A COMPREHENSIVE MATHEMATICAL MODEL OF STEM CELL PROLIFERATION WHICH REPRODUCES MOST OF THE PUBLISHED EXPERIMENTAL RESULTS

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ABSTRACT

On the basis of experimental knowledge about haemopoietic stem cells a catalogue of fundamental statements is formulated. From this a simple mathematical model of haemopoietic regulation mechanisms is developed. The functional net effects of regulatory processes which are still unknown or unmeasurable are estimated using evolution arguments. The model is developed in three steps. It allows description of the self-replication of stem cells after direct destruction as well as their reaction to increased or reduced needs in the erythropoietic system. The most important experimental data about changes in CFUs, BFUe and CFUe after acute or chronic irradiation, anaemia, hypoxia, hypertransfusion or direct erythropoietic stimulation can be reproduced within the model. The model allows us to understand most of the results of experimental stem cell research. Furthermore, it can be applied for a more precise analysis of the existing data. Predictions about the results of certain experiments can be made.

Over the last 20 years different in vivo and in vitro methods have been developed which allow measurement of the morphologically unidentified haemopoietic precursors. For the pluripotential stem cells these are the colony-forming units CFUs (Till & McCulloch, 1961; McCulloch & Till, 1964, 1971). As erythroid precursors we find in vivo the erythropoietin responsive cells (ERC) (Gurney et al., 1962; Bruce & McCulloch, 1964) and in vitro erythropoietin sensitive cells (CFUe) (Stephenson et al., 1971; Iscove, Sieber & Winterhalter, 1974) and burst forming units (BFUe) (Axelrad et al., 1974; Iscove & Sieber, 1975) which can be influenced only slightly by erythropoietin. These BFUe can be further subdivided into different age compartments (BFUe_{a1}, BFUe_{a2}, etc.) (Gregory & Eaves, 1978; Adamson, Torok-Storb & Lin, 1978) and seem to lie between CFUs and CFUe (Iscove & Sieber, 1975; Gregory & Eaves, 1978).

The experiments investigating the reactions of the stem cell system to different forms of stress include acute and continuous irradiation, hypoxic and anaemic hypoxia, hyperoxia.
A mathematical model of stem cell proliferation

(1) There is a compartment S of pluripotent stem cells. These are self-replicating and replenish the early differentiated cells of erythropoiesis, granulopoiesis and thrombopoiesis. We restrict our attention to erythropoiesis. From these pluripotent stem cells S (whose normal value is set to S = 1) the part \( a \) S is in the active, proliferative cell cycle and the part \( g_a \) S is in a quiescent phase. We define \( a \) as the proliferation function with \( a = 1 - g_a \). Under normal conditions \( a \) is small (10-20%). It increases with increased proliferative requirements (maximum = 100%) and decreases to a minimum in the absence of stimulation. The proliferative stem cells may have the generation time \( \tau_S \).

(2) After each mitosis, the fraction \( p \) of the postmitotic cells remains in the stem cell compartment while the fraction \( 1 - p \) differentiates. We define \( p \) as the remaining function. Under steady state conditions \( p = 0.5 \). For \( p > 0.5 \), S increases, while S decreases for \( p < 0.5 \) since in this case more than 50% of the newly formed cells differentiate.

(3) The committed precursor cells of erythropoiesis are defined as \( E' \). We assume that the \( E' \)-compartment has a rigorous age structure and that all cells are in the proliferative cycle. Let the factors which stimulate erythropoiesis be called ESF. The \( E' \)-compartment is subdivided into an ESF-independent part B and an ESF-dependent part E (\( E' = B + E \)). The corresponding generation times, \( \tau_B \) and \( \tau_E \), are assumed to be constant. The number of mitoses in \( B, n_B \), is assumed to be constant, while the number of mitoses in E, \( n_E(ESF) \), may be ESF-dependent.

(4) The biological regulatory system must react to the direct destruction of stem cells, as well as to perturbations of erythropoiesis. Thus, one must assume that the essential regulatory terms of the model, namely the proliferation function \( a \) and the remaining function \( p \), depend on S, \( E' \) and ESF. However, general functions \( a = a(S, E', ESF) \) and \( p = p(S, E', ESF) \) have too many degrees of freedom to be derived unequivocally from the data. Therefore, the following simple structure allows direct and graphic biological derivation as well as later generalization.

