Patterns of Granulocyte Kinetics in Health, Infection and in Carcinoma

By Peter R. Galbraith,* Leslie S. Valberg and Malcolm Brown

HEMOLYTIC ANEMIA may be found in association with solid tumors and cross transfusion studies indicate that hemolytic factors are resident in the circulation.1-3 Although there have been many studies of erythrocyte production and destruction4-4 the production and destruction of granulocytes have not been reported in nonleukemic malignant disease. The present study was undertaken to see if granulocyte kinetics are altered in carcinoma and the results have been compared with findings in patients with infection.

MATERIALS AND METHODS

White Blood Cell Survival Studies

A) Labeling the cells. The leukocytes were labeled with radioactive diisopropylfluorophosphate (DFP32) by a modification of the technic described by Mauer et al.5 One hundred μc of DFP32 (Radiochemical Centre, Amersham, England) diluted in sterile anhydrous propylene glycol were added to 500 ml of whole blood freshly drawn into a tared siliconized bottle containing 150 ml of dextrose and sodium citrate solution (Baxter Laboratories, Alliston, Ontario). The total amount of DFP added to the blood ranged from 0.18 to 0.48 mg. The blood was gently mixed for 45 minutes and 30 ml were removed for the determination of granulocyte count and of radioactivity in the leukocytes. The bottle was reweighed and the remainder of the blood was reinfused into the patient over a period of 15 minutes. Thirty ml of blood were taken with a plastic syringe (Stylex®, Pharmaseal Laboratories, Glendale, California) containing 1 ml of 5 per cent disodium ethylenediaminetetraacetate in distilled water at 15 minutes and at 1, 3, 6, 8 and 24 hours after completion of the infusion.

B) Isolation of leukocytes. Glassware was siliconized and all operations were carried out at 4 C, in either an ice bath or a refrigerated centrifuge. The blood sample was added to a test tube, 7" by 1/4", and mixed thoroughly with 3 per cent dextran (M.W. 227,000, Pharmachem Corporation, Bethlehem, Pa.) in saline. After the erythrocytes had sedimented for 1 hour, the supernatant was transferred to a 40 ml centrifuge tube and centrifuged at 130 x g for 10 minutes. The supernatant was discarded, the cells were resuspended in 10 ml of normal saline and then sedimented by centrifugation at 55 x g for 10 minutes. The supernatant was discarded and 10 ml of 0.15 M sodium acetate buffer at pH 7.35 was added. The tube was covered with Parafilm® (American Can Company, Menasha, Wisconsin) the leukocytes were suspended in the buffer by gentle shaking and 0.1 ml of freshly prepared 1 per cent saponin (Fisher Scientific Co., Fair Lawn, New Jersey) in normal saline was added. The suspension was chilled for 4 minutes at 4 C and then centrifuged at 690 x g for 10 minutes. The supernatant was discarded.

The button of leukocytes was transferred with a Pasteur pipette to a tared aluminum...
Table 1. — Leukokinetic Data in Control Subjects

<table>
<thead>
<tr>
<th>19 Control Subjects</th>
<th>Body Weight (Kg.)</th>
<th>Blood Granulocytes (G per cu.mm.)</th>
<th>T 1/2 (hrs.)</th>
<th>BGM (G x 10^9)</th>
<th>GTR (G x 10^9/hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>72.1</td>
<td>4067</td>
<td>6.44</td>
<td>38.00</td>
<td>4.08</td>
</tr>
<tr>
<td>Range</td>
<td>54.6–88.6</td>
<td>2013–6946</td>
<td>5.1–7.7</td>
<td>19.9–56.4</td>
<td>2.51–5.50</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>±9.1</td>
<td>±1380</td>
<td>±.74</td>
<td>±10.0</td>
<td>±.920</td>
</tr>
</tbody>
</table>

planchet (No. AC-12, Nuclear Chicago Ltd., Chicago, Illinois) and spread thinly over the surface with an applicator stick. The samples were dried at 40 C. in an incubator and then in a vacuum oven at 40 C. for at least 4 hours. The planchets were reweighed to obtain the dry weight of the cells.

