Granulocytopoiesis. I. Senescence and Random Loss of Neutrophilic Granulocytes in Human Beings

By T. M. Fliedner, E. P. Cronkite and J. S. Robertson

In order to understand and describe quantitatively a cell proliferation process like that of myelopoiesis, it is necessary to define the various subcompartments of proliferation, maturation and storage and the functional compartment as has been done by Killmann et al. However, of equal importance is the nature of the losses from the functional compartment, namely the circulating blood, and its quantitative description. The purpose of this paper is to analyze the disappearance of segmented neutrophils based on the assumption that there are two distinct means by which neutrophilic granulocytes disappear from the peripheral blood, namely random emigration and senescence, and to define the relationships between these two processes. The attainment of these objectives was made possible by the in vivo tritiated thymidine (H3TDR) labeling of granulocytes. Simultaneous serial sampling of granulocytes from the blood and from extravascular sites gives information on the loss of granulocytes by migration. Comparison of the sequence of labeling in segmented neutrophils and in their circulating pyknotic and karyorrhectic forms, described first by Undritz, provides data to estimate some time parameters of the process of senescence of the granulocytes.

Materials and Methods

Tritiated thymidine was administered intravenously to six patients. The initial clinical and hematologic diagnoses, amount of thymidine given, average number of segmented neutrophilic granulocytes per mm.³ blood and fraction of pyknotic granulocytes are given in table 1.*

Neutrophilic granulocytes in blood in their segmented and pyknotic form were studied in smears of concentrated leukocytes. Concentrates were prepared by sedimentation of red cells with dextran for 30 minutes (2 ml whole blood incubated at room temperature for 1 hour with 0.25 ml of 10 per cent dextran in 5 per cent dextrose and 0.25 ml of 1 per cent EDTA in 1.4 saline). The supernatant, containing mainly leukocytes and platelets with a few red cells is carefully pipetted off and spun at 1000 rpm for 5 minutes. The cell-free supernatant is then removed leaving enough to resuspend the button of leukocytes to give a concentration of about 200–300,000/mm.³ Smears are made on carefully cleaned microscope slides, rapidly air dried, fixed in absolute methyl alcohol by three successive changes of 10 minutes each. Then the slides are processed for autoradiography according

From the Medical Research Center, Brookhaven National Laboratory, Upton, New York. Research supported by the U. S. Atomic Energy Commission.

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†Na₂ ethylenediamine tetraacetate.

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to the methods described in principle by Pelc\textsuperscript{5} AR10 stripping film as well as NTB\textsuperscript{2} liquid emulsion is used. Exposure times were determined by taking sample slides off at various intervals to get maximum label of about 60–80 grains per cell. Development, fixation, washing of the autoradiographs as well as staining with Giemsa were performed as described in the past.\textsuperscript{6}

Neutrophilic granulocytes in an extravascular site are studied in oral lavage preparations. These are prepared by washing the mouth with 50 ml. of isotonic saline. The saline is centrifuged at 1000 rpm for 5 minutes. The saline is decanted and the button of cells and mucous is resuspended in about 2 ml. of autologous serum. Care is taken to break up clumps as much as possible. This suspension is centrifuged at 1000 rpm for 3 minutes and most of the serum removed. The button is resuspended in minute amounts of serum and smeared like a blood smear on microscopic slides. Thereafter, the smears are handled the same as the leukocyte concentrates and processed for autoradiography.

At each time interval, at least 500 clearcut segmented neutrophilic granulocytes are counted in the smears of the leukocyte concentrate in order to determine the fraction that is labeled. A neutrophil is classified as segmented, if the nucleus shows at least one segment connected with the remainder of the nucleus by a filamentous chromatin fiber. In the same smears, the frequency of pyknotic neutrophilic granulocytes per 1000 segmented forms is determined and at least 25 pyknotic forms counted to determine the fraction that is labeled. (It is recognized that the determination of the labeling indices based on at least 25 pyknotic forms for each point does not have a high statistical reliability. However, in order to find this many pyknotic forms, about 5000 granulocytes have to be scanned.) A cell is classified as a pyknotic neutrophilic granulocyte in accordance with the description of Heilmeyer and Begemann\textsuperscript{7} and Undritz\textsuperscript{8} of “Abbauformen.” In oral lavage preparations, at least 200 clearcut segmented neutrophilic granulocytes were counted in order to determine the fraction of labeling. Simultaneously, the appearance and disappearance of label in other cells present (epithelial cells, lymphocytes, monocytes) was recorded, but the results will be given elsewhere.\textsuperscript{9}

RESULTS

Senescence of Neutrophilic Granulocytes in the Peripheral Blood

In figure 1, an example of an unlabeled pyknotic neutrophilic granulocyte in leukocytic concentrates of the patients studied is shown. These cells are distinctly different from all other segmented forms because of the loss of nuclear structure in the nuclear remnants, which appear as structureless “chromatin droplets” in an intact cytoplasm of normal neutrophilic appearance. The filamentous connections between individual lobes or segments have disappeared.

