSA | $S02_{art}$ | Fractional saturation of oxygen in arterial blood | ND |
| *OSV | $S02_{ven}$ | Fractional saturation of oxygen in renal vein | ND |
| ** | TOM | Tissue $P0_2$ effect on oxygen utilization | ND |

| GUYTON NOTATION | THIS REPORT | DEFINITION | UNITS |
|---|---|---|---|
| - | $V02_{art}^{max}$ | Maximum oxygen flow rate in arterial blood | ml/min |
| *Q02 | $V02_{tis}$ | Total oxygen volume dissolved in renal tissue fluid | ml |
| ** | $\dot{V}02_{tis}$ | Rate of oxygen accumulation in renal tissue fluid | ml/min |

* Guyton computes this variable for non-renal, non-muscle tissue and therefore it is not equivalent to the corresponding variable in a renal model.

** Not computed explicitly in Guyton model.

- No comparable term in Guyton model.

ND- No dimension

FIGURE 5

COMPARISON OF RED BLOOD CELL CONTROL MODELS

| Process | Mylrea and Abbrecht | Hodgeson | Guyton |
|---|---|---|---|
| Oxygenation | $PO_2$(atm) → $PO_2$(art) → $SO_2$(art) | Input: $SO_2$(art) * | Pulmonary Model → $SO_2$(art) |
| Blood Flow to Kidney | Not a model parameter; Considered to be constant | Input: Renal Blood Flow* | Circulatory Model → non-renal blood flow |
| Oxygen Extraction | Not Considered | Input: Metabolic Rate | a) $O_2$ Diffusion * b) Variable Metabolic Rate * |
| Stimulus for EP Release | "Effective" [HbO] (art) = [HbO] × viscosity factor | Renal Tissue $PO_2$ * | Non-renal Tissue $PO_2$ |
| Plasma [EP] | $\tau$ (clearance); $Vd_{EP}$ | Mean life span, $T_{EP}$; $Vd_{EP}$ | Not Considered * |
| RBC Production Rate | a) $P = P_m(1 - e^{-k[EP]} + P_o$ b) Maturation time = f( EP ) | $P = f(\log [EP])$ | $P = K_{gain} \times (P_{bias} - PO_{2,tis})$* |
| RBC Destruction Rate | RBC Life Span | $D = RC /$ Mean life span | $D = RBC \times \tau_{clearance}$ * |
| Distribution in PV | Input variable: PV * | Input variable: PV * | Fluid Shift Model → PV |

* DENOTES PROPOSED USE IN PRESENT MODEL

$PO_2$ = Oxygen Tension

$SO_2$ = Oxyhemoglobin Saturation

HbO = Oxyhemoglobin Concentration

[EP] = Erythropoietin Concentration

$Vd_{EP}$ = Volume of Distribution of EP

PV = Plasma Volume

$\tau$ = Clearance Constant

P = Production Rate

Oxygen Extraction by Tissue (2/3; 3/3&4; 4/2-14)

Although recognizing the importance of oxygen extraction in determining the amount of oxygen available to the tissue, Mylrea and Abbrecht do not consider this factor, per se, in their model because of "inadequate data". However, they found that their simulations did not agree with experimental responses to hypoxia until they added a "viscosity effect" to their model. The stated purpose of using this term was to account for a reduction in blood flow (and hence a decrease in oxygen delivery) due to increasing hematocrit. However, since blood flow was not used explicitly in their model the actual effect was to obtain an "effective oxyhemoglobin concentration" in arterial blood lower than the true value. The overall result is a reduction in the amount of oxygen being delivered to the tissues. This same effect was achieved more realistically in Hodgson's model by including a term for tissue oxygen consumption and in Guyton's model by accounting for both tissue metabolism and transcapillary oxygen diffusion. The Guyton model allows for a variable rate of metabolism and diffusion resistance.

Stimulus for Erythropoietin Release and Plasma $\left[EP\right]$ (2/4&5; 3/5-8; 4/15)

Mylrea and Abbrecht postulate that their "effective oxyhemoglobin concentration" is the stimulus for erythropoietin release. The relationship between these two variables is a monotonically decreasing function derived from experimental data on small animals. A time delay, also based on experimental observation, accounts for the delay between changes in (Hb0) and the associated erythropoietin release. Hodgson postulates that the renal tissue oxygen partial pressure is the stimulus for erythropoietin release. It is assumed that venous-capillary $P0_2$ is identical to tissue $P0_2$ and this term is computed by comparing rates of oxygen delivery to, and oxygen extraction by, the renal tissue. Guyton does not account for erythropoietin release, per se, but uses the tissue oxygen partial pressure as the stimulus for erythrocyte production. An inverse linear function relating tissue $P0_2$ to erythrocyte production is assumed.

