A mathematical model of erythropoiesis in mice and rats
Part 3: Suppressed erythropoiesis

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Abstract. A mathematical model of erythropoietic cell production and its regulation process has been proposed in a preceding paper. It is primarily based on the assumption that the number of cell divisions taking place in the CFU-E and erythropoietic precursor stages can be regulated depending on the oxygen supply to the tissue. Here we provide evidence that this model adequately describes situations of suppressed erythropoiesis. In detail this implies a quantitative description of the following processes: (1) changes in tissue oxygen tension (P_{to_2}) due to increase in red cell numbers (red cell transfusion, posthypoxia), decrease in plasma volume (dehydration) or increase in atmospheric oxygen pressure (hyperoxia), (2) P_{to_2} dependent reduction of erythropoietin (EPO) production, (3) dose-response of reduced EPO-levels on erythropoietic amplification (omission of three to five mitoses).

Model simulations are compared to experimental data obtained from red cell transfusion, posthypoxia, hyperoxia and dehydration. A satisfactory agreement suggests that the model adequately describes and correlates different ways to suppress erythropoiesis. It quantifies the role and relative contribution of the haematocrit, haemoglobin concentration, atmospheric oxygen pressure, tissue oxygen pressure and plasma volume as triggers in erythropoietic suppression under various conditions. In conjunction with the preceding two papers it could be shown that one unique set of model parameters is sufficient to describe erythropoiesis in steady state, stimulation and suppression. Limitations of the model are discussed and experiments for a more detailed investigation of the feedback mechanisms are proposed.

A mathematical model of erythropoiesis in mice and rats has been developed. In the first part (Loeffler *et al.*, 1989) of a series of three papers, the model description was given and it was shown that the model is able to reproduce the *equilibrium* conditions experimentally found. The second part (Wichmann *et al.*, 1989) proved the validity of the model during and after several *stimulations* of erythropoiesis. Now, we complete the comprehensive analysis of the regulating mechanisms in erythropoiesis by comparing the experimental results of erythropoietic

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Table 1. Model simulation of experiments on suppressed erythropoiesis

Hypertransfusion
- Initial values for reticulocytes and erythrocytes are elevated according to the number of transfused cells
- The transfused red cells are destructed at random (average lifespan 10 days)
- The plasma volume remains constant

Posthypoxia
- The reduced arterial oxygen pressure returns immediately to normal (80 or 95 mmHg in mice or rats respectively)
- The reduced plasma volume increases linearly to its normal value within 10 days

Hyperoxia
- The arterial oxygen saturation is maximum (100%)
- The tissue oxygen pressure is artifically elevated using a constant factor to mimic the effect of the physically soluted oxygen
- The plasma volume remains constant

Dehydration
- The plasma volume is reduced according to the measurements
- The production of erythropoietin is reduced due to deprived nutrition of a changed metabolism

suppression with the model calculations. It is one of the major assumptions that the erythropoietic feedback acts on the number of cell divisions taking place during the differentiation process. During situations of suppression fewer than the normal number of mitoses is assumed to take place while a largely normal maturation process can continue. Evidence for this concept is provided subsequently.

MODEL SIMULATIONS

In Table 1 the characteristics of the experimental manipulations are described in terms of the model to give an indication of how the simulations are performed.

Hypertransfusion
In animals having received a red cell transfusion, the haematocrit declines more rapidly than would be expected if all erythrocytes had a normal lifespan of over 40 days. Based on such data (Gurney *et al.*, 1961; Hara & Ogawa, 1977) one has to conclude an average lifespan of approximately 10 days. In the model, the transfused cells are added to the compartment of reticulocytes (RETI) and stress erythrocytes (ERYR) and the transit time τ_{ERYR} is reduced to 10 days. The reduction of plasma volume (PV) after transfusion of erythrocytes was found to be small (Birkhill *et al.*, 1951; Pribilla, 1977). Thus it seems reasonable to neglect these changes and to assume a constant plasma volume during the whole simulation.