In figures 2 a,b,c,d and in 4, the appearance of label in segmented neutrophils and in pyknotic neutrophils as a function of time after H\textsuperscript{3}TDR injection is shown for the six patients studied. The first labeled segmented neutrophils appeared in the blood between the second and fifth day after H\textsuperscript{3}TDR administration, varying somewhat from patient to patient. In three patients, the granulocytes emerged between the third and fourth day. Regardless of the emergence time of labeled segmented granulocytes, labeling was not observed in the pyknotic granulocytes until 24 to 36 hours later. Thereafter,
Fig. 1.—Pyknotic neutrophilic granulocyte in leukocytic concentrate smear of patient Mr. H. Note the loss of chromatin structure in nuclear droplets of the pyknotic cell compared to the distinct patterns in the other neutrophils.

the ascending slope of labeling is parallel for the segmented and pyknotic granulocytes until the maximum labeling index is reached. For comparable per cent of labeling, the difference between the curves is between 24 and 36 hours. At later time intervals, the curves are similar; in Mr. B (fig. 4) it appears that the labeling curve of the pyknotic forms lags somewhat behind that of the segmented forms in the blood and in the oral lavage preparations at all time intervals, but is similar in the general pattern.
SENESCENCE AND LOSS OF NEUTROPHILIC GRANULOCYTES

FIG. 2.—Appearance of labeled segmented neutrophils and of labeled pyknotic cells in the peripheral blood of four patients.

**Appearance of Labeled Neutrophils in Extravascular Sites**

In figure 3, the cytology of oral lavage preparations is demonstrated. Neutrophilic segmented granulocytes can be detected without any difficulty: "Neither in blood film nor in fixed tissue sections can they be confused with any other cell," (Bunting 1938). The most frequent cell, however, is the epithelial cell with a distinct round to oval shaped nucleus and a delicate, fine nuclear structure and usually an ill defined cytoplasmic outline. More difficult is the identification of lymphocytes and monocytes or other round cells. Bacteria are present usually in large amounts and clumps. Red cells are not present in the oral lavages, demonstrating that the granulocytes are not a contaminant from minute hemorrhages but rather the result of active emigration which occurs under normal environmental circumstances.

In figure 4 the appearance of labeled neutrophils in the peripheral blood and in oral lavages are compared in two patients (Mr. B and Mr. D.). It will be noted that labeled segmented granulocytes simultaneously appear in the oral lavages and in the peripheral blood although the time of appearance is between 84 and 96 hours in Mr. B. and 108 and 120 hours in Mr. D. At most time intervals, the fraction that is labeled in oral lavage preparations is greater than the labeling index in the peripheral blood, but the general pattern of intermediate rises and declines is similar.

**DISCUSSION**

The fate of neutrophilic granulocytes after discharge into the peripheral blood and the precise description of the time parameters involved is puzzling.
Two concepts have been proposed in the past. Sabin, Cunningham, Doan and Kindwall\textsuperscript{11} were the first to attempt to quantify neutrophil turnover. From their study of the occurrence of showers of dying, non-motile leukocytes in the circulation they concluded that about 6 per cent of neutrophils die in 8 hours or about one-fifth of all neutrophils in 24 hours. Although this report was not confirmed by Smith and McDowell\textsuperscript{12} it indicates one line of reasoning for the ultimate fate of granulocytes, namely dying in the circulation and removal by the reticulo-endothelial cells primarily in the spleen and liver. The fact that granulocytes are able to undergo an aging process and become pyknotic was shown by Osgood\textsuperscript{13} in blood cultures of normal human beings.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{fig3}
\caption{Smears of cell concentrate of oral lavages. Note labeled granulocyte in 3a; an unlabeled granulocyte is shown in 3b among many epithelial cells. Usually, large numbers of various bacteria are present.}
\end{figure}
Within 24 to 72 hours, most granulocytes disappear from the blood culture after development of karyorrhexis and karyolysis. In 1919, Kaznelson described "rare cell forms of the circulating blood." He described macrophages containing chromatin droplets of various sizes signifying phagocytosis of nucleated cells in a case of bacteremia. In another case, he was able to follow this process from the beginning of the pyknosis of a leukocyte nucleus to the formation of structureless nuclear droplets which finally became vasoules. In 1933, Zadeck described extensively the stages of leukocytic degradation in inflammatory exudates. Undritz was the first to describe pyknotic granulocytes or "Abbauformen" in blood smears of normal persons and in various disorders. Heilmeyer-v.Mutius reviewed the present knowledge of the occurrence of pyknotic granulocytes and gives a detailed description of the cytology of this distinct granulocytic form. However, senescence is not the only possible fate of granulocytes since they obviously