Erythrocyte Production in Bone Marrow (2/6; 3/9; 4/16)

In the Mylrea and Abbrecht model, hemoglobin production rate (which is assumed to be similar to erythrocyte production) is postulated to have a small basal value and asymptotically approaches a maximum value as erythropoietin concentration increases. The model incorporates a normal erythrocyte maturation time delay which decreases from 4 to 2.5 days as erythropoietin concentration increases. Hodgson takes erythrocyte production rate to be a linear function of $\ln [EP]$ which is similar to the dose response curve proposed in Mylrea and Abbrecht's model, but based on different data. Guyton assumes red cell production to be proportional to the difference between oxygen demand and supply (as measured in terms of oxygen partial pressure). This "drive factor" for erythrocyte production has a minimum value and is multiplied by a gain factor which describes the overall sensitivity of the erythropoietin release - erythrocyte production circuit. In spite of the fact that Guyton does not account for an erythropoietic stimulating factor in his model, his overall schema of relating tissue oxygen supply to red cell production is quite similar to those adopted by both Mylrea and Abbrecht and Hodgson.

Red Cell Destruction and Distribution (2/7-12; 3/10&11; 4/17-21)

It was assumed in Mylrea and Abbrecht's model that the red blood cells have a finite life span and that the cells destroyed at any given time are distributed in a normal manner about a mean value. Total circulating red blood cell volume was calculated from the net total circulating hemoglobin by using the appropriate hematologic indices. Hodgson accounted for red cell destruction by multiplying the production rate of red cells by the mean red cell life span to give the net number of red cells released. Red cell destruction, in the Guyton model, is accounted for by using a clearance time constant (based on the mean life span) and multiplying this by the present red cell volume to give the rate of destruction. The net red cell volume is determined by integrating the difference between the rates of production and destruction. In all three

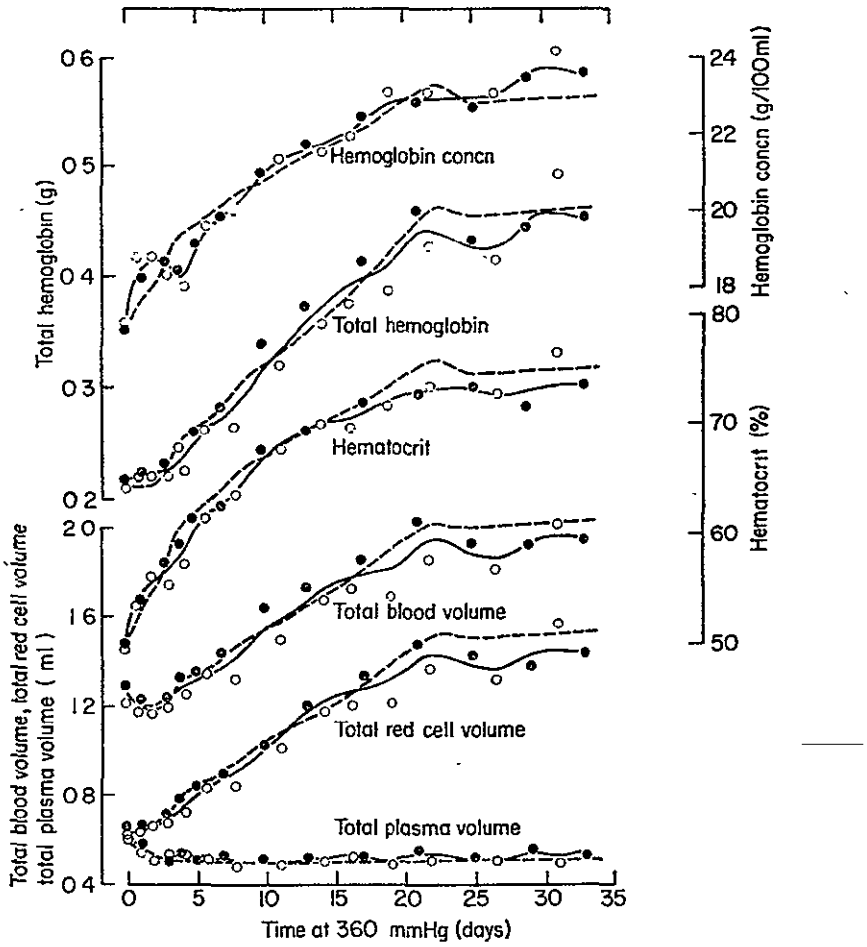
models the hematocrit of circulating blood is computed by dividing the present red cell volume by the total blood volume. Plasma volume is an input variable in Mylrea and Abbrecht and Hodgson's models while Guyton computes plasma volume from an intercompartmental fluid shift model. In the red cell production block (Figure 4), plasma volume is considered to be an input term.