(C) Determination of radioactivity. The samples were counted to a total of 2000 counts in a low background beta counter equipped with an automatic sample changer (Nuclear Chicago Ltd., Chicago, Illinois). The total count was corrected for background and for decay of the isotope. The results, expressed as counts per mg. of dried leukocytes, were plotted on semilogarithmic paper and the corrected specific activity of the leukocytes at the completion of the infusion (T_o) was taken as 100 per cent. The half-life of the labeled leukocytes in the circulation (T 1/2) was determined by the method of least squares. Blood granulocyte mass (BGM) was determined by isotope dilution and it was expressed in terms of granulocytes (G) x 10^9. Granulocyte turnover rate (GTR) calculated from the equation: GTR = \( \frac{\text{BGM}}{T_{1/2}} \times 0.693 \) was expressed as G x 10^9/hour.

(D) Evaluation of technic. The coefficient of variation of the technic determined from duplicate estimations of leukocyte radioactivity in 54 blood samples was 3.0 per cent. Repeated examination of the leukocyte preparations under the phase microscope showed no contamination by platelets or erythrocytes. After 48 hours the leukocyte radioactivity, reduced to less than 1 per cent of the T_o value, disappeared at a different rate. This might have been due to light labeling of other leukocytes which disappeared at a different rate, or to slight contamination by platelets and erythrocytes, which were still heavily labeled at this time. In any event, this constitutes insignificant contamination of leukocyte preparations.

(E) Selection of patients. Normal values were established in 19 healthy male control subjects with normal blood counts who ranged in age from 21 to 70 years. Studies were also performed on 6 subjects with infection, on 11 patients with carcinoma who were free of infection, and on 3 patients with untreated carcinoma of the bronchus with superimposed infection. Relevant clinical data on the patients are given in tables 2, 3, and 4.

Three patients, 2 with cancer and 1 with infection, in whom the disappearance of the labeled granulocytes from the blood was not a simple exponential function were excluded from the study because these cases were obviously not in a steady state with respect to BGM.

RESULTS

The results of leukokinetic studies in the control subjects are shown in table 1. The mean T 1/2 was 6.44 hours with a range of 5.1 to 7.7 hours. The mean BGM was 38 x 10^9 cells with a range of 19.9 to 56.4 x 10^9 cells. The mean GTR was 4.08 x 10^9 cells per hour with a range of 2.51 to 5.50 x 10^9/hour. There was a direct linear relationship between the BGM and the T 1/2 in the control group (fig. 1). The coefficient of correlation was 0.62 (p < 0.01) and the F value for linearity was 10.12 (p < 0.01).

The results of leukokinetic studies in 6 subjects with infection are shown in table 2. The peripheral blood granulocyte concentration varied from 1368...
to 12,238 per cu.mm. The BGM was increased and the GTR was either increased or at the upper limit of normal in each case, but there was no correlation between BGM and T ½ (fig. 1).

Leukokinetic data on subjects with carcinoma are given in table 3. Although the mean granulocyte count was slightly increased, in all save 3 subjects (Nos. 7, 9 and 11) the granulocyte count fell within the normal range of 2013 to 6946 per cu.mm. The mean T ½ was increased and values were above the normal range in 5 cases (Nos. 3, 7, 8, 9 and 10). The mean BGM was raised and in 5 patients the BGM was above normal (Nos. 7, 8, 9, 10 and 11). No correlation was observed between BGM and T ½ (fig. 1). The GTR was decreased in 2 patients (Nos. 3 and 4), increased in 2 patients (Nos. 6 and 11) and within the normal range in the others.

The leukokinetic data in subjects with carcinoma and superimposed infection given in table 4 and in figure 1 show that these patients, like the subjects with infection, sustained larger than normal blood granulocyte masses and had increased granulocyte turnover rates.

**DISCUSSION**

The present method for the determination of leukocyte radioactivity has two advantages over the methods described by Athens et al. First, saponin which has been used instead of lysolecithin and gramicidin for the hemolysis of erythrocytes in the leukocyte suspension produces consistent results and is commercially available, whereas lysolecithin has to be prepared in the laboratory. Secondly, leukocyte radioactivity is expressed in terms of dry weight rather than leukocyte nitrogen, which eliminates a procedure with its own possibilities of error. The results obtained by both methods are, however, comparable.

