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Occurrence of periodic oscillations in the differential blood counts of congenital, idiopathic, and cyclical neutropenic patients before and during treatment with G-CSF

Caroline Haurie[a], David C. Dale[d], and Michael C. Mackey[a,b,c]

Departments of [a]Physiology, [b]Physics, and [c]Mathematics, Centre for Nonlinear Dynamics, McGill University, Montreal, Quebec, Canada; [d]Division of Hematology, Department of Medicine, University of Washington, Seattle, WA

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Using techniques developed in astrophysics to deal with unequally sampled data sets, we have analyzed serial differential cell counts from 45 congenital, idiopathic, and cyclic neutropenic patients before and during treatment with recombinant human G-CSF (rhG-CSF). Our results show that the occurrence of significant cycling in the absolute neutrophil count (ANC) of neutropenics not classified as cyclical is much more prevalent than had been previously thought, and that not all the patients classified as cyclic show significant ANC periodicity. In these patients, cycling in more than one cell line may be involved. The range of periods encountered in these patients is much broader (between 11 and 52 days) than is usually associated with classical cyclical neutropenia, and there is no obvious connection between the range of periods and the patient's diagnostic category. Administration of rhG-CSF is able to induce significant cycling in neutropenic patients that were not cycling prior to treatment. In patients who had significant cycling before treatment, rhG-CSF may either decrease the period to between 11 and 14 days, or may obliterate any statistical evidence of cycling. **Published by Elsevier Science Inc.**

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Introduction

Severe chronic neutropenia (SCN) is a general term for a group of conditions characterized by a persistent absolute neutrophil count (ANC) in the blood lower than 0.5×10^9cells/L. The neutrophil half-life in the circulation is usually normal, and the function of the cells is normal or only moderately impaired [1,2]. These conditions were attributed to reduced or ineffective production of neutrophils by the bone marrow based on marrow morphology and kinetic studies [1]. In many cases there is a dramatic reduction in the absolute number of neutrophil precursors in the bone marrow. The origin of this marrow depression is unknown.

SCN includes congenital neutropenia (ConN) or congenital agranulocytosis, which is usually recognized soon after birth; idiopathic neutropenia (IN), which is acquired during childhood or adulthood; and cyclical neutropenia (CN). Cyclical neutropenia has been described as regularly occurring episodes of severe neutropenia with a period of 3 weeks [3]. Approximately two-thirds of CN cases have a family history suggesting an autosomal dominant inheritance, but the disease can also occur as an acquired disorder. Grey collie dogs have cyclical neutropenia inherited as an autosomal recessive disorder. In the grey collie, the monocytes, eosinophils, platelets, and reticulocytes oscillate with the same period as the neutrophils but around or above normal values [4,5]. In humans with CN, the platelets (often the monocytes and eosinophils) and occasionally the reticulocytes, also oscillate [6]. Serial bone marrow examination reveals a wave of cell production propagating successively from the colony forming units to the mature cells in each lineage [7–12]. The stem cell origin of this disorder is strongly suggested by the fact that it can be transferred and cured by bone marrow transplantation [13,14]. Both human and canine cyclic neutropenia are reviewed in [3–6,15,16].

Human recombinant granulocyte colony-stimulating factor (rhG-CSF) has been successfully used in severe chronic neutropenia to increase the nadir ANC to normal levels and to prevent recurrent infections [17–20]. Studies of the differential blood counts of five CN patients further showed an increase in the amplitude of the oscillations during G-CSF administration coupled with a decrease of the period of the oscillations from 21 to 14 days in all the cell lineages [17]. In another patient, probably having acquired CN, G-CSF abolished the oscillations [17]. There have been some re-

Offprint requests to: Michael C. Mackey, Department of Physiology, 3655 Drummond Street, Room 1124, Centre for Nonlinear Dynamics, McGill University, Montreal, Quebec, Canada H3G 1Y6; E-mail: mackey@cnd.mcgill.ca

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ports of oscillations in the ANC of congenital and idiopathic neutropenic patients during G-CSF administration [18,19].

We report here on an extensive analysis of serial blood counts from 45 neutropenic patients with CN, ConN, or IN who were treated with G-CSF during a Phase III clinical trial [21]. Using periodogram analysis, we tested for the presence of statistically significant periodic oscillations in the serial blood counts of the patients before and during treatment with G-CSF, and determined these periods.