(a) The proliferation function \( a \) depends only on the number of pluripotential stem cells: \( a = a(S) \).

(b) The remaining function \( p \) depends only on the pluripotent cells and on the erythropoietic precursors: \( p = p(S, E') \).

(c) ESF influences only the number of divisions in the ESF-dependent compartment E: \( n_E = n_E(ESF) \).

(5) Since few data are available to test whether any assumed function \( a(S) \) or \( p(S, E') \) is adequate we formulate an evolution hypothesis. Evolution has favoured those systems of blood formation in which, after acute perturbations of erythropoiesis, the normal state is reached as early as possible and with oscillations as small as possible. Mathematically speaking, this means that the time \( t_i \) when \( E' \) reaches its normal value \( E'^{norm} \) and the area enclosed between \( E' \) and \( E'^{norm} \) shall be a minimum.

Derivation of the model equations

Formulae and parameters. The above assumptions lead to three differential equations for the independent cellular compartments S, B and E:

\[
\dot{S}(t) = (2p - 1) aS(t)/\tau_S \tag{1}
\]

\[
\dot{B}(t) = \dot{B}^{in}(t) + \dot{B}^{in}(t - \tau_B) + \ldots + 2^{n-1} \dot{B}^{in}(t - n_B \tau_B) - \dot{B}^{out}(t) \tag{2}
\]
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\[
\dot{E}(t) = \dot{E}^a(t) + \dot{E}^b(t - \tau_E) + \ldots + 2^{s-1} \dot{E}^s(t - n_E \tau_E) - \dot{E}^{out}(t)
\]  

(3)

For the E' compartment we have

\[
\dot{E}'(t) = \dot{B}(t) + \dot{E}(t), E'(t) = B(t) + E(t), n_{E'} = n_E + n_E
\]  

(4)

The input and output rates are:

\[
\dot{S}^{out}(t) = 2(1 - p) aS(t)/\tau_s
\]  

(5)

\[
\dot{B}^{in}(t) = a_E \dot{S}^{out}(t), \dot{B}^{out}(t) = 2^n \dot{B}^{in}(t - n_E \tau_E)
\]  

(6)

\[
\dot{E}^{in}(t) = \dot{B}^{out}(t), \dot{E}^{out}(t) = 2^n \dot{E}^{in}(t - n_E \tau_E)
\]  

(7)

The following specific model assumptions will be referred to later in greater detail:

Proliferation function \(a = a(S) = 1/(A + B \exp(CS)) + D\)  

(8)

where A, B, C, D are determined from \(a(0), a(0.5), a(1)\) and \(a(S > 1); g_0 = 1 - a\).

Remaining function \(p = p(S, E')\) with \(p(1, E'_{norm}) = 0.5\)  

(9)

\(p\) increasing strictly with decreasing \(S\) and decreasing strictly with decreasing \(E'\).

ESF-dependence only in the number of mitoses in E: \(n_E = n_E\) (ESF).  

(10)

Evolution hypothesis: \(\tau_1 \approx \min \int_0^\infty |E'(t) - E'_{norm}| \, dt \approx \min \)  

(11)

From the literature, the cellular parameters (generation times, number of mitoses, fraction of erythroid differentiation) are chosen as

\[
\tau_s = \tau_b = \tau_E = 8 \text{ hr}, n_b = 5, n_E (\text{ESF} = \text{normal}) = 5, \alpha_E = 0.1
\]  

(12)

In equilibrium (\(S = B = E = E' = 0\)) we have the normal values

\[
S_{norm} = 1, B_{norm} = 0.31, E_{norm} = 9.92, E'_{norm} = 10.23
\]  

(13)

Derivation. Equation (1) describes the time variation of the number of pluripotent stem cells. Per unit time the fraction \(dS/\tau_s\) of proliferating stem cells \(dS\) divides if \(\tau_s\) is the generation time and a random process is assumed (Wichmann, 1979). After mitosis the fraction \(p.2aS/\tau_s\) remains in the stem cell pool. The difference in these rates gives the temporal change \(S\) (Eqn 1). The rest \((1 - p)2aS/\tau_s\) differentiate (Eqn 5). The proportion \(\alpha_E\) of these cells goes into the erythroid line.