It should be apparent that these models are not exactly alike. For example, Guyton does not explicitly consider an erythropoietic stimulating agent while Mylrea and Abbrecht and Hodgson use experimental data to compute release rates, clearance rates, and plasma concentrations of erythropoietin. On the other hand, Mylrea and Abbrecht consider renal blood flow to be constant while it appears that a variable flow rate can have important consequences on red cell production in the models of Hodgson and Guyton.

The most important test of a model is its ability to predict experimental observations using parameters that have physiological significance and using values for those parameters that are biologically plausible. Validation was only attempted for one of these models, that of Mylrea and Abbrecht's, and that was for the case of mice under chronic hypoxic conditions. An example of the results they obtained are shown in Figure 6. It can be seen that the prediction of several important hematologic variables was in good agreement with experimental data. Neither Hodgson nor Guyton have reported any attempt to subject their models to similar verification.

New Model Proposed by Guyton-White

Recently Drs. Guyton and White have been attempting to formulate an improved version of their erythropoiesis model. Their new model is quite preliminary and still untested, and it is described here briefly in the interest of completeness. It is based on a new concept of the renal tissue site that is believed to sense oxygen supply and regulate the release of erythropoietin.




Experimental data (Mylrea & Abbrecht, 1970) and the model results for mice exposed continuously to a total pressure of 360 mmHg ($p_{O_2}$ = 75 mmHg). Each point is the average of values obtained for nine mice. Different symbols represent different runs. The solid lines were obtained by first doing a linear interpolation to obtain daily values for the variables for each run, and then averaging the daily values for all runs at that altitude. Broken lines show the model output for this altitude, with the exception of the lowest curve, which shows the empirically derived relationship used for plasma volume in the model. Experimental values shown for time "0" were obtained on control mice kept at atmospheric pressure.

FIGURE 6

They have ascribed several characteristics to this oxygen sensing-erythropoietin releasing tissue within the kidney: 1) the blood flow rate to this tissue is assumed constant due to excellent intrarenal autoregulation, 2) the oxygen consumption rate is also assumed to be constant, and 3) the erythropoietin releasing system is considered to be a fast responding, high gain system, especially in hypoxic situations. The constancy of blood flow and tissue metabolism in effect make this tissue a sensor of blood hematocrit for the reasons that follow. Since oxygen delivery to tissue is dependent on basically two parameters, the blood flow rate and hemoglobin concentration in the arterial blood (proportional to the hematocrit), a system that can keep blood flow constant will deliver oxygen at a rate proportional only to the hematocrit. In addition, by requiring a constant rate of oxygen consumption, the tissue $PO_2$ will vary in direct proportion to the hematocrit. It is postulated that erythropoietin release is inversely proportional to hematocrit and is much more sensitive to changes in hematocrit below normal than above normal.

There are some good arguments for an erythropoietic control system that is not dependent on blood flow. Primarily it is felt that, in most normal circumstances, a change in tissue oxygen supply that is not in balance with demand can be compensated for by a rapid adjustment in blood flow and perhaps blood oxygenation by respiratory and circulatory reflexes. The more slowly responding erythropoietic system is only required to be brought into play in those more unusual situations such as sustained breathing from hypoxic atmospheres that require additional correction.

GE Model for Control of Erythropoiesis

The model represented in Figure 4 is being proposed as a starting point for simulating the human erythropoietic system. In particular we desire to investigate the decrease in red cell mass that is observed in astronauts upon their

return from mission and the subsequent red cell mass increase following recovery. The model will be used to test several hypotheses, discussed in the next section, to explain this erythropoietic response.

The proposed model is, in large measure, derived from a portion of the Guyton-White formulation (13, 14). Two segments of that model have been removed for study on a stand-alone basis: a) computation of net red cell mass from subroutine "BLOOD", and b) computation of tissue $P0_2$ from subroutine "AUTRG". Some obvious changes were necessary in extracting a section of a larger model. Primarily these changes were concerned with input/output flow. Other changes were made within the model itself in order to make it more physiologically plausible. These modifications are outlined below:

1. Plasma volume (PV), blood flow (BF), arterial blood oxygen saturation ($S02_{art}$) and the autonomic stimulatory effect on metabolism (AOM) are computed from other physiological systems in the Guyton model, but they will be considered to be input terms in the present model.