Data and methods

Adult and pediatric patients with severe IN, CN, or ConN were evaluated, including some cases of congenital agranulocytosis (Kostmann's syndrome), Schwachman-Diamond syndrome, and myelokathexis from a randomized controlled clinical trial [21]. Patients with congenital agranulocytosis (Kostmann's syndrome) had severe neutropenia recognized soon after birth because of recurrent fevers and infections. Typically, the marrow showed some early neutrophil precursors, but very few cells beyond the promyelocyte stage, often with accompanying increased eosinophils in the marrow. In most cases, no other family members were affected. Patients were diagnosed as having Schwachman-Diamond syndrome if they had severe ConN associated with findings of pancreatic insufficiency. Patients with myelokathexis had severe leukopenia, as well as neutropenia, with very pycnotic nuclei in the blood neutrophils. Patients with CN had 3 to 5 days of neutrophils $< 0.5 \times 10^9$/L at regularly spaced, usually 3-week intervals of a 6-month period. IN was the category for patients lacking symptoms or findings of neutropenia during the first years of life, but developing these changes later in life. Generally, the severity of neutropenia and the associated complications were less severe in patients with IN than in the other categories.

Eligible patients were then randomized to one of two treatment groups. One group began a 4-month observation period after which they received G-CSF therapy for 5 months. The other group received the same treatment, begun immediately. G-CSF was administered subcutaneously in doses sufficient to raise the blood neutrophil count to between 1.5×10^9 and 10×10^9 cells/L, with dose adjustments to maintain counts in this range. Serial blood cell counts were performed two to three times per week throughout the study period [21].

We used the Lomb periodogram to detect periodicity in the blood counts before and during treatment with G-CSF [22]. The Lomb periodogram is equivalent to power spectrum analysis but is tailored for unevenly sampled data sets [22,23]. In the case of discrete time series, the periodogram is calculated for a discrete number of frequencies. For each frequency, the value taken by the periodogram is inversely correlated with the distance between the data set and a sinusoidal wave and the statistical significance (p value) of any peak in the periodogram can be calculated [23].

Specifically, let x_j be the number of a particular type of cell as measured at times t_j, where $j = 1, \cdots, N$ and N is the number of data points. As usual, the mean and variance of the data values are given by:

$$\bar{x} \equiv \frac{1}{N}\sum_{i=1}^{N} x_j \qquad \sigma^2 \equiv \frac{1}{N-1}\sum_{i=1}^{N}(x_i - \bar{x})^2 . \tag{1}$$

Then the Lomb normalized periodogram $P(T)$ at a period T is defined by:

$$PT \equiv \frac{1}{\sigma^2}\left\{ \frac{\left[\sum_{j=1}^{N}(x_j - \bar{x})\sin\frac{2\pi(t_j-\tau)}{T}\right]^2}{\sum_{j=1}^{N}\sin^2\frac{2\pi(t_j-\tau)}{T}} + \frac{\left[\sum_{j=1}^{N}(x_j - \bar{x})\cos\frac{2\pi(t_j-\tau)}{T}\right]^2}{\sum_{j=1}^{N}\cos^2\frac{2\pi(t_j-\tau)}{T}} \right\}, \tag{2}$$

where the constant τ is defined implicitly by:

$$\tan\left(\frac{4\pi\tau}{T}\right) = \frac{\sum_{j=1}^{N}\sin(4\pi t_j/T)}{\sum_{j=1}^{N}\cos(4\pi t_j/T)}. \tag{3}$$

The value of $P(T)$ indicates the likelihood of a periodicity with period T in the data set. We implemented Equation 2 for a series of different periods T. A judgment must be further made as to whether or not there is a period for which the power $P(T)$ is significantly high. The estimation of the significance level of $P(T)$ is straightforward as long as some rules are followed for the choice of the range and the number of periods that are scanned [23,24]. We implemented an adaptation of the procedure proposed in [24] using Matlab. Copies of this program are available from the authors for the analysis of analogous data.

Once a significant periodicity T has been detected through periodogram analysis, the estimation of the phase (ϕ) and amplitude (A) of the sine wave that fits best the data can be calculated by a simple linear least-square fitting procedure [22,23] of the data x_j using:

$$x_j = A\sin\left(\frac{2\pi t_j}{T} + \phi\right), \qquad j = 1,\ldots,N. \tag{4}$$

Note that there is an uncertainty in the estimation of the period because only a discrete set of periods can be tested.

Results

Of the 45 patients we analyzed, 38 had significant periodicity at the $p = 0.1$ level in at least one cell type, before or during treatment with G-CSF. Tables 1 and 2 summarize the results of all of our determinations of significant periodicities and their levels of significance (indicated only if $p \leq 0.10$) for the neutrophils, lymphocytes, monocytes, and platelets.