Fig. 4.—Appearance of labeled granulocytes in blood and oral lavages and of pyknotic granulocytes in blood in two patients. The background correction was performed using a modification of the method published by Stillstrom.
participate in inflammatory reactions. In addition, Isaacs and Danielian were
the first to demonstrate large numbers of leukocytes in saliva. These leuko-
cytes did not come from the salivary glands since the saliva obtained by
catherization of the salivary ducts was practically free of granulocytes. These
authors concluded that mucous membranes of the mouth (and probably that
of other parts of the gastrointestinal tract) are sites at which granulocytes
emigrate from the blood. Whether this phenomenon is part of a normal regu-
laratory method or a response to the presence of commensal bacteria is not
clear. The work of Ambrus and Ambrus as well as the studies of Bieman
suggest that the lung acts as a filter for leukocytes in general and thus plays
a major role in regulating leukocyte concentration by trapping cells when
the count is high and releasing cells when the count is low. Some insight into
the role of granulocyte emigration into areas covered by a high density of
commensal bacteria can be gained by the studies on the role of the granulo-
cyte in the development of infecton by commensal organism after whole
body irradiation and by the first successful transfusions of homologous
granulocytes. By transusion of fresh granulocytes into fatally irradiated
dogs with aplastic marrows and no granulocytes of their own, it was clearly
shown by Cronkite, Brecher and Wilbur that the transused granulocytes
eigrated into the areas that are frequently the portals of entry for bacte-
rial infection setting up a defensive wall against the commensal organisms
and thus changed the histologic picture of radiation injury. From these
studies one can infer that the commensal organisms may have a
chemotactic influence that induces the granulocytes to emigrate into these
areas.

If one accepts the pyknotic forms as the normal mode of senescence irre-
spective of the mechanism of the emigration, there are clearly at least two
routes by which granulocytes are lost from the blood: (1) emigration out of
the blood stream (2) Removal of pyknotic cells presumably by the reticulo-
histioytic system. For the present purposes it will be assumed that the
pyknotic cells described here are a consequence of senescence of neutrophilic
granulocytes. Other mechanisms for the production of pyknosis are imagi-
able but the available data tend to support the assumption of senescence.
The data presented in this paper show that both aspects of the end of the life
cycle of neutrophils can be studied simultaneously. The fact that labeled
granulocytes appear at the same time (within an error of 6 hours due to
sampling intervals) both in oral lavages and in blood indicates that there is
a random process of emigration of these cells from the circulation since
granulocytes in oral lavages must have passed through a capillary wall
at least once into tissue and to the surface. The fact that the proportion of
labeled cells is at all times somewhat higher than in the blood could be
interpreted that the newly formed cells have a preference for migration over
older cells. However, the findings of the labeling pattern of pyknotic cells in-
dicates that the random loss by emigration is apparently truncated by an
aging process which terminates the life of the granulocytes.

Mauer et al. have labeled autologous granulocytes in human beings in
vitro with DFP. The autologous transfusion of these labeled cells in a large series of normal human beings has demonstrated clearly a random disappearance of the label from the peripheral blood with a mean half-time of 6.6 ± 1.4 hours. This half-time is compatible with the survival of transfused Pelger cells. Our studies give cytologic and autoradiographic evidence for a random loss thus supporting the numbers obtained in the DFP study. In order to make calculations on the time spent in pyknosis a diagrammatic model incorporating the concepts discussed above is shown in figure 5. The numerical estimates utilize this model and various assumed values for the half-time of granulocytes in the blood distributed around Mauer's average of 6.6 hours.

