Periodic haematological diseases: mystical entities or dynamical disorders?

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> ... regularity is a sign of health, and that irregular body functions or habits promote an unsalutary condition. Pay close attention to fluctuations in a patient's symptoms, his good and his bad days in times of health and illness.
>
> *Hippocrates*

Nearly 2,400 years ago Hippocrates associated disease with a change in the regularity of a physiological process. Present day clinical medicine often focuses on diseases in which these changes occur on time scales ranging from milliseconds to hours, for example, the generation of cardiac and respiratory arrythmias, tremors and seizures. More puzzling have been those diseases, collectively referred to as the 'periodic diseases', in which symptoms recur at 7-day intervals, or multiples thereof [1]. The best known of these disorders are the periodic haematological diseases, ie cyclic neutropenia (also known as periodic haematopoiesis) [2,3], cyclic thrombocytopenia [4], cyclic eosinophilic myositis and hyperimmunoglobulin E syndrome [5], and the periodic variants of chronic myelogenous leukaemia [6,7] and autoimmune haemolytic anaemia [8,9].

It has long been suspected that periodic haematological diseases arise because of abnormalities in the feedback mechanisms that regulate blood cell number [10–16]. Indeed this observation has provided a major impetus for mathematicians to determine the conditions for oscillation onset in these mechanisms. There have been two surprising predictions of these studies [17,18]: (1) qualitative changes can occur in blood cell dynamics as quantitative changes are made in feedback control; (2) under appropriate conditions, these feedback mechanisms can produce aperiodic, irregular fluctuations ('chaotic' in the current vernacular) which could easily be mistaken for noise and/or experimental error [19–21]. The clinical significance is that it may be possible to develop new diagnostic and therapeutic strategies based on manipulation of feedback [17,18,21–23]. Here we examine these theoretical developments and discuss their clinical implications in a manner that avoids the use of mathematics.

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Control of blood cell production

The organisation of normal haematopoiesis is shown in Fig. 1. It is generally believed that there exists a self-maintaining pluripotential stem cell population (PPSC) capable of producing committed stem cells (CSC) specialised for the erythroid, myeloid or thromboid cell lines [24]. The influx of cells from the PPSC to the CSC lines is regulated by two types of feedback mechanisms: (1) long-range humoral mechanisms, eg renal erythropoietin; (2) local environmental mechanisms which are as yet poorly characterised (labelled as LR in Fig. 1). An intrinsic property of these feedback mechanisms is the presence of time delays which arise, for example, because of finite cell maturation times. Thus most investigators have studied models of delayed feedback in order to investigate the periodic haematological diseases [10–15,17,18,25–30].

In order to appreciate how oscillations develop in blood cell number and their properties such as period and morphology, three steps are necessary: (1) development of a simple, but physiologically realistic, model for the relevant control mechanism (Figs 2a and 3a); (2) investigation of the properties of the model, typically by use of computer simulations (Figs 2b,c and 3b); (3) comparison of the model's predictions with experimental and/or clinical observations (Figs 2c and 3c). Current numerical experiments measure the time-dependent changes in blood cell number as certain quantities, referred to as control parameters, are varied. Control parameters are the quantities that, in comparison with blood cell number, either do not change with time, or change very little and hence are considered by the investigator to be constant. Examples of control parameters in the regulation of haematopoiesis are the maturation times and the peripheral destruction rate(s). It must be emphasised that quantitative predictions are usually unique to the individual model. Here we discuss only those qualitative properties of delayed feedback mechanisms that appear to be more generally applicable.

