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This report details the simulation tasks performed with the computer model of erythropoietic regulation originally developed by GE. A primary objective was to convert the model already validated for simulating human erythropoietic studies to a model suitable for the mouse system. Dr. Dunn's background was particularly appropriate for this task because of his involvement with NASA's hematologic spaceflight program and his current studies at the University of Tennessee using the mouse as a potential experimental model for space-flight. Included in this report are validation studies using data from Dr. Dunn's previous study of the dehydrated mouse.

J. I. Leonard

Attachment
/db

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RESEARCH REPORT

USE OF A COMPUTER MODEL IN THE UNDERSTANDING OF ERYTHROPOIETIC CONTROL MECHANISMS

by

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The General Electric Company
Houston

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SUMMARY

During an eight-week visit approximately 200 simulations using the computer model for the regulation of erythropoiesis were carried out in four general areas: with the human model simulating hypoxia and dehydration, evaluation of and simulation of dehydration using the mouse model. The experiments led to two new considerations for the model. Firstly, a direct relationship between erythropoietin concentration and bone marrow sensitivity to the hormone and, secondly, a partial correction of tissue hypoxia prior to compensation by an increased hematocrit. This latter change in particular produced a better simulation of the effects of hypoxia on plasma erythropoietin concentrations. The model produced excellent qualitative changes of dehydration. In addition, a greater appreciation of the gaps in our knowledge of the regulation of erythropoiesis became evident. There was a considerable cross-fertilization of ideas and concepts between the author and the computer group. As a result, at least four publications are in the formulation stage.

INTRODUCTION

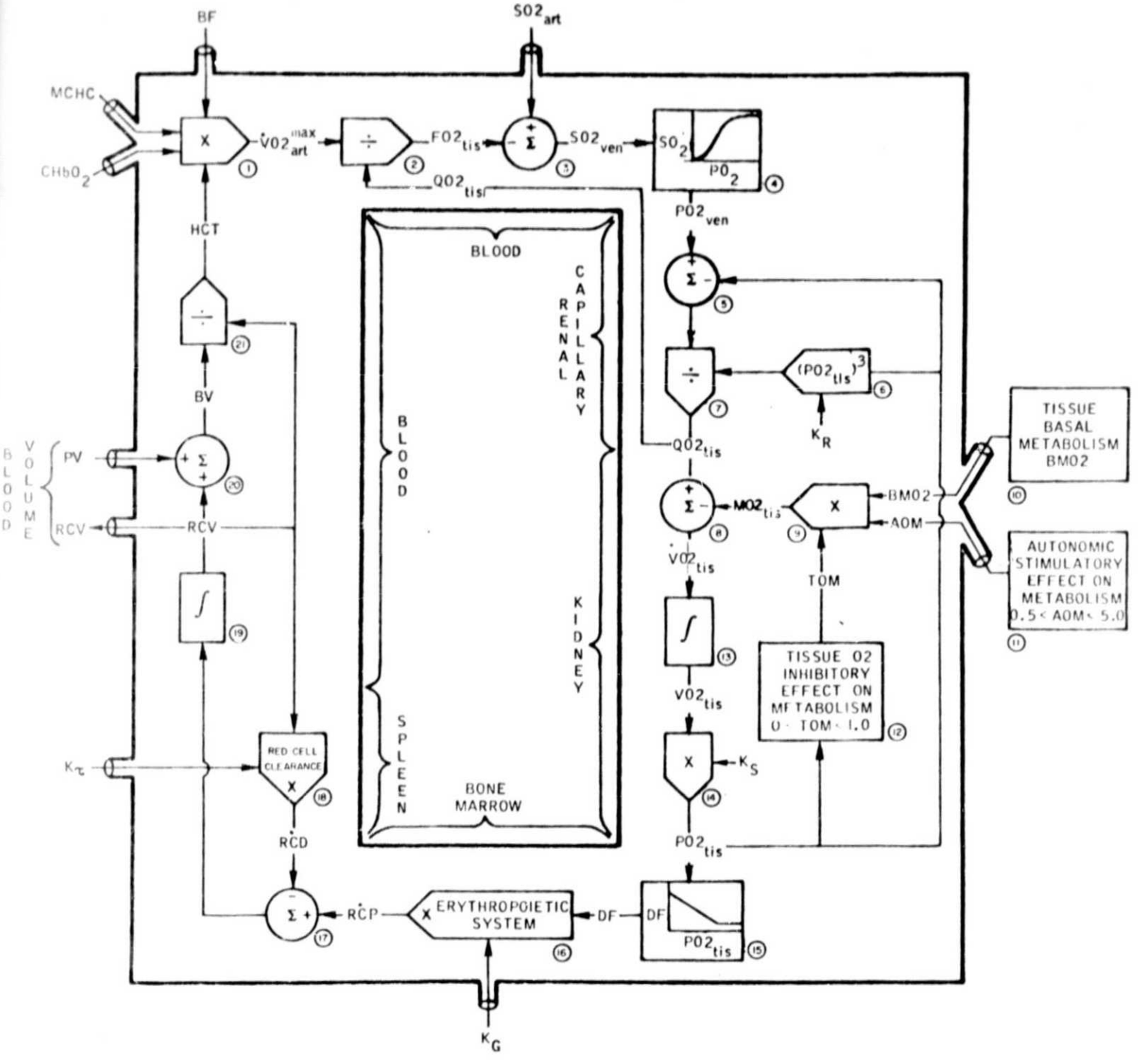
A computer model for the study of erythropoietic control mechanisms with particular emphasis on the "anemia" of space flight has been developed and described by Leonard (1,2,3). The model is capable of simulating the effects of various erythropoietic stimuli on red cell production. However, a full appreciation of the model was difficult as it was developed by personnel with principally a mathematical background with little input from biologists. The primary purpose of the present author's leave of absence from the University of Tennessee to The Johnson Space Center was to interact with the computer groups with the aim of further validating the model of erythropoietic control mechanisms and to determine how well a modified model for mouse parameters responded to data obtained from a potential animal model of the "anemia" of space flight. As a secondary objective the author was asked to advise in the most appropriate role, from a grantee's viewpoint, for NASA scientists in the Spacelab Life-Sciences Program. The leave of absence extended from 14 August to 5 October 1978.

THE MODEL

A detailed description of the General Electric model for the control of erythropoiesis can be found in the reports by Leonard (1,2,3) and Grounds (4). Salient points only will be reviewed in this report. The model is summarized in Figure 1 (from reference 1). It consists of 69 parameters of which 24 are variable, the remainder being changed automatically in response to the input. The model was established using numerical values appropriate for the human and it has been shown to realistically simulate a variety of erythroid perturbations eg: compensated hemolytic anemia, red cell infusion (2). Hypoxia and the "anemia" of space flight cannot be directly simulated by the model (3).

FIGURE 1

GE MODEL FOR CONTROL OF ERYTHROPOIESIS (DERIVED FROM GUYTON)



RESULTS AND DISCUSSION

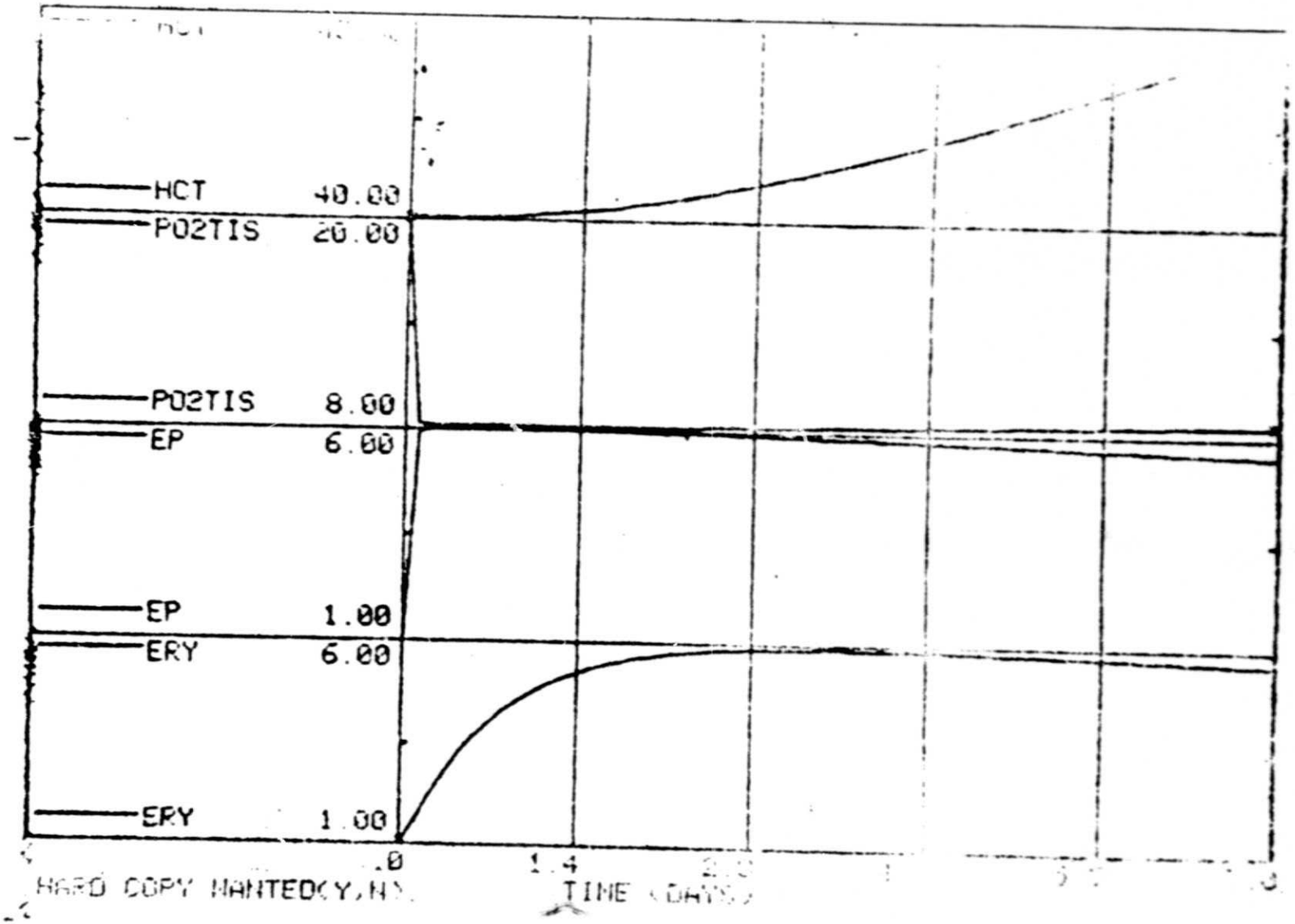
Approximately 200 simulations were carried out. These can be grouped into four categories:

1. Simulation of hypoxia using the human model,
2. Simulation of dehydration using the human model but with data "scaled-up" from studies in mice,
3. Evaluation of a model established with numerical values appropriate for mice,
4. Simulation of dehydration using the mouse model.