Figures 1 and 2 show the Lomb periodograms for the serial blood counts of five CN patients, three ConN patients, and two IN patients before and during treatment with G-CSF. Peaks in the periodogram can occur in one or more cell lines in all three groups of patients. In some patients, there is no peak in the periodogram of the ANC but a clear peak in the periodogram of another cell line (patients 50 and 102 before treatment, and patient 58 during treatment with G-CSF). In

Table 1. Periodicities (in days) estimated through periodogram analysis before treatment with G-CSF

Diagnosis	Patient no.	Neutrophils	Lymphocytes	Monocytes	Platelets
CN	104	—	—	—	27 ± 1.8 (0.001)
CN	39	—	—	—	—
CN	42	30 ± 1.7 ($4.9e^{-8}$)	—	—	30 ± 1.7 ($3e^{-6}$)
CN	43	20.2 ± 0.9 (.009)	—	—	—
CN	50	—	—	—	16 ± 0.5 (.002)
CN	69	—	—	—	13 ± 0.3 (0.07)
CN	116	—	—	—	34.8 ± 2.7 (0.06)
CN	25	—	—	20.4 ± 0.7 (0.08)	—
CN	18	—	44.4 ± 4.9 (0.07)	—	—
CN	54	17.8 ± 0.8 (0.04)	—	11.8 ± 0.3 (0.07)	—
ConN	10	—	—	—	—
ConN	102	—	—	—	35.7 ± 2.7 (0.001)
ConN	105	—	—	—	22.4 ± 1.1 (.008)
ConN	106	—	—	—	—
ConN	108	15.4 ± 0.5 (0.01)	15.4 ± 0.5 (0.02)	15.4 ± 0.5 (0.003)	15.4 ± 0.5 (0.009)
ConN	11	—	—	—	—
ConN	114	13 ± 0.4 (0.07)	26.4 ± 1.6 (0.02)	—	28 ± 1.8 (0.06)
ConN	32	—	—	20 ± 0.9 (0.005)	52.4 ± 5.2 (0.08)
ConN	4	—	—	—	22.5 ± 1.1 (0.002)
ConN	60	—	—	—	—
ConN	63	—	—	—	—
ConN	66	—	—	—	—
ConN	74	—	—	—	—
ConN	95	—	—	—	26.4 ± 1.6 (0.04)
ConN	97	—	—	—	17 ± 0.6 (0.03)
ConN	115	—	—	—	—
ConN	111	—	—	—	27 ± 1.8 (0.07)
IN	103	—	—	24 ± 1.3 (0.08)	32.6 ± 2.5 (0.004)
IN	29	—	—	—	—
IN	58	—	—	—	31.7 ± 2.3 (0.02)
IN	7	46.2 ± 4.6 (0.05)	—	—	—
IN	77	19.8 ± 0.9 (0.03)	—	—	—
IN	78	—	—	—	20.7 ± 0.9 (0.05)
IN	80	—	—	—	—
IN	98	—	—	—	22.7 ± 1.1 (0.05)
IN	23	52 ± 5.2 (0.008)	—	—	—
IN	24	—	—	—	—
IN	26	11.2 ± 0.3 (0.05)	—	—	—

Periodicities (±the uncertainty inherent to periodogrm analysis) with their significance level (in paranthesis), when the significance levels $p \leq 0.10$, before treatment with G-CSF. CN = cyclic; ConN = severe congenital; IN = idiopathic; — = not periodic; / = not enough data.

other patients (patients 104, 43, 114, and 80 before treatment, and patient 102 during G-CSF treatment), the presence of a peak at the same period in the periodograms of two or more different cell types strongly suggests significant periodicity even though the power may not be significant for a given cell type.

Occurrence of periodicity in the ANC before treatment

We found significant ($p \leq 0.10$) periodicity in the ANC of nine patients, of which three were CN, two were ConN, and four were IN patients. The ANC period was between 18 and 30 days in four of these (three CN and one IN). In the remaining five patients (two ConN and three IN) with significant periodicity, the periods found were 11, 13, 15, 46, and 52 days, respectively. Clearly, cyclicity is a property shared by all three patient groups and the criteria for establishing the diagnosis are insufficient to predict the presence or absence of statistically significant periodicity in the ANC.

Occurrence of periodicity in the other cell types before treatment

Of the nine patients that showed significant periodicity in the ANC, two patients (one CN and one ConN) also showed significant oscillations with the same period in one or more other cell type (platelets, monocytes, and/or lymphocytes). The periods of the oscillations in these patients were 30 days (patient 42) and 15 days (patient 108), respectively. Even if the periodogram analysis clearly indicated periodicity in all the cell types as in patient 108 (see Fig. 3), it may be hard to detect it by visual inspection of the serial blood counts because of the irregular sampling frequency and the high level of noise.

