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PERIODIC AUTO-IMMUNE HEMOLYTIC ANEMIA: AN INDUCED DYNAMICAL DISEASE

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Experimentally induced auto-immune hemolytic anemia (AIHA) in rabbits is characterized either by constant depressed erythrocyte numbers, or by oscillatory erythrocyte numbers about a depressed level (periodic auto-immune hemolytic anemia).

Here the experimentally observed characteristics of AIHA are satisfactorily accounted for by a simple model for erythropoiesis, assuming only the peripheral erythrocyte destruction rate is elevated with all other parameters normal. The onset of periodic AIHA is identified with the occurrence of a Hopf bifurcation in the model dynamics for certain values of the erythrocyte destruction rate.

Pathology in physiological system function is often marked by the onset of periodic behaviour in normally constant system variables, or by the alteration of a normally periodic variable. The term dynamical disease has been applied to those pathologies characterized by the operation of a basically intact control system in a region of physiological parameters that produces pathological behaviour (Cronin, 1977; Gurel, 1975; Mackey and Glass, 1977; May, 1978; Morley, 1970). Based on this criteria, several haematological disorders have been tentatively classified as periodic dynamical diseases (Glass and Mackey, 1978; Mackey, 1978a, b).

In an intriguing series of experiments (Orr *et al.*, 1968) it has been shown that the induction of auto-immune hemolytic anemia (AIHA) in rabbits is sometimes marked by a steady depression of hemoglobin levels, and at other times by sustained oscillations in hemoglobin concentration and reticulocyte numbers with a period of 16 to 17 days. The primary defect in this induced AIHA is presumably an increase in the erythrocyte destruction rate. Here I consider a simple model for the regulation of circulating erythrocyte numbers. This study examines the role of the

peripheral erythrocyte destruction rate in determining erythrocyte dynamics in AIHA, and offers circumstantial evidence that periodic AIHA is an induced dynamical disease.

It is generally accepted that in mammals there exists a pluripotential stem cell (PPSC) population capable of providing differentiated cells for the erythroid series. Once a cell from the PPSC is committed to the erythroid series, it undergoes a series of nuclear divisions and enters a maturational phase for a period of time before release into the blood as a mature erythrocyte. A fall in erythrocyte numbers leads to a decrease in hemoglobin levels and thus in arterial oxygen tension. This decrease in arterial oxygen tension triggers the production of a substance, renal erythropoietin (REP). Increased levels of REP, in turn, increase the cellular production rate within the early committed erythroid series cells and, ultimately, circulating erythrocyte numbers (Wintrobe, 1976).

To understand this process, I use the following paradigm. The peripheral erythrocyte destruction rate is γ (day^{-1}) while β (cells/kg/day) is the cellular production rate in the early erythroid series cells. The total average time between the entrance of a cell into the erythroid series and the release of a mature erythrocyte into the blood is τ (days). The circulating density of erythrocytes is E (cells/kg), so their dynamics are described by

$$\frac{dE}{dt} = -\gamma E + \beta(E_\tau), \tag{1}$$

where $E_\tau = E(t-\tau)$. The erythrocyte production rate is a function of the circulating erythrocyte numbers at a time τ previously because of the finite time needed for cell maturation. Similar models for blood cell production have been considered previously (Mackey and Glass, 1977; Glass and Mackey, 1978; Mackey, 1978a, b; Wazewska-Czyzewska and Lasota, 1976).

The *in vivo* erythrocyte production rate in rats has the form of a Hill function, showing saturation at low hemoglobin levels (Hodgson and Eskuche, 1966). Thus I take

$$\beta(E) = \frac{\beta_0 \theta^n}{\theta^n + E^n}, \tag{2}$$

where β_0 (cells/kg/day) (the maximum production rate), θ (cells/kg), and n are parameters to be determined. Combining (1) and (2) gives

$$\frac{dE}{dt} = -\gamma E + \frac{\beta_0 \theta^n}{\theta^n + E_\tau^n}. \tag{3}$$

The single steady state E^* of the model is defined by $(dE/dt)=0$ or implicitly by

$$\gamma E^* = \beta_0[1+(E^*/\theta)^n]^{-1}. \tag{4}$$

Increases in n or γ, or decreases in β_0 or θ, lead to a decrease in the steady state erythrocyte numbers E^*.