1. Simulation of hypoxia using the human model:

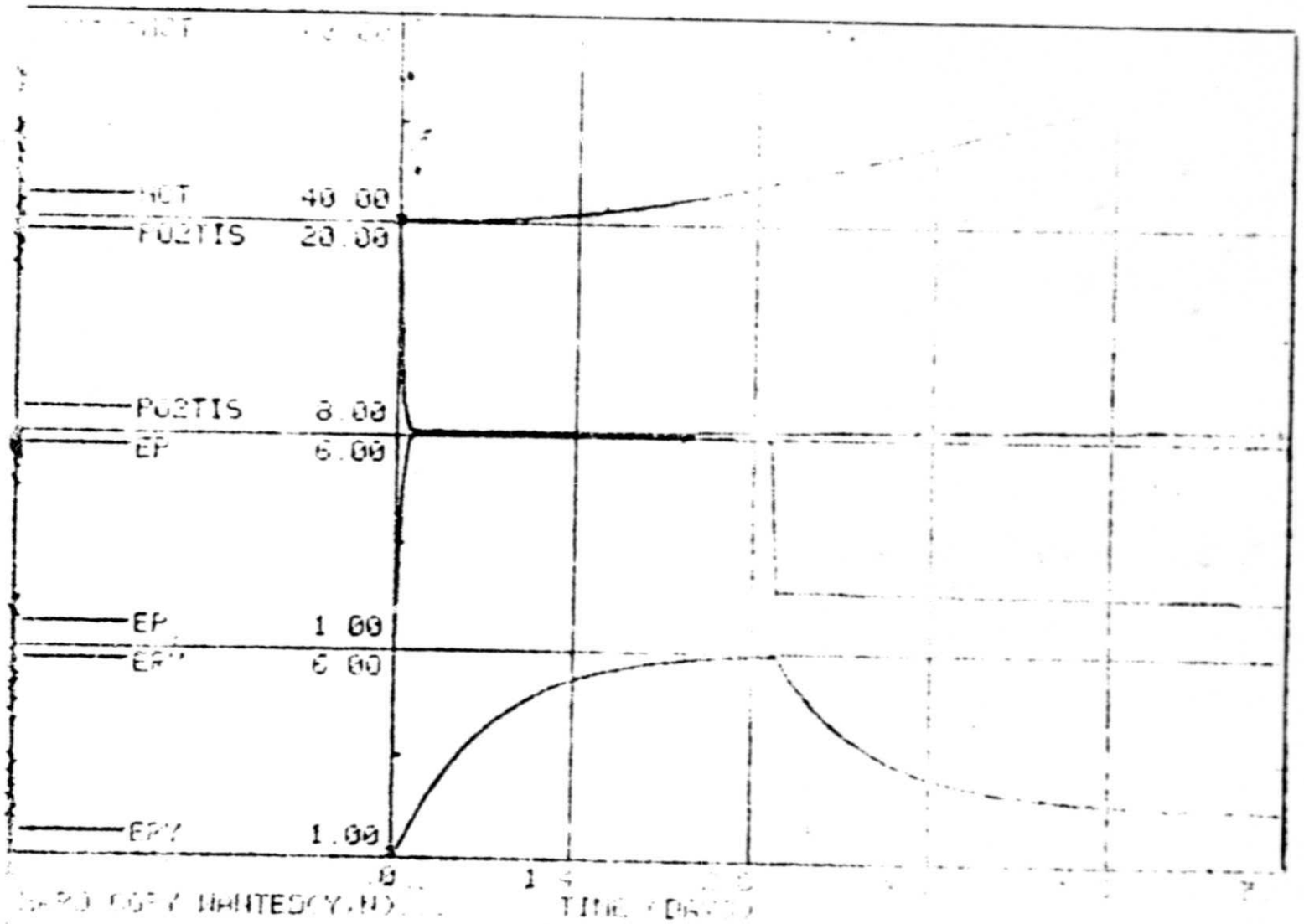
The model responds to 7 days of hypoxia with an acceptable change in hematocrit (HCT, Figure 2) and red cell volume (RCV, data not shown). However it predicts that erythropoietin production (EP) and plasma erythropoietin concentration (ERY) reach peak levels by the third day and are maintained at these high levels for the duration of hypoxia (Figure 2). In contrast, experimental data suggest that plasma erythropoietin concentrations respond to hypoxia by reaching a peak at 1-3 days and then fall abruptly to titers only slightly above normal despite continuation of the stress (5-9). The object of the initial simulations was to determine the affect on the HCT of allowing ERY to reach maximum values and then reducing it to a level approximately twice control. ERY has altered by changing EPO (Mnemonic #49); the extrapolated value of EP at zero tissue oxygenation. Simulations determined that if EPO was altered prior to day 3 of hypoxia the maximal level of ERY was not reached and that a reduction of EPO from 20.09 to 8.0 was necessary to reduce ERY to approximately twice normal. The effect of changing EPO at day 3 in a 7 day exposure to hypoxia is shown in Figure 3. As might have been anticipated, such

FIGURE 2



SIMULATION OF HYPOXIA (PO2 ART = 55.) USING THE HUMAN MODEL.

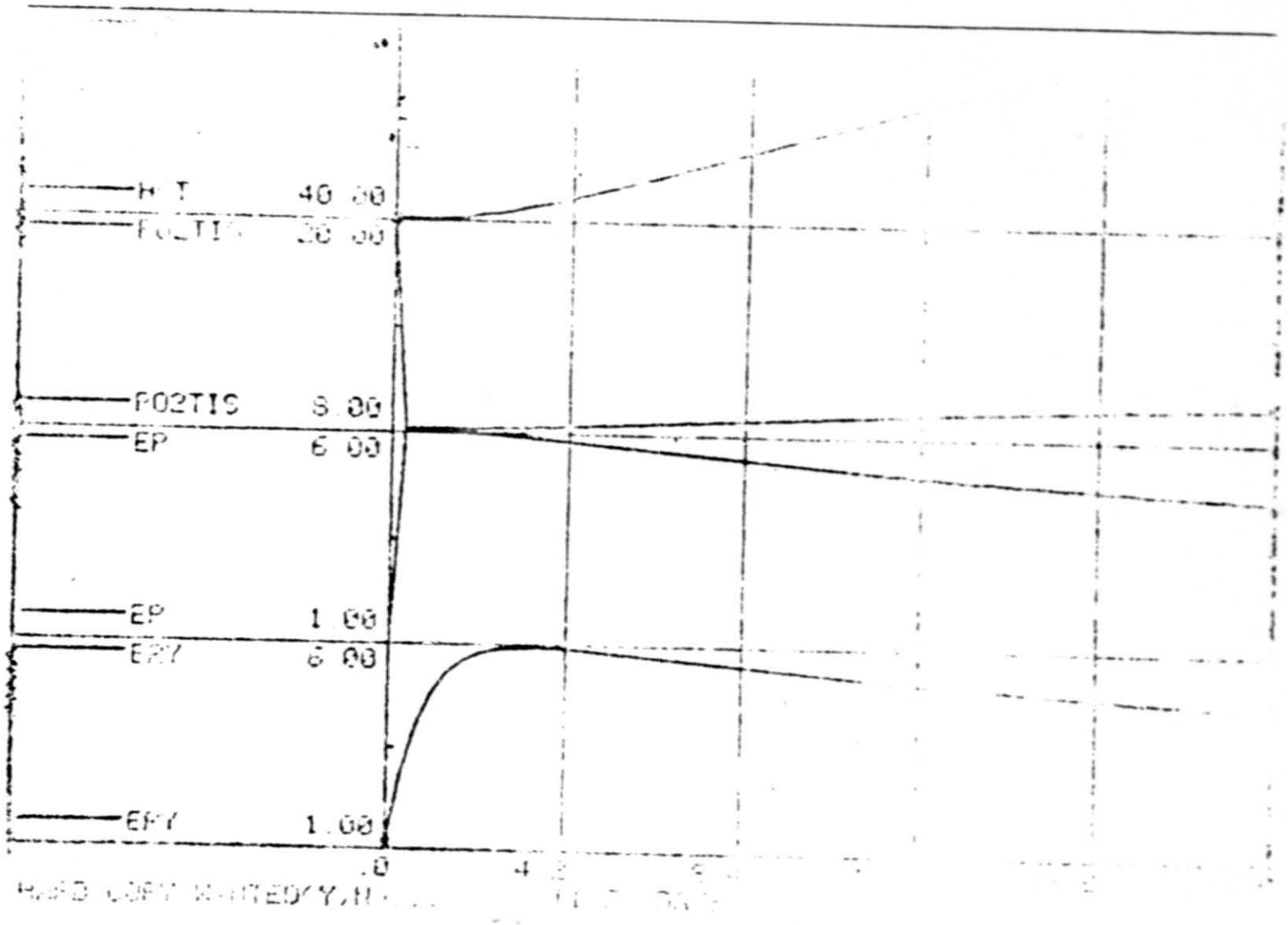
FIGURE 3



SIMULATION OF HYPOXIA (PO2 ART = 55.) IN THE HUMAN MODEL WITH A REDUCTION IN EPO FROM 20.09 TO 8.0 ON DAY 3.

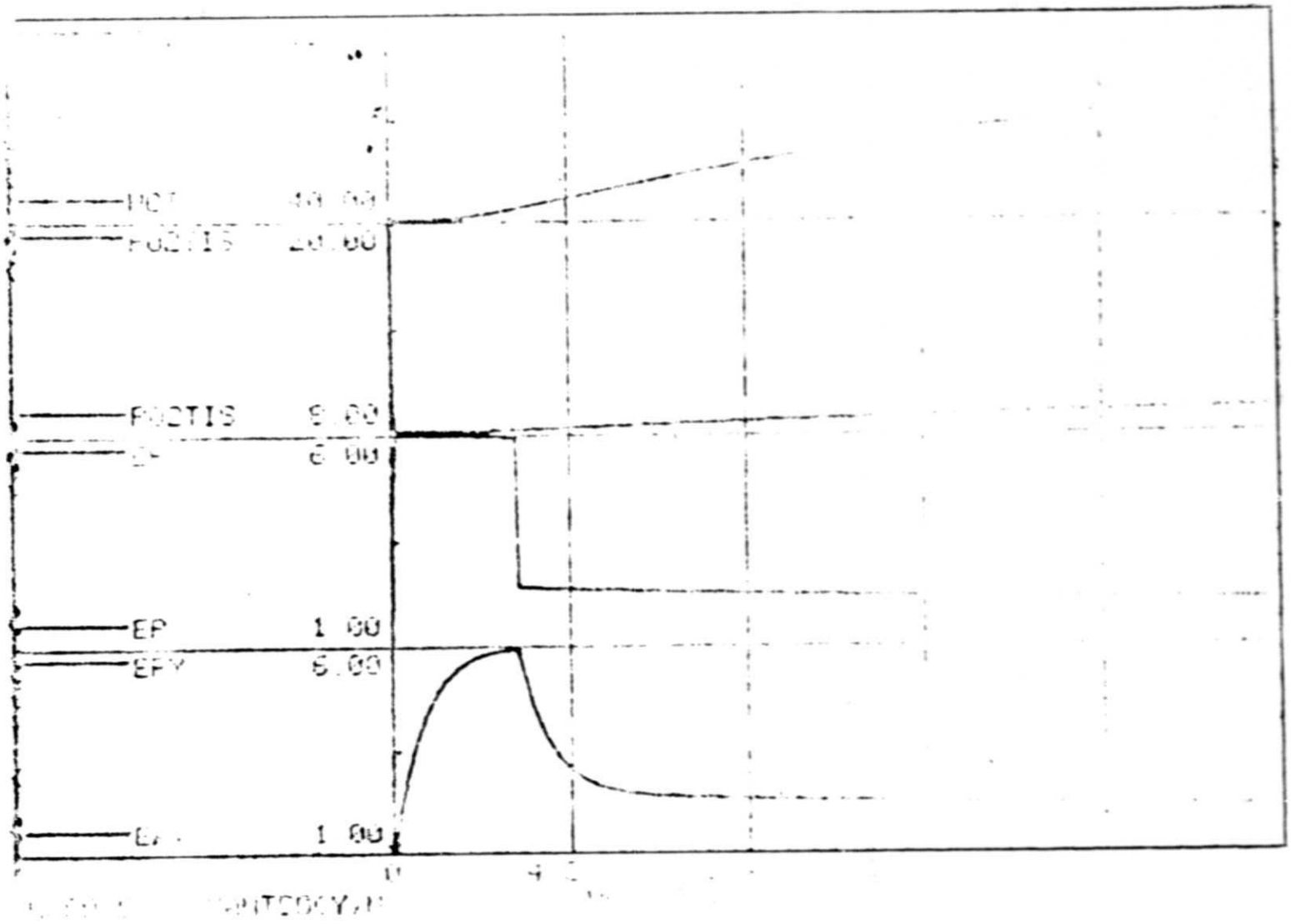
a change resulted in a smaller increment in HCT than was observed when ERY was allowed to remain high (compare Figures 2 and 3). This difference became more marked if the duration of hypoxia was extended to 21 days when the HCT only reached 46.8% (Figure 5, compared to 50.9% when ERY was allowed to remain high (Figure 4). Further simulations were done in an attempt to bring the HCT up to levels observed when ERY was allowed to remain high. The rationale for the following simulations was based on recent studies using *in vitro* clonal assays for Erythropoietin Responsive Cells (ERC). These investigations (10,11), together with earlier computer simulations (12), have suggested a direct relationship between ERY and the number and/or sensitivity of the ERC population. This change in number and/or sensitivity is best expressed in the present model by a change in G2; viz, the Gain factor relating erythropoietin production to red cell production. Adjusting G2 from 2 to 4 at the end of day 1 of hypoxia and bringing ERY down to twice normal on day 3 (Figure 6) results in increases in HCT, RCV and Blood Volume (BV) comparable to that seen (Figure 4) when ERY is allowed to remain at values approximately six times normal for the duration of exposure to the hypoxia stress. Other simulations (not shown) determined that a doubling of G2 on day 1 was the minimum change necessary to elecit the necessary increment in HCT although a similar response could be obtained by altering P1 - a comparable parameter to EPO but relating to the bone marrow response (Figure 7). Subsequent studies (not shown) demonstrated that G2 could change in parallel with ERY or could remain high throughout hypoxia with little effect on the HCT at the end of 21 days of hypoxia; G2 could, therefore, be directly related to ERY. Partial confirmation of this hypothesis was obtained by discussions with Dr. C. Peschle at the annual meeting of the