Table 2. Periodicities (in days) estimated through periodogram analysis during G-CSF treatment

Diagnosis	Patient No.	Neutrophils	Lymphocytes	Monocytes	Platelets
CN	104	13.7 ± 0.3 (0.06)	—	—	14.4 ± 0.4 (0.001)
CN	39	17.4 ± 0.5 (0.03)	—	—	17.9 ± 0.6 (0.04)
CN	42	38.9 ± 2.8 (0.003)	—	53.1 ± 5.3 (0.03)	30.1 ± 1.7 (0.001)
CN	43	—	—	—	—
CN	50	18.7 ± 0.6 (0.008)	19.1 ± 0.6 ($2e^{-4}$)	18.5 ± 0.6 ($2.8e^{-5}$)	18.5 ± 0.6 ($1.8e^{-15}$)
CN	69	11.8 ± 0.3 (0.05)	—	—	11.3 ± 0.2 (0.03)
CN	116	13.6 ± 0.4 (0.02)	13.3 ± 0.3 (0.008)	13.7 ± 0.3 (0.004)	13.7 ± 0.3 ($1.2e^{-05}$)
CN	25	—	—	—	33.8 ± 2.3 (0.06)
CN	18	—	—	—	—
CN	54	—	—	—	—
ConN	10	10.8 ± 0.2 (0.002)	—	—	—
ConN	102	12.7 ± 0.3 (0.007)	—	—	12.7 ± 0.3 (0.002)
ConN	105	52.4 ± 5.8 (0.07)	11.9 ± 0.3 (0.09)	—	12.5 ± 0.3 (0.02)
ConN	106	64 ± 8.0 (0.04)	—	—	—
ConN	108	11.5 ± 0.2 (0.006)	—	—	11.8 ± 0.2 (0.04)
ConN	11	52 ± 5.2 (0.02)	—	47.7 ± 4.3 (0.08)	—
ConN	114	11.4 ± 0.2 (0.0004)	11.1 ± 0.2 (0.03)	11.4 ± 0.2 (0.05)	11.6 ± 0.2 (0.06)
ConN	32	11.3 ± 0.2 (0.02)	—	—	—
ConN	4	—	—	—	58 ± 5.8 (0.08)
ConN	60	12.4 ± 0.3 (0.04)	12.4 ± 0.3 (0.08)	—	28.6 ± 1.5 (0.02)
ConN	63	—	—	—	24.2 ± 1.2 (0.09)
ConN	66	12.9 ± 0.3 (0.04)	—	—	12.9 ± 0.3 (0.02)
ConN	74	—	—	—	58.4 ± 6.5 (0.05)
ConN	95	11.7 ± 0.2 (0.01)	—	—	—
ConN	97	—	—	56.4 ± 6.3 (0.01)	—
ConN	115	/	—	22.3 ± 0.9 (0.04)	22.3 ± 0.9 (0.007)
ConN	111	—	—	41.8 ± 3.5 (0.07)	—
IN	103	—	—	—	—
IN	29	—	—	—	50.9 ± 5.1 (0.04)
IN	58	—	15.6 ± 0.4 (0.07)	15.9 ± 0.5 (0.02)	7.4 ± 0.1 (0.05)
IN	7	12.4 ± 0.3 (0.0002)	—	—	12.4 ± 0.3 (0.001)
IN	77	—	—	/	—
IN	78	13 ± 0.3 (0.03)	—	—	13.2 ± 0.3 (0.003)
IN	80	12.7 ± 0.3 (0.0009)	12.4 ± 0.3 (0.04)	12.4 ± 0.3 (0.09)	12.7 ± 0.3 (0.003)
IN	98	/	—	—	—
IN	23	—	—	—	—
IN	24	—	—	25.6 ± 1.2 (0.07)	—
IN	26	25.2 ± 1.3 (0.07)	—	—	—

Periodicities (±the uncertainty inherent to periodogrm analysis) with their significance level (in paranthesis), when the significance levels $p \leq 0.10$, during G-CSF treatment. CN = cyclic; ConN = severe congenital; IN = idiopathic; — = not periodic; / = not enough data.

In two patients, oscillations occurred in different cell lineages with different periods: in patient 54, the period was 18 days in the neutrophils and 12 days in the monocytes; and in patient 114, the period was 13 days in the neutrophils, 26 days in the lymphocytes, and 28 days in the platelets. A similar difference in periods between cell types in the same patient has been previously reported in a CN patient [25], where the neutrophils oscillated with a period of 20 days and the platelets oscillated with a period of 35 days.

Significant oscillations in the lymphocytes, monocytes, or platelets can also occur independent of oscillations in the ANC. Of the 35 patients with no periodicity in the ANC before treatment, 17 patients had significant periodicity in one or more other cell lineages, with periods ranging from 13 to 44 days (cf, Table 1).

