The Pelger-Huët Anomaly in Three Families and Its Use in Determining the Disappearance of Transfused Neutrophils from the Peripheral Blood

By WENDELL F. ROSEE AND CLIFFORD W. GURNEE

The Pelger-Huët anomaly, first described by Pelger in 19281 and confirmed by Huët in 1931,2 is a familial, congenital anomaly of the leukocytes characterized by decreased segmentation of the nucleus, distinctive nuclear forms and pyknosis of the nuclear chromatin out of proportion to the nuclear area. These changes are best seen in the neutrophilic series. The anomaly has been reported in persons of Caucasoid, Oriental and Negroid stock.3-17

The purpose of this paper is twofold: (1) to report 13 further cases of Pelger-Huët anomaly in three families, including the second reported occurrence among Negroes, and (2) to report the results of the use of Pelger-Huët cells in demonstrating the disappearance of transfused leukocytes from the peripheral blood. The literature prior to 1955 has been reviewed extensively by Klein, Hussar and Bornstein,7 and any further systematic review would be superfluous. A discussion of Harm’s morphologic classification18 and other facets of the anomaly will be included insofar as they are related to the present cases.

Case Reports

A. Case 1. Mrs. S. De W. K., age 20, a student nurse of Dutch extraction, was admitted to Nebraska Methodist Hospital in July, 1955, with complaints of aching pain in the right upper quadrant of the abdomen, a mild fever and mild jaundice and scleral icterus. The liver was enlarged and tender; subsequent laboratory tests established the diagnosis of infectious hepatitis. On admission, the total white blood count was 5,500 cells per cu. mm. and the differential blood count was as follows: segmented neutrophils, 33%; stab and metamyelocytes, 36%; lymphocytes, 22%; monocytes, 5%; eosinophils, 3%; and basophils, 1%. The hemoglobin was 12.6 Gm. %. Typical Pelger-Huët cells were seen in the peripheral blood smears; no segmented neutrophils had more than two lobes of the nucleus. The presence of the anomaly was further established by examination of peripheral blood smears of members of her immediate family; the pedigree is shown in figure 1 and table 1.

During hospitalization, subsequent blood counts disclosed no significant change. The patient was discharged in August, 1955, on a program of conservative therapy and was apparently well until an exacerbation of her hepatitis occurred in the summer of 1956. At that time, the blood picture was essentially the same as when first seen. Neither she nor any members of her family gave a history of previous serious, repeated or recurrent illnesses.

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The authors wish to express their gratitude to Dr. John R. Schenken, Pathologist, Nebraska Methodist Hospital, for equipment and facilities he provided for the transfusion experiments; to the members of his laboratory group; and to Martin P. Dumler for his great assistance during the transfusions. Especial thanks are given to the long-suffering members of the families described herein.

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B. Case 2. Mrs. K. S., a 35-year-old Negro woman, was seen in the University of Nebraska Hospital in October, 1955, where she delivered a normal child without puerperal complications. Examination of her peripheral blood smear at that time revealed typical Pelger-Huët cells; no segmented neutrophils had nuclei with more than two lobes. In addition, 96.6 per cent of 1000 red blood cells were elliptocytes. The blood of the child, then two days old, showed typical Pelger-Huët cells without significant elliphtocytosis of the red blood cells. Examination of that part of her immediate family that was available confirmed the presence of both conditions as shown in figure 2 and table 2. The percentage of elliptocytes is indicated for each member. At the time of examination, one brother, C. S., was undergoing treatment for chronic kidney infection; otherwise no member of the family gave a history of chronic, serious, debilitating or recurrent illness. Her father had died some years previously of a "heart condition." No anemia was known to exist in the family.