The cells which enter compartment E' per unit time, \(\dot{B}^{in}\), double after each generation time \(\tau_b\) until \(n_b\) mitoses have taken place. Thus, after the transit time \(n_b \tau_E\) for each cell having entered B, \(2^n\) daughter cells leave the compartment. This is formulated in equations (2) and (6). The same arguments hold true for compartment E and equations (3) and (7), while equation (4) covers B and E.

Equations (8) and (9) embody the critical simplifications about the regulatory mechanisms. They cannot be derived straightforward since they are not measurable, but some boundary conditions can be formulated. We assume that the proliferation function \(a(S)\) approaches 1 asymptotically for small values of S (Becker et al., 1965; Lajtha et al., 1969; Renericca et al., 1970; Gidali, & Lajtha, 1972; Necas, Ponka & Neuwirt, 1976) that the normal value \(a(1)\)
is 0.1 to 0.2 (Becker et al., 1965; Lajtha, 1971; Vassort et al., 1973) and that \( a(S) \) approaches a minimum (which can be zero) asymptotically if \( S \) becomes greater than 1. A simple mathematical function with these properties is given in equation (8) and drawn in Fig. 2.

![Graph showing proliferation fraction \( a(S) \) vs. \( S \)](image)

**Fig. 2.** The proliferative fraction \( a \) of cells in compartment \( S \) is assumed to depend only on \( S \): \( a = a(S) \). The function \( a(S) \) has a logistic form (Eqn 8). Its parameters are determined from \( a(S = 0) \), \( a(S = 0.5) \), \( a(S = 1) \) and \( a(S \gg 1) \). The shaded area can be excluded by the evolution hypothesis. The middle curve is used for the simulation of experimental data.

The boundary conditions for the remaining function \( p(S, E) \) are formulated in equation (9) and will be specified later as well as the ESF-dependence \( n_0(ESF) \) in equation (10). Equation (11) is the mathematical formulation of the evolution hypothesis.

The generation times for pluripotent and committed cells have been estimated by several authors. They give values between 6 hr and 11 hr (Blackett, 1968; Hanna, Tarbutt & Lamerton, 1969; Lajtha, 1971; Vassort et al., 1973; Hodgson et al., 1975; Wu Chu Tse & Lajtha, 1975). We chose \( \tau_0 \), \( \tau_p \), \( \tau_E \) and \( \tau_{rE} \) all equal to 8 hr (Eqn 12). Lajtha (1971) and Wu Chu Tse & Lajtha (1975) estimate the number of mitosis of erythroid precursors, \( n_E \), to be 10 (with great variability). From data of Iscove (1977) and Gregory & Eaves (1978) we computed \( n_E \) normally to be 4 or 5. We chose \( n_E = 5 \) and then found \( n_0 = n_E - n_E = 5 \) (Eq. 12). The value for \( \sigma_E \) is taken from Iscove & Sieber (1975) to be 10%.

These values are not critical for the model since no detailed quantitative reproduction of measured data is intended. The normal value for \( S \) is arbitrarily set to 1. Then the normal values for \( B, E \) and \( E' \) follow from \( \dot{S} = \dot{B} = \dot{E} = \dot{E}' = 0 \) (Eqn 13; see Wichmann, 1979). The differential equations (1), (2) and (3) are solved numerically.
Biological meaning of the model compartments. The compartment S corresponds mainly to the CFUs pool in the bone marrow. Compartment B includes the early BFUe cells (like BFUE\textsubscript{eh}) as they show a clearly smaller ESF-dependence than CFUe. In E all ESF-dependent non-identified erythroid precursor cells are included. Thus, E corresponds mainly to CFUe and ERC. As ESF we consider erythropoietin only.

RESULTS

In order to achieve an explicit form for \( a(S) \) and \( p(S, E') \) and to calculate their consequences a stepwise approach is chosen.

Model step 1 (autonomous proliferation in S)

In the first step two additional restrictions are made:

(A) ESF-dependent feed-back influences are negligible compared with the massive self-replication of the stem cell system:

\[ n_e = \text{constant}. \]  \hspace{1cm} (14)

Discrimination between ESF-independent and ESF-dependent erythroid precursors B and E is then meaningless and we consider only the compartments S and E'.