FIGURE 4



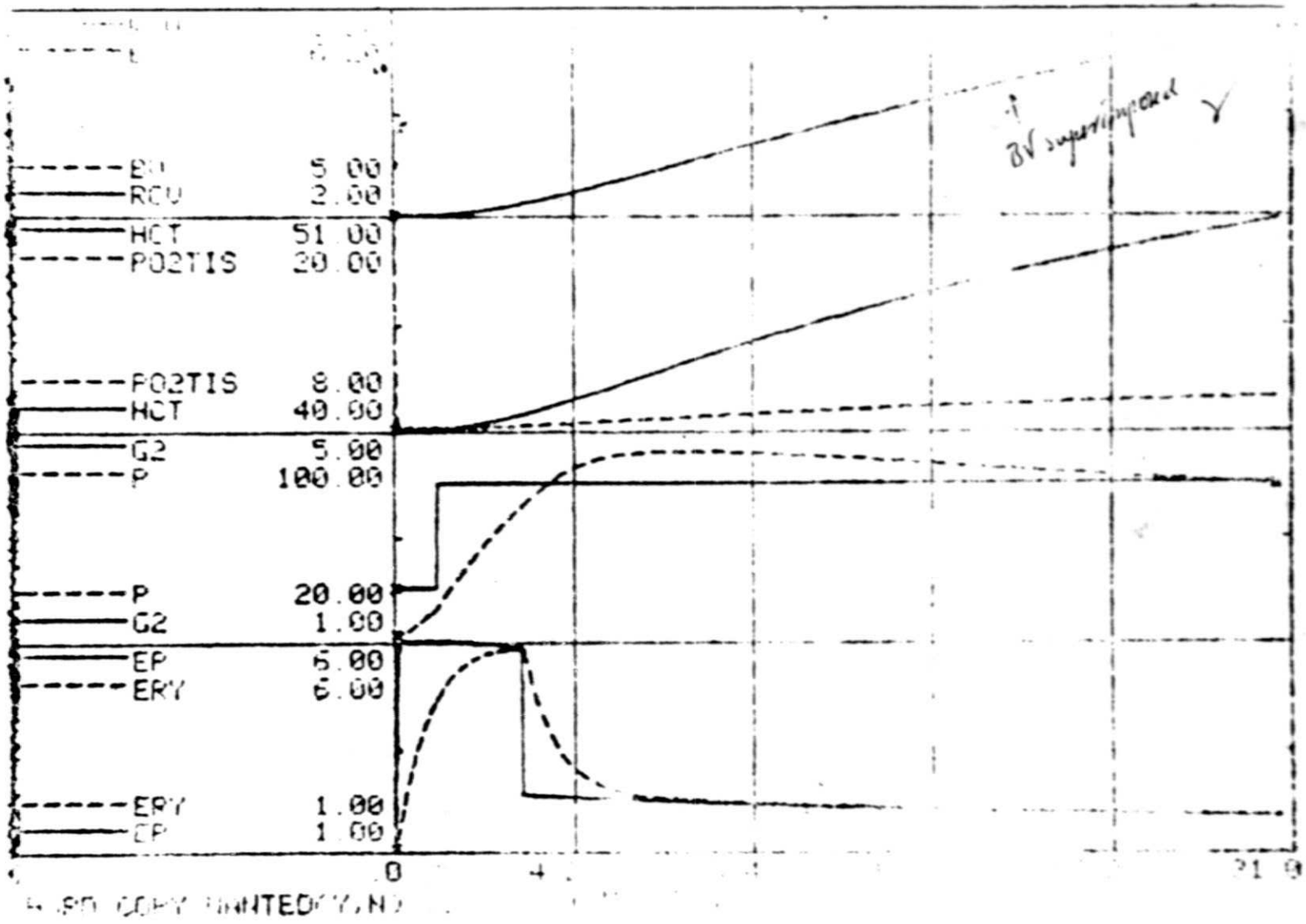
SIMULATION OF HYPOXIA (P02 ART = 55.) IN THE HUMAN MODEL.

FIGURE 5



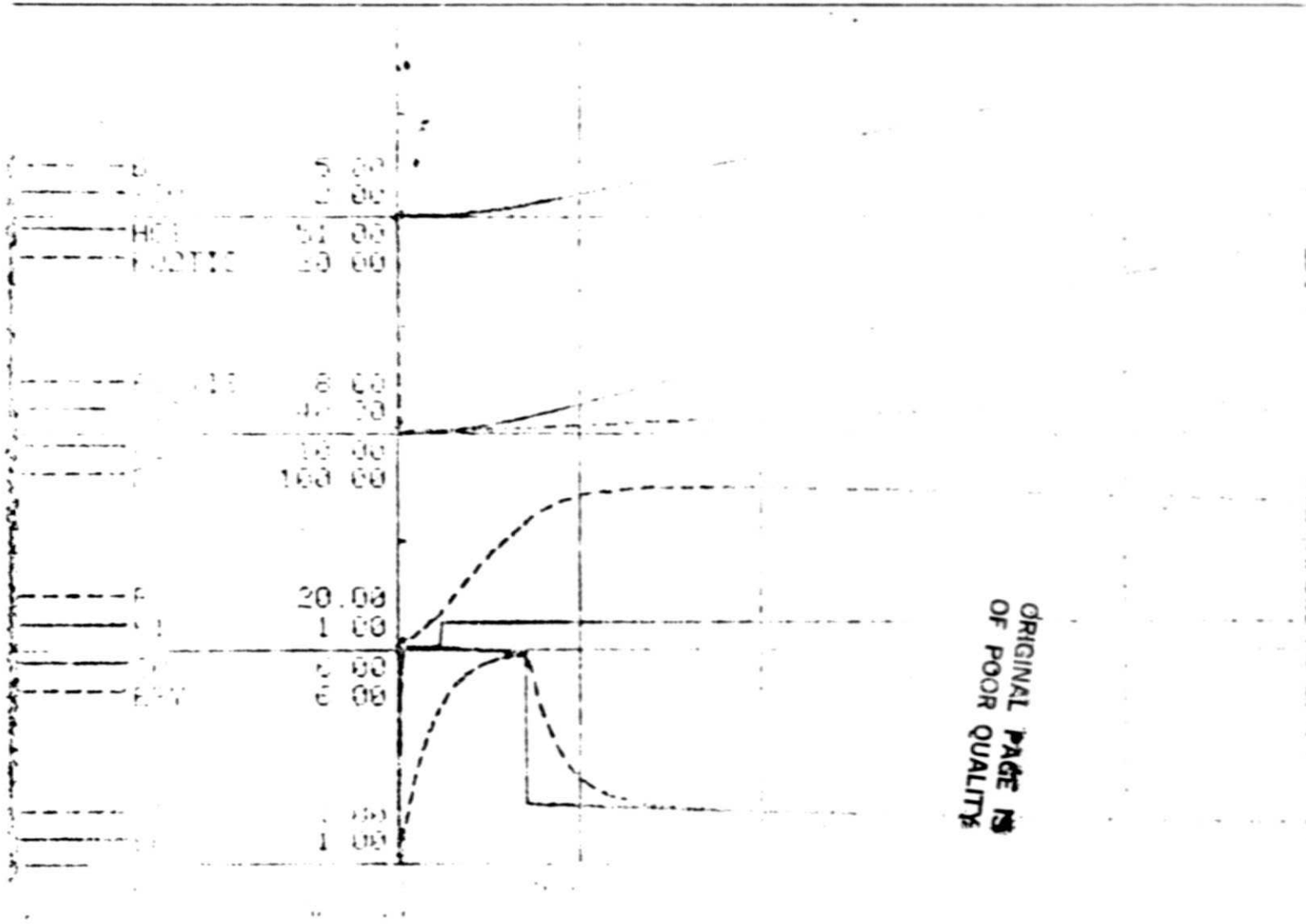
SIMULATION OF HYPOXIA (PO2 ART = 55.) IN THE HUMAN MODEL WITH A REDUCTION IN EPO FROM 20.09 TO 8.0 ON DAY 3.

FIGURE 6



SIMULATION OF HYPOXIA (P02 ART = 55.) WITH CHANGES IN G2 (DAY 1) AND EPO (DAY 3).

FIGURE 7



SIMULATION OF HYPOXIA (PO2 ART = 55.) WITH CHANGES IN P1 (DAY 1) AND EPO (DAY 3).

International Society for Experimental Hematology. His, currently unpublished, data suggest that there are temporary net increases in ERC in response to hypoxia although these cells in the bone marrow and spleen behave somewhat differently. There is, therefore, some evidence that ERY can directly influence a factor that may be mathematically designated G2. However, at this time the biological mechanism whereby ERY would decrease in the face of maintained hypoxia was uncertain.

In order to more fully understand the relationship between G2 and ERY changes post-hypoxia were simulated with (Figure 8) or without (Figure 9) changes in G2 and a reduction in EPO. There was little evidence that changes in G2 and EPO had a detrimental effect on the simulation of the post-hypoxia changes; in fact, it was in the situation where G2 and EPO were altered (Figure 8) that a more realistic post-hypoxia suppression of P was obtained.

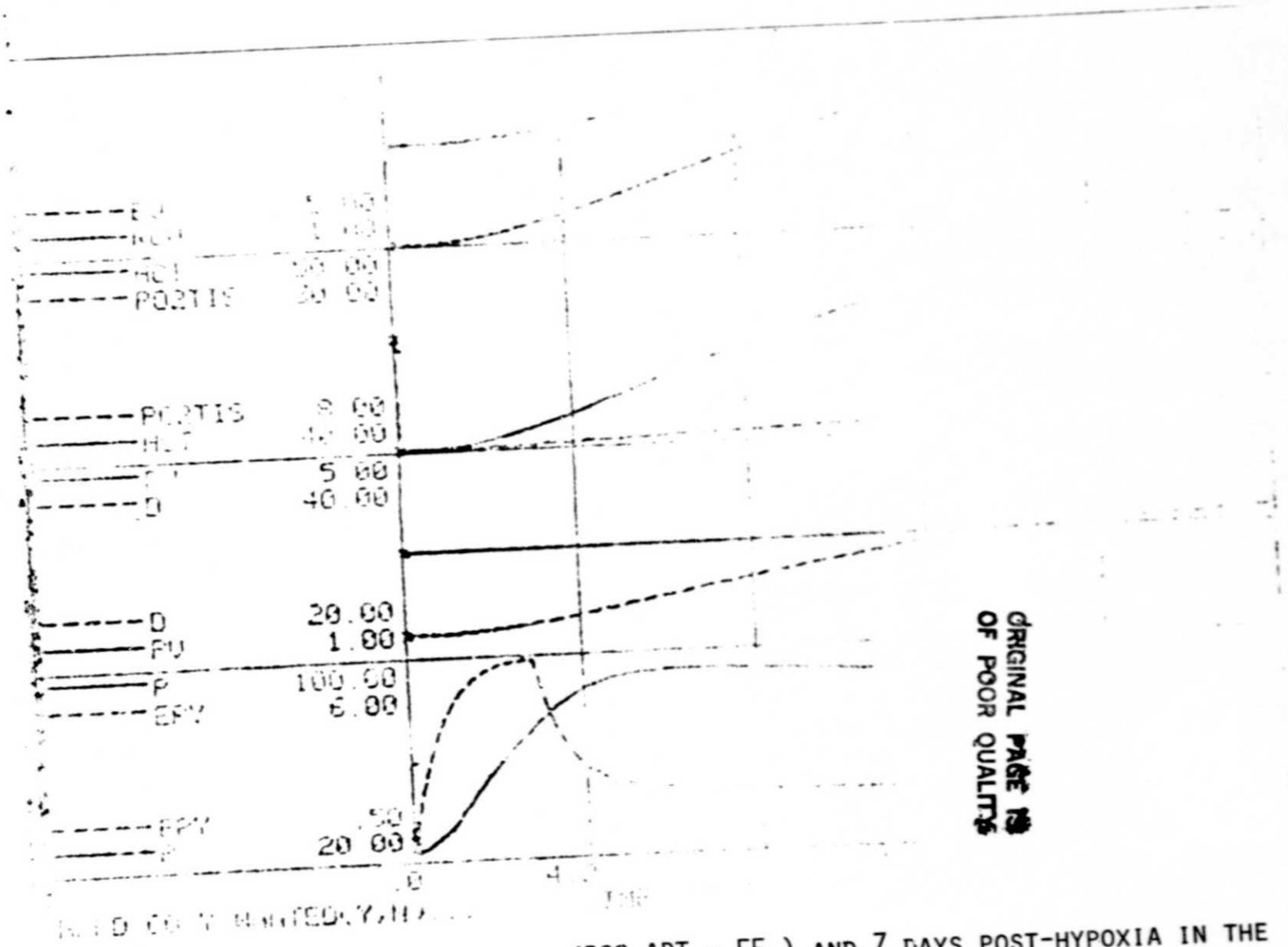
In conclusion to this part of the study it appeared that if G2 was altered in a way which reflected changes in ERY, then ERY could be brought back to titers approximately twice control without a detrimental effect on red cell production. The original model did not consider this possibility or a mechanism for bringing ERY down from its peak levels. Two modifications were made to the model:

(i) a direct numerical relationship between ERY and G2 was incorporated into the Subroutine Blood, i.e.,

$$G2 = ERY \times 2$$

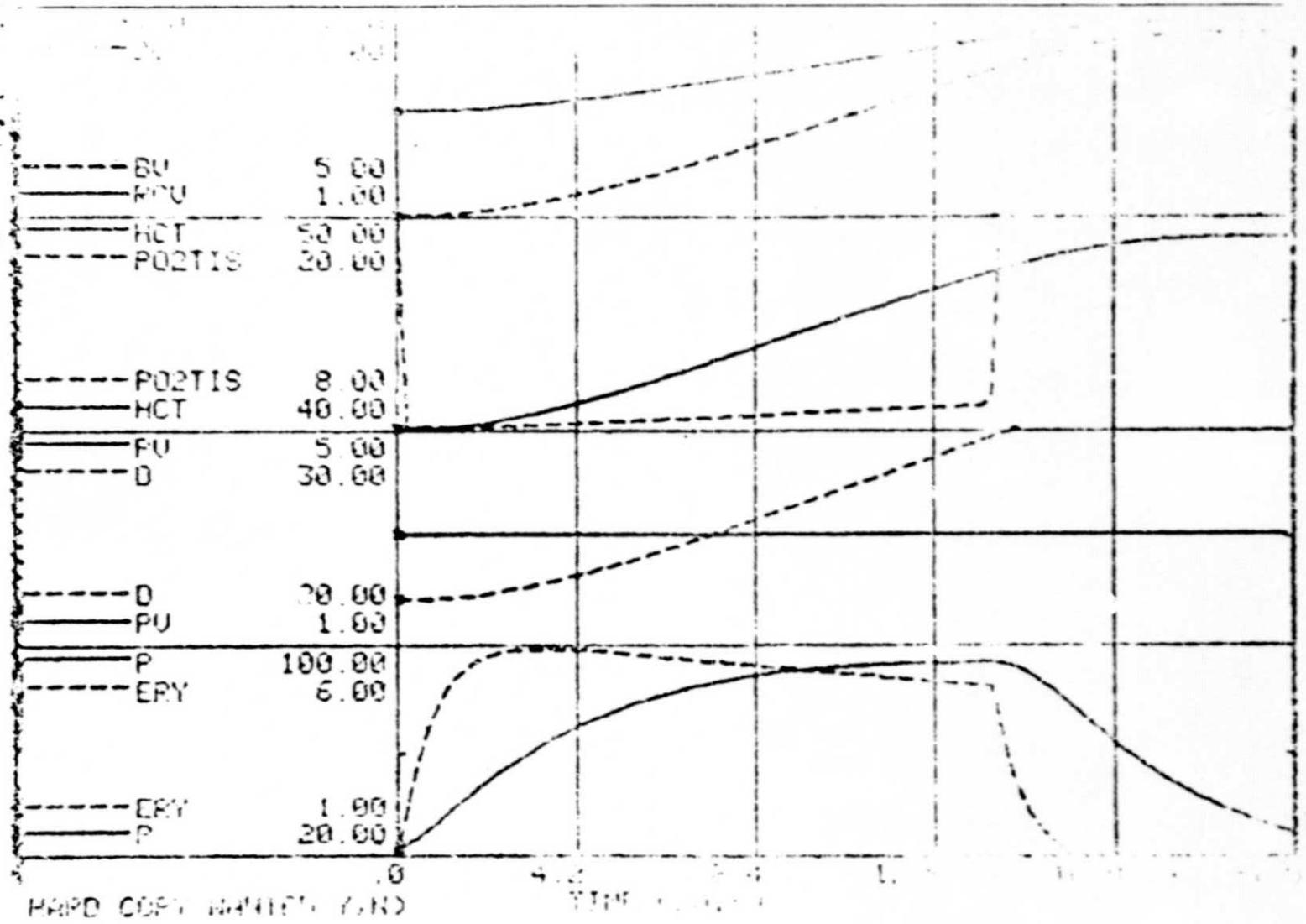
(ii) Since the only 'trigger' in the model for changes in erythropoietin production is tissue oxygenation, it was presumed that a mechanism would be operative whereby tissue oxygenation would be brought back almost to control levels before the hematocrit completely

FIGURE 8



SIMULATION OF 14 DAYS OF HYPOXIA (PO2 ART = 55.) AND 7 DAYS POST-HYPOXIA IN THE HUMAN MODEL WITH CHANGES IN G1 (DAY 1) AND EPO (DAY 3).

FIGURE 9



SIMULATION OF 14 DAYS OF HYPOXIA (PO2 ART = 55.) AND POST-HYPOXIC CHANGES IN THE HUMAN MODEL.

compensated for the hypoxia. It was postulated that such a mechanism could occur by changes in blood flow, rate of oxygen diffusion, or in the oxygen-carrying capacity of the blood i.e., the p50. On this basis the following formula was inserted into Subroutine Tissue, line 24:

$$RDIFO2 = \bar{RDIFO2} + (PO2TIS^3/SENS - RDIFO2)/DAMPF$$

Where RDIFO2 = rate of oxygen diffusion, $\bar{RDIFO2}$ = original rate of oxygen diffusion, PO2TIS = level of tissue oxygenation and SENS and DAMPF = numerical values to alter the level of sensitivity of the new model. In addition a delay parameter, DLAY, was introduced to allow a variable period of time to occur before partial correction of the tissue hypoxia was instituted.

These modifications were incorporated into a modified model designated "@ ADD THERM.LOADCD." Nineteen simulations were performed to optimize the 3 new variables at

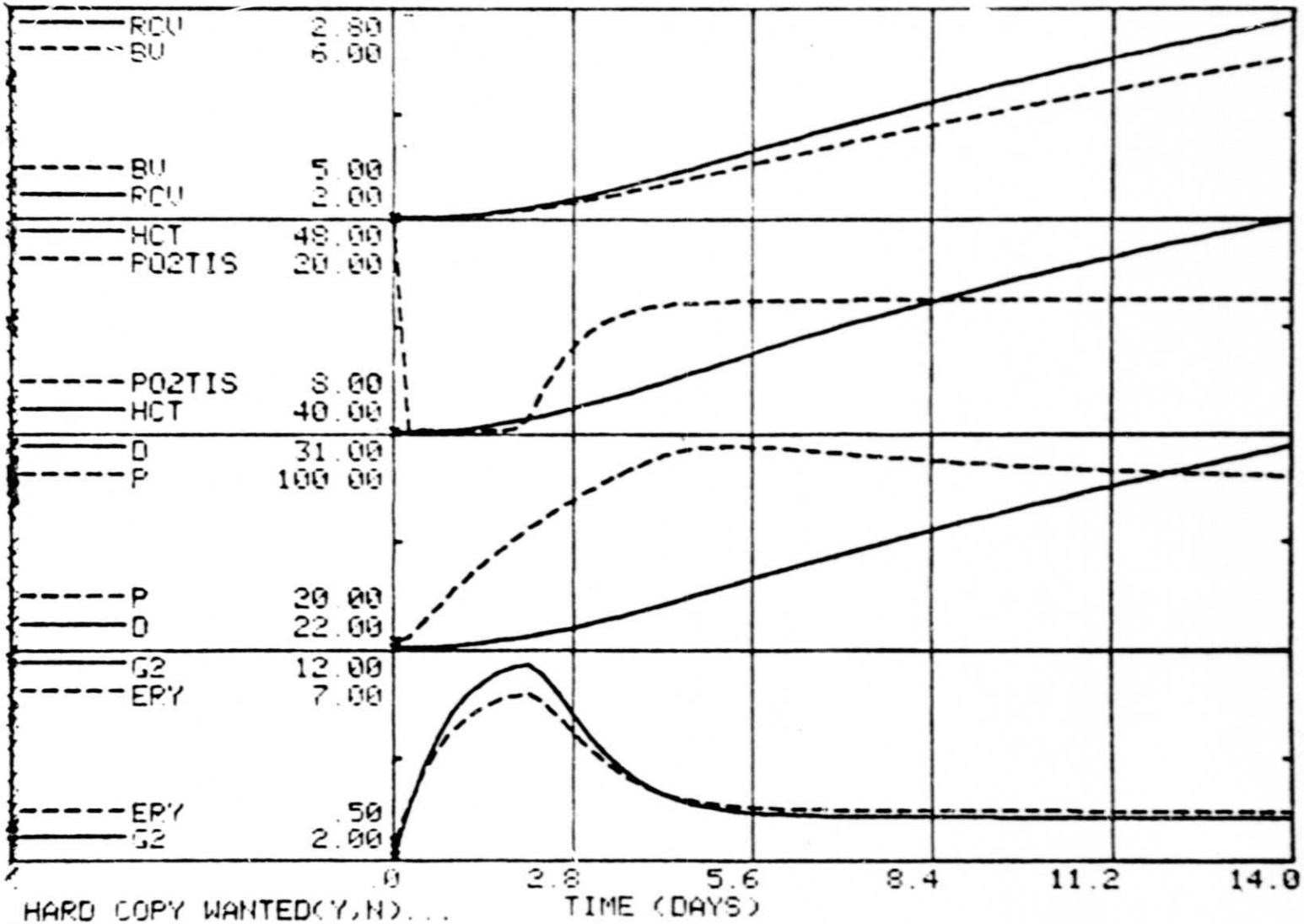
DLAY = 2880 minutes

DAMPF = 5760 minutes

SENS = 0.55

and the simulation of hypoxia shown in Figure 10 was obtained with this model. Note the changes in HCT, RCF and BV compare well with the original model (Figure 4) in which ERY was allowed to remain high. Note also the partial correction of PO2TIS which accounts for the decrease in ERY (and, therefore, G2). Preliminary experiments in this laboratory using mice exposed to hypoxia suggest that there are dramatic shifts in the p50 which might biologically explain the partial correction of PO2TIS. "Dose/response"

FIGURE 10



SIMULATION OF HYPOXIA (PO2 ART = 55.) PRODUCED BY A MODIFIED (@ ADD THERM.LOADCD) HUMAN MODEL FOR THE REGULATION OF ERYTHROPOIESIS.

relationships to various degrees of hypoxia and the changes during the following 14 days post-hypoxia are summarized in Figures 11 through 14. At hypoxia levels of PO2ART $\leq$ 35 the system aborts.