In order to use this model as a basis for developing a mathematical explanation for the rate of disappearance of labeled granulocytes from the circulation, we shall use the following notation:

\[ N = \text{number of normal granulocytes in the circulation} \]
\[ P = \text{number of pyknotic granulocytes in the circulation} \]
\[ \lambda_1 = \text{fraction of } N \text{ becoming } P \text{ in unit time} \]
\[ \lambda_2 = \text{fraction of } P \text{ leaving the circulation in unit time} \]
\[ \lambda_3 = \text{fraction of } N \text{ leaving the circulation in unit time} \]

It is assumed that during the period of interest, \( N, P, \) and the \( \lambda \)'s are constant. For this to be true, the rate of production of pyknotic cells must equal their rate of loss from the circulation. Symbolically:

\[ \lambda_1 N = \lambda_2 P \]  \hspace{1cm} (1)

from which:

\[ \frac{\lambda_1}{\lambda_2} = \frac{P}{N} \]  \hspace{1cm} (2)

Equation (2) indicates that the fractional rate of conversion of \( N \) to \( P \) is to the fractional rate of removal of the pyknotic cells as \( P \) is to \( N \). If one assumes that pyknotic granulocytes are present in the ratio of about 1:500 to the normal cells present, \( \lambda_2 \) is 500 times \( \lambda_1 \). Thus, if the fractional rate of removal of the pyknotic cells, \( \lambda_2 \), is known, \( \lambda_1 \) can be calculated. If it can further be assumed as being known, that the cells become pyknotic only after remaining some 30 hours (\( t_n \)) in the circulation, the product \( \lambda_1 N \) represents a final (rather than a random) rate process leading to the disappearance of normal cells. In the meantime, the cells constituting \( N \) have been subject to random loss described by \( \lambda_3 N \). The relationships involved are diagrammed in figure 6. The rate of inflow of normal cells must equal the total rate of loss, \( (\lambda_1 + \lambda_3) N \). Thus it is necessary to find a value for \( \lambda_3 \) such that for \( t_n = 30 \) hours (or whatever time is established for the conversion of \( N \) to \( P \)), the rate of flow of a given cohort of cells, \( \Delta N \), is diminished from \( (\lambda_1 + \lambda_3) N \) to \( \lambda_1 N \) by an exponential process describing the random rate of loss:

\[ \lambda_1 N = (\lambda_1 + \lambda_3) N \cdot e^{-\lambda_3 (t_n)} \]  \hspace{1cm} (3)

which leads to:

\[ \lambda_3 = \lambda_1 \left( e^{\lambda_3 (t_n)} - 1 \right) \]  \hspace{1cm} (4)

With equation (4), \( \lambda_3 \) can be calculated for a given \( \lambda_1 \) (by use of the series expansion of \( e^{\lambda_3 (t_n)} \)) or \( \lambda_1 \) can be calculated for a given \( \lambda_3 \). Table 2 indicates some examples of the relationship among \( \lambda_1, \lambda_2 \) and \( \lambda_3 \), for \( \lambda_2 = 500 \lambda_1 \) and for \( t = 30 \) hours. In equation (4) the value of \( \lambda_1 \) is restricted to \( \lambda_1 < \frac{1}{30} \) because larger values of \( \lambda_1 \) require negative values for \( \lambda_3 \). This restriction in turn means that for \( \lambda_2 = 500 \lambda_1 \) the half-time for \( P \) must be greater than about 2.5 minutes. Because of the mutual dependencies of \( \lambda_1, \lambda_2 \)
**Fig. 5.**—Diagrammatic model illustrating relationships among rate of entry of granulocytes into the circulation [(λ₁ + λ₃) N], conversion to pyknotic cells [λ₁N], removal of pyknotic cells [λ₂P] and loss from the circulation by random processes [λ₃N]. Degeneration of N to P is a terminal, not a random process.

**Fig. 6.**—Conversion of figure 5 to a model including the role of time as it affects the number of a given cohort of granulocytic, and later pyknotic, cells in the circulation. An entering cohort, ΔN = (λ₁ + λ₃) NΔt, diminishes in number exponentially due to random losses expressed by λ₃, until t₅₀, when a terminal pyknosis described by λ₁N occurs, with subsequent removal from the circulation by λ₂P.

and λ₃, experimental determination of any one makes it possible to calculate the other two, provided that P/N and t₅₀ are also known. As may be seen in table 2 very short half-times for the pyknotic cells call for small values of λ₃, with correspondingly long half-times for the loss from N by random processes.