We have departed from the nomenclature of Athens et al. by the use of the term blood granulocyte mass instead of total blood granulocyte pool. This was done to avoid confusion which may arise because we have expressed the blood granulocyte mass in absolute terms rather than in relation to body weight. This departure from the standard expression of results was prompted by the finding in control subjects that there was no relationship between BGM and body weight, and therefore no relationship between blood granulocyte mass and blood volume. It also facilitates the comparison of leukokinetic data of the control group with the results in patients with carcinoma or infection in whom alterations in body weight may occur independently of blood volume.

Granulocytes spend a variable part of their potential lifespan in the blood stream. The vast majority of these cells are randomly removed and their transit time bears no relationship to their potential for circulatory survival.

In leukokinetic studies we assume the presence of a steady state where granulocyte production equals granulocyte removal, and the BGM remains at a constant level. Under these conditions the T ½ gives a reliable indication of the circulating phase of the granulocytes' life. The magnitude of T ½ is directly related to the size of the BGM if the GTR remains constant because it takes longer for the labeled cells to be removed by this random mechanism and to be replaced by unlabeled cells from the bone marrow.
Table 2.—Leukokinetic Data in Patients with Infection

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex and Age</th>
<th>Weight (Kg.)</th>
<th>Infection</th>
<th>Hb (Gm. per 100 mL)</th>
<th>ESR* (mm. in 1 hr)</th>
<th>Granulocyte Concentration (per cu. mm.)</th>
<th>T ½ (hrs.)</th>
<th>BGM (Gx 10⁹)</th>
<th>GTR (Gx 10⁹/hr.)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M - 63</td>
<td>54.6</td>
<td>Chronic bronchitis</td>
<td>19.4</td>
<td>4</td>
<td>1368</td>
<td>10.3</td>
<td>287.7</td>
<td>19.4</td>
<td>Cr₅¹ RBC mass normal.</td>
</tr>
<tr>
<td>2</td>
<td>M - 71</td>
<td>54.6</td>
<td>Chronic bronchitis</td>
<td>15.9</td>
<td>6</td>
<td>6213</td>
<td>9.2</td>
<td>69.9</td>
<td>5.3</td>
<td>Bone marrow normal.</td>
</tr>
<tr>
<td>3</td>
<td>M - 73</td>
<td>50.5</td>
<td>Chronic bronchitis</td>
<td>12</td>
<td>29</td>
<td>8580</td>
<td>7.0</td>
<td>126.7</td>
<td>12.5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>M - 80</td>
<td>75.5</td>
<td>Abscess of buttock</td>
<td>14.4</td>
<td>15</td>
<td>4181</td>
<td>7.9</td>
<td>64.4</td>
<td>5.6</td>
<td>Infection nearly resolved.</td>
</tr>
<tr>
<td>5</td>
<td>M - 73</td>
<td>55.9</td>
<td>Acute bronchitis</td>
<td>9.4</td>
<td>122</td>
<td>12,238</td>
<td>8.2</td>
<td>92.5</td>
<td>7.8</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>M - 37</td>
<td>61.4</td>
<td>Acute bronchitis</td>
<td>15.2</td>
<td>18</td>
<td>9796</td>
<td>10.1</td>
<td>78.9</td>
<td>5.4</td>
<td>-</td>
</tr>
</tbody>
</table>

Mean | 62.1 | 7063 | 8.8 | 120.0 | 9.3 |

*Westergren
The blood granulocyte concentration does not always reflect the size of BGM, and distribution of the majority of the granulocytes into the marginal pool may result in "leukopenia" when BGM is normal or increased. Marginated granulocytes are in dynamic equilibrium with those in the axial blood. In contrast, cells damaged during prolonged labeling, in vitro, rapidly leave the axial blood and do not reappear, and results, through artifact, in high values of BGM. Hematologic and leukokinetic studies suggest that the leukopenia observed in one patient (Case No. 1, table 2) is an example of 'leukopenia" due to marginal distribution of the granulocytes.