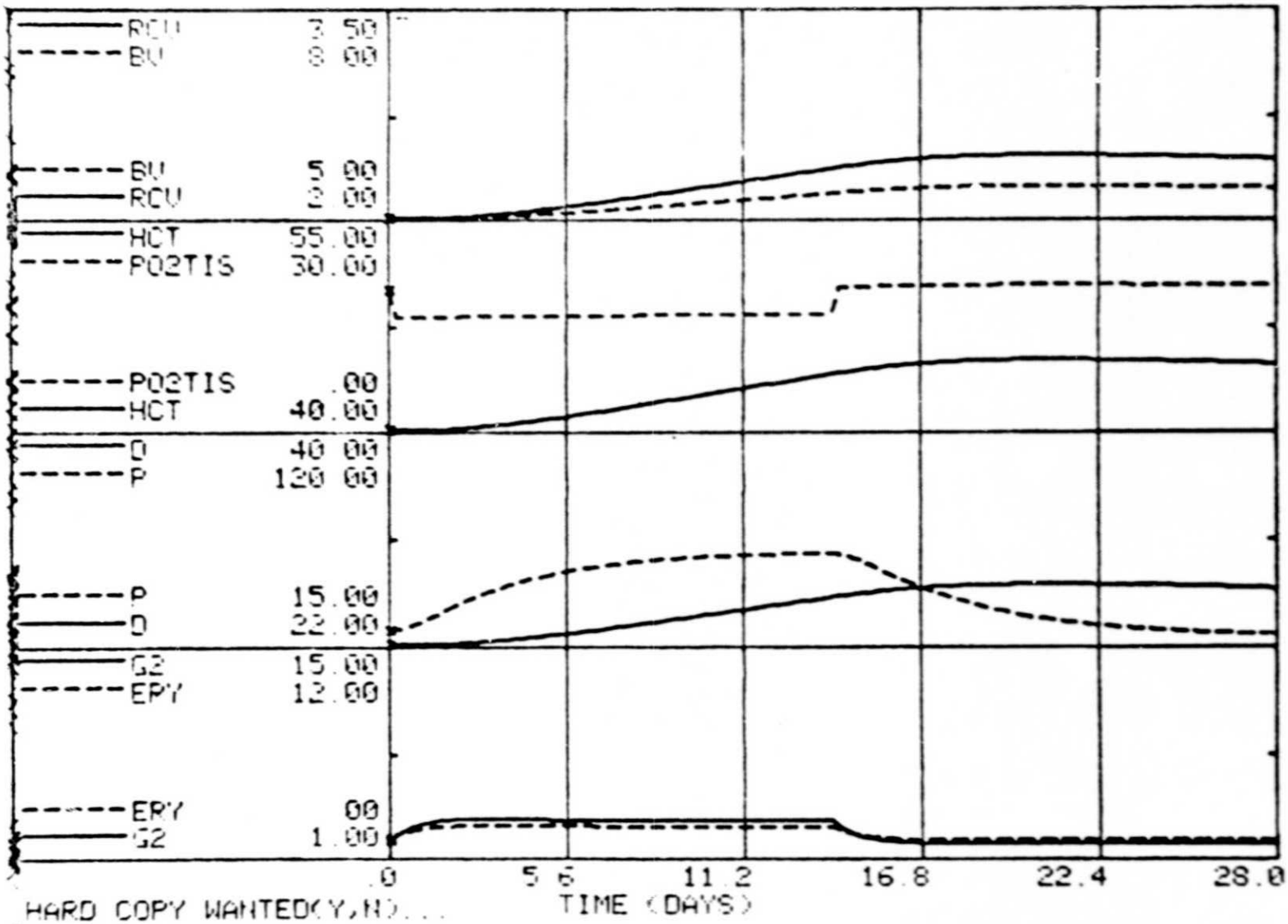
2. Simulation of dehydration using the human model but with data "scaled-up" from studies in mice:

We (13,14) have obtained much information regarding the effects of dehydration and/or food consumption on erythropoiesis in mice. Thus we have data on changes in plasma volume (PV), ERY, in the sensitivity of the target tissues to erythropoietin (G2), in red cell production (P) and an indication of changes in metabolic rate (AOM) assumed to be reflected by a change in body weight. By changing PV, G2 and AOM as dictated by experimental findings we hoped to simulate the changes in P and ERY. Since the data had been accumulated in mice, results expressed as percentage changes were used in the human model.

(i) Simulations in the original model:

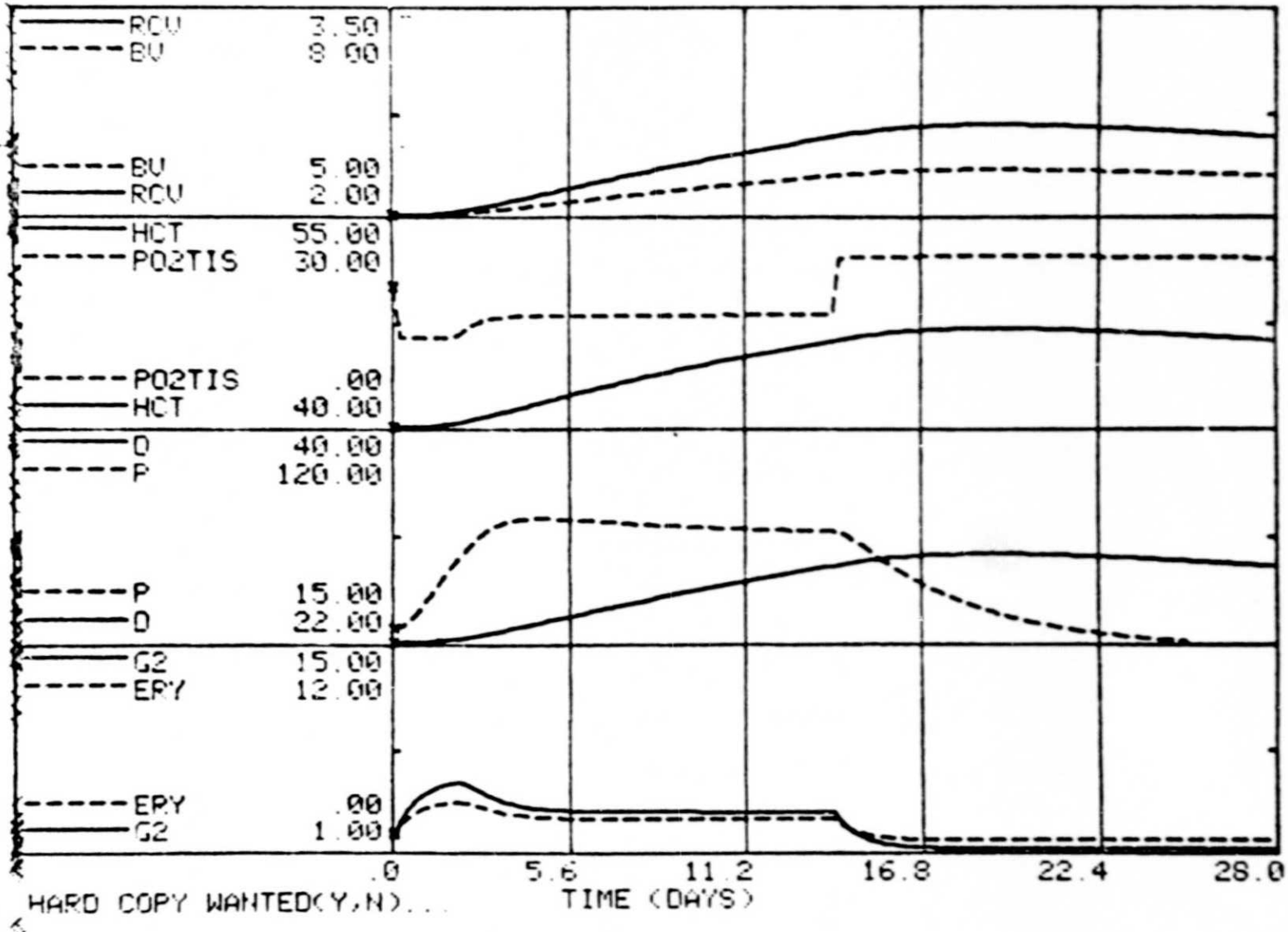
The effects of programmed changes in PV, G2 and AOM on P and ERY over a three day period are shown in Figure 15. Note that in contrast to the experimental findings (13) ERY was decreasing at the end of day 1. In addition, suppression of P was much less than was observed experimentally (13,14). Suppression of P to values comparable to those seen in the mice at 24 hours could be accomplished by reducing the parameter (Z) for bone marrow cell transit time from 5760 minutes to 1 minute (Table 1). ERY can be maintained above 0.9 of control by reducing renal blood flow (BF) from 1.2 to 1.0 (Table 2) but under these circumstances P is higher than expected from the experimental data. A three day

FIGURE 11



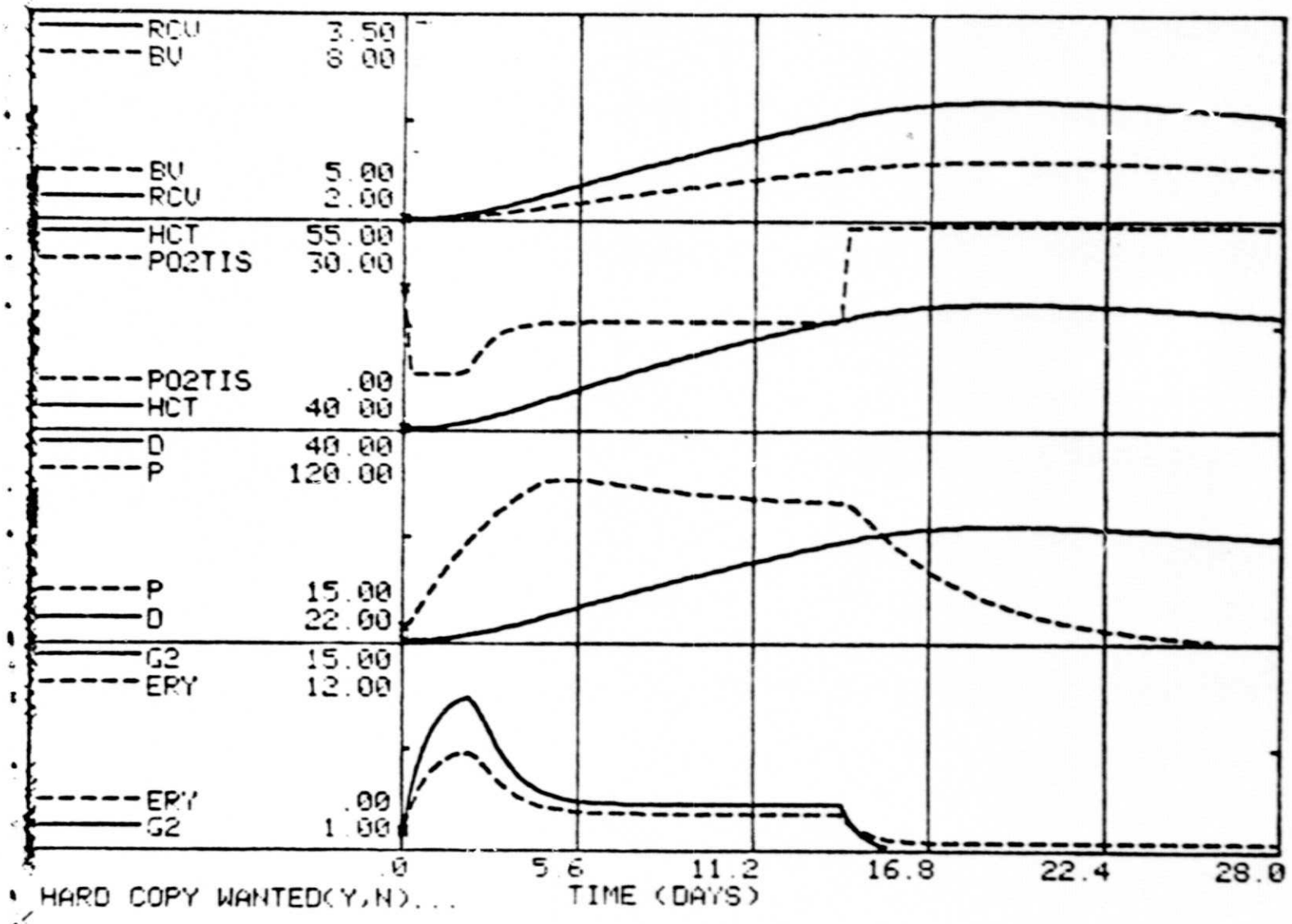
SIMULATION OF HYPOXIA (P02 ART = 75.) AND POST-HYPOXIA WITH THE MODIFIED HUMAN MODEL.