Posthypoxia
The simulation of the initial hypoxic period has been described in Part 2 (Wichmann *et al.*, 1989) (i.e. reduction of the arterial oxygen pressure, reduction of PV, initial peak of erythropoietin). A termination of the hypoxic stimulus in the model is simulated by switching the arterial oxygen tension (Pto_2) immediately back to normal and by linearly increasing the plasma volume (PV) to its normal value within 10 days.

Hyperoxia

In most experiments on hyperoxia, the atmospheric oxygen pressure is elevated to three to five times normal (Linman, 1968; Fishman *et al.*, 1973; Birks *et al.*, 1976; Moccia *et al.*, 1980). This leads to an increase of both the arterial oxygen tension and saturation (Gray & Steadman, 1964). To simulate hyperoxia it is assumed that Sao_2 equals 100% which corresponds to an increase of the normal tissue tension Pto_2 by 4–8 mmHg. Furthermore, the fraction of oxygen dissolved physically in the arterial blood is increased during hyperoxia. This is simulated in a simplified way by multiplying Pto_2 with a constant factor $k = 1.4$ which is estimated from the experimental data. The effect of the physically dissolved oxygen corresponds to a further elevation of the tissue oxygen tension by 17–20 mmHg.

Dehydration

The regulatory influences of dehydration are mediated via the decreased plasma volume. The time course of the plasma volume used in the model simulation is adjusted to the experimental data (see Fig. 4d). In an additional step, possible effects of dehydration on the production of erythropoietin (EPO) are considered. During the period of dehydration, the production of EPO is reduced to 33% of the model value calculated in the first step. This reduction is assumed to describe an influence of deprived nutrition or changed metabolism on EPO-production as discussed by Dunn *et al.* (1981).

RESULTS: MODEL CURVES VERSUS EXPERIMENTAL DATA

Hypertransfusion

In polycythaemia, erythropoiesis is suppressed and according to the model dose-response curve three to five mitoses may be omitted in the erythropoietic cell lineage (see Part 1). Consequently the number of erythroblasts may decline to 2% of the normal value in mice and to 13% in rats. Compared to this a prolongation of the marrow transit time by about 2% is of minor importance.

To simulate the experiments on hypertransfusion, the pool of erythrocytes and reticulocytes is elevated according to the number of transfused cells. Furthermore, a shortened lifespan of 10 days is assumed for the transfused cells.

Figure 1 shows the resulting model curves in comparison with the experimental data. The decrease of the EPO-level is deeper in the model than in the experiment. However, the changes calculated for CFU-E, reticulocytes and Hct agree well with the data. The erythropoietic production rate (i.e. the efflux from the compartment of the erythroblasts, Fig. 2c) corresponds to the rate of ^{59}Fe-incorporation measured by Okunewick & Fulton (1970).

Posthypoxia

Figure 2 shows model curves during and after a hypoxic period of 8 days according to an altitude of 7 km and comparable experimental data. The end of the hypoxic period is denoted as day zero. The time courses for the progenitors (CFU-E) and precursors (erythroblasts) are reproduced by the model (Fig. 2a–c). Unfortunately, the measurements have been terminated before the steady states were reached. The blood values represented by the haematocrit and the percentage of reticulocytes reach their normal levels in the model slightly later than in the experiment (Fig. 2d–e).

