

### Cyclic oscillations of neutrophils, monocytes, and CD8-positive lymphocytes in a healthy subject

We describe an asymptomatic subject with cyclic variations (22-day intervals) of neutrophils, monocytes, and CD8<sup>+</sup> lymphocytes. This case may be interpreted as an amplification of the mechanisms which regulate the production and circulation of human blood cells. Identifying this phenomenon may help interpret cases with unexplained neutropenia.

Sir,

Hematopoiesis has been suggested to show a cyclic behavior under both normal and pathologic conditions,<sup>1-3</sup> although other studies have not confirmed such a hypothesis.<sup>4,5</sup>

We report a peculiar case characterized by cyclic oscillations of neutrophils, monocytes and CD8<sup>+</sup> lymphocytes in an asymptomatic subject. These findings suggest the existence of periodic hematopoiesis with a clinical expression intermediate between normality and the pathologic features which characterize cyclic

neutropenia (CN).<sup>6</sup>

A 21-year old male presented with asymptomatic, intermittent neutropenia, (neutrophils 1-1.2×10<sup>9</sup>/L in some blood samples). During our first observation, hematologic parameters were: Hb 15.1 g/dL; Hct 44.3%; MCV 86 fL; PLT 179×10<sup>9</sup>/L; WBC 3.7×10<sup>9</sup>/L; neutrophils 1.47×10<sup>9</sup>/L; lymphocytes 1.75×10<sup>9</sup>/L; monocytes 0.27×10<sup>9</sup>/L; eosinophils 0.11×10<sup>9</sup>/L; basophils 0.02×10<sup>9</sup>/L; LUC 0.12×10<sup>9</sup>/L. May-Grünwald-Giemsa stained neutrophils showed normal morphology. The known causes of neutropenia,<sup>7</sup> including anti-neutrophil antibodies, were excluded. Bone marrow aspiration, carried out during the first observation, revealed normal hematopoiesis and karyotype. Consent to repeat other bone marrow aspirations was not given. The subject had no brothers or sisters, and his parents did not have blood abnormalities.

Blood cell counts were performed twice a week<sup>6</sup> for 64 days; then our observation was continued for another 56 days to complete a 120-day follow-up. We found 5 episodes of neutropenia (neutrophils < 1.5 ×10<sup>9</sup>/L), with approximately 22-day intervals (Figure 1A); nadir values ranged between 1.0-1.2×10<sup>9</sup>/L. Six episodes of monocytopenia (< 0.3×10<sup>9</sup>/L) were detected (Figure 1A).

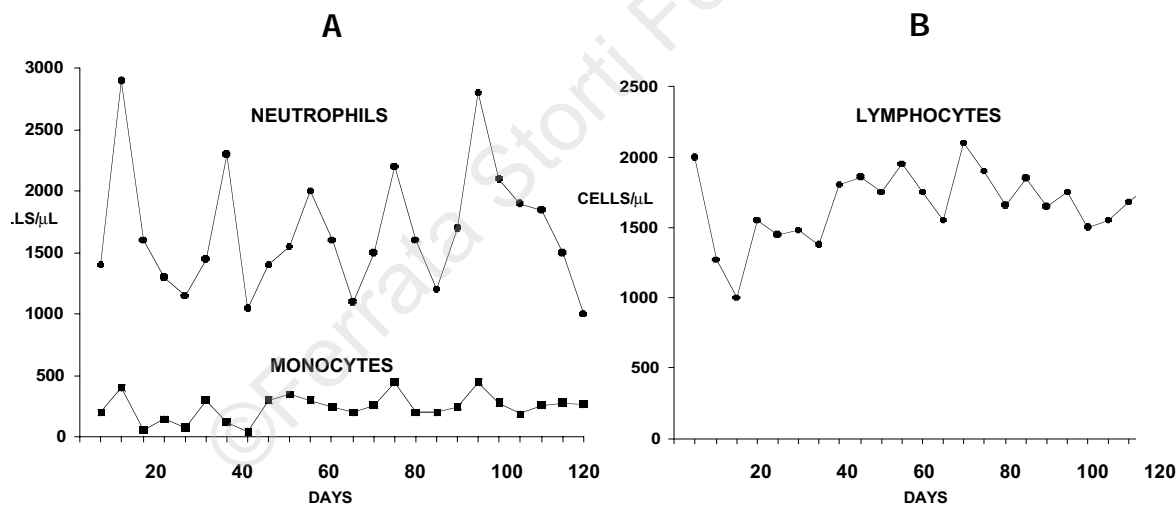


Figure 1 (above). Neutrophil, monocyte (A), and lymphocyte (B) behavior during the study.

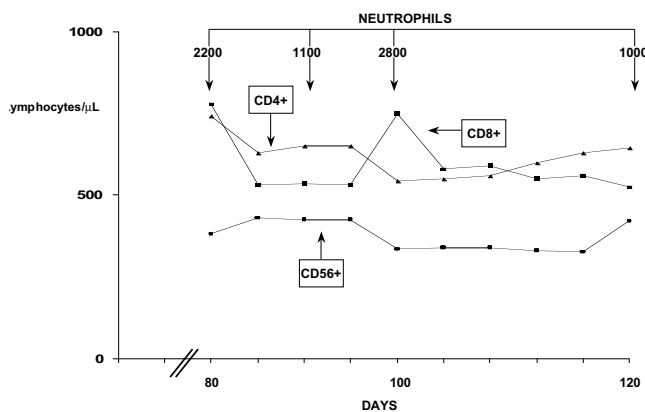


Figure 2 (left). Behavior of CD4<sup>+</sup>, CD8<sup>+</sup>, and CD56<sup>+</sup> lymphocytes during one of the cycles of neutrophil variation.

The overall lymphocyte population did not show cyclic variations (Figure 1B). However, during one of the cycles, we studied lymphocyte phenotype (CD3, CD4, CD8, CD19, CD56), using monoclonal antibodies and flow cytometry, and found that CD8<sup>+</sup> lymphocytes showed a cyclic behavior, synchronous with that of neutrophils (Figure 2; peak values 0.78 and  $0.75 \times 10^9/L$ , n.v.  $0.3-0.6 \times 10^9/L$ ). There were relatively high percentages of CD56<sup>+</sup> lymphocytes (18-26%; absolute values  $0.32-0.53 \times 10^9/L$ ; n.v.  $0.1-0.5 \times 10^9/L$ ), but without any cyclic behavior (Figure 2). No increase in the percentage of large granular lymphocytes was detected in peripheral blood smears.

Platelets, eosinophils, and basophils did not change significantly during the study (data not shown). Plasma cortisol levels, measured at 8 a.m., did not show any correlation with neutrophil counts (data not shown).

Some of the peripheral blood cells of the subject under study showed a behavior mimicking CN. However, this was self-limiting behavior and the severe laboratory and clinical features of CN were not observed. In addition, lymphocyte behavior was different from the rare cases of CN in which T8 lymphocytes were found to cycle,<sup>8,9</sup> and no increase of large granular lymphocytes<sup>10</sup> was detected. Although the existence of cyclic variations of neutrophils in normal subjects is a debated matter,<sup>4,5</sup> we think that our case may be consistent with an amplification of the homeostatic mechanisms which regulate the production and circulation of human blood cells. From a clinical point of view, identifying and studying such a phenomenon may help to interpret cases characterized by unexplained neutropenia.

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#### Key words

*Cyclic neutropenia, hematopoiesis, neutrophils, monocytes, lymphocytes.*

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