FIGURE 12



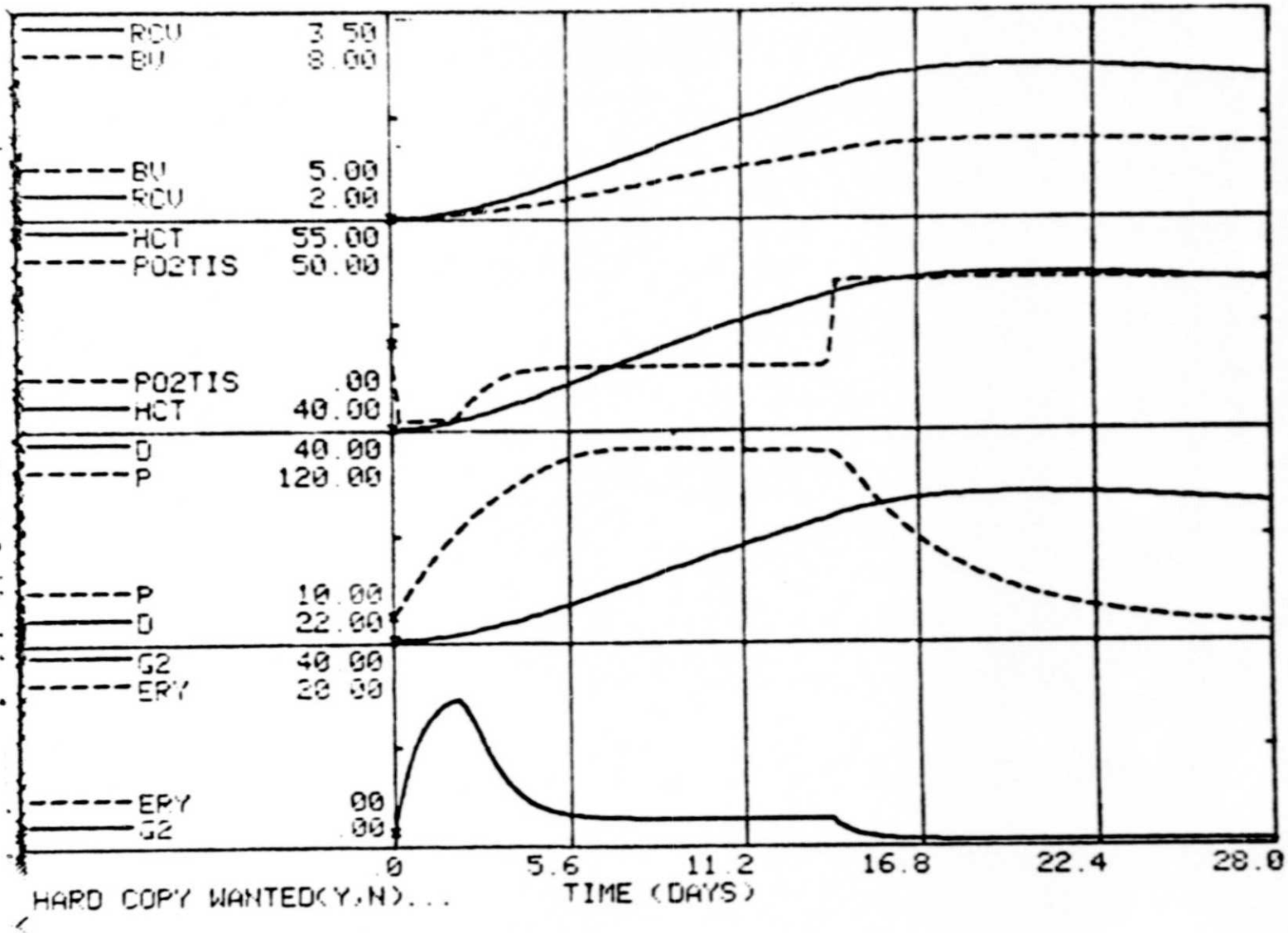
SIMULATION OF HYPOXIA (PO2 ART = 65.) AND POST-HYPOXIA WITH THE MODIFIED HUMAN MODEL.

FIGURE 13



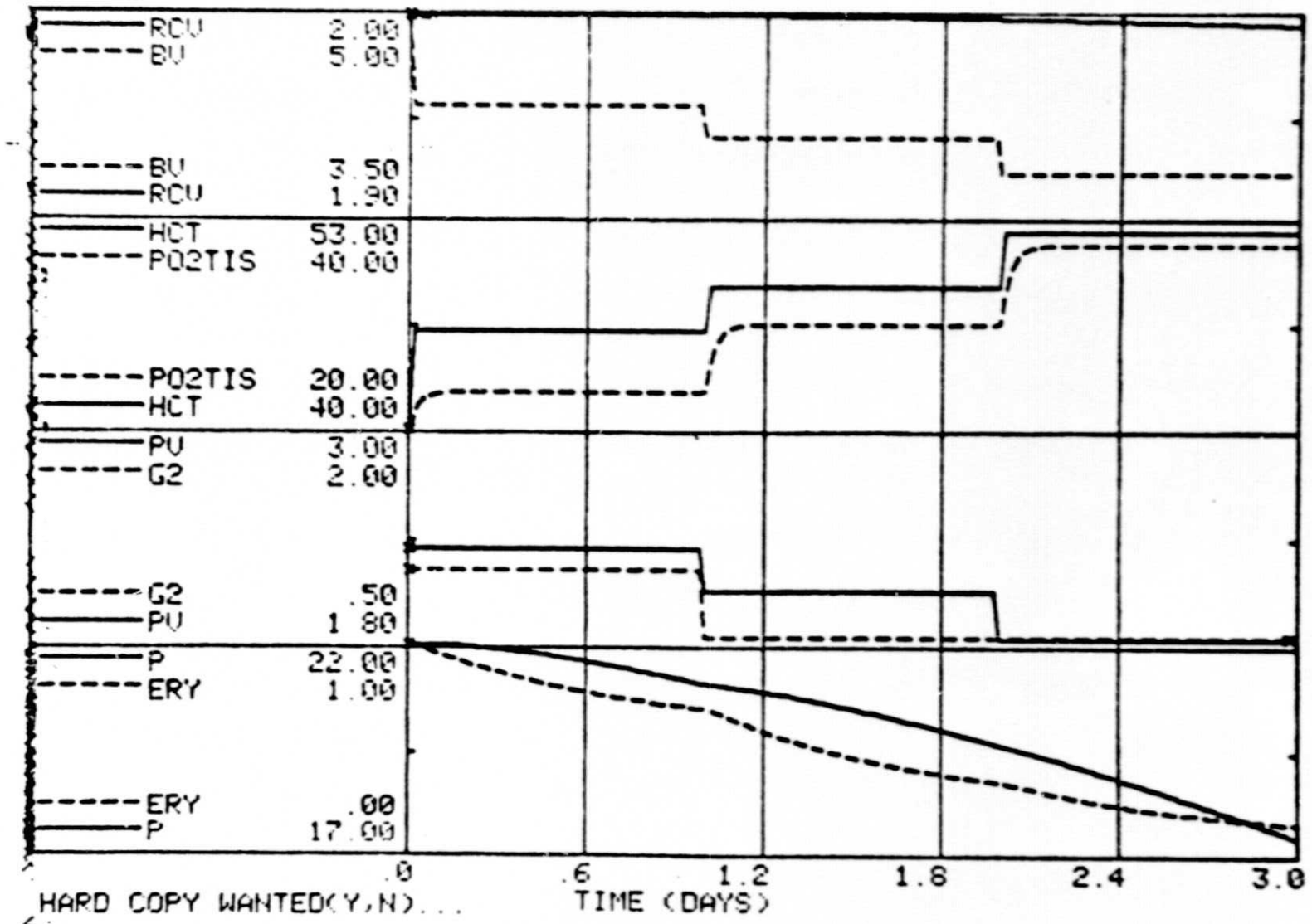
SIMULATION OF HYPOXIA (PO2 ART = 55.) AND POST-HYPOXIA WITH THE MODIFIED HUMAN MODEL.

FIGURE 14



SIMULATION OF HYPOXIA (PO2 ART = 45.) AND POST-HYPOXIA WITH THE MODIFIED HUMAN MODEL.

FIGURE 15



SIMULATION OF DEHYDRATION BY CHANGES IN PV, G2 AND AOM USING THE ORIGINAL HUMAN MODEL.

TABLE 1

DAYS	RCV	BV	HCT	PO2TIS	PV	G2	P	ERY
.00	2.000	5.000	40.000	20.000	2.340	1.620	22.000	1.000
.20	2.000	4.340	46.079	23.495	2.340	1.620	18.970	.913
.40	1.999	4.339	46.069	23.496	2.340	1.620	16.424	.835
.60	1.998	4.338	46.052	23.496	2.340	1.620	14.590	.776
.80	1.996	4.336	46.032	23.496	2.340	1.620	13.256	.731
1.00	1.994	4.334	46.009	23.484	2.340	1.620	12.282	.698

SIMULATION OF DEHYDRATION BY CHANGES IN PV, G2 AND AOM AND BY REDUCTION IN Z FROM 5760 TO 1 MINUTE IN THE ORIGINAL HUMAN MODEL.

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TABLE 2

DAYS	RCV	BV	HCT	POZTIS	PV	G2	P	ERY
00	2.000	5.000	40.000	20.000	2.340	1.620	22.000	1.000
.20	2.000	4.340	46.082	20.668	2.340	1.620	21.283	.980
.40	2.000	4.340	46.080	20.668	2.340	1.620	20.647	.962
.60	1.999	4.339	46.076	20.668	2.340	1.620	20.170	.948
.80	1.999	4.339	46.071	20.668	2.340	1.620	19.811	.937
1.00	1.999	4.339	46.065	20.668	2.340	1.620	19.541	.929

SIMULATION OF DEHYDRATION BY CHANGES IN PV, G2, AOM AND Z AND BY REDUCTION OF BF FROM 1.2 TO 1.0 IN THE ORIGINAL HUMAN MODEL.