Comparison of the dashed and full lines in Fig. 2 shows that the normalization of the plasma volume (which was reduced to 73% during hypoxia, see part 2) accelerates the normalization of the haematocrit but has no strong influences on erythropoietic proliferation, at least during the first 10 days.
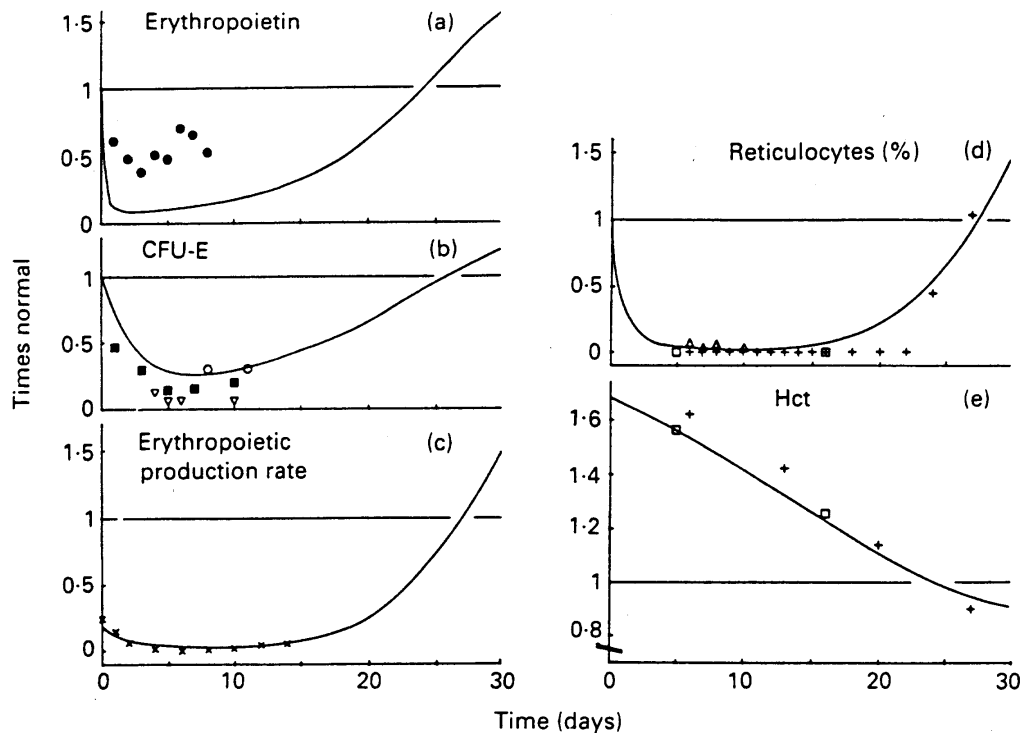
Fig. 1. Changes in erythropoiesis after transfusion of red blood cells to mice. Data from: Moccia *et al.* (1980), ●; Iscove (1977), ○; Hara (1980), ■; Hara & Ogawa (1977), □; Gregory *et al.* (1973), ▽; Okunewick & Fulton (1970), ×; Seidel & Opitz (1979), △; Gurney *et al.* (1961), +. Model curves (—) are calculated for an elevation of the total mass of Hb to 5·3 times normal.

Hyperoxia

Hyperoxia is simulated by increasing arterial oxygen saturation to a maximum which is responsible for a small increase of the tissue tension Pto_2. This leads to a reduced erythropoietic production (Fig. 3, full lines). The theoretical curve of EPO shows a decrease similar to the experimental data. However, the resulting decrease of the precursors and reticulocytes is too small to reach the experimental values.

If, in addition, the physically dissolved oxygen is considered to play a role in the regulation of EPO production (Fig. 3, dashed lines), the EPO-level decreases further and the blasts and reticulocytes reach values closer to the experimental data.

Dehydration

Figure 4 shows the influence of dehydration on erythropoiesis. The plasma volume is reduced to 50% of normal within 3 days resulting in an increase of Hct to 1·33 times normal. Thus, the production of erythropoietin and erythroblasts is suppressed which is reproduced by the model calculations.