Overall, we detected significant periodic oscillations in one of the blood cell lines in 26 of the 46 neutropenic patients before treatment. Figure 4 shows the histogram of the periods (T) found in all the cell lines before treatment. Even though periodicities between 20 and 25 days are the most frequent, the occurrence of periods outside this range is also quite common. There are no discernible differences between the three diagnostic groups since $11 \leq T \leq 44$ for CN, $13 \leq T \leq 52$ for ConN, and $11 \leq T \leq 46$ for IN.

Effect of G-CSF on the periodicity in the ANC

Modification or abolition of ANC periodicity with G-CSF. Three of the nine patients showing periodicity in the ANC before treatment (two ConN and one IN) had a reduction in their periods during G-CSF treatment (cf, Table 2). Before treatment, these three had periods $13 \leq T \leq 46$ days, while during treatment $11 \leq T \leq 14$ days as reported previously

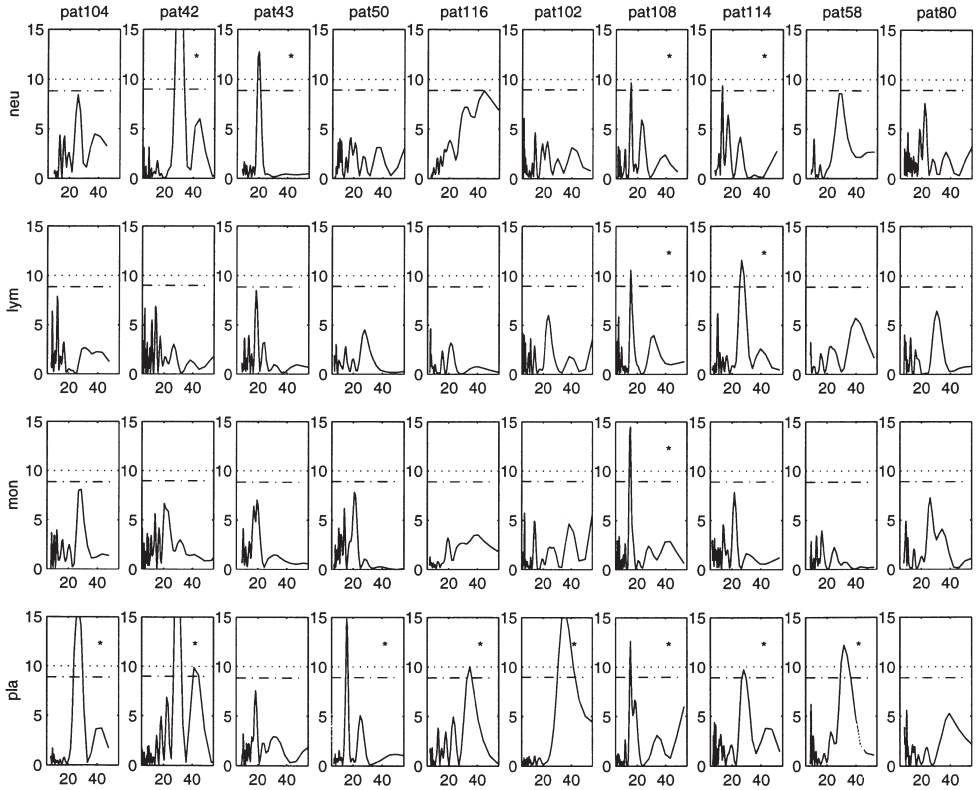

Figure 1. Lomb periodogram P(T) [power P versus period T in days] of the blood cell counts of five cyclical neutropenia (CN), three congenital neutropenia (ConN), and two idiopathic neutropenia (IN) patients before treatment. The dotted lines in the Lomb periodogram give the $p = 0.10$ (lower dash-dot line) and $p = 0.05$ significance levels (upper dotted line); *indicates periodicity with significance $p \leq 0.10$; neu = neutrophils; lym = lymphocytes; mon = monocytes; pla = platelets.

[17,26]. In two cases (patients 42 and 26), the period *increased* during G-CSF administration from 30 days to 39 days and from 11 to 25 days, respectively. Furthermore, G-CSF therapy abolished significant oscillations in four patients (two CN and two IN). This effect was also described earlier [17].

Induction of ANC oscillations with G-CSF. In 16 patients (five CN, nine ConN, two IN), the data of Tables 1 and 2 show that G-CSF induced significant oscillations in the ANC where none existed before treatment. Eleven of these patients had ANC oscillations with periods $11 \leq T \leq 14$ days, which is the same range reported for the period of CN patients treated with G-CSF [17], while the other five had periods of 17, 19 (two patients), 52, and 64 days.