2. The use of "non-muscle, non-renal" tissue oxygen tension as the primary stimulus for erythropoiesis in the original Guyton model does not appear to be consistent with present physiological concepts. Consequently, the proposed model will assume that blood flow, tissue oxygen consumption, and tissue oxygen tension are variables associated with the kidney rather than with non-muscle, non-renal tissue.

3. An algorithm has been included in the present model that computes percent saturation of blood hemoglobin from the blood oxygen partial pressure and vice-versa. This algorithm is based on an empirical formulation of the entire oxy-hemoglobin saturation curve (15). The Guyton model computes these terms by assuming a constant slope of the saturation curve in the appropriate range of oxygen tension.

Detailed Description and Assumptions of the GE Model

The flow chart of Figure 4 will be described more completely, especially those segments that differ from the Guyton model (14).

The computation of venous $P0_2$ is described in Blocks 1 through 4. Block 1 computes the maximum oxygen flow possible, $\dot{V}02_{art}^{max}$, in the blood for a given hematocrit (HCT) and blood flow (BF). The mean corpuscular hemoglobin concentration (MCHC) and the oxygen carrying capacity of the hemoglobin molecule ($CHb0_2$) are considered constant. The fraction of the maximum oxygen flow that is delivered to the tissues ($F02_{tis}$) is computed in Block 2. The difference between the fraction of maximum oxygen flow in arterial blood ($S02_{art}$) and the fraction of maximum oxygen flow diverted to the tissues (Block 3) is equal to the fraction of maximum oxygen flow remaining in the venous blood ($S02_{ven}$). Block 4 represents the oxyhemoglobin dissociation curve used to compute venous $P0_2$.

The computation of tissue $P0_2$ (Blocks 5 through 14) is quite similar to the development in the Guyton model. It is postulated that the "oxygen detector" site is located at the venous end of the capillary and therefore capillary $P0_2$ is identical to venous $P0_2$. This is derived from the assumption that the erythropoietin releasing tissue should be highly sensitive to oxygen lack and that small changes in blood oxygen pressure would effect the venous $P0_2$ to a relatively greater extent than arterial $P0_2$. Tissue oxygen consumption ($M02_{tis}$), Block 9, has a basal level, but can change due to: a) overall autonomic stimulation (AOM), and b) an inhibitory effect caused by insufficient oxygen supply (TOM).

The calculation of net red cell production rate is computed in Blocks 15 through 17. This segment of the model is nearly identical to the Guyton formulation. Erythropoietin production, per se, is not considered in this