The preceding calculations utilized an assumed N/P ratio of 500, an experimental approximation of 30 hours for the t₅₀ and various values for the half-time of granulocytes in the blood to show the variations in λ₂ as the half-time in the blood is varied. If it is considered desirable to make precise estimates of the half-time of pyknotic cells in various disease states one can appreciate the necessity of precision in determination of t₅₀, N/P and the T½ of granulocytes in the blood by the DFP³² method. In our studies t₅₀ can not be determined more precisely than 6 hours because this interval was used in sampling our patients. The ratio N/P can be determined to any degree of accuracy desired by counting larger numbers of cells. The half-time of granulocytes in the blood is subject to the errors that are discussed by Mauer et al. In normal individuals, the half-time was 6.6 ± 1.4 hours. The range among 45 normal males was 4.0 to 9.0 hours. With such a range among normal individuals and the great sensitivity of equation (4) to variations in λ₃ it would be necessary to determine the DFP³² half-time in
Table 1

<table>
<thead>
<tr>
<th>Patient's Initial and Weight</th>
<th>Clinical(^1) and Hematologic(^2) Diagnosis</th>
<th>Amount of Thymidine Given in (\mu\text{c./Gm. Body Weight})</th>
<th>Average Number of Pyknotic Granulocytes per 1000 Neutrophils</th>
<th>Total WBC (% Seg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr. S. (64.5 Kg.)</td>
<td>1. Glioblastoma multiforme 2. Compensated steady state</td>
<td>0.31 (\mu\text{c./Gm.}) (Spec. act. 1.3 C/mM)</td>
<td>8.5</td>
<td>13,000 (72% Seg.)</td>
</tr>
<tr>
<td>Mr. D. (88.5 Kg.)</td>
<td>1. Osteoarthrosis 2. Compensated steady state</td>
<td>0.1 (\mu\text{c./Gm.}) (Spec. act. 1.9 C/mM)</td>
<td>3.6</td>
<td>6,500 (53% Seg.)</td>
</tr>
<tr>
<td>Mr. B. (67.5 Kg.)</td>
<td>1. Polycythemia vera 2. Compensated steady state p. therapy</td>
<td>0.1 (\mu\text{c./Gm.}) (Spec. act. 1.9 C/mM)</td>
<td>1.5</td>
<td>13,300 (75% Seg.)</td>
</tr>
<tr>
<td>Mr. H. (62.5 Kg.)</td>
<td>1. Myelofibrosis 2. Extramedullary hemopoiesis</td>
<td>0.08 (\mu\text{c./Gm.}) (Spec. act. 1.3 C/mM)</td>
<td>5.5</td>
<td>68,000 (53% Seg.)</td>
</tr>
<tr>
<td>Mrs. N. (53 Kg.)</td>
<td>1. Lymphosarcoma 2. Compensated steady state</td>
<td>0.18 (\mu\text{c./Gm.}) (Spec. act. 1.9 C/mM)</td>
<td>5.2</td>
<td>7,400 (48% Seg.)</td>
</tr>
<tr>
<td>Mrs. Sk. (51.3 Kg.)</td>
<td>1. Pernicious anemia 2. Leukopenia</td>
<td>0.1 (\mu\text{c./Gm.}) (Spec. act. 1.9 C/mM)</td>
<td>3.0</td>
<td>3,600 (70% Seg.)</td>
</tr>
</tbody>
</table>

Table 2.—Rate Constants Consistent with \(t_N = 30\) Hours and N/P = 500

<table>
<thead>
<tr>
<th>(T_{1/2}) N Hours</th>
<th>(\lambda_1) Hours(^{-1})</th>
<th>(\lambda_2) Hours(^{-1})</th>
<th>(\lambda_3) Hours(^{-1})</th>
<th>(T_{1/2}) P Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>0.139</td>
<td>0.00218</td>
<td>1.09</td>
<td>65.4</td>
</tr>
<tr>
<td>6.93</td>
<td>0.10</td>
<td>0.00524</td>
<td>2.62</td>
<td>15.9</td>
</tr>
<tr>
<td>11.5</td>
<td>0.06</td>
<td>0.01188</td>
<td>5.94</td>
<td>7.0</td>
</tr>
<tr>
<td>23.1</td>
<td>0.03</td>
<td>0.02055</td>
<td>10.28</td>
<td>4.0</td>
</tr>
<tr>
<td>69.3</td>
<td>0.01</td>
<td>0.02857</td>
<td>14.28</td>
<td>2.9</td>
</tr>
<tr>
<td>(\infty)</td>
<td>0</td>
<td>0.03333</td>
<td>16.66</td>
<td>2.5</td>
</tr>
</tbody>
</table>