Effect of G-CSF on the oscillations in the other cells
During G-CSF treatment, 16 patients had significant oscillations both in the ANC and in another cell lineage, 5 patients had oscillations only in the ANC, and 10 patients had no oscillations in the ANC but significant oscillations in another cell lineage. The period in these latter 10 patients ranged from 7 to 58 days. Of these patients, five had no significant periodicity in any cell type before G-CSF treatment. As with the neutrophils, G-CSF could either abolish, modify, or induce significant oscillations in all the blood cells. Thus, periodicity during G-CSF treatment is not dependent on the existence of periodicity before treatment.

Figure 3 shows the cycling of all the cell lineages with a period of 11 days during G-CSF administration in patient 114. Before treatment with G-CSF, the neutrophils were oscillating with a period of 13 days, and the lymphocytes and the platelets were oscillating with a period of 26 days. Administration of G-CSF induced significant periodic oscillations in the monocyte counts and decreased the period of the oscillations in all the other cell types.

The histograms of the significant periods found during G-CSF treatment shows an increase in the occurrence of significant oscillations and a concentration of the periods in the 10- to 15-day range for all the diagnostic groups (see Fig. 4).

Discussion

The typical pattern of CN is easily recognizable because of large fluctuations in the ANC from very low to normal values. The period of the oscillations in the ANC of human CN patients is typically taken to be in the range of 19–21 days [3]. Other reviews have suggested a larger range of periods

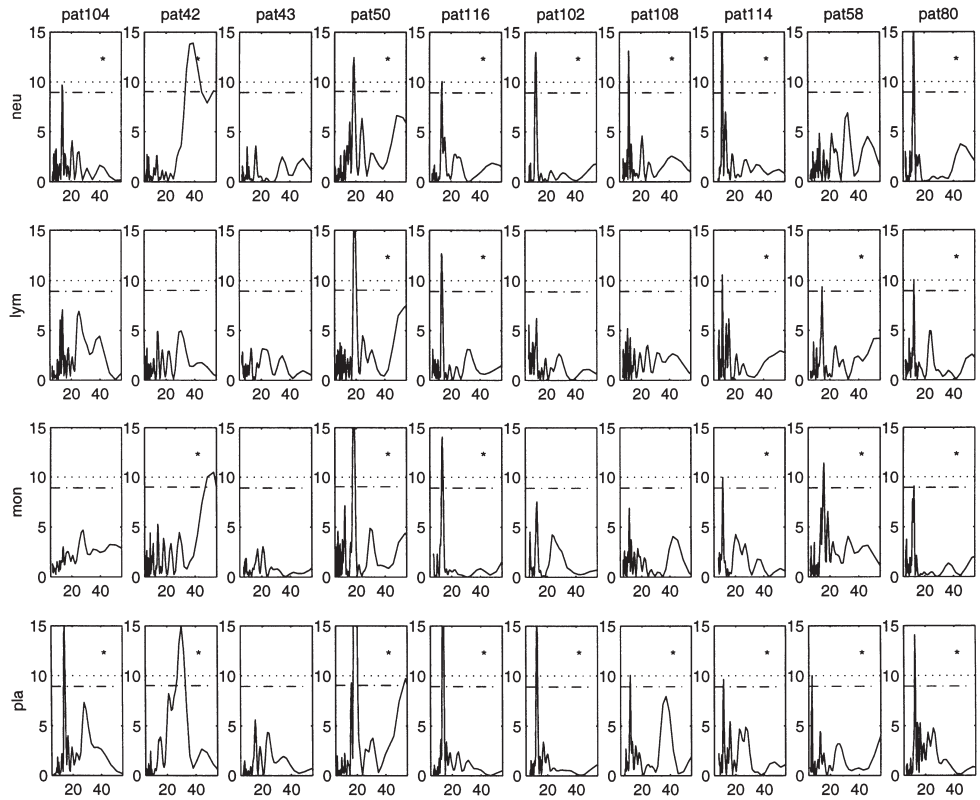

Figure 2. Lomb periodogram of the blood cell counts of the same five cyclical neutropenia (CN), three congenital neutropenia (ConN), and two idiopathic neutropenia (IN) patients shown in Figure 1 but during G-CSF treatment. *Indicates periodicity with significance $p \leq 0.10$; neu = neutrophils; lym = lymphocytes; mon = monocytes; pla = platelets.

(18–30 days) [15,16], and a case of neutropenia with a period of 100 days has been reported [27]. There has been one description of a case of human CN with a period of 14 days [28].