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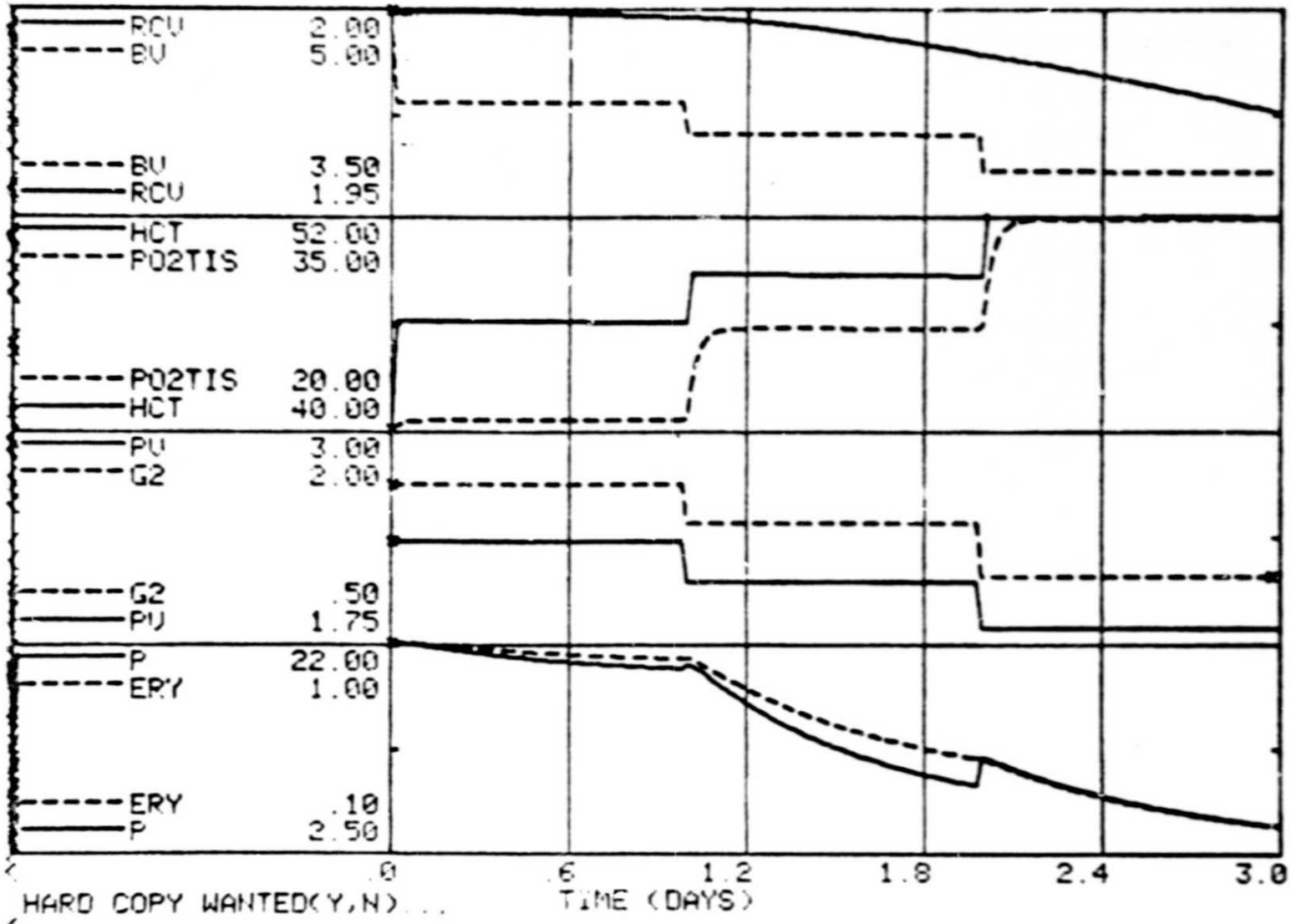
FIGURE 16



SIMULATION OF DEHYDRATION IN THE ORIGINAL HUMAN MODEL USING EXPERIMENTALLY-DICTATED CHANGES IN PV, G2 AND AOM AND Z = 1.0 AND BF = 1.0 THROUGHOUT.

TABLE 3

	EXPERIMENTAL DATA†	COMPUTER SIMULATION
PV	1.83	1.83††
G2	0.96	0.96††
AOM	0.75	0.75††
RCV	1.75	1.98
BV	3.68	3.8
HCT	47.5	51.9
PO2TIS	---	34.7
P	2.0	4.9
ERY	< 0.01	0.21

†= NORMALIZED FROM MOUSE DATA TO HUMAN VALUES.

††= VALUES DICTATED BY EXPERIMENTAL FINDINGS AND USED TO DRIVE THE MODEL.

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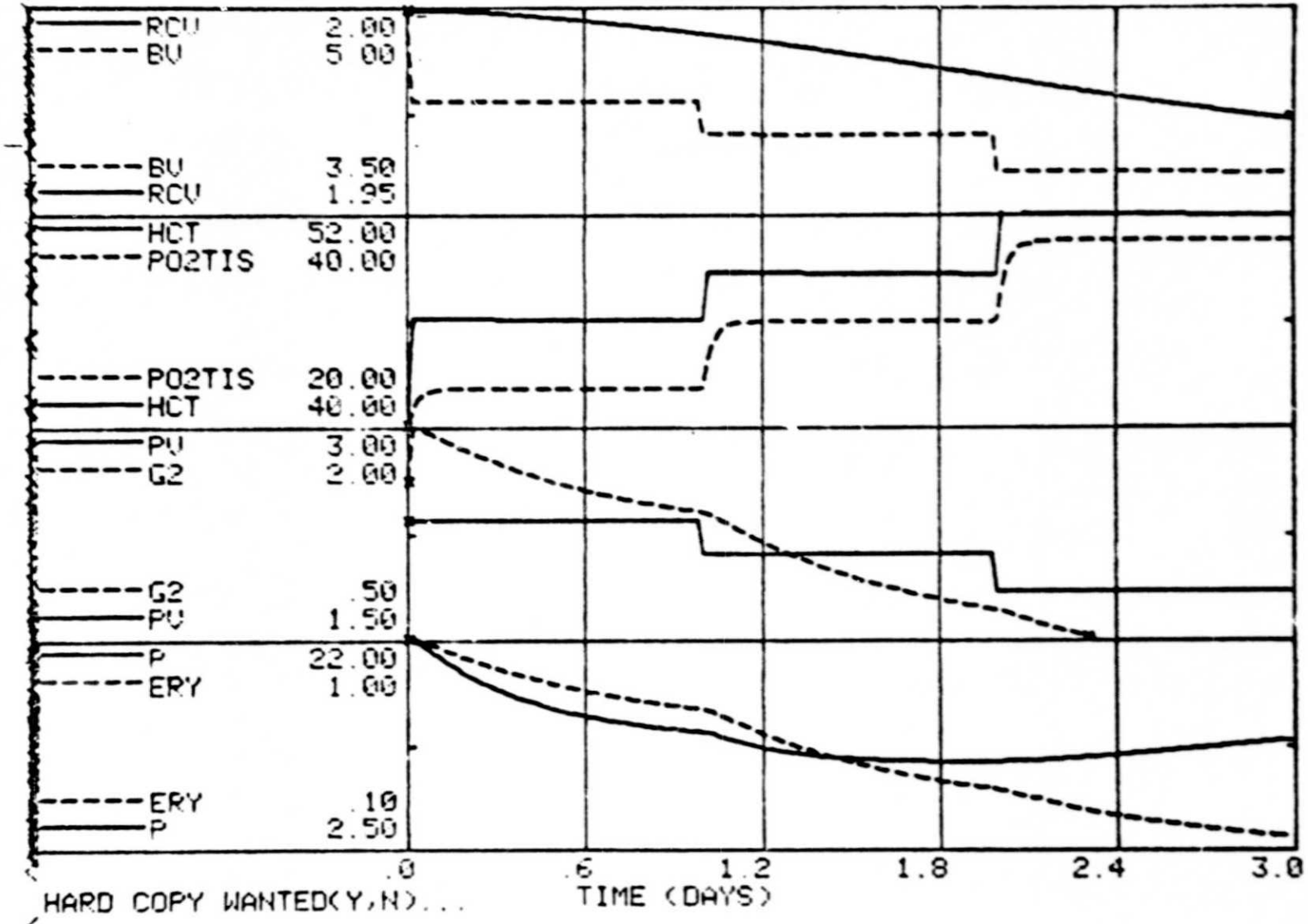
A COMPARISON OF DATA ON DEHYDRATION OBTAINED EXPERIMENTALLY OR BY COMPUTER SIMULATION USING THE ORIGINAL MODEL.

FIGURE 17



SIMULATION OF DEHYDRATION WITH THE LOADCD FILE USING EXPERIMENTALLY-DICTATED CHANGES IN PV AND AOM.

(iii) Simulation of rehydration with the original model:

Following three days of experimentally-dictated changes in PV, G2 and AOM (Figure 16) these parameters were returned to control values (rehydration) and the model run for a further seven days. The simulation is listed in Table 4. An excellent simulation of the experimental data (14) was obtained even to the slight decrease in HCT and small increase in P.

3. Evaluation of a model established with numerical values appropriate for mice:

A mouse model was established with the designation "@ ADD THERM.LOADM." This model responded appropriately to hypoxia (PO2ART = 55. or 35.) but inappropriately to infusions of erythropoietin (ENIF), to changes in e ythropoietin production (ERYO), erythropoietin half-life (EHL), infusions of red cells (RCFLO), changes in BF, PV, red cell destruction (RKC), basal metabolic rate (BMOTIS), and hemoglobin oxygen-carrying capacity (CHbO2). These inappropriate responses were eventually traced to the number of significant figures used in the integration steps. When these were increased the model responded appropriately to the above stimuli in 18 simulations. As an example of the behavior of this model, Figure 18 depicts simulation of a typical erythropoietin assay similar to those carried out routinely in our laboratory. Mice were presumed to be exposed continuously to 6% oxygen (PO2ART = 25) for 14 days before return to an ambient environment (PO2ART = 78). On the seventh day after return the animals were infused with erythropoietin at a dose twenty times the normal, pre-hypoxia, plasma concentration and the model run for a further four days. A qualitatively good simulation of the changes which are thought to occur during hypoxia and post-hypoxia were obtained. However, changes in PV during

TABLE 4

*WAIT-LAST	RCV INPUT	BV IGNORED*	HCT	PO2TIS	PV	G2	P	ERY
4.00	1.961	4.961	39.528	19.822	3.000	2.000	14.223	.804
5.00	1.958	4.958	39.487	19.807	3.000	2.000	20.827	.973
6.00	1.958	4.958	39.492	19.807	3.000	2.000	22.669	1.015
7.00	1.959	4.959	39.509	19.807	3.000	2.000	23.125	1.026
8.00	1.961	4.961	39.528	19.807	3.000	2.000	23.238	1.029
9.00	1.963	4.963	39.548	19.831	3.000	2.000	23.188	1.027
10.00	1.964	4.964	39.567	19.831	3.000	2.000	23.135	1.026

<

SIMULATION OF REHYDRATION USING THE ORIGINAL HUMAN MODEL.

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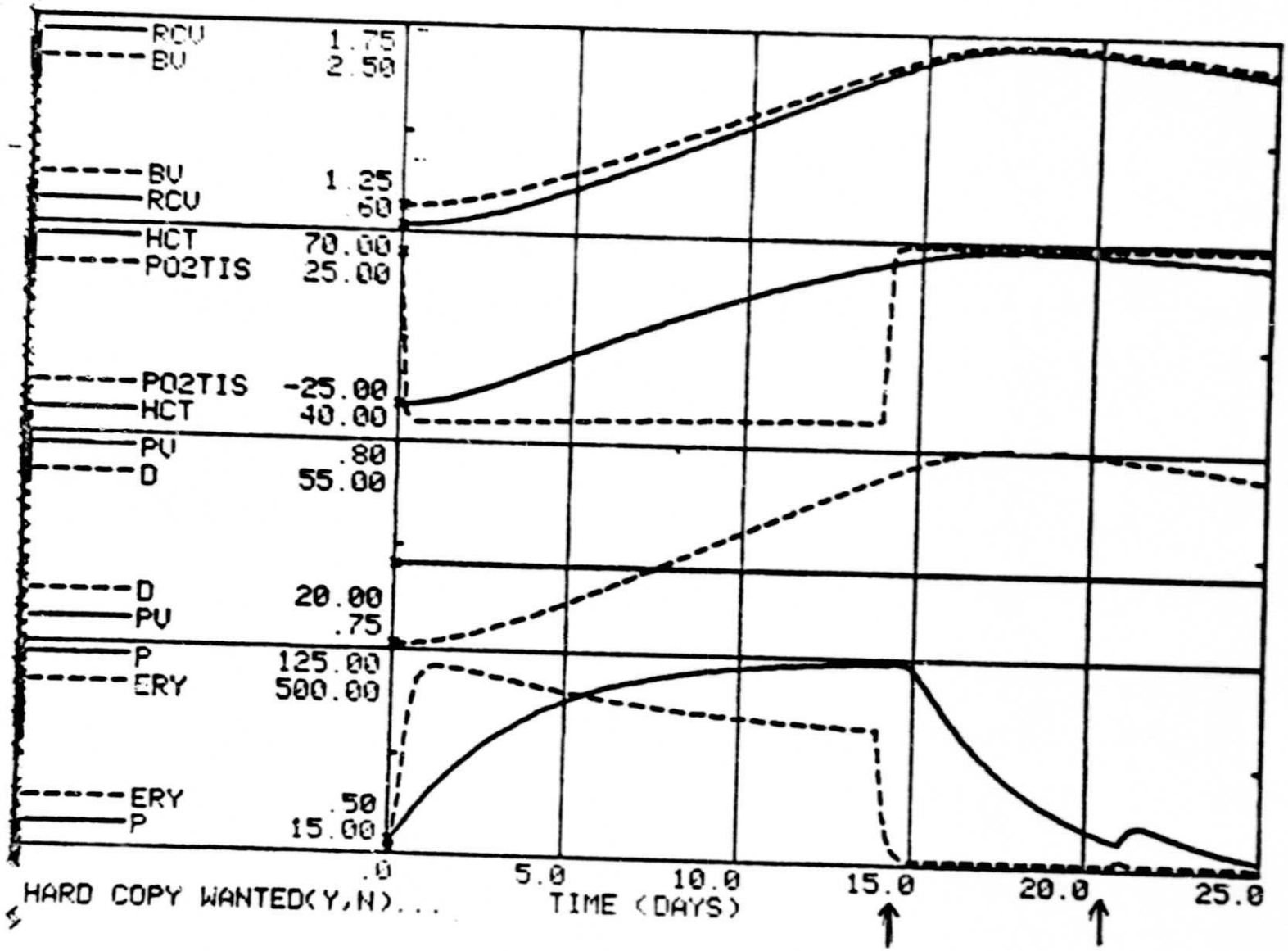
FIGURE 18



SIMULATION OF AN ERYTHROPOIETIN ASSAY.

hypoxia may occur. Note the small increases in ERY and P in response to ENIF in comparison to those produced by exposure to hypoxia. Note also that P does not fall as much during the post-hypoxic period as experimental studies with radioiron would lead us to expect.