To take the effect of deprived nutrition on EPO-production into account (as discussed by Dunn *et al.* (1981)) the EPO-production is reduced further to 33% of the previous model simulation (Fig. 4, dashed lines). However, this shows no strong influence on the time courses of EPO and the cell numbers.
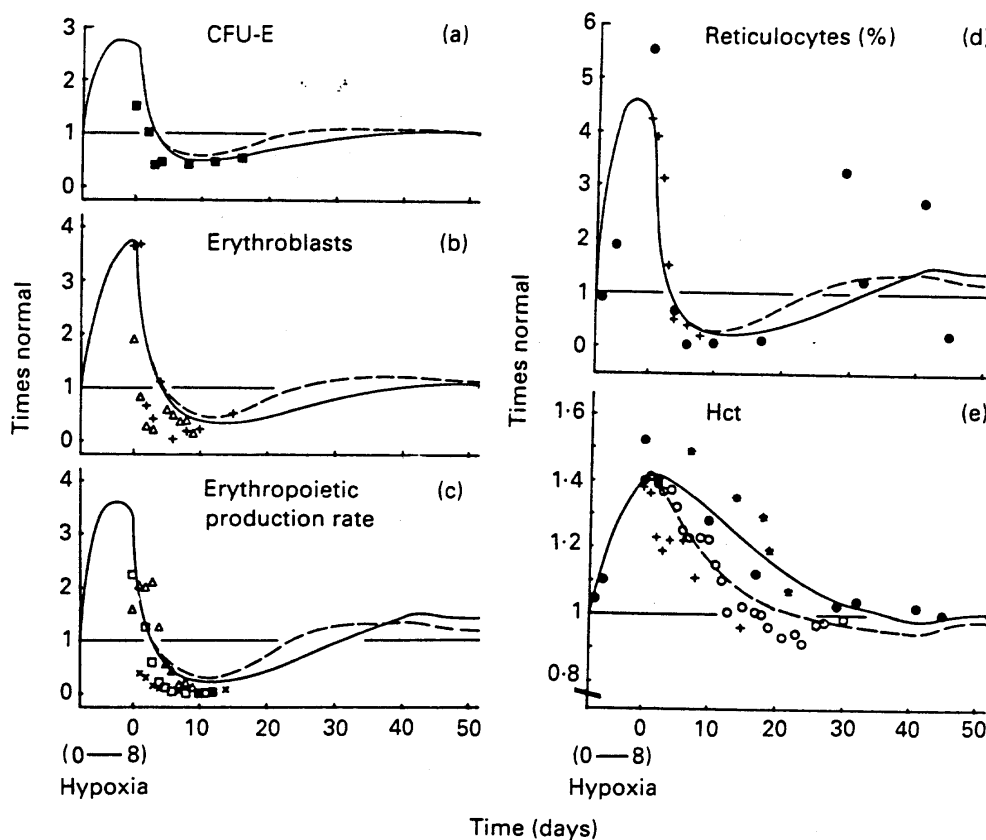
Fig. 2. Changes in murine erythropoiesis after hypoxia in mice. Data from: Wagemaker *et al.* (1977), ■; Beran & Tribukait (1971), +; Peschle *et al.* (1977), □; Turner *et al.* (1967), △; Okunewick & Fulton (1970), ×; Rothman *et al.* (1970), ●; Tribukait (1968), ○; Zanjani (1976), ∗. Model curves simulate recovery after a preceding hypoxia of 8 days corresponding to an altitude of 7 km with (——) or without (– – –) restoration of the decreased plasma volume.

DISCUSSION

The suppression of erythropoiesis is mainly characterized by a strong reduction of the amplification factor of CFU-E and erythropoietic precursors caused by a decreased level of EPO. The total erythropoietic production in mice decreases rapidly to approximately 1/32 indicating that at least five amplifying cell divisions can be skipped under such circumstances while cell differentiation may still be going on. In rats the erythropoietic production does not drop below 10% of normal, indicating that only three to four cell divisions are skipped.