Infection was characterized by the presence of enlarged BGM and increased GTR. In the 11 patients with cancer kinetic patterns were more variable. The BGM was increased in 5 patients but the GTR was increased above the normal range in only one of these; in the other 4 cases it was in the upper normal range. This pattern was similar to, but less marked than, that seen in the patients with infection and reflects a slight increase in granulopoiesis, probably due to the stimulation of the bone marrow by tumor or tissue necrosis. In the 6 cancer subjects with normal BGM values the GTR was slightly increased in 1 case, normal in 2 cases and at the lower limits of normal in 3 cases. In these subjects the deviation of BGM from the mean control value was accompanied by a proportionate deviation in the GTR in all except one patient (No. 3, table 3). The ability of this patient to maintain a normal BGM with reduced granulocyte production suggests the possibility that the tumor altered the ability of the granulocytes to leave the circulation by some unknown mechanism. This possibility is also suggested in Case Nos. 7, 8 and 9 who show
Table 3.—Leukokinetic Data in Patients with Carcinoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex and Age</th>
<th>Weight (Kg.)</th>
<th>Site of Primary Tumor</th>
<th>Extent of Disease</th>
<th>Hemoglobin (Gm. per 100 ml.)</th>
<th>ESR* (mm. in 1 hr.)</th>
<th>Blood Granulocyte Concentration (per cu. mm.)</th>
<th>T 1/2 (hrs.)</th>
<th>BGM (G x 10⁶)</th>
<th>GTR (G x 10⁶/hr.)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M – 47</td>
<td>65.9</td>
<td>Testis</td>
<td>Para-aortic and pulmonary metastases</td>
<td>14.4</td>
<td>23</td>
<td>5225</td>
<td>7.0</td>
<td>40.3</td>
<td>4.0</td>
<td>No weight loss</td>
</tr>
<tr>
<td>2</td>
<td>M – 53</td>
<td>63.2</td>
<td>Orbit</td>
<td>Extensive local invasion of adjacent sinuses</td>
<td>9.5</td>
<td>47</td>
<td>4654</td>
<td>7.7</td>
<td>40.6</td>
<td>3.7</td>
<td>12 lb. wt. loss in 3 months</td>
</tr>
<tr>
<td>3</td>
<td>F – 74</td>
<td>48.2</td>
<td>Breast</td>
<td>Brain bone</td>
<td>10.6</td>
<td>68</td>
<td>5607</td>
<td>10.8</td>
<td>37.4</td>
<td>2.4</td>
<td>No weight loss</td>
</tr>
<tr>
<td>4</td>
<td>F – 68</td>
<td>63.4</td>
<td>Colon</td>
<td>Palpable colonic mass; no evidence of metastases</td>
<td>12.1</td>
<td>75</td>
<td>2446</td>
<td>7.2</td>
<td>25.2</td>
<td>2.4</td>
<td>No weight loss</td>
</tr>
<tr>
<td>5</td>
<td>M – 68</td>
<td>59.0</td>
<td>Kidney</td>
<td>Widespread</td>
<td>8.7</td>
<td>110</td>
<td>3985</td>
<td>6.7</td>
<td>23.9</td>
<td>2.5</td>
<td>Cachexia present; 5 lb. wt. loss in 20 days</td>
</tr>
<tr>
<td>6</td>
<td>M – 70</td>
<td>57.3</td>
<td>Prostate</td>
<td>Widespread osteoblastic metastases</td>
<td>11.9</td>
<td>23</td>
<td>3906</td>
<td>6.4</td>
<td>52.5</td>
<td>5.6</td>
<td>No recent wt. loss</td>
</tr>
<tr>
<td>7</td>
<td>M – 57</td>
<td>57.7</td>
<td>Tongue</td>
<td>Invasion of neck, lungs; necrotic tumor at autopsy</td>
<td>11.1</td>
<td>80</td>
<td>8505</td>
<td>11.6</td>
<td>90.1</td>
<td>5.4</td>
<td>Marked cachexia</td>
</tr>
<tr>
<td>8</td>
<td>M – 78</td>
<td>72.7</td>
<td>Unknown</td>
<td>Generalized lymph node, liver and bone metastases</td>
<td>7.9</td>
<td>160</td>
<td>5104</td>
<td>10.3</td>
<td>64.0</td>
<td>4.4</td>
<td>Marked wt. loss</td>
</tr>
<tr>
<td>9</td>
<td>M – 78</td>
<td>61.4</td>
<td>Kidney</td>
<td>No metastases; tumor necrotic</td>
<td>18.1</td>
<td>1</td>
<td>7304</td>
<td>12.3</td>
<td>81.3</td>
<td>4.6</td>
<td>Marked wt. loss</td>
</tr>
<tr>
<td>10</td>
<td>M – 59</td>
<td>73.2</td>
<td>Parotid</td>
<td>Local recurrence only</td>
<td>12.7</td>
<td>40</td>
<td>5038</td>
<td>8.0</td>
<td>58.3</td>
<td>5.5</td>
<td>Marked wt. loss</td>
</tr>
<tr>
<td>11</td>
<td>F – 60</td>
<td>54.6</td>
<td>Colon</td>
<td>Hepatic and lymph node involvement</td>
<td>11.2</td>
<td>52</td>
<td>8580</td>
<td>6.1</td>
<td>111.0</td>
<td>12.6</td>
<td>No weight loss</td>
</tr>
</tbody>
</table>