(B) The self-replication of S is more important than supply of E'. Thus, it is assumed that \( p \) depends only on S:

\[ p = p(S). \]  \hspace{1cm} (15)

A biological situation for which (A) and (B) seem adequate is severe acute or chronic irradiation which largely depletes the pluripotent stem cell pool. To find the optimum functions using the evolution hypothesis for acute perturbation recovery, \( a(S) \) and \( p(S) \) are varied within the boundary conditions (8) and (9). For \( p(S) \) an arbitrary polygonal curve fulfilling \( p(1) = 0.5 \) and decreasing strictly with S is assumed. In the first step \( p(S) \) is optimized by the evolution criterion while \( a(S) \) is fixed. Then, in the second step, \( a(S) \) is optimized for fixed \( p \) curves from the appropriate area found in the first step. The results are shown in Figs 2 and 3.

The optimum area for \( p(S) \) hardly exceeds \( p = 0.6 \). This value has already been found by Vogel, Niewisch & Matioli (1968) from different considerations. The steeper increase in \( p \) for values of S below 0.1 (Fig. 3) which follows from the evolution hypothesis has also been found qualitatively by Chervenick & Boggs (1971). The normal value \( a(1) \) plays a less important role for the recovery of S than for the recovery of E'.

It does not seem to be justified to derive smaller areas for \( a(S) \) and \( p(S) \) from the evolution hypothesis than those in Figs 2 and 3 since this is only a qualitative principle. Thus, if we want to compare our results with experiments we have to change our strategy. We no longer ask 'What can be derived from simple assumptions', but rather 'Do there exist functions \( a(S) \) and \( p(S) \) lying within these "optimum" areas which allow us to reproduce simultaneously most of the experimental data?' We find the middle curves in Figs 2 and 3 fulfill this criterion. Thus, they will be used in all of the following calculations.
A mathematical model of stem cell proliferation

Recovery after acute irradiation

Figure 4 shows the recovery of S and E', compared with experimental results for CFUs and ERC after acute irradiation. The model curves show similar characteristics, but the agreement for S in the first few days and for the final E' normalization is not good enough. This is due to lack of E' feed-back. Regulated by such feed-back, the E' compartment could receive a larger fraction of differentiating cells from S at the beginning. This would keep S low. During the E'-overshoot more dividing cells could remain in S. Thus, in this phase E' would decrease earlier and S would increase faster. This will be investigated in model step 2.

Continuous irradiation

For recovery after continuous irradiation, good agreement for S and CFUs data is found (Fig. 4). Figure 5 shows the simulation of continuous irradiation. It is assumed that the cells in S and E' are destroyed proportionally to their number. Thus, the differential equations (1) and (4) are modified with the terms -kS and -kE', respectively, where k is the kill rate and has been estimated from the dose–response curve, Lajtha, Gilbert & Guzman, 1971; Wu Chu Tse & Lajtha, 1975) to be $k = 0.016$/hr for a dose rate of 0.45 Gy (45 rad)/day. The CFUs
results in Fig. 5 are reproduced well by the S-curve. The E'-curve is not drawn since simplification (A) cannot meet the experimental situation in E'.

Model step 2 (erythroid feed-back on the differentiation rate in S)

We now omit simplification (B) from step 1 and consider $p$ depending on $S$ and $E'$: $p = p(S, E')$. Once again we choose a simple form for $p$ assuming that the $p(S)$-dependence already found is completed by a linear $p(E')$-dependence:

$$p = p(S, E') = p(S) - p(E') = p(S) - f \times (1 - E'/E'_\text{norm})$$

(16)

with $p(S)$ from Fig. 5. $f$ will be called erythroid feed-back intensity (for $f = 0$ one has model step 1).

Equation (16) can be suggested biologically, assuming that for decreased $E'$ ($E'/E'_\text{norm} < 1$) and normal $S(S = 1)$ more cells will differentiate from $S$ into $E'$ ($p < 0.5$). From the evolution criterion $f$ can be restricted to values between 0 and 0.15. Good agreement with experimental data is found for $f = 0.09$. For this $f$ Fig. 6 shows several model curves.
A mathematical model of stem cell proliferation

Fig. 5. Continuous irradiation. Model curve for S and corresponding experimental data for CFUs in rats [Blackett, 1967, 0.45 Gy/45 rad/day].