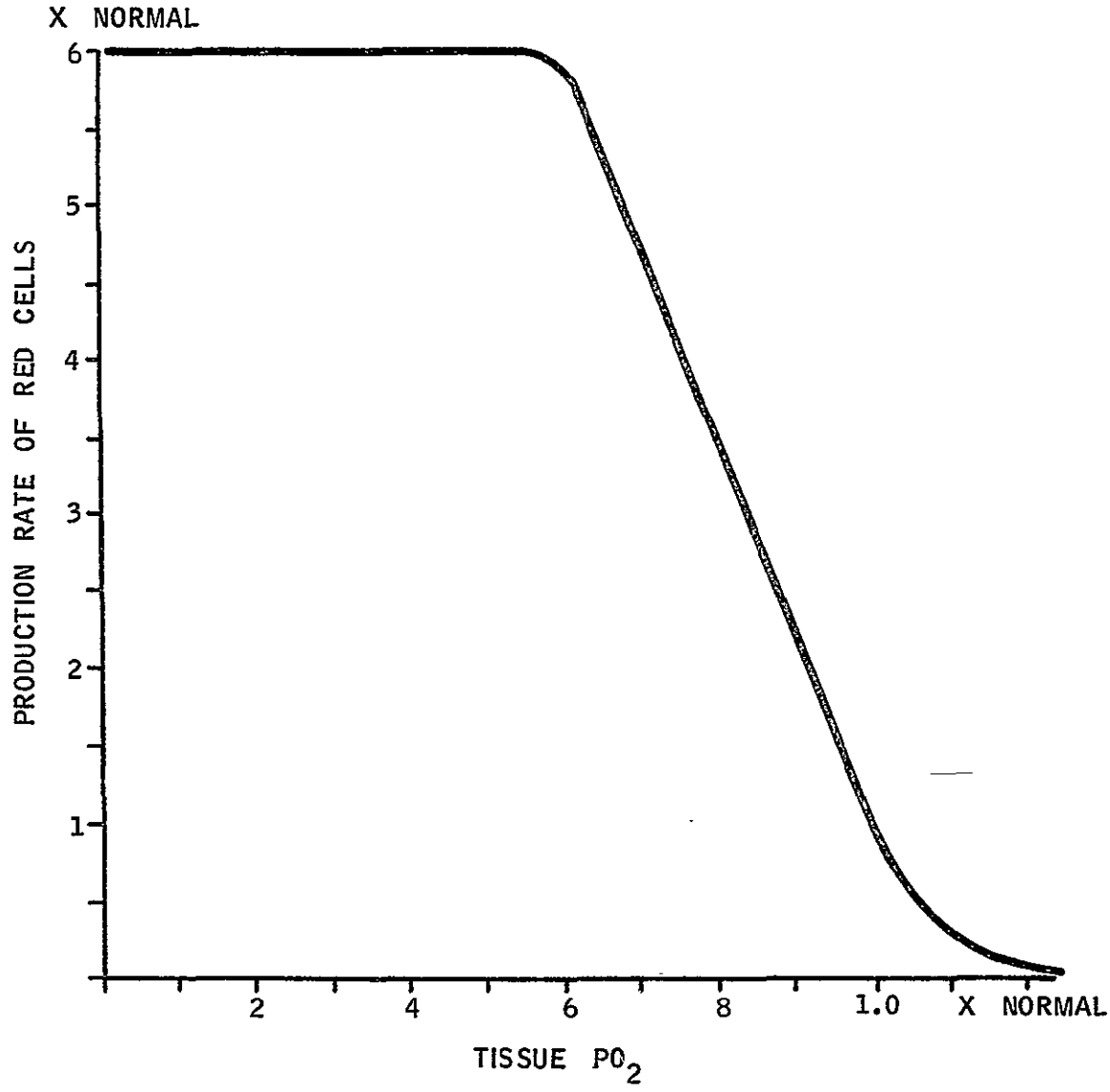
preliminary version of the model inasmuch as information is not available regarding changes in plasma erythropoietin during space flight. The drive factor, DF (Block 15) represents the difference between tissue oxygen demand and supply in terms of oxygen tension. The gain factor $K_G$ (Block 16) is merely the slope of a dose - response curve relating tissue $P0_2$ to red cell production. Since the source of the data for generating the Guyton erythrocyte production curve (Blocks 15 and 16) is not apparent, the proposed model will utilize a dose-response curve derived from the data of Hodgson (see Figure 7). This is an extremely important element in the model because it represents the system that directly controls erythrocyte production. It should be recognized that the controlled variable is not red cell production or red cell mass, but a related term, tissue $P0_2$. This is consistent with the accepted concept that the red-cell-hemoglobin mass is maintained at such a level that the tissue requirements for oxygen are optimally met.

The calculation of hematocrit from the instantaneous red cell mass is described in Blocks 19 through 21. Plasma volume is an input variable. This completes the analysis of the closed loop system of Figure 4.

This model has recently been programmed for interactive-demand terminal use on the Univac 1110. An example of the response of the model, illustrating the associated graphics capability, is presented in Figure 8.

## 4.0 CONCLUSIONS

If the systems analysis presented here is basically correct (even though some of the details will be improved), it provides us with a systematic approach to investigate the heretofore unexplained changes in red cell mass observed in the Skylab program. For example, the analysis has identified five primary input variables, each of which could have a crucial effect on the response of the erythropoietic system: blood flow, plasma volume, mean red cell life span, sensitivity of the erythropoietin-erythrocyte producing circuit, and the




EFFECT OF TISSUE $PO_2$ ON RED CELL PRODUCTION

(DERIVED FROM HODGSON, 1970)