C. Case 3. Mr. R. T., a 34-year-old man of Swedish extraction, was seen in the outpatient department of Nebraska Methodist Hospital in December, 1955, complaining of abdominal pain in the lower right quadrant. Acute appendicitis was suspected; however, on initial examination and subsequent observation, there was no fever, rigidity of the abdominal muscles or rebound tenderness. The total white blood count at that time was 6,200 per cu. mm., with the following differential: segmented neutrophils, 24%; stabs and metamyelocytes, 35%; lymphocytes, 34%; monocytes, 4%; eosinophils, 2%; and basophils, 1%. The leukocytes were typical Pelger-Huët cells; because of this, the "shift to the left" was disregarded, and because of the lack of physical findings, the patient was sent home where his recovery was uneventful. Investigations of his immediate family revealed the incidence of Pelger-Huët anomaly as shown in figure 3 and table 3. All three members of the family have been in good health, and none has had chronic, recurrent, debilitating or severe illness.

**DISCUSSION OF CASES**

These cases are interesting from several points of view. This is the second time that the anomaly has been reported to be found in Negroes. It is difficult to say whether this family (Case 2) was of pure racial stock; however, all known members were Negroid. In van der Sar's study, the father in the first generation was Caucasoid and had married twice. Only the descendants of his Negro wife had the anomaly; this is presumptive but not conclusive evi-
<table>
<thead>
<tr>
<th>Patients</th>
<th>Differential Counts of 100 Leukocytes</th>
<th>Differential Counts of 100 Neutrophils</th>
<th>C</th>
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A, B, C = the three types of neutrophils according to Harm's classification.
C, type C bilobed cells are divided according to symmetry; symmetrical cells are roughly equivalent to pince-nez forms.
PM = pseudo-myelocyte; PMM = pseudo-metamyelocyte.
Roman numerals = number of lobes in the nucleus.
USE OF PELGER-HUËT ANOMALY

Fig. 2.—Pedigree of Case 2.

dence that she had the anomaly since the blood of the first generation was not examined.

The simultaneous incidence of the Pelger-Huët anomaly and elliptocytosis in the same family is thought by us to be fortuitous since such a combination has not been reported previously. As can be seen, the leukocyte anomaly occurs without concomitant erythrocyte anomaly (Case 3, patients W. S. Jr., and C. S.). The converse is also true (Case 3, patient B. S.). However, it is interesting to note that congenital and/or familial anomalies in association with the Pelger-Huët anomaly have been reported with some frequency.6,19,20,22

The tables showing differential counts of peripheral blood for the members of the families investigated follow Harm’s18 classification. By this system, neutrophilic leukocytes stained with Romanowsky stain may be divided into three types: type A (normal), type B (intermediate) and type C (typical Pelger-Huët). Type C cells characteristically have fewer nuclear lobes. Cells with unsegmented nuclei often predominate, and those with more than two nuclear lobes are rare. The nuclear chromatin of these cells is very basophilic and densely clumped, giving a “pitted” appearance. The nuclear outline is smooth. The nuclei of unsegmented cells are round, ovoid or short, thick, plump rods (figs. 4 and 5). Bilobed cells are either symmetrical with lobes of equal area (figs. 6 and 7) or asymmetrical, with one round and one ovoid lobe (fig. 8). The most characteristic and diagnostic cell is the so-called “pince-nez” form (fig. 6) in which the two lobes of the nucleus are round, symmetrical and joined by a thin chromatin strand.

The type B cells exhibit these properties to a lesser extent and tend toward the appearance of normal cells. The chromatin is clumped less densely and
### Table 2.—Differential Counts of the Peripheral Blood of Members of the Family of Case 2

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<th>Patients</th>
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<th>Eo</th>
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<th>I</th>
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<th>V</th>
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<th>II</th>
<th>III</th>
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</table>

A, B, C = the three types of neutrophils according to Harm's classification.
C, bilobed cells are divided according to the symmetry of the lobes of the nucleus. Cells with symmetrically divided nuclei (sym.) are roughly equivalent to pince-nez forms. See text for fuller explanation.

PM = pseudo-myelocyte; PMM = pseudo-metamyelocyte.
Roman numerals = number of lobes in the nucleus.
the nuclear forms are less characteristic and smooth in outline (see figs. 12 and 13). These cells are present in normal smears (0-15 per cent of all neutrophils) and in the blood of persons with Pelger-Huet anomaly (0-30 per cent).