The estimation of these parameters is straightforward. The $t_{\frac{1}{2}}$ for the exponential disappearance of ^{51}Cr labeled erythrocytes is 30 days (Wintrobe, 1976) so normally $\gamma = 2.31 \times 10^{-2}$ (day^{-1}). In man the normal number of circulating erythrocytes is $E^*_{\text{norm}} = 3.3 \times 10^{11}$ (cells/kg) (Wintrobe, 1976). Thus the erythrocyte flux to death is $\gamma E^*_{\text{norm}} = 7.62 \times 10^9$ (cells/kg/day) and this must equal the normal steady state production rate: $\gamma E^*_{\text{norm}} = \beta_{\text{ss}}$. It is estimated (Giblett *et al.*, 1956) that the maximum erythrocyte production rate is at most ten times the steady state rate so $\beta_0 = 7.62 \times 10^{10}$ (cells/kg/day). The average elapsed time between the entry of a cell into the committed erythroid series and release into the circulation is $\tau = 5.7$ days (Dormer, 1973). In rabbits (Orr *et al.*, 1968) a decrease in hemoglobin levels to 0.75 normal leads to a five-fold increase in erythropoiesis. This implies that $n = 7.6$, consistent with the hemolytic anemia response in rats produced by phenylhydrazine, (Hodgson and Eskuche, 1966). Finally, $\theta = E^*_{\text{norm}}/\sqrt[n]{9} = 2.47 \times 10^{11}$ (cells/kg).

Techniques do not presently exist for characterizing analytically the full behaviour of the solutions $E(t)$ of (3). However, we may examine the behaviour of the solutions near the steady state E^*. Set $z(t) = E(t) - E^*$, and take the linear portion of (3) near E^* to obtain

$$\frac{dZ}{dt} = -\gamma z + \beta' z_\tau, \tag{5}$$

where $\beta' = (\partial\beta/\partial E_\tau)_{E^*}$. Hayes (1950) has established necessary and sufficient criteria for the eigenvalues $\lambda = \mu \pm i\omega$ of (5) to have real parts less than zero, $\mu < 0$. For (5), Hayes' criteria reduce to

$$-\gamma\tau < 1 \quad \text{and} \quad -\gamma\tau < -\beta'\tau < \sqrt{\gamma^2\tau^2 + \omega^2\tau^2}, \tag{6a}$$

where $\omega\tau \in [0, \pi]$ is the solution of

$$\omega\tau = -\gamma\tau \tan(\omega\tau). \tag{6b}$$

These criteria thus define the necessary and sufficient conditions on the

parameters γ, β_0, θ, n, and τ for the steady state erythrocyte density E^* to be stable.

Under the assumption that the parameters β_0, n, τ, and θ for the erythrocyte control system remain at the normal values determined above, (6a, b) predicts that the steady state E^* of (3) will be stable for all erythrocyte hemolysis rates $\gamma \lesssim 5.12 \times 10^{-2}$ (day^{-1}) and $\gamma \gtrsim 2.70 \times 10^{-1}$ (day^{-1}). Thus the normal steady state (E^*_{norm}), with $\gamma = 2.31 \times 10^{-2}$ (day^{-1}), is locally stable.

When the eigenvalues of (5) become pure imaginary ($\mu = \text{Re}\,\lambda = 0, \lambda = \pm i\omega$),

$$\omega\tau = \cos^{-1}(\gamma/\beta'),$$

where $\omega^2 = (\beta')^2 - \gamma^2$ (Mackey, 1978a). Exactly at this point a Hopf bifurcation occurs in (5) and solutions of Hopf period $T = 2\pi/\omega$ arise (Chow and Mallet–Paret, 1978). With the normal values of β_0, n, τ, and θ it is calculated that a Hopf bifurcation will occur at $\gamma \simeq 5.12 \times 10^{-2}$ and $\gamma \simeq 2.70 \times 10^{-1}$ (day^{-1}). The approximate predicted Hopf periods for the solutions occurring at these two bifurcation points are 20.6 and 16.6 days respectively.