In the model, the amplification factors f for CFU-E and erythroblasts are the most important parameters. The dose-response curves of these factors (f_{CFU-E} and f_{PEP}) depending on EPO are the main hypotheses put forward by this model. This implies a prediction about the dose-response relationship of erythropoietic feedback *in vivo* which at present cannot be measured directly. In comparison to the relevance of the amplification factor f the changes of the bone marrow transit time are small during suppressed erythropoiesis. With this concept it is possible to interpret most of the experimental observations. The findings deserve several comments.

Elevation of red blood cell counts (hypertransfusion, posthypoxia)
After the increase of Hct by transfusion of erythrocytes or after hypoxia, erythropoiesis may be
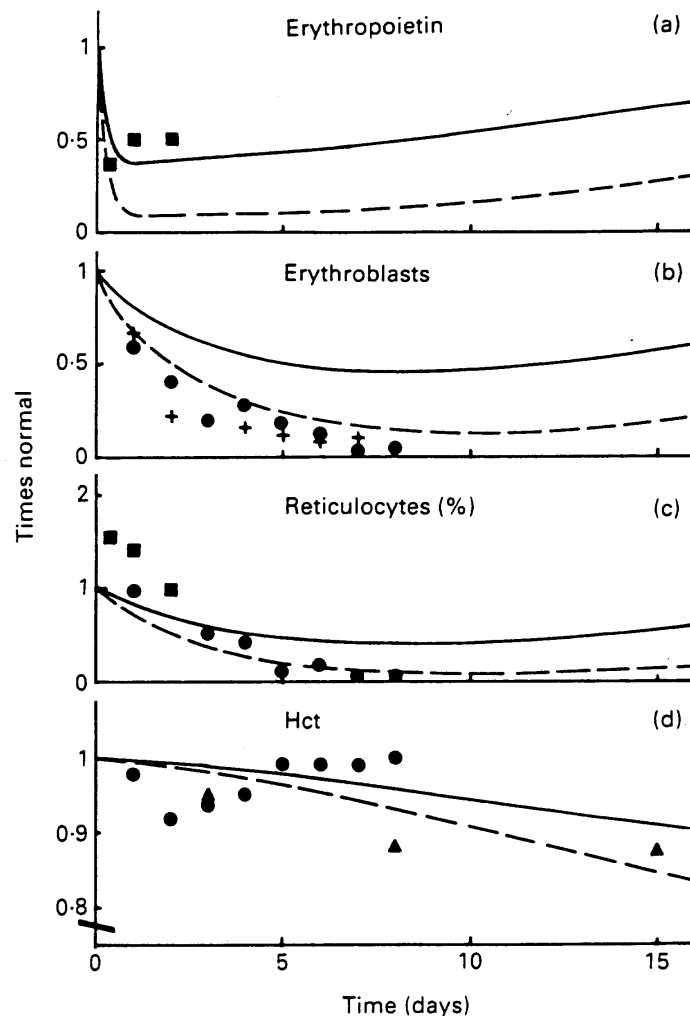
Fig. 3. Changes in erythropoiesis during hyperoxia in mice. Data are taken from: Moccia *et al.* (1980), ■: 100% O_2; Fishman *et al.* (1973), +: 60% O_2; Linman (1968), ●: Po_2 = 4 atm); Birks *et al.* (1976), ▲: Po_2 = 3 atm). Model curves are calculated without (——) and with (———) considering the oxygen dissolved physically.

suppressed for 25 days. The lifespan of the erythrocytes is reduced after red cell transfusion or after hypoxia but for different reasons. During hypoxia, predominantly 'stress erythrocytes' have been generated which are predicted to have a lifespan of 15–20 days. In contrast, a large fraction of erythrocytes in animals having received transfusion seem to have a shortened lifespan of 10 days probably due to some effects related to the experimental procedure. Thus, although different in cause the elevated haematocrit normalizes much earlier after hypertransfusion or hypoxia than should be expected from the normal life span of erythrocytes in mice (42 days).