Delayed negative feedback mechanisms

The concept of delayed negative feedback can be introduced by considering the control of erythrocyte production as represented schematically in Fig. 2a. A

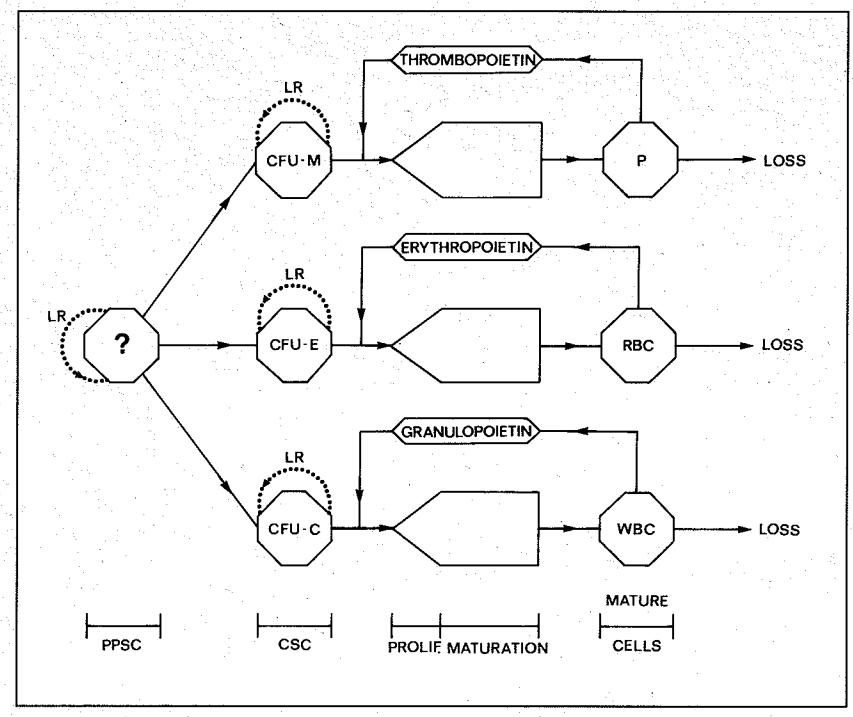

Fig. 1. *Haematopoietic regulation architecture.*
A schematic representation of the control of platelet (P), erythrocyte (RBC) and white blood cell (WBC) production, adapted from [24]. There are peripheral control loops mediated by the various poietins, as well as local regulatory (LR) loops within the various stem cell compartments. CFU refers to the various colony-forming units (M = megakaryocytic, E = erythroid, C = granulocyte/macrophage) which are thought to be the *in vitro* analogues of the *in vivo* committed stem cell (CSC) populations, all of which arise from the pluripotential stem cells (PPSC).

fall in circulating erythrocyte numbers leads to a decrease in haemoglobin levels and thus in arterial oxygen tension. This decrease in turn triggers the production of renal erythropoietin which increases the cellular production rate within the early committed erythrocyte series cells, and ultimately augments circulating erythrocyte numbers (ie negative feedback). Measurements *in vivo* of erythrocyte production rates in rats [31] indicate that the feedback function saturates at low haemoglobin levels and has the shape shown in Fig. 2a. The augmentation of circulating erythrocyte number does not occur instantaneously. Once a cell from the PPSC is committed to the erythroid series, it undergoes a series of nuclear divisions and enters a maturation phase for a period of time (~5.7 days) before release into circulation (ie delayed negative feedback). It is well established that, in appropriate circumstances, delayed negative feedback mechanisms can produce oscillations. To illustrate this point we consider the following two examples.

Periodic autoimmune haemolytic anaemia (AIHA)

Periodic AIHA is a rare form of haemolytic anaemia in humans [8,9], but it has been induced in rabbits by using red blood cell auto-antibodies [32]. Rabbit AIHA is one of the best understood periodic haematological diseases and arises from increases in the destruction rate of circulating erythrocytes.

In general, the period of an oscillation produced by a delayed negative feedback mechanism is at least twice the delay [11,33]. Moreover, for the model of erythrocyte production in Fig. 2a it can be shown that the period of the oscillation should be no greater than 4 times the delay [12]. Since the maturation delay for erythrocyte production is ~6 days, we would expect to see oscillations in erythrocyte numbers with periods ranging from 12 to 24 days. This is in excellent agreement with the observed periods of 16–17 days in rabbit AIHA [32]. What is surprising is the fact that these oscillations are so rarely observed. This paradox is illuminated by the following observations.

Figure 2b shows a computer simulation of the model in Fig. 2a as a function of the peripheral destruction rate (γ). As can be seen, when γ is low, as it normally is, oscillations in erythrocyte number do not occur. As γ increases, regular oscillations appear whose period increases as γ increases. However, for high γ, no oscillation occurs. Interestingly, depending on the severity of the haemolytic anaemia induced in the rabbit model, reticulocyte levels were observed either to be depressed at constant levels or to oscillate [32].