The results of the periodogram analysis reported here show that:

- The occurrence of significant ANC cycling in neutropenics not classified as cyclical neutropenic is much more prevalent than had been previously thought.
- Not all the patients classified as cyclic show significant ANC periodicity.
- Periodicity occurs before and during G-CSF treatment as frequently in the platelet counts as in the ANC, and less often in the other cell types (although the platelet, monocyte, and lymphocytes counts are normal). In several patients, significant periodicity occurred in platelets and/or monocytes and not in the neutrophils, especially before treatment with G-CSF. Thus, the occurrence of significant cycling in at least one (neutrophil, lymphocyte, monocyte, or platelet) cell line is much more common than is usually thought to be the case with neutropenic patients (10 of the 11 CN patients showed cycling in at least one of these lines, as did 17 out of 20 ConN patients, and 12 out of 14 IN patients).
- The range of periods encountered in these patients is much broader (in this study the range of significant periods involving any one of the cell lines shows that $11 \leq T \leq 52$ days) than is usually associated with classical cyclical neutropenia. Periods larger than 60 days may be due to long-trend effects associated with the start of G-CSF administration.
- Significant periodicity was more frequent during G-CSF treatment than before treatment, and the periods found were not as uniformly spread between 10 and 50 days: a majority of the oscillations found during treatment ranged between 11 and 14 days. Also, G-CSF increased the average number of cells cycling per patient.

These observations suggest that "cyclical hematopoiesis," broadly defined as the presence of statistically significant cycling in at least one cell line, is probably highly prevalent in neutropenic patients (39 of the 45 patients of this study fell into this definition). However, periodicity may be detectable only during G-CSF treatment. When irregular sampling occurs, periodicity can sometimes be very hard to detect without the use of periodogram analysis. This may explain why we found significant periodicity in neutropenic patients that had not been classified as cyclic.

Since significant periodicity occurs before and during

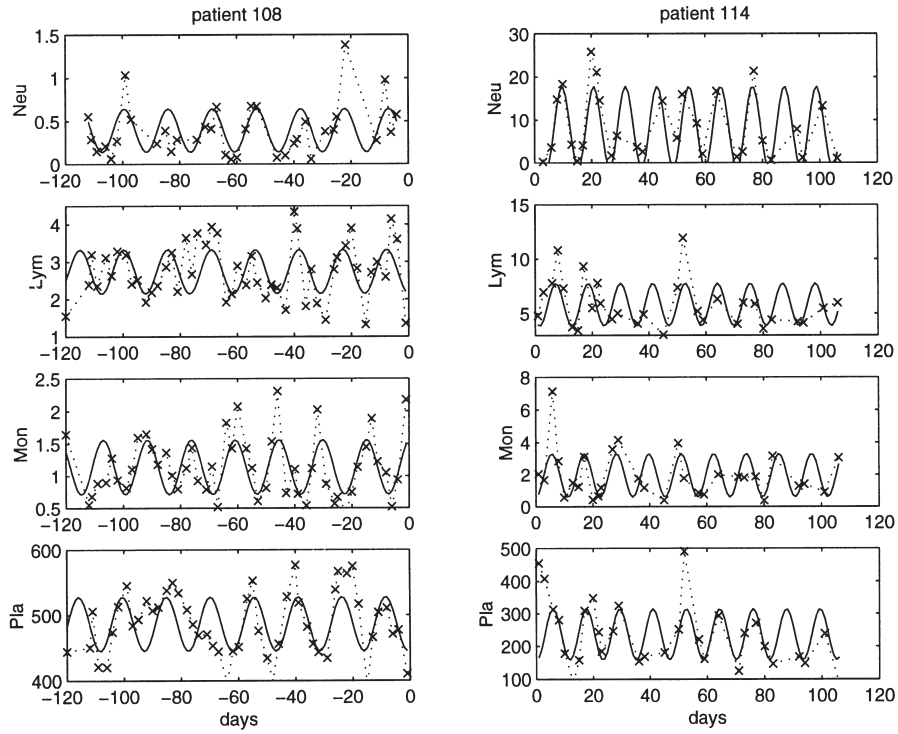

Figure 3. Sine wave fitting of the differential blood counts of congenital neutropenic patient 108 before treatment and congenital patient 114 during treatment with G-CSF.

G-CSF administration in these three types of neutropenic patients, we conclude that the occurrence of periodic oscillations is very strongly linked to the occurrence of the neutropenia itself. Hematopoiesis is regulated by a complicated network of cytokines that are produced in part by the hemopoietic cells. Thus, it is very likely that the alteration of one of the major hemopoietic compartments will affect the regulation and the dynamics of early hemopoietic cells and/or the other cell lineages.

Studies of the serial neutrophil counts in normal individuals showed no significant cycling [29,30]. Periodic cycling of the blood counts has been observed in other untreated hematologic disorders associated with bone marrow defects such as chronic myelogenous leukemia and aplastic anemia, with periods between 30 and 100 days [6]. The present finding that oscillations with periods as large as 52 days also occur in CN and other types of neutropenia sheds new light on the relation between these apparently disparate disorders. Similar mechanisms controlling the dynamics of pluripotential stem cells may be responsible for the occurrence of periodic fluctuations of the blood counts in these different disorders. This is consistent with the finding that CN can be a premalignant manifestation of acute lymphoblastic leukemia [31].