The Pelger-Huet anomaly was found in rabbits and other animals, and the genetically homozygous form of the anomaly was produced in rabbits by Nachtsheim. Only one case of this form in man has been described. In the homozygous form of the anomaly in both man and rabbits, nearly all the granulocytic cells are round or ovoid and less than 5 per cent show any segmentation. The clumping of the nuclear chromatin is even more marked than in the heterozygous form.

The so-called "partial-carrier" form of Pelger-Huet anomaly has been noted in which cell types A, B and C are present simultaneously. This is now thought to be a separate entity in that it is inherited similarly to the classical form of the condition. It is rarely if ever found in families that have the classical form, which tends to exclude the possibility that it is merely a manifestation of variable expressivity. These facts are substantiated in a limited way by the cases presented in that no type C cells were seen in the smears of members having type A cells.

The cases presented illustrate several further important facts about the anomaly. Genetically, the dominant inheritance and absence of sex linkage are clearly seen. The presence of the anomaly in one child (G. S., Case 2) two days following birth is evidence that it is congenital. But most importantly, the propositus of the last case (R. T.) illustrates the importance of differentiation from a true left shift. The anomaly is recognized easily if the characteristics of the cells are kept in mind, and its presence may be verified in most cases by the same condition in other members of the family.
### Table 3.—Differential Counts of the Peripheral Blood of Members of the Family of Case 3

<table>
<thead>
<tr>
<th>Patients</th>
<th>Differential Counts of 100 Leukocytes</th>
<th>A</th>
<th>Differential Counts of 100 Neutrophils</th>
<th>C</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Lympho</td>
<td>Mono</td>
<td>Eo</td>
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<td>R. T.</td>
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</table>

A, B, and C are the three types of neutrophils according to Häm's classification. C, type C bilobed cells are divided according to symmetry of the lobes of the nucleus. Cells with symmetrically divided nuclei are roughly equivalent to pince-nez forms. See text for fuller explanations.

PM = pseudo-myelocyte; PMM = pseudo-metamyelocyte.

Roman numerals = number of lobes in the nucleus.
Fig. 4.—Type C pseudo-metamyelocyte (upper) and lymphocyte from patient with Pelger-Huët anomaly (x 2050).
Fig. 5.—Type C-I neutrophil (stab form) (x 2050).
Fig. 6.—Type C-II neutrophil with round lobes, symmetrical (typical "pince-nez" form) (x 2050).
Fig. 7.—Type C-II neutrophil with symmetrical ovoid lobes (x 2050).

The Pelger-Huët anomaly must be distinguished from several other conditions that give similar blood pictures. Cells resembling both the typical heterozygous\textsuperscript{28} and the homozygous\textsuperscript{29} forms of the condition have been found in patients with chronic myelogenous leukemia. To date, two cases of leukemia have been found in patients with personal or family histories of the anomaly.\textsuperscript{30,31} Other pseudo Pelger-Huët blood pictures are seen in enteritis.\textsuperscript{32}
Fanconi's panmyelopathy,\textsuperscript{33} viral diseases (exanthema subitum),\textsuperscript{29} malaria\textsuperscript{25} and mongoloidism.\textsuperscript{4} Careful attention to details of cellular structure will again make possible the differentiation of these diseases from the apparently harmless anomaly; further substantiation may be found in the appropriate familial incidence.