Mean = 61.5
Range (48.2–73.2)

*Westergren
### Table 4.—Leukokinetic Data in Subjects with Carcinoma of the Lung and Superimposed Pulmonary Infection

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex and Age</th>
<th>Weight (Kg.)</th>
<th>Extent of Disease</th>
<th>Hemoglobin (Gm. per 100 ml.)</th>
<th>ESR* (mm. in 1 hr.)</th>
<th>Blood Granulocyte Concentration (per cu. mm.)</th>
<th>T ½ (hrs.)</th>
<th>HGM (G x 10⁹)</th>
<th>GTR (G x 10⁹/hr.)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M – 49</td>
<td>57.8</td>
<td>Metastases to lymph nodes, kidneys, liver, adrenals, heart pelvis and bones</td>
<td>10.0</td>
<td>107</td>
<td>8280</td>
<td>12.4</td>
<td>239.2</td>
<td>13.4</td>
<td>Had a purulent bronchitis</td>
</tr>
<tr>
<td>2</td>
<td>M – 54</td>
<td>61.4</td>
<td>Inoperable. No distant metastases</td>
<td>14.7</td>
<td>88</td>
<td>13,464</td>
<td>9.2</td>
<td>95.7</td>
<td>7.2</td>
<td>Aware of weight loss; had purulent sputum</td>
</tr>
<tr>
<td>3</td>
<td>M – 69</td>
<td>45.5</td>
<td>Operable. No evidence of metastases</td>
<td>8.0</td>
<td>90</td>
<td>6619</td>
<td>6.7</td>
<td>93.0</td>
<td>9.6</td>
<td>Aware of weight loss: acute and chronic large abscess at operation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td></td>
<td>9454</td>
<td>9.4</td>
<td>142.6</td>
</tr>
</tbody>
</table>

*Westergren
deviations from the normal mean BGM unaccompanied by proportionate increases in GTR. These results contrast with the findings in Case No. 11 who had a marked expansion of BGM associated with a marked increase in the GTR.

The 3 patients with infection superimposed upon carcinoma were able to respond with an appropriate increase in leukocyte production and showed no evidence that their tumors altered this response.

None of the cancer patients showed evidence of failure of granulopoiesis and in this respect the granulocytic series fares better than the erythroid. In the one patient (No. 11) with a marked increase in the loss of granulocytes the random removal mechanism suggests increased utilization rather than cell destruction in the circulation. No evidence for an hemolysis equivalent was found in the group of subjects with carcinoma.

If the assumption that a steady state exists is incorrect, the conclusions reached are to some extent changed. Alterations in T½ with respect to BGM would merely reflect the variations in cell production rate characteristic of any negative feedback system, and the greater variation in the diseased patients would reflect greater disturbances in homeostasis or failure of negative feedback control mechanisms. This might explain the absence of a correlation between BGM and T½ in diseased subjects. No matter what the stability of BGM, carcinoma does not apparently suppress granulopoiesis significantly. If steady state conditions did not exist the suggestion made previously that tumor may inhibit the exodus of granulocytes from the circulation would have to be abandoned in favor of the simple explanation that the negative feedback mechanism had shut off granulopoiesis to allow the BGM to return towards normal.