For all positive values of \( f \) the following characteristics appear.

(a) The S-curve has a plateau, or even a temporary slight decrease, before recovery starts. This means that for equal destruction of S and E' erythropoiesis has priority for recovery. Comparison with Fig. 4 shows that the S-curve for \( f = 0.09 \) reproduces the CFUs data much better than the curve for \( f = 0 \). Thus, it can be understood why many CFUs curves show plateaus or dips (Blackett & Roylance, 1964; Lamerton, 1968; Okunewick et al., 1972; Sauer, 1977).

(b) With increasing feedback intensity \( f \) the E'-curve shows two peaks. The first corresponds to an early E'-increase at the expense of S, the second is parallel to the recovery of S. It seems noteworthy that for a wide range of simple monotonic functions \( p(S, E') \) these two peaks occur. Thus, they seem to be an essential effect which comes from the erythropoietic feed-back on the remaining function \( p(S, E') \).

(c) The demands of the evolution hypothesis are better fulfilled if an E' feed-back is assumed (\( f > 0 \)).

Figure 6 also shows the strong influence of the starting points in the case of feed-back (\( f = 0.09 \)). For larger initial values the first E'-peak is higher than the second one, for small initial values it is vice versa. Beyond a critical value (which is 5% for S and E' here) the system dies out. This strong influence of the initial values (possibly combined with inter- and intra-individual differences in feed-back intensity) has been found in experiment as shown in Fig. 7 for the iron-incorporating erythropoietic compartments. Thus, the large experimental variations can possibly be understood on this basis.

It is an interesting question whether the stem cell system can collapse by regulation. In model step 1 (missing E'-influence on \( p \)) this is impossible since for small values of S we find
Fig. 6. Consequences of the feed-back from E' on p, the fraction of postmitotic stem cells remaining in S \( p = p(S, E') \), model step 2. The recovering E' curves (above) have two peaks, their form depends mainly on the initial values. The S curves (below) show a small initial decrease or a long plateau. For very small initial values and a sufficient erythroid feed-back intensity the system dies out. Model curves: erythroid feed-back intensity \( f = 0.09 \), initial values 0.3(---), 0.2(-----), 0.1(· · ·) and 0.05(----, system dies out).

\[ p(S) > 0.5, \text{i.e., S recovers. However, using a sufficient erythroid feed-back intensity in model step 2 it is possible that for small starting values of S and E' } p(S, E') \text{ stays less than 0.5. Then S decreases and finally dies out. Experimental evidence of such a 'regulatory death' seems to exist (Reincke et al., 1979).} \]

Model step 3 (ESF-stimulation)

Simplification (A) from step 1 is omitted to consider the influence of ESF on the erythroid precursor cells. E' is divided into early part B which is not ESF-sensitive and an ESF-dependent part E as shown in Fig. 1. We assume that the number of divisions in E increases with ESF stimulation and decreases in its absence. Since only the qualitative effect of the influence of ESF is to be investigated we assume a roughly estimated number of mitoses (e.g., Iscove, 1977)

\[ n_g(ESF) = \begin{cases} +1 \text{ or } +2 \text{ for a moderate or strong ESF stimulus} \\ +0 \text{ for a normal ESF stimulus} \\ -1 \text{ or } -2 \text{ for a decreased or absent ESF stimulus} \end{cases} \] (17)
The functions \( a \) and \( p \) do not depend on ESF. Thus, all ESF-mediated regulatory effects only influence \( S \) and \( B \) indirectly. Since \( E \) is much larger than \( B \) (normal ratio \( E:B = 32:1 \)) we can use \( p(S, E) \) instead of \( p(S, E') \) in equation (16):

\[
p(S, E) = p(S) - f(1 - E/E_{\text{norm}}) \approx p(S, E').
\]

Some special cases will now be investigated qualitatively.