In discussing the anomaly, most of the attention has been directed toward the neutrophilic series. However, similar but less noticeable changes are seen in the other leukocytes. The nuclei of the eosinophils (fig. 9) and basophils (fig. 10) have some of the same characteristics as those of the neutrophils,
USE OF PELGER-HUËT ANOMALY

Fig. 12.—Type B-I neutrophil from patient with Pelger-Huët anomaly (x 2050).
Fig. 13.—Type B-III neutrophil (upper) contrasted with Type A-III neutrophil from sibling of patient with Pelger-Huët anomaly (x 2050).
Fig. 14.—Type A-I neutrophil (upper) contrasted with Type C-I neutrophil (lower). Following injection of normal blood into Pelger-Huët patient (x 2050). Note monocyte (center).

although this is sometimes difficult to demonstrate in routine preparations. The monocytes (fig. 14) and lymphocytes (fig. 11), especially the small round type, show greater clumping of the chromatin of the nucleus. These changes are markedly exaggerated in the one case of homozygous Pelger-Huët anomaly in a human being.24 The cytoplasm of the lymphocytes is said to be more basophilic than normal and to show a clear perinuclear zone: this, however, is not always demonstrable. It was noted in the course of our observations that the cytoplasm of the monocytes often contained larger eosinophilic
granules than are commonly encountered in normal smears. However, the folding-over (or pseudo-segmentation) of the monocytic nucleus was apparently unaffected by the presence of the anomaly.

**THE INTRAVASCULAR SURVIVAL OF INJECTED NEUTROPHILS**

Since Pelger-Huët neutrophils are morphologically distinct from normal neutrophils, they can be employed as a biologic tracer when injected into a person with normal neutrophils. Likewise, normal cells injected into a person with Pelger-Huët anomaly can be easily distinguished. These facts were used to investigate the survival time within the vascular system of injected neutrophils.

**METHOD**

**Experiment 1:** 430 ml. of whole blood from patient R. T. (Case 3, WBC 5,500; blood type A Rh CcDee) were removed rapidly by phlebotomy into 120 ml. of A.C.D. solution, using a siliconized needle, tubing and bottle. Preliminary studies had shown the absence of normal (type A) neutrophils. The blood of the donor and recipient had been matched previously, using saline and albumin suspensions of the red blood cells and the Coombs' cross-match technic. Upon completion of the phlebotomy, the blood was infused immediately into the recipient (blood type A Rh CCDee). The total time of infusion was less than 15 minutes. Previous peripheral blood smears from the recipient had shown the absence of typical Pelger-Huët (type C) neutrophils.

At specified time intervals, samples of the peripheral blood of the recipient were obtained by finger puncture; total white counts were performed with two pipettes, and four smears were made. The latter were stained with Wright's stain. The slides were relabeled and counted without knowledge of the sequence in which they had been taken. The usual differential count was done on 400 cells (100 per slide), and a total of 1000 neutrophils (250 per slide) was counted for each sample. Only type C cells were considered donor cells, all type B cells being considered recipient leukocytes. From these data, the total number of Pelger-Huët cells per cu. mm. was calculated for the time at which each sample was obtained.

**Experiment 2:** normal blood (type O RhCCDee) was given to a patient (S. DeW. K., blood type O RhCCDee) with the Pelger-Huët anomaly. In this way, the survival of transfused normal leukocytes could be determined. The donor cells were normal (WBC 8,500) and the recipient's (S. DeW. K., propositus Case 1) Pelger-Huët. The slides were again counted as unknowns, and the total number of normal cells per cu. mm. was calculated for each time interval.

**RESULTS**

The results of these experiments are given in tables 4 and 5 and figure 15. The data indicate that there is rapid decline in the number of infused cells, more than half disappearing from the peripheral blood stream within six to eight hours. The longest time any donor cells were observed was 49.2 hours. Observations in this experiment were continued to 72 hours.

**DISCUSSION**

In recent years, much evidence has accumulated to suggest the existence of a large extravascular pool of viable leukocytes. Since our investigations were not continued for a long period after disappearance of transfused leukocytes from the recipient's circulation, we cannot comment on the degree to
USE OF PELGER-HUÉT ANOMALY

Fig. 15.—Survival of injected neutrophils, as determined by using the Pelger-Huét anomaly.