**Summary**

Leukokinetic studies were performed using granulocytes labeled in vitro with radioactive diisopropylfluorophosphate (DFP32). The half-time of the granulocytes in the circulation, blood granulocyte mass and granulocyte turnover rates were determined.

In control subjects the mean half-life was 6.44 hours with a range of 5.1 to 7.7 hours. The mean blood granulocyte mass was \(38 \times 10^9\) cells with a range of 19.9 to 36.4 \(\times 10^9\) cells and the granulocyte turnover rate was \(4.08 \times 10^9\) cells per hour with a range of 2.51 to 5.50 \(\times 10^9\) cells per hour. There was a direct relationship between the half-life and the blood granulocyte mass in the control subjects.

In 6 subjects with infection the blood granulocyte mass was uniformly increased. The mean half-life and mean granulocyte turnover rate were both increased above the normal range.

In 11 subjects with carcinoma several different leukokinetic patterns were found. The blood granulocyte mass was raised in 5 patients, but in only one of these was the granulocyte turnover rate increased above the normal range. In 6 subjects the blood granulocyte mass was within the normal range and deviations from the mean control value were accompanied by proportionate changes in the granulocyte turnover rate in all but 1 patient.
No relation was found between the half-life and the blood granulocyte mass in subjects with infection and/or carcinoma. The possibility that this was due to the establishment of a new steady state of blood granulocyte mass at altered levels of granulocyte production, or that steady state conditions did not exist has been considered. However the data are interpreted no evidence for suppressed granulopoiesis was found in subjects with advanced malignant disease.

**SUMMARIO IN INTERLINGUA**

Studios leucocinetic esseva effectuate con le utilisation de granulocytos marcate in vitro con diisopropylfluorophosphato radioactive ($\text{DFP}^{32}$). Esseva determinate le tempore de medie valor del granulocytos in le circulation, le massa del granulocytos in le sanguine, e le rapiditate del transition del granulocytos.

In subjectos de controlo le valor medie del tempore de medie valor esseva 6,44 horas con un distribution ab 5,1 ad 7,7 horas. Le valor medie del massa de granulocytos in le sanguine esseva $38 \times 10^9$ cellulas con un distribution ab 19,9 ad $36,4 \times 10^9$ cellulas. Le rapiditate del transition del granulocytos esseva al media $4,08 \times 10^9$ cellulas per hora con un distribution ab 2,51 ad $5,50 \times 10^9$ cellulas per hora. Esseva constatate un relation directe inter le tempores de medie valor e le massas de granulocytos in le sanguine in le caso del subjectos de controlo.

In 6 subjectos con infection, le massa del granulocytos del sanguine esseva uniformemente augmentate. Le valor medie del tempore d medie valor e etiam le valor medie del rapiditate del transition del granulocytos esseva elevate a nivellos supra le norma.

In 11 subjectos con carcinoma, plure differente configurations leucocinetic esseva observate. Le massa del granulocytos del sanguine esseva elevate in 5 patientes, sed in solmente 1 de iste 5 esseva notate un accelerate transition del granulocytos in comparation con le norma. In 6 patientes, le massa del granulocytos del sanguine esseva intra le area del norma, e deviationes ab le valor medie trovate in le subjectos de controlo esseva accompaniate de alterationes proportional in le rapiditate del transition del granulocytos in omne le casos con un sol exception.

Nulle relation esseva trovate inter le tempores de medie valor e le massas del granulocytos del sanguine in ulle del subjectos con infection ni in ulle del subjectos carcinoma. Es discutite le possibilitate que iste observation reflecte le establimiento de un nove stato stabile pro le massa del granulocytos del sanguine a alterate nivellos in le production del granulocytos e etiam le possibilitate que illo reflecte le absentia de un stato stabile. In omne caso, nulle evidentia esseva trovate pro un supprimite granulopoiese in subjectos con avantiate morbo maligne.

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