After transfusion of RBC, the reduction of EPO is more pronounced in the model than in the corresponding experiments. This may have to do with the difficulties of measuring subnormal EPO-concentrations (see below). Alternatively, this can be explained by an effect of the enlarged blood viscosity which leads to a reduction of tissue perfusion and, thereby, to a
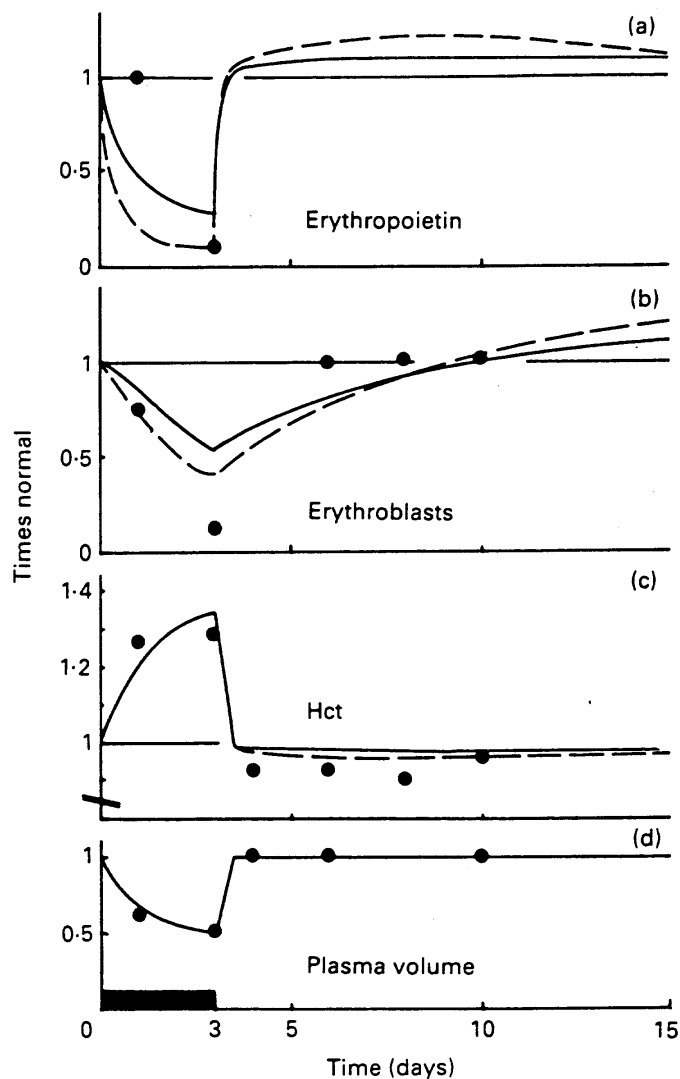
Fig. 4. Changes in erythropoiesis during and after a period of water restriction (3 days) in mice. Data from Dunn *et al.* (1981), ●. Model curves are calculated for an unaffected production of EPO (——) and for a reduced EPO production (---, reducing factor = 0·33).

somewhat less optimal oxygen supply as one might expect. This would elevate the level of EPO-production slightly.

Elevation of the oxygen pressure (hyperoxia)

The elevated atmospheric pressure leads to a better oxygen supply of the body. Thus, the oxygen tension in the tissue increases and the production of EPO declines.

In the model, it is not sufficient to consider the influence of hyperoxia on the desaturation of haemoglobin since the normal arterial oxygen saturation is already close to the maximum. In contrast, it is necessary to assume that the physically dissolved oxygen increases the tissue tension. With this assumption the model fit to the measurements is improved.

Since the lifespan of red cells is normal during hyperoxia the number of erythrocytes decreases much slower than after hypertransfusion or after hypoxia.

If, however, the lifespan of the erythrocytes is reduced for other reasons (e.g. in haemolytic anaemia), the administration of oxygen may be disadvantageous. This could be demonstrated for erythropoiesis in man where oxygen therapy in patients with sickle cell anaemia led to reduction of erythropoietic proliferation by more than 80% within one week (Wichmann *et al.*, 1976).