Table 4.—Results of Experiment 1. 430 ml. of Whole Blood from Donor (R. T. Case 3) with Pelger-Huét (Type C) Neutrophils Injected into Recipient with Normal (Type A) Neutrophils

<table>
<thead>
<tr>
<th>Hours After Injection</th>
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<th>% Neutrophils</th>
<th>No. Neutrophils per mm.³</th>
<th>No. Type C Cells per 1000 Neutrophils</th>
<th>No. Type C Cells per mm.³</th>
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<td>18</td>
</tr>
<tr>
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<td>12,300*</td>
<td>70</td>
<td>8,610</td>
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</tr>
<tr>
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<td>12,300*</td>
<td>70</td>
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<tr>
<td>36</td>
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<tr>
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<td>12,300*</td>
<td>69</td>
<td>8,490</td>
<td>0</td>
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</tbody>
</table>

*Total white counts were not done at these times. The figure given is the average of the previous total white counts.

which leukocytes were sequestered in the extravascular pool to return at a later time to the blood stream. Therefore, this discussion will be confined to the demonstration of leukocytes in the peripheral blood during the initial phase extending from transfusion to complete disappearance from the peripheral blood. Even in this short period of time we can draw no conclusions about rates of disappearance from and re-entry into the vascular compartment. Rather, we are assessing the net decline in transfused leukocytes in this initial period.

One of the problems encountered in determining the length of survival in the peripheral blood of transfused leukocytes is tagging the exogenous cells
Table 5.—Results of Experiment 2. 430 ml. of Whole Blood from Donor with Normal
(Type A) Neutrophils Injected into Recipient (S. DeW. K.) with
Pelger-Huet (Type C) Neutrophils

<table>
<thead>
<tr>
<th>Hours After Injection</th>
<th>No. Leukocytes per mm.(^3)</th>
<th>% Neutrophils</th>
<th>No. Neutrophils per mm.(^3)</th>
<th>No. Type A Cells per 1000 Neutrophils</th>
<th>No. Type A Cells per mm.(^3)</th>
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<tr>
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<td>67</td>
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<tr>
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<tr>
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<tr>
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<td>6,700</td>
<td>62</td>
<td>4,150</td>
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</table>

so that they may be distinguished from the endogenous cells. The prime requirements in this regard are (1) distinctiveness and (2) preservation of cellular integrity. Distinctive cells have been obtained by labeling with radioactive phosphorus,\(^34\) radioactive chromium\(^35\) and Atabrine,\(^39\) or by using leukemic cells.\(^40\),\(^41\) The necessity for distinctiveness may be circumvented by studying the total leukocyte concentrations where that of the donor is markedly higher than that of the recipient;\(^42\),\(^43\) in animal experiments, the normal output of leukocytes may be suppressed by total-body irradiation.\(^41\),\(^44\),\(^45\)

Cellular integrity becomes a major factor when in vitro-tagging processes are used. During the time that the tagging is taking place, unknown and unaccountable changes are undoubtedly occurring that probably have deleterious effects upon the viability of the leukocytes.

In the above experiments, the tagging was biologic and involved no changes in the transfused cells. In making cellular counts, care was taken that only the cells entirely foreign to the recipient (type C in experiment 1, and type A in experiment 2) were recorded. The reduction of the time from removal from the donor to infusion into recipient as well as the use of siliconized equipment probably reduced the factor of altered cellular integrity to a minimum.

The results obtained by this method are comparable to those obtained by other methods. In working with humans, the maximum survival time has been estimated to be from 90 minutes\(^39\) to 65 hours in one case described by Bierman et al.\(^46\) Our results are most comparable to those of McCall and her associates\(^38\) who, using in vivo tagging with radioactive chromium, found that 80 to 85 per cent of the leukocytes were removed from the circulation within 24 hours, but that some cells apparently persisted for as long as 5 days. The longest time (49.5 hours) infused cells could be found in our experiments may have been a reflection of necessarily limited sampling. All investigators...
using human subjects noted rapid decline in the number of infused cells in
the peripheral blood; this same phenomenon was noted to a
greater extent in rodents.

Kline and Clifton, using P32 as a labeling device, and Weisberger and
Levine, using radioactive sulphur-labeled cysteine, both observed that the
normal survival time for leukocytes is 14 days. Patt has discussed reasons
why