FIGURE 7

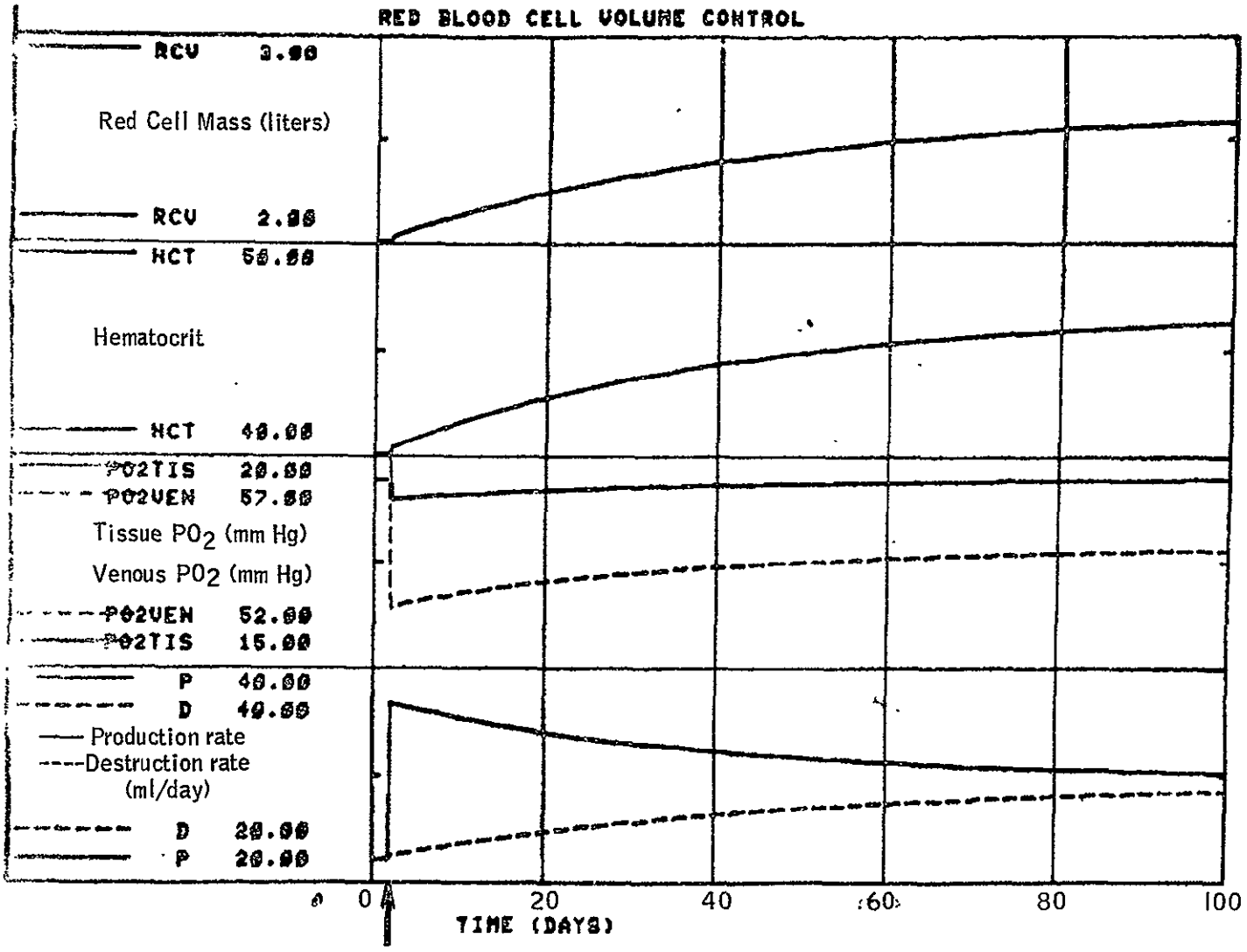



FIGURE 8

Example of the computer generated graphics capabilities associated with the conversational mode of simulating the erythropoietic model of Figure 4. At t = 2 days (arrow) the arterial oxygen tension is changed from 95 mm Hg to 75 mm Hg, simulating a change in altitude from sea level to 5,000 ft. The sudden decrease in blood oxygen tension stimulates erythrocyte production which gradually decreases to a new steady state value as the increased red cell mass is now able to provide sufficient tissue oxygenation. Changes in oxygen-hemoglobin affinity, blood flow and plasma volume which are known to occur in hypobaric hypoxia were not considered in this example.

autonomic effect on cell metabolism. It is proposed to utilize digital computers to simulate the response of this model and to investigate the effects of the above mentioned parameters on the behavior of the circulating red cell mass.