**Increased ESF stimulus (bleeding, hypoxia, ESF injection)**

In the model an increased ESF stimulus is simulated by 1 or 2 additional mitoses in \( E \). Since \( S \) is normal, the remaining function \( p(S, E) \) becomes greater than 0.5 (Eqn 18). Therefore, \( S \) is positive and \( B \) is negative (Eqns 1, 2, 5, 6), i.e., \( S \) increases and \( B \) decreases. The decrease in \( B \) is followed by a decrease of \( E \) some days later. On the other hand, the increasing \( S \) and the decreasing (but already enlarged) \( E \) lowers \( p \) until with \( p(S, E) = 0.5 \) a new steady state is reached. We then find an enlarged \( S \) and \( E \) and a decreased \( B \) as long as the ESF stimulus persists.
For bleeding this is shown in Fig. 8 (top). By experiment, most authors found similar behaviour (Fig. 8, bottom). The only contradictory data are reported by Rencicca et al. (1970) for CFUs in CF1-mice (Table 1).

![Graphs showing relative compartment size versus time](image)

**Fig. 8.** Acute severe anaemia in model (top) and experiment (bottom). Data from Adamson et al. (1978) (mice, CFUs, BFUe, CFUe, △); Iscove (1977) (mice, BFUe, CFUe, ○); Hara et al. (1977) (mice, BFUe, CFUe, ●).

For hypoxia and ESF injection the model also predicts increased S and E values and decreased B values. Here the experimental data of nine authors support these findings while the CFUs measurements in CF1-mice from Kumanek et al. (1968a) contradict them (Table 1).

**Decreased or absent ESF stimulus (hypertransfusion, hyperoxia post-hypoxia)**

In the model, these situations are simulated by the omission of 1 or 2 mitoses in E. We find the mirror-image of the ESF-stimulation: Now S decreases, B increases and E decreases.

For hypertransfusion this is drawn in Fig. 9 (top). The experimental data show the same characteristics (Fig. 9, bottom). Corresponding curves follow for hyperoxia and post-hypoxia. Here, only data for CFUs are available which correspond to the model results in three and contradict them in one case (Table 1).

**DISCUSSION**

**Model structure**

The feed-back mechanisms within the stem cell area and between blood cells and stem cells determine the behaviour of the blood forming system. Since they cannot be measured directly,
ERRATUM:

page 555, Table 1

Quantitatively or qualitatively reproduced data:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>Kubanek et al. (1968a): CFUs, CAF₁-mice</td>
</tr>
<tr>
<td>Posthypoxia</td>
<td>Peschle et al. (1977): BFUs, CFUs, mice</td>
</tr>
<tr>
<td></td>
<td>Lord &amp; Schofield, personal communication (1979): CFUs, mice</td>
</tr>
<tr>
<td></td>
<td>Murphy &amp; Lord, personal communication (1980): CFUs, mice</td>
</tr>
</tbody>
</table>

Contradictory data

Phenylhydrazine

('Bleeding')  | Rencricca et al. (1970): CFUs, CF₁-mice |
|              | Wright & Lord (1977): CFUs, BDF₁-mice |
|              | Hodgson et al. (1968): CFUs, B10D2-mice |

Hypertransfusion | Monette et al. (in press): CFUs, CD1-mice |
|                 | Shadduck et al. (1972): CFUs, CF₁s-mice |
|                 | Schooley & Lin (1972): CFUs, C3H-mice |

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**Table 1.** List of experimental data compared with the model results