The observations in Fig. 2 indicate that whether or not a suggested mechanism for periodic AIHA produces an oscillation critically depends on whether the value of the control parameter, ie the peripheral destruction rate (γ), lies in some crucial range. This may explain why oscillations in erythrocyte number are so rarely seen in patients.

It should be noted that the morphology of the oscillations shown in Fig. 2b is simple, ie there is only one maximum per period. To date, all studies of delayed negative feedback mechanisms have indicated that only oscillations with this simple morphology can be produced [17, 18, 34, 35]. More complex waveforms (ie more than one maximum per period) are, however, possible with multiple delayed negative feedback loops [36] and with multiple time delays [37].

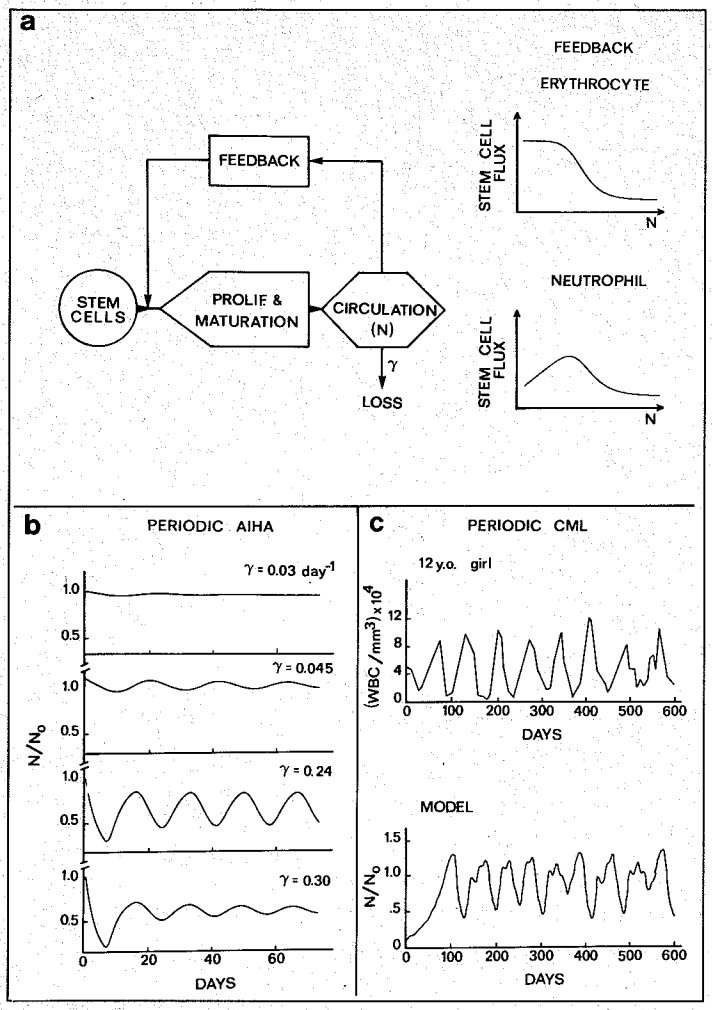

Fig. 2. *Peripheral haematopoietic regulation.*
(a) The genetic peripheral regulatory system of Fig. 1, with the qualitative dependence of the feedback mechanisms on circulating cell numbers (N) for erythrocyte and neutrophil production. γ is the rate of random loss of cells from the circulation. **(b)** Computer simulations of the model for erythrocyte production for four different peripheral destruction rates, γ. The predicted reticulocyte numbers have been plotted relative to normal values, N_0. See text for discussion. **(c)** A comparison between the temporal evolution of WBC numbers in a patient with periodic CML (redrawn from [6]) and the predictions of the model in (a) [17,18] when the neutrophil production delay is abnormally long. See text for further discussion.

Periodic haematopoiesis (PH)

The most common periodic haematological disease is PH. In humans, PH is a disease characterised by 17–28 day periodic oscillations in circulating neutrophil numbers from approximately normal values to barely detectable numbers [2, 3]. In addition to neutrophils, oscillations are seen for all the formed elements of blood with the same period. The oscillations for each blood cell line are out of phase and the phase differences between the cell lines are consistent with the differences in the maturation times. Recurrent illness is characterised by malaise, fever, aphthous stomatitis and cervical adenopathy [2, 3]. Neutropenic episodes place the patients at increased risk for infective processes (eg abscesses, pneumonia, septicaemia) and up to 20% of patients have died during these episodes.

An abnormality in the regulation of the PPSC in PH is suggested by the observation that the disorder can be transferred by bone marrow transplantation [38, 39]. Consequently, most investigators have looked to abnormalities in the regulation of the PPSC and delayed negative feedback mechanisms as an explanation for PH [11, 13–15, 25–30]. Recent evidence has suggested that the abnormality in feedback may be related to defective lymphocyte production of granulocyte/macrophage colony-stimulating activity (GM-CSA) in response to a monocyte-derived recruiting activity [40, 41].

The control mechanisms within the PPSC compartment are not as well understood as the control mechanisms for regulating the CSC compartment. A schematic representation of a possible PPSC regulatory mechanism is shown in Fig. 3a. Experimental study of periodic haematological disorders has been facilitated by the availability of suitable animal models. All grey collies have PH [38, 42] and periodic erythropoiesis can be induced in mice by the administration of a single dose of marrow-seeking radioisotope ^{89}Sr [42, 43]. Here we interpret the effects of an increase in the rate of irreversible loss from the proliferating phase of the PPSC (β in Fig. 3a) on blood cell production.

Figure 3b shows the results of a computer simulation of the model for PPSC production shown in Fig. 3a as a function of the control parameter β. As expected, an increase in β is accompanied by a decrease in the average number of circulating cells. For certain

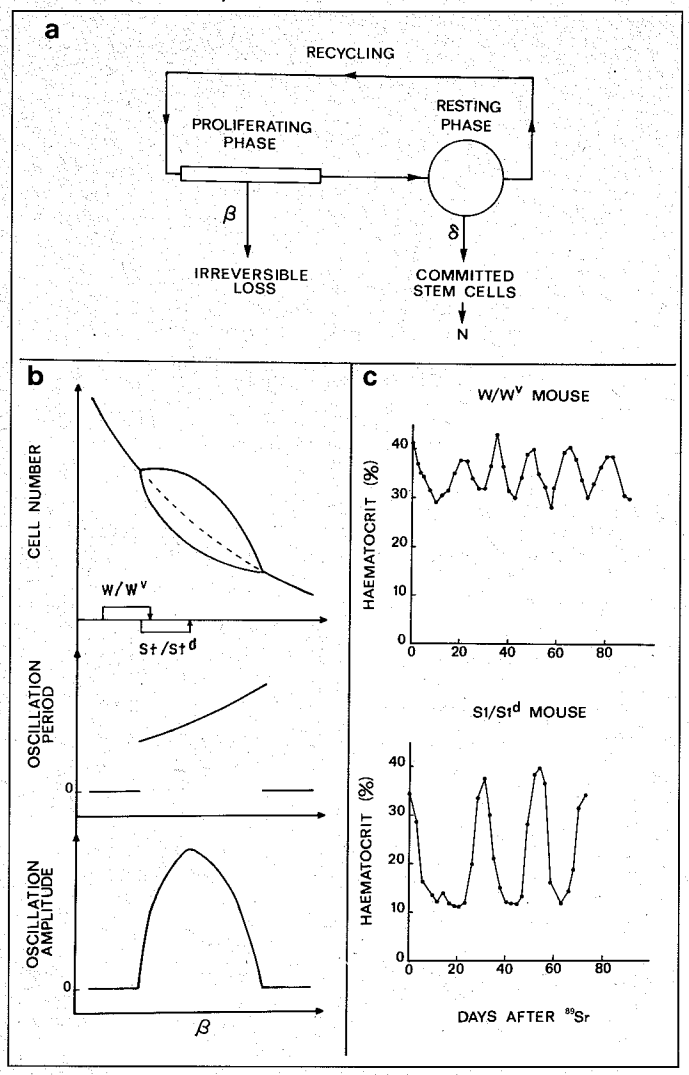

Fig. 3. *Central haematopoietic regulation*
(a) A schematic representation of the control of PPSC regeneration. Proliferating phase cells include those cells in G_1, S (DNA synthesis), G_2, and M (mitosis), while the resting phase cells are in the G_o phase. Local regulatory influences are exerted via a cell number dependent variation in the fraction of circulating cells. δ is the normal rate of differentiation into all the CSC populations, while β represents an abnormal loss of proliferating phase cells. See [11,13] for further details. **(b)** The qualitative behaviour of the model in (a) as β is increased from 0 (normal) to higher values with all other parameters at their normal values. In the top panel, the dashed portion of the curve indicates the range of β over which cell numbers oscillate with a period that increases as β increases (middle panel). The solid lines bounding the dashed line indicate the maximum and minimum values of the oscillating cell numbers, from which the variation in the amplitude of the oscillation with β can be determined (bottom panel). **(c)** Variations in haematocrit for two congenitally anaemic strains of mice after injection of a single dose of 0.5 μCi/g body weight ^{89}Sr. The data are taken, respectively, from [43] and [44].

values of β an oscillation appears. The period of this oscillation is at least twice the delay, and computer simulations indicate that the period is actually longer. For example, for an average intermitotic delay of ~2.2 days [11], the period is 10–14 days, in good agreement with that observed for PH in grey collies. Over the range of β in which an oscillation occurs, the period increases as β increases. However, the amplitude of the oscillation first increases and then decreases. Similar observations occur for the model of AIHA as the control parameter γ is increased (data not shown).

To illustrate the preceding discussion with a concrete example, we will compare the predictions in Fig. 3a to experimental observations obtained for ^{89}Sr-induced erythropoiesis in two congenitally anaemic strains of mice, W/W^v and S1/S1^d (Fig. 3c) [43,44]. W/W^v mice suffer from a defect in the PPSC, and in S1/S1^d mice the haematopoietic micro-environment is defective. Let us assume that the difference between W/W^v and S1/S1^d mice is solely related to differences in β. The observation that S1/S1^d mice are more refractory to erythropoietin than W/W^v suggests that β is higher in S1/S1^d. From Fig. 3a we see that a higher β would make it more likely for an oscillation in erythrocyte number to occur. Indeed, in contrast to W/W^v, about 40% of S1/S1^d mice have 'spontaneous' oscillations in their haematocrits [44]. In both strains of mice, a single dose of ^{89}Sr is sufficient to increase β into a range associated with oscillations in erythrocyte number. Since the value of β for S1/S1^d was greater than that for W/W^v prior to ^{89}Sr, it is reasonable to expect that it will also be higher following administration of ^{89}Sr. Thus, as predicted from Fig. 3b, the period of the oscillation is longer, the amplitude is larger and the mean haematocrit is lower in S1/S1^d mice.

Delayed 'mixed' feedback mechanisms

Up to this point we have only considered delayed negative feedback mechanisms. However, this is not the only type of feedback that can occur. A more complicated type of feedback arises for the control of circulating neutrophil numbers. A schematic representation of the regulation of neutrophil production is

similar to that for erythrocytes shown in Fig. 2a, except that the feedback function is different. Over a wide range of circulating neutrophil levels, the neutrophil production rate decreases as the number of neutrophils increases (ie negative feedback). However, owing to a variety of factors, it is expected that at very low neutrophil numbers the production rate falls to zero. Thus, in the range of low neutrophil numbers, the production rate must increase as neutrophil number increases (ie positive feedback). This type of feedback is a mixture of positive and negative feedback, ie 'mixed' feedback [34,35,45].

In order to contrast the dynamics that arise in delayed negative and mixed feedback mechanisms we will consider the disorder periodic chronic myelogenous leukaemia (CML). Periodic CML is a variant of CML in which peripheral neutrophil numbers oscillate around elevated levels with a period of 30–70 days even in the absence of clinical interventions [6,7]. In most patients the oscillations in neutrophil numbers range from approximately normal values to levels that are approximately 10 times normal. Although occasionally parallel oscillations in thrombocytes and reticulocytes have been reported [7], here we consider only those patients with oscillations in neutrophil levels. This disorder may be more common than is generally appreciated, since it is known that oscillations can occur in the number of S-phase CFU-C in CML patients in the absence of peripheral leukocyte oscillations [46].

Figure 2c shows the serial white cell counts [6] in a 12-year-old girl with periodic CML. There are oscillations in neutrophil number with a period of ~60–70 days. On closer inspection it can be seen that the number of days between successive maximum numbers of neutrophils is not constant, but varies by a few days. Moreover, the morphology of each waveform differs slightly and there are shoulders on some of them. The standard explanation for the origin of these departures from a regular periodic oscillation is that they reflect sampling errors and/or the influence of uncontrollable 'random' fluctuations in blood cell number. Here we discuss the possibility that these irregularities are intrinsic properties of the underlying control mechanism.

There is evidence in CML that the neutrophil precursor maturation time is prolonged [47]. Thus we will examine the influence of an increase in the maturation time on the neutrophil dynamics predicted by the model in Fig. 2a. As the time delay is increased there is first the appearance of simple oscillations with periods at least twice the delay and then more complex periodic oscillations (data shown in [17,18]). However, this is not all of the behaviour that can be seen. Figure 2c shows a computer simulation when the maturation time is increased to 20 days. Not only does the simulation correctly predict the overall period of the observed oscillations in the CML patient, it also has irregular fluctuations. This is in contrast to the general conception that random fluctuations are caused by random inputs. Here the model predicts that levels of circulating neutrophils are random simply as a consequence of their own deterministic evolution.

The complex, aperiodic fluctuations produced by deterministic mechanisms are currently referred to as 'chaos' [19]. The realisation that physiological control mechanisms can generate exceedingly complex oscillations, such as chaos, is a subject of great interest at present [17–21]. It is quite possible that both interesting and relevant dynamical changes are often observed, but their significance is wrongly ascribed to environmental noise and/or experimental error. Careful attention to these dynamical behaviours may eventually provide important insights into the properties of the underlying control mechanisms.

Concluding remarks

In summary, delayed feedback mechanisms are important for regulating blood cell numbers. Under certain conditions, delayed feedback mechanisms can produce oscillations whose period typically ranges from 2 to 4 times the delay, but which may be even longer. The observation that periodic haematological diseases have periods that are multiples of 7 may simply be a consequence of the combination of delayed feedback mechanisms with maturation times which are of the order of 5–7 days. Thus, it is not necessary to search for illusive and mystical entities [48], such as ultradian rhythms, to explain the periodicity of these disorders.

The observations in Figs 2 and 3 emphasise that an intact control mechanism for the regulation of blood cell numbers is capable of producing behaviours ranging from no oscillation to periodic oscillations to more complex irregular fluctuations, ie chaos. The type of behaviour produced depends on the nature of the feedback, ie negative or mixed, and on the value of certain underlying control parameters, eg peripheral destruction rates or maturation times. Pathological alterations in these parameters can lead to periodic haematological disorders.

As an extension to the concept of periodic diseases introduced by Riemann [1] in 1963, the term 'dynamical disease' has been introduced [17,18,21–23]. A dynamical disease is defined as a disease that occurs in an intact physiological control system operating in a range of control parameters that leads to abnormal dynamics. Clearly the hope is that it may eventually be possible to identify these altered parameters and then readjust them to values associated with healthy behaviours. Developments in biotechnology and the analysis of physiological control mechanisms are proceeding at such a rapid pace that the feasibility of such an approach may be just around the corner.

Often overlooked in the advance of medical science is the essential role of the practising physician. The identification of a dynamical disease as well as its response to clinical manoeuvres can only be assessed at the bedside. Indeed it is possible that both interesting and relevant dynamical changes have been observed but not published, because their theoretical significance is not fully appreciated by the clinician. In

the words of the French neurologist J. M. Charcot, 'Disease is very old and nothing about it has changed. It is we who change as we learn to recognise what was formerly imperceptible'.

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