Hypothesis for Erythropoietic Adaptation to Weightlessness

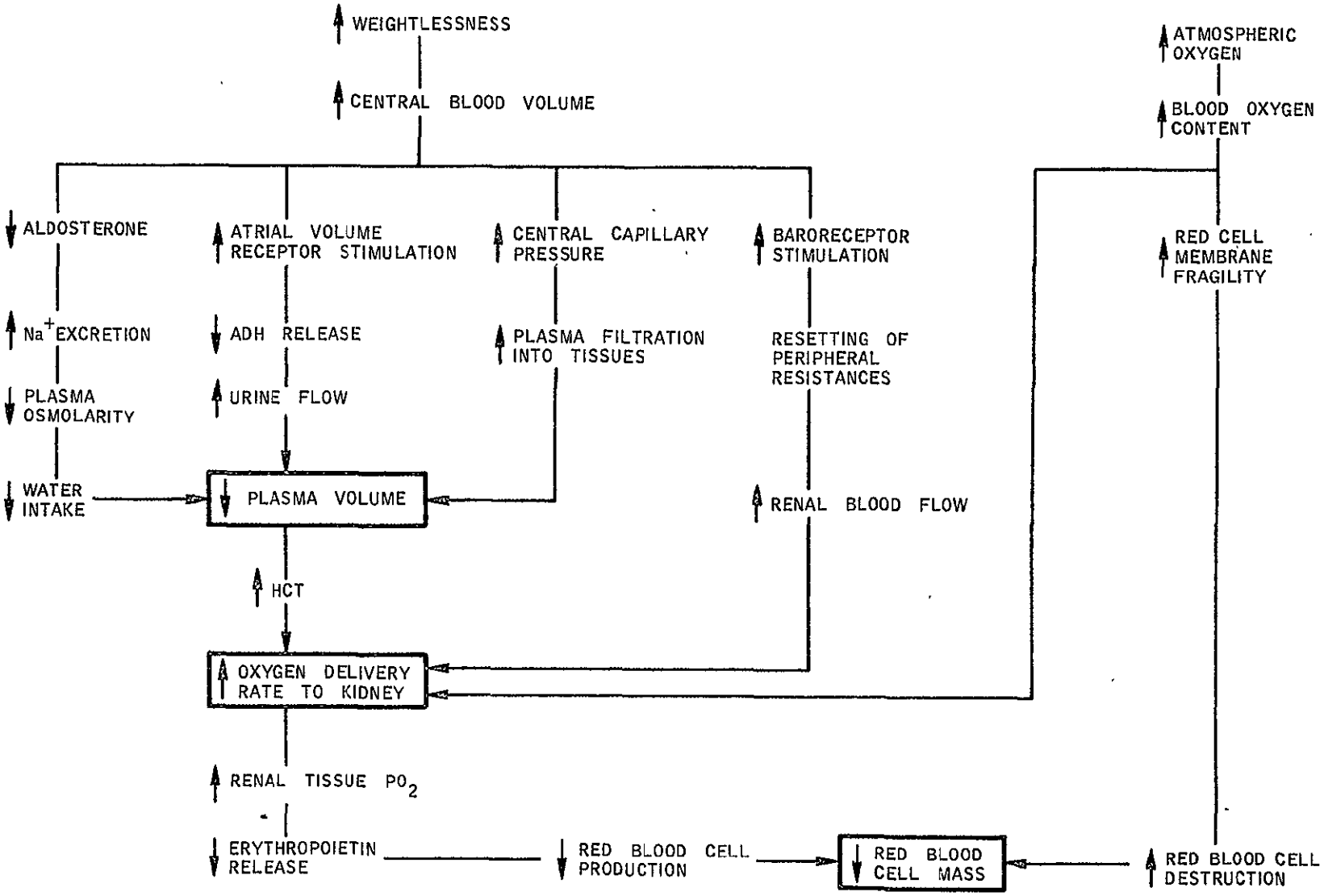
Based on this characterization of potentially important variables and taking additional physiological facts into consideration, it was possible to make some preliminary testable hypotheses as a starting point for investigating the decreased red cell mass observed during space missions. It is postulated (Figure 9) that the stress of the zero-g environment decreases plasma volume and increases renal blood flow. These factors have already been implicated in the systems analysis as potentiators for decreasing erythrocyte production.

Preliminary data from the Skylab experiments strongly suggest that plasma volume decreases, at least early in the mission, leading to an increased hematocrit. It is certainly compelling to assume that this condition of "stress induced hypovolemic polycythemia" results in a relative tissue hyperoxia and eventual shut-down of the erythrocyte producing circuit until the hyperoxic condition is relieved. But this has yet to be established in fact. Other unknown factors, induced by the still obscure physiological effects of weightlessness, may be acting on the erythropoietin releasing-stem cell differentiation axis.