<table>
<thead>
<tr>
<th>Situation</th>
<th>Quantitatively or qualitatively reproduced data: authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute irradiation</td>
<td>Porteous &amp; Lajtha (1965): CFUs, ERC, mice; Hennessy &amp; Kretchmar (cells showing Fe-uptake), Blackett &amp; Roylance, Harris; all taken from Okunewick (1967); Baum (1967): ERC, rats; Brescher <em>et al.</em> (1967), Guzman &amp; Lajtha (1970), Lajtha <em>et al.</em> (1971), Hendry &amp; Lajtha (1972), Vos (1972), Kondratenko (1975): CFUs, mice; Okunewick <em>et al.</em> (1972): CFUs, ERC, rats</td>
</tr>
<tr>
<td>Continuous irradiation</td>
<td>Blackett (1967): repopulating ability, rats; Kalina <em>et al.</em> (1975): CFUs, mice</td>
</tr>
<tr>
<td>Post-irradiation</td>
<td>Blackett (1967): repopulating ability, rats; Wu Chu Tse &amp; Lajtha (1975): CFUs, rats</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Iscove (1977), Hara &amp; Owaga (1977): BFUs, CFUs, mice; Adamson <em>et al.</em> (1978): CFUs, BFUs, CFUs, mice</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Bruce &amp; McCulloch (1964), Lord &amp; Murphy (1973): CFUs, mice; Kubanek <em>et al.</em> (1968a): CFUs, CF₁, mice; Okunewick, Hartley &amp; Darden (1969): CFUs, ERC, mice; Peschle <em>et al.</em> (1977): BFUs, CFUs, mice</td>
</tr>
<tr>
<td>ESF injection</td>
<td>Kubanek <em>et al.</em> (1968b): CFUs, mice; Gregory <em>et al.</em> (1974): CFUs, CFUs, mice; Hara &amp; Owaga (1977), Peschle (1978): BFUs, CFUs, mice</td>
</tr>
<tr>
<td>Hypertransfusion</td>
<td>Gregory, McCulloch &amp; Till (1973): CFUs, CFUs, mice; Iscove (1977), Hara &amp; Owaga (1977), Iscove &amp; Gilbert (1978): BFUs, CFUs, mice; Adamson <em>et al.</em> (1978): CFUs, BFUs, CFUs, mice</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>Fishman <em>et al.</em> (1973): CFUs, mice</td>
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<tr>
<td>Posthypoxia</td>
<td>Peschle <em>et al.</em> (1977), Lord &amp; Schofield (personal communication): CFUs, mice</td>
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</table>

Assumptions about their structure can only be tested indirectly by analysing reactions to different stimuli.

To have clear and interpretable conditions we have tried to manage with a minimum number of assumptions. One needs at least two independent feedback terms in the stem cell area (in our model $a$ and $p$) to describe the different experimental situations. If only the proliferative fraction of the pluripotent stem cells was variable and the probability of differentiation held constant (equal to 0.5) then the stem cells could never recover after an injury although high proliferation could maintain erythropoiesis by an increased output of differentiated cells. Such observations have never been reported. On the other hand, a constant proliferative fraction of CFUs would contradict, e.g., the $[^3]H$thymidine and hydroxyurea suicide data (Becker *et al.*, 1965; Lajtha *et al.*, 1969; Rencricca *et al.*, 1970; Vassort *et al.*, 1973; Necas & Neuwirth, 1976).

Furthermore, at least the probability of differentiation must depend on both pluripotent and committed cells (in our model this is considered in $p = p(S, E) \approx p(S, E')$). Otherwise
Fig. 9. Severe hypertransfusion in model (top) and experiment (bottom). Data from Gregory et al. (1973) (mice, CFUs, CFUs, O; Hara et al. (1977) (mice, BFUe, CFUe, ); Iscove (1977) (mice, BFUe, CFUe, ).

Simultaneous and co-ordinated recovery of both compartments would not be possible. In addition, during all kinds of indirect stress (as discussed in model step 3) the stem cells would remain totally unaffected. This contradicts the experimental data.

Finally, the assumption that only the number of mitoses in the last part of the erythroid precursors compartment depends on ESF is a minimum assumption too.

These minimum assumptions and the model equations derived from them by biological arguments, allow one to reproduce most of the experimental results, at least qualitatively. However, this does not prove the assumptions. It only shows that they are sufficient at the present accuracy of measurement.

Biological interpretation of the model structure

The model terms do not yield definite interpretations on the cellular level. Thus, nothing is assumed about the micro-environment in which the simulated processes take place. For example, the regulation of stem cell proliferation by simultaneous action of stimulators and inhibitors (Wright & Lord, 1978) does not conflict with our model assumption of only one proliferation function. We describe only the net effect of the underlying biological mechanisms. Similarly, the remaining function p leaves open how the mitoses of stem cells occur. The question of symmetrical or asymmetrical stem cell division is not affected (Lajtha, Oliver & Gurney, 1962).
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In addition, it is possible to separate the compartments B and E into subcompartments \( B = B_1 + B_2 + \ldots, \) \( E = E_1 + E_2 + \ldots, \) since they have an age-dependent structure. The same is possible for S by adding age-dependent compartments \( S = S_1 + S_2 + \ldots. \)

These examples show already that very different cellular phenomena can possibly be described with nearly the same mathematics. So, for example, in the controversy about unlimited v. limited reproductive capacity of stem cells (Hayflick, 1965; Reineke et al., 1975) nearly the same mathematical model can be used.