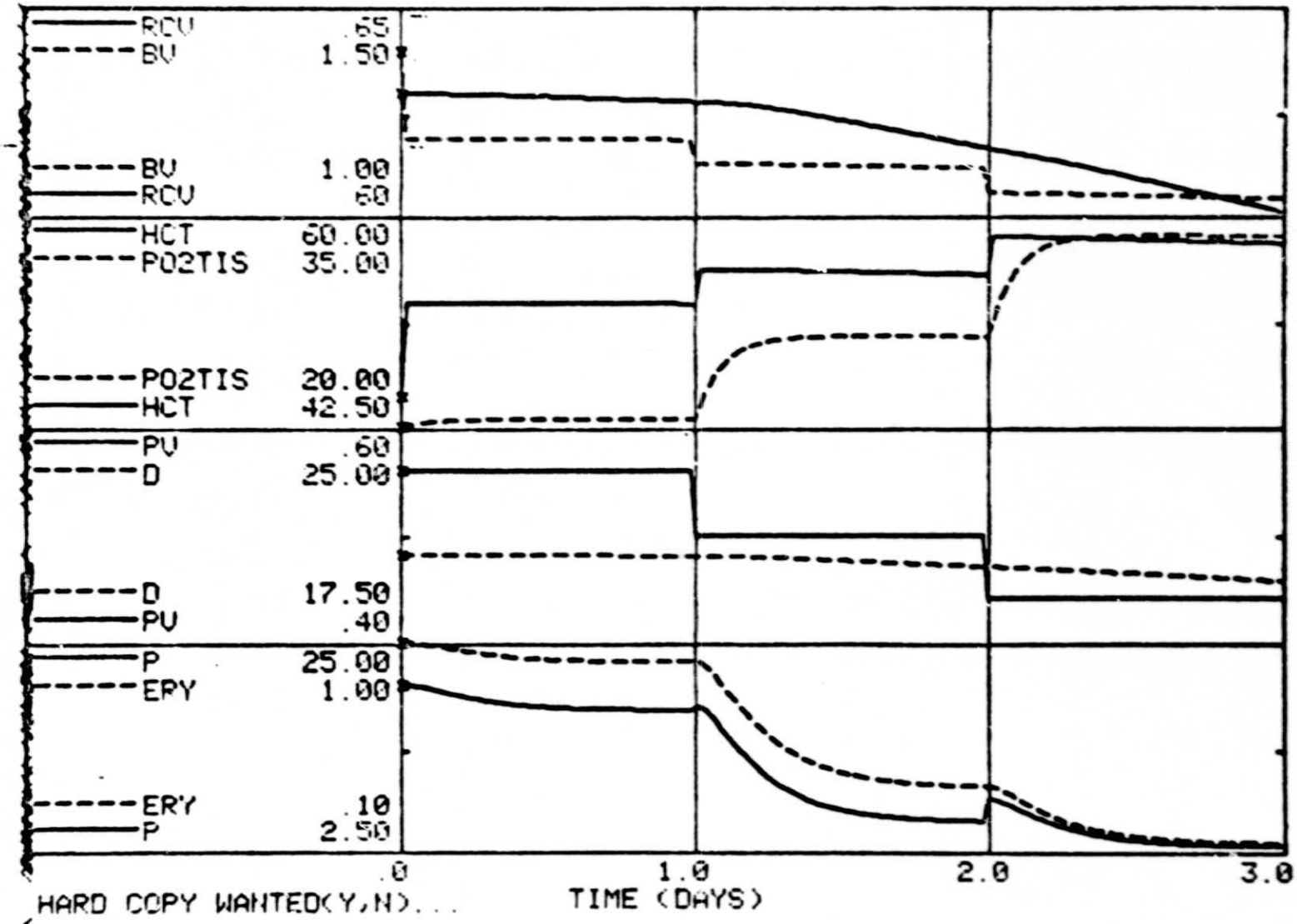
As part of the validation of this model the balance between the sensitivity of the erythropoietin producing mechanism (G1) and that of the bone marrow response to erythropoietin (G2) was elucidated. It was found that numerical values of G1 = 2.5 and G2 = 2.4 provided the most satisfactory increases in ERY and P in response to hypoxia.

4. Simulation of dehydration using the mouse model:

As detailed in Section 2 (above) we utilized our knowledge of changes in PV, G2 and AOM to determine how the model, specifically ERY and P, would respond to dehydration. The mouse model responded to the results obtained with mice in a similar way to the human model (Figures 15 and 16) using proportional changes from animal data. Like in the human model, optimum simulation of dehydration (Figure 19) was obtained only if the bone marrow maturation time (Z) and renal blood flow (BF) were both reduced to 1.0 and 0.0015 respectively. Even under these conditions, red cell production (P) and red cell mass (RCM) did not fall to the low levels seen experimentally. Similar to the trials with the human model the HCT was subnormal and P slightly increased during the excellent simulation of rehydration -- during which time Z and BF were returned to control values (Table 5).

The reasoning behind the implementation of changes in Z and BF to get acceptable simulations of dehydration are not clearly understood. A decrease in blood volume (BV) might simplistically be expected to decrease BF unless

FIGURE 19



SIMULATION OF DEHYDRATION IN THE MOUSE MODEL USING EXPERIMENTALLY-DICTATED CHANGES IN PV, G2 AND AOM AND Z = 1.0 AND BF = 1.0 THROUGHOUT.

TABLE 5

*WAIT-LAST	RCV INPUT	BV IGNORED*	HCT	PO2TIS	PV	D	P	ERY
4.00	.594	1.334	44.533	19.864	.740	19.378	20.851	1.007
5.00	.596	1.336	44.608	19.885	.740	19.437	21.267	1.018
6.00	.598	1.338	44.680	19.896	.740	19.494	21.183	1.016
7.00	.599	1.339	44.746	19.919	.740	19.546	21.083	1.013
8.00	.601	1.341	44.805	19.937	.740	19.592	20.968	1.010
9.00	.602	1.342	44.858	19.948	.740	19.635	20.882	1.008
10.00	.603	1.343	44.907	19.958	.740	19.673	20.813	1.006

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SIMULATION OF REHYDRATION USING THE MOUSE MODEL.

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other compensating mechanisms eg. heart rate, were increased. On the other hand, decreasing the time (Z) for a cell to mature through the bone marrow from 5040 minutes to 1.0 minute is probably unrealistic. A possible explanation of this dichotomy might be that dehydration inhibits cell proliferation at a stage late in the maturation sequence. A reduction of cell output from the marrow would, therefore, occur earlier than when the inhibition occurred at a more primitive cell level. However, even this theory is not entirely compatible with experimental data as it would suggest changes in the marrow morphology during dehydration. No such change has been observed (14).

On the basis of the above simulations and discussions of a theoretical nature with Drs. Leonard and Kimzey, four papers are in the formulation stage.

CONCLUSIONS AND RECOMMENDATIONS

The visit to the NASA group was a thought-provoking experience. It has led to a considerable "cross-fertilization" of ideas between people trained in different disciplines; i.e., between a mathematically-oriented group and the author whose major experience is in the biological sciences. As an example of this greater appreciation of our common interests in the regulation of erythropoieses, I was able to provide to the computer group an idea of the accuracy of the numerous assays involved and an indication of whether computer simulated data might be significantly different from those generated biologically. In addition, several areas in which the model might be improved were recognized; e.g., relating ERY to G2, rapidly correcting for tissue hypoxia by mechanisms which we are currently attempting to elucidate. In return, it became evident from the simulations performed and from discussions with the

computer group that an understanding of the regulation of erythropoiesis is not as complete as we had all thought. This has led to a greater appreciation of erythropoietin control mechanisms and underlined the gaps in our knowledge, some of which could be filled by experiments in my laboratory. These ideas have been generated as a direct consequence of the visit to NASA. Certainly, a clearer understanding of the erythropoietic effects of hypoxia and dehydration were gained and several avenues of research which could be performed in our potential animal model for the "anemia" of space flight (13,14) were recognized. These experiments will be enhanced by access to the computer model now established on The University of Tennessee's computer system -- another direct "spin-off" from the visit to Houston. The planned joint publications using the model will also act to the mutual advantage of both groups.

On the basis of my visit it is recommended that the concept of having an outside scientist to work with the computer group for a couple of months per year be continued. This will allow different inputs into the erythropoietic control model with the result that more and more realistic simulations are obtained. In addition, as more and more scientists use the model it will certainly become more widely known and probably appreciated to a greater degree. There seems little doubt that working in parallel between the computer model and the laboratory bench will greatly enhance our understanding of the regulation of erythropoiesis.

Three improvements are suggested which may make subsequent visits by other scientists even more useful: (a) the visiting scientist should attempt to spend one or two days with the computer group perhaps a month before the planned leave of absence to familiarize himself with the computer systems;

(b) at least one member of the computer group be allowed *de facto* leave from his usual responsibilities and given the sole job of interacting with the visitor. These two suggestions apply particularly to visiting scientists whose knowledge of computer technology is severely limited; (c) the possibility of "return visits" by one or more of the computer group to the visiting scientist's laboratory -- obviously there are many factors which would need to be clarified before this could be made operative.

By way of summing up the two months' stay at the NASA facilities in Houston, the visit was very useful and thought-provoking. It has led to a greater appreciation of the gaps in our knowledge regarding erythropoietic control mechanisms and identified areas of future research both for the computer group and author. I am exceedingly grateful to friends and colleagues both in Knoxville and Houston who made the visit possible in the first place and for making it so pleasant and successful.

REFERENCES

1. Leonard, J. I., (1974). NASA Report TIR 741-MED-4012.
2. Leonard, J. I., (1976). NASA Report TIR 782-MED-6004.
3. Leonard, J. I., (1977). NASA Report TIR 782-LSP-7012.
4. Grounds, D. J., (1978). NASA Report TIR 741-LSP-8004.
5. Dunn, C. D. R., *et al.*, (1976). *Exp. Hemat.*, *4*, 365.
6. Miller, M. E., *et al.*, (1973). *New Engl. J. Med.*, *288*, 706.
7. Abbrecht, P. H., and Littell, J. K., (1972). *J. Appl. Physiol.*, *32*, 54.
8. Rothman, I. K., *et al.*, (1970). *J. Clin. Invest.*, *49*, 2051.
9. Mylrea, K. C., and Abbrecht, P. H., (1971). *J. Theor. Biol.*, *33*, 279.
10. Wagemaker, G., *et al.*, (1977). In: "Experimental Hematology Today," Ed. J. Baum and G. D. Ledney. Springer-Verlag, New York, p. 103.
11. Gregory, C. J., *et al.*, (1973). *J. Cell. Physiol.*, *81*, 411.
12. Kretchmar, A., (1966). *Science*, *152*, 367.
13. Dunn, C. D. R., (1978). *Aviat. Space Environ. Med.*, *49*, 990.
14. Dunn, D. C. R., and Lange, R. D. Submitted.