The increase in renal blood flow during weightlessness has not been confirmed, but there is sufficient evidence to show that changing posture from an erect to supine position (which is often used to simulate the circulatory responses to weightlessness) can increase renal flow appreciably (11, 16). There are at least two reasons for such an increase: 1) cardiac output increases about 20% in the supine position and the renal blood flow, which is normally about a fifth of the cardiac output, receives a share of this extra flow, and

# FIGURE 9

HYPOTHESIS TO EXPLAIN DECREASED RED CELL MASS DURING WEIGHTLESSNESS AND HYPEROXIA
(STRESS & ADAPTATION STAGE)



2) the normal centrally mediated reflexes which provide peripheral vasoconstriction and increased arteriolar resistance in the erect position are abolished to a large extent in the recumbent position and this results in as much as a 20% decline in renal vascular resistance. (A mathematical model has recently been reported that is capable of simulating renal circulatory function during adaptation to changing gravitational forces (17) ). Furthermore, it is known that this increased renal plasma flow during recumbency results in a less than proportional increase in glomerular filtration rate (16). This suggests that the recumbent renal flow is higher in all parts of the kidney vasculature including the vessels beyond the renal corpuscle. It is quite possible that under these circumstances the erythropoietin producing tissues are subject to an increased blood flow as well, leading to a relative hyperoxic state. Also of interest is the fact that renal flow is known to decrease as a result of exercise, even in the recumbent position (18). This may help to explain the smaller decreases in red cell mass observed in those Skylab crewmembers who were known to have engaged in the heaviest exercise regime.

As suggested in Figure 9 an increase in atmospheric oxygen tension has been found to suppress the release of erythropoietin (19) as well as increase the rate of red cell destruction (1). While an increase in atmospheric oxygen tension was not a major factor in the Skylab missions, this hypothesis can explain the fact that in certain Gemini flights (an atmosphere of 100% oxygen at 258 mm Hg) the decline in red cell mass was greater than could be accounted for by a complete shutdown of erythrocyte production alone (2, 20).

Recommendations for Future Study

As a result of this review and analysis several areas of potential interest have been identified for more detailed study: 1) the response of renal blood flow to the stimulus of weightlessness, 2) the relationship of renal blood flow and production of erythropoietic factor, and 3) the relationship between the response

of the cardio-respiratory system and the erythropoietic system to abnormal tissue oxygen balance. Where possible, the present literature survey will be expanded to include coverage of these items.

In addition, current periodicals will be reviewed on a continual basis to keep abreast of new developments in the field of erythropoietic control especially as concerns identification of other chemical agents or neural components that affect red cell production and the clarification of the role of tissue oxygen as a stimulus for erythropoietin production.

A model claiming to represent the control of erythropoiesis should be able to simulate not only the data obtained during the Skylab program, but should also be capable of simulating the responses to a wide range of hemotologic disturbances such as hypoxia, hyperoxia, hemorrhage, anemia, polycythemia, and hemolytic diseases, as well as responses to immersion and bedrest. For this reason, a literature survey will be made to locate data regarding these events.

Many factors have been discussed that are known to affect erythropoiesis, but have not been included in the proposed model. Performing computer simulations of a mathematical model is not unlike performing experiments in the laboratory on an unknown system, starting from asking simple and easily understood questions and progressing to the more complex world of reality. It is probably a mistake to try to start from too realistic a system. Accordingly, it is believed that at least some, if not all, of the following factors may eventually be necessary in a more complete model: 1) a description of an erythropoietic stimulating factor (ESF), 2) a description of a still-not-confirmed second erythropoietic factor that is perhaps a precursor to ESF, 3) a description of the kinetics of stem cell differentiation in the bone marrow, 4) a more accurate description of the renal sensor site(s) of oxygen tension, 5) consideration of a possible shift in the affinity of hemoglobin for oxygen, and 6) consideration of possible extrarenal sites of ESF production.

## Assessment of the Systems Analysis Approach

It is believed that the utility of the systems analysis approach as an investigative tool in the Skylab hematological experiments may be limited by the scarcity of measurements of certain potentially crucial parameters, as well as an incomplete understanding of the mechanisms affecting erythropoiesis. However, it is felt that mathematical modeling and simulation can be quite useful in several ways: 1) identification of important parameters and their sensitivity on the overall system, 2) a method to test hypotheses rapidly, 3) identification of specific elements that must be further quantified, and 4) prediction of the behavior of certain unmeasured or difficult to measure parameters of the system in response to specific stress states.

There is every reason to suspect that this study, in its initial stages, will suggest more questions than answers. However, this should help point the way toward the kind of clarifying experiments that might be performed and the type of data that should be collected. As the simulation study progresses it may be possible to incorporate more and more diverse kinds of experimental results into a single model, each of which alone would not support a generalized theory, but taken together might point to a coherent picture of erythropoietic control.

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