Reduction of the plasma volume (dehydration)

The restriction of food and water uptake during 3 days leads to haemoconcentration indicated by an increase of Hct. This increase is accompanied by a marked reduction of EPO production and subsequently of the erythropoietic precursor counts.

It is discussed that the production of EPO is further reduced during the phase of dehydration by metabolic changes (Dunn *et al.*, 1981). The model calculations show that this would not cause a strong influence on erythropoietic regulation.

At the end of this series of three papers on modelling the erythropoietic system some general problems derived from the model simulations for stimulated and suppressed erythropoiesis deserve discussion.

(1) The good reproduction of most of the experimental data measured for different perturbations of erythropoiesis supports the main assumptions of the model (especially the dose-response curves for the amplification factors of CFU-E and proliferative erythropoietic precursors depending on EPO). However, the exact mechanisms of the production and metabolism of the regulating hormone erythropoietin remain unclear. Neither the parameters influencing directly the activation of EPO in the kidney nor the disappearance of EPO during or after different experimental treatments (consumption of EPO by the progenitors or precursors?) can be exactly determined by our model analysis. An important problem in this case seems to be the determination of EPO-levels. The development of experimental methods started with the *in vivo* bioassay using polycythaemic mice (Fogh, 1966; Zivny *et al.*, 1970; Fishman *et al.*, 1973) and was followed by the more valid *in vitro* bioassays using, e.g. fetal liver cells or haemaglutination-inhibition. Today the radioimmunoassay (RIA) is a common method to determine EPO in animals as well as in man. Although the variation of EPO-levels measured by the RIA is lower than the results derived from *in vitro* bioassays (De Klerk *et al.*, 1982) it ranges between 5·8 and 36 mU/ml plasms in haematologically normal human subjects as measured by Rege *et al.* (1982). Thus, it is difficult to interpret moderate differences between the EPO-values derived from the model calculations and the corresponding experiments.

(2) The influence of imbalances of the iron metabolism is neglected in the model calculations. Deficiency of iron may occur after severe acute bleeding or during a moderate but continuous loss of blood cells. On the other hand, iron-overloading might become relevant after severe or repeated transfusions of red blood cells. Both imbalances may reduce the response of the erythropoietic system because iron can be a limiting factor (bleeding anaemia) or work as a toxic agent (haemochromatosis as a result of severe iron-overloading). A more realistic model would have to take iron metabolism into account which was so far neglected.

(3) The model is able to reproduce quantitatively the behaviour of the erythropoietic system although the influences of splenic erythropoiesis, the effects of changes of the stem cell level, as well as interaction with granulopoiesis have been neglected. The indirect effects of erythropoietic stimulation on CFU-S and BFU-E are small compared with the effect produced by EPO on the CFU-E and the erythropoietic precursor cells (Loeffler & Wichmann, 1980; Wichmann & Loeffler, 1985). Preliminary model calculations which separately consider splenic

erythropoiesis show that the proliferative reserve is higher for splenic CFU-E than for marrow CFU-E (Pantel *et al.*, 1988). This is especially important for the regeneration from severe bleeding and for the adaptation to chronic anaemia or to severe hypoxia.

(4) The present analysis deals mainly with temporary reactions of the erythropoietic system on experimental treatment where erythropoiesis finally returns to the normal steady state. However, the model is also able to reproduce permanent changes leading to new steady states, as shown for chronic hypoxia (see Part 2). Thus, it becomes possible to reproduce new steady states for different kinds of haematological disorders by making special assumptions for the pathomechanism of each disease. This has earlier been done for man (Wichmann *et al.*, 1976) and presently work is underway in our group to investigate and analyse the aplastic anaemia in congenitally anaemic W/W^V-mice.