The effects of G-CSF on the dynamics of the various cell lines showed a variety of patterns ranging from modification (usually a decrease) of the period of oscillation in the ANC or other cell lines, an abolition of any significant periodicity, an initiation of a significant periodicity, or no effect on periodicity.

G-CSF is the only cytokine known to affect the period of the oscillations in CN. Granulocyte-monocyte colony stimulating factor (GM-CSF) led to an increase in neutrophil count by a factor of between 1.5 and 3.5 (much less that achieved by G-CSF) and obliterated all signs of the cycling [20]. Although recombinant canine SCF (re-SCF) did not cause neutrophillia in the grey collie, it did obliterate the oscillations of CN. Lithium therapy in grey collies [10,32] and humans with CN [33,34] has uniformly yielded an elimination of the severe neutropenic phases, and a diminution in the amplitude of the oscillations without any apparent change in the period of the oscillation.

It is likely that the modification in the period of the oscillations is a consequence of an effect of G-CSF on the pluripotential early hematopoietic stem cell (HSC), since several blood lineages are affected simultaneously, while the increase in the mean white blood cell counts can be explained by the specific effect of G-CSF on the amplification of white blood cells precursors.

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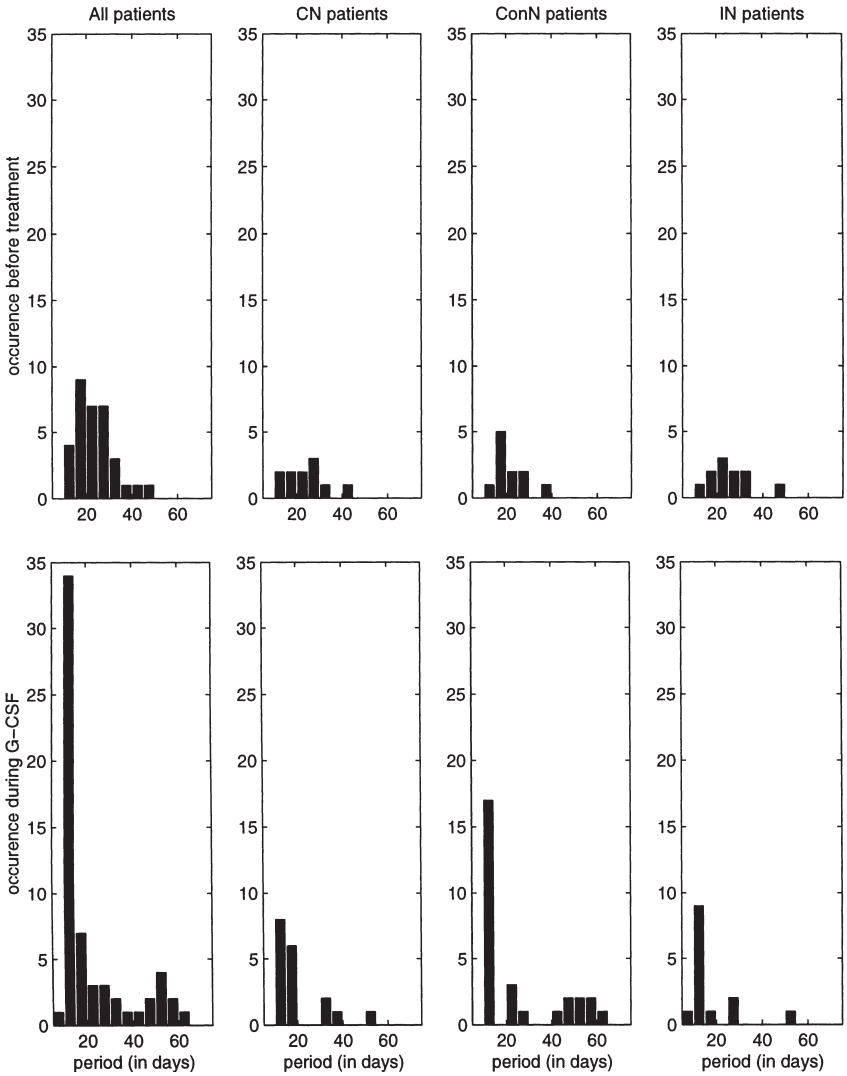

Figure 4. Histograms of the significant periods found in all the patients in the neutrophils, lymphocytes, monocytes, and platelets before and during treatment with G-CSF.

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