Interpretation of the results

The model presented here has been tested against experimental stem cell data for various stresses. Some typical experimental results can be interpreted by means of the model.

(a) The steep increase and overshoot in ERC and CFUs after acute irradiation may follow mainly from the activation of the dormant CFUs (in the model, the proliferation function \( \alpha(S) \) increases from 10–20% to nearly 100%).

(b) The post-irradiation plateau or temporary decrease in CFUs can be understood assuming a higher priority for erythroid replenishment than for CFUs recovery at low CFUs values [in the model, the remaining function \( \rho(S, E) \) is less than 0.5 for small \( E \)]. An additional consequence of this mechanism is the possibility of a ‘regulatory death’ for sufficiently severe acute irradiation. Here, the stem cell system may die out slowly (although the stem cells proliferate maximally) because the erythroid cells do not reach nearly normal values early enough.

(c) The same argument, namely the competition of the CFUs and the CFUe compartments for the newly formed cells, may explain the two peaks found in CFUe and \(^{59}\)Fe data. First CFUe are fed. After the saturation of this compartment CFUs follow. The intermittent CFUe dip results from a time delay between the action of CFUe, on the differentiation probability and its manifestation in CFUe cell numbers. In the model all the remaining functions \( \rho(S, E) \) used, even in the simplest linear form, lead to \( E \)-curves with two peaks. Thus, the often-used speculative interpretation of the first peak as an ‘abortive rise’ can be abandoned. Here it was assumed that radiation injures some stem cells which go through a few divisions before they and their progeny die (Bond, Fiedler & Archambeau, 1965; Okunewick & Kretchmar, 1967).

(d) From the erythroid feedback on the differentiation probability of stem cells further consequences follow. This may explain the large variability of recovery curves after irradiation. Our calculations show that there is an extreme sensitivity to the amount of destruction (in the model, the initial values) and to the degree of feedback (in the model, the erythroid feedback intensity \( f \)). Perhaps this makes the embarrassing variety of results understandable.

(e) For all indirect stimulation mediated by ESF, first the far-reaching autonomy of erythropoiesis is remarkable. Even with strong stimulation CFUs and BFUe (as well as \( S \) and \( B \) in the model) are only slightly affected. In the model this follows from the reproductive power of 2 divisions in \( E \). This can change the erythropoietic proliferation by a factor between 4 and 0.25.

(f) Although the experimental data are not unequivocal, to a certain degree they show parallel reaction of CFUs and CFUe and an opposite reaction of BFUe. In the model \( S, B \) and \( E \) show the same behaviour. With ESF stimulation \( S \) and \( E \) increase and \( B \) decreases. The opposite behaviour is found with an absent ESF stimulus.
Further applications and predictions

In the above model calculations we have used certain functions \( a \) and \( p \) and then determined the time courses of the cell numbers S, B and E. This procedure can be inverted. Thus, it seems possible to learn something about the unknown functions \( a(S) \), \( p(S, E) \) and the feed-back intensity \( f \) from experimental curves for CFUs, BFUe and CFUe. This method will be described in detail in a later paper.

An extension of the model to diseases and abnormalities of the stem cell system is intended. Furthermore, the stem cell model will be added to existing models of erythropoiesis (Wichmann et al., 1976) and thrombopoiesis (Wichmann, Gerdhardt & Spechtmeyer, 1979).

Areas in which the model allows predictions which can be verified (or not) are: simultaneous measurements of CFUs, BFUe and CFUe which have not yet been performed (gaps in Table 1); combination of experiments from Table 1; further experiments like fractionated manipulations or destruction of specific cell stages; comparison of our proliferation function with curves for stem cell stimulators and inhibitors; identification of cell stages responsible for feed-back; indirect estimation of the pattern of destruction by \(^{59}\text{Fe}\)-electrons.

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REFERENCES


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