\(\lambda_3 = \lambda_1 (e^{\lambda_1 (30)} - 1)\).
\(\lambda_2 = 500 \lambda_1\).
See figures 5 and 6 for meanings of \(\lambda\)'s.

each individual under consideration in order to have useful numbers. However, if there are myelocytes in the peripheral blood (e.g. metaplasias etc), which also label with DFP,\(^{32}\) one will not measure only granulocyte half-time. Experimentally the problem is further complicated in attempting to determine \(t_N\) since the latter is dependent upon a precise estimate of the initial emergence of labeled granulocytes from the marrow into the blood. Since the latter can not be predicted for a given individual,\(^{24}\) it would be necessary to sample at intervals that are impractical. For example, if \(t_N\) needs to be known within 1 hour, hourly samples would be needed over about a 3–5 day period.
In table 1 we present the P/N ratios for our patients. In view of the
preceding discussion emphasizing the dependency of $A_2$ upon precise estimates
of $t_s$ and granulocyte half-time we could see no reason to compute the
pyknotic half-time since it might be in serious error because of the various
reasons discussed above.

**Summary and Conclusions**

Tritiated thymidine labeling of DNA with a subsequent autoradiographic
and cytologic study of the peripheral blood and oral lavages reveal:

1. Direct cytologic evidence for a random loss of granulocytes from the
blood into the oral cavity is given. Presumably there are larger random losses
in the gastrointestinal tract. This observation supports the conclusions based
upon disappearance of radioactivity from the blood after autotransfusion of
DFP$^{32}$ labeled granulocytes.

2. The delayed appearance of label in the pyknotic granulocytes (Ab-
baufomen) is strong evidence that those cells are older degenerating granulo-
cytes and that it takes about 24–30 hours for labeled granulocytes to age to
the point of becoming pyknotic senescent granulocytes.

3. The process of senescence truncates the exponential curves of random
disappearance of granulocytes from the blood.

4. A model showing the relationship between random loss and senescence is
constructed and discussed.

5. A mathematical description of this model is presented. The equations
developed are highly sensitive to variations in input data thus limiting their
practical usefulness for computations unless precise measurements are possi-
ble and are made on each subject studied for each variant in the equation.

**Summario in Interlingua**

Le sequente factos esseva establite per un investigation utilisante marcation
de acido deoxyribonucleic con thymidina tritiate, sequite de studios auto-
radiographic e cytologic del sanguine peripheric e de lavages oral:

1. Il existe directe evidentia pro un perdita aleatori de granulocytos ab le
sanguine ad in le cavitate oral. Il pote esser supponite que plus considerabile
perditas aleatori occurre in le vias gastrointestinal. Iste observation supporta
le conclusiones que es basate in le disparition de radioactivitate ab le sanguine
post le autotransfusion de granulocytos marcate con radioactive diisopropyl-
fluorophosphato (DFP$^{32}$).

2. Le tardive apparition del marcage in le granulocytos pyknotic (= Ab-
baufomen) representa un forte evidentia pro considerar ille cellulas como
vetule granulocytos in stato de degeneration e pro le these que circa 24 a 30
horas es requisite pro que marcate granulocytos avantia al puncto de devenir
senescente granulocytos pyknotic.

3. Le processo del senescentia produce un truncation del curvas exponential
del disparition aleatori de granulocytos ab le sanguine.

4. Es construite e discutite un modello que monstra le relation inter le
perdita aleatori e le senescentia.
5. Es presentate un description mathematic de ille modello. Le equationes obtenite es altemente sensibile pro variationes in le datos experimental, lo que reduce le utilitate de ille equationes pro objectivos de computation practic, excepte si precisissime mesurationes es possibile e pote esser repetite in omne studiate subjecto individual pro omne variabile individual in le equationes.

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Theodor M. Fliedner, M.D., Medical Klinik d. Universitat, Freiburg/Breisgau, Germany

Eugene P. Cronkite, M.D., Head, Division of Experimental Pathology, Medical Research Center, Brookhaven National Laboratory, Upton, Long Island, N. Y.

James S. Robertson, M.D., Ph.D., Head, Division of Medical Physics, Medical Research Center, Brookhaven National Laboratory, Upton, Long Island, N. Y.
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