(5) The model consists of a series of compartments representing the maturing erythropoietic cell lineage. These compartments are connected by influxes and effluxes which are determined by differential equations. Neither a reflux of cells into preceding compartments nor a premature loss of cells is assumed in this system. The maturation steps take place chronologically and irreversibly. They require a certain time which may be subject to EPO-control. The process of amplification is regulated largely independent of maturation. At each cell stage the number of cell divisions taking place may not be a fixed value but could be subject to modulation. However, there exist limitations to this modulation which is expressed by the upper and lower limits of the sigmoidal shape of the dose-response curves obtained for the amplification factors (see Fig. 3, Part 1, p. 20). The model describes a system in which the cells leave their stage of maturation (compartment) by a stochastic process; only the average number of mitoses and average transit time of the whole cohort is controlled. Therefore, on each model cell stage there exist slowly and rapidly maturing cells and the speed of maturation of individual cells may change from one cell stage to the next. This view may be a somewhat oversimplistic description of the erythropoietic differentiation and proliferation process on the single cell basis. However, with respect to cell cohorts of many cells the coefficient of the total marrow maturation time and of the maturation time in any compartment (e.g. CFU-E) must be large (at least ±30%). This is concluded from a stability analysis of the regulated model (Wichmann, Loeffler & Schmitz, 1988). If small variation coefficients are assumed the model would tend to start oscillations. Biologically, this conclusion implies that although maturation continues irreversibly and chronologically it most likely is not synchronous for initially closely related cell cohorts. Thus, it may be a different thing to describe a mass phenomenon of *in vivo* haemopoiesis or to describe single cell developments.

(6) Experimental values of the dose response curves for the production of erythropoietic cells are not available under *in vivo* conditions except for the minimum, maximum and normal values. Thus, it might become an important aim of experimental research to obtain more operation points on these curves *in vivo*. This could be done by driving the systems to different *steady states* of suppressed or stimulated erythropoiesis by subjecting it, e.g. to a continuous (recombinant) EPO stimulus. Furthermore, experiments would be helpful which investigate possible mechanisms of EPO-binding or of EPO-consumption by EPO-sensitive cells.

(7) The dose-response curve of the EPO-production related to the renal oxygen tissue pressure at the sites of EPO-production is also experimentally unknown. In the model, the corresponding values of the whole body oxygen supply were used fitting the experimental results sufficiently well. Future experiments might determine more exactly the oxygen supply of different tissue areas (renal and extrarenal) in correlation with the production of EPO.

(8) It was concluded that erythrocytes produced under stimulated conditions are destroyed at random with a shortened life span. Teleologically speaking the production of such 'stress'

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erythrocytes with a lower quality may be the price the system pays for shortening the marrow transit time under severe stimulations. The major target of this mechanism could be to compensate a severe demand of red blood cells rapidly paying less attention to long term deficits which can be dealt with by increased amplification. However, it remains unclear at which stage of the erythropoietic cell lineage the switch from normal to stress-production occurs and how it is precisely regulated. We suspect that it occurs in precursor cell stages rather than at the level of reticulocytes where the switch is located in the model for technical reasons. Further investigations of biochemical differences between normal and stress erythrocytes might be warranted.

(9) In an earlier version of the model (Wichmann *et al.*, 1976) erythropoiesis in man has been investigated for different kinds of anaemia (aplastic anaemia, pernicious anaemia, sickle cell anaemia and other haemolytic anaemias). In future, we will extend this work to investigate further haematological disorders as, e.g. found in chronic renal failure. From these studies, we will try to get a better understanding of the quantitative influences of the different defects caused by the uraemic toxins (inhibited proliferation of erythropoietic progenitors or precursors; destruction of red blood cells) or the impaired production of EPO (Fisher *et al.*, 1983). We hope that this investigation will lead to a more effective use of therapeutic methods against the haematological disorders in uraemia, e.g. optimal dose scheduling of recombinant EPO to treat the reduced production of endogenous EPO (Eschbach *et al.*, 1987). Thus, the model also may contribute to the solution of actual problems in clinical research.

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