Thus the *linear analysis* of (3) predicts that elevations in γ from its normal value will result in a stable but ever decreasing steady state erythrocyte density E^* until $\gamma \simeq 5.12 \times 10^{-2}$ day^{-1}. At this value of γ, E^* will become unstable and a periodic hemolytic anemia should occur with period approximately 21 days. Once $\gamma \gtrsim 2.70 \times 10^{-1}$ (day^{-1}), E^* will be stable once again, and further increases in the hemolysis rate will only serve to make the anemia more severe. This linear analysis offers no insight into the behaviour of the solutions of (3) for hemolysis rates in the range $5.12 \times 10^{-2} \lesssim \gamma \lesssim 2.70 \times 10^{-1}$ (day^{-1}).

To examine the complete nature of the predicted erythrocyte dynamics in the face of elevated values of the erythrocyte destruction rate, I numerically integrated (3) using an integration step size of 0.01 days, an initial condition $E(0) = E^*_{\text{norm}} = E(t-\tau)$ for $t \in [-\tau, 0]$, and the normal estimated values of β_0, n, τ, and θ. The results are shown in Figure 1. As predicted from the linear analysis, increasing the erythrocyte destruction rate up to about 0.05 (d^{-1}) results in a steady depression in the predicted number of circulating erythrocytes. However, for erythrocyte destruction rates between about 0.05 and 0.27 (d^{-1}), the erythrocyte numbers oscillate about a depressed level. The period of the oscillation decreases from about 17.9 to 16.8 days as γ is increased through the oscillatory zone. Finally, for destruction rates greater than 0.27 (d^{-1}) a depressed constant steady state level of circulating erythrocytes is again reached. Note that although the linear bifurcation analysis of (3) closely predicts values of γ for the onset

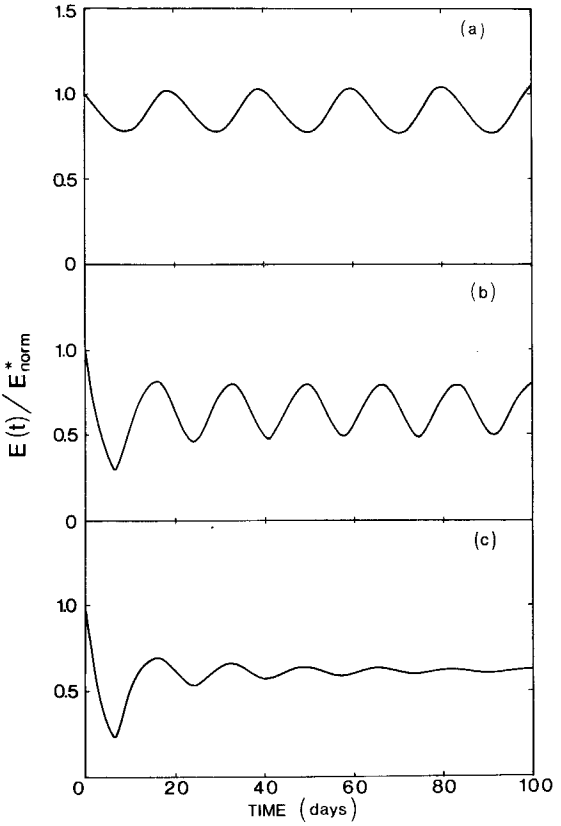

Figure 1. Predicted numbers of circulating erythrocytes, relative to $E^*_{\text{norm}} = 3.3 \times 10^{11}$ (cells/kg), as a function of time as obtained by numerically integrating (3). All parameters were assumed normal, with the exception of γ. (a) $\gamma = 6.0 \times 10^{-2}$ (day^{-1}); (b) $\gamma = 2.4 \times 10^{-1}$ (day^{-1}); (c) $\gamma = 3.0 \times 10^{-1}$ (day^{-1})

and cessation of numerically computed periodic solutions to (3), the predicted Hopf period ($T \simeq 21$ days) at $\gamma \simeq 5.12 \times 10^{-2}$ does not closely correspond to the period of the computed solution ($\simeq 18$ days). However, the range of periods (16.8 to 17.9 days) of the *numerically computed* solutions to (3) is in close agreement with the observed erythrocyte periods in periodic AIHA (16 to 17 days).

Thus, from both the linear analysis and numerical integration of (3), it seems likely that the induction of AIHA by Orr *et al.* (1968) resulted in periodic or simple AIHA depending only on the erythrocyte destruction rate γ achieved by the administration of red blood cell antibody. Viewed in this context, periodic auto-immune hemolytic anemia is perhaps the clearest example of a dynamical disease whose origin can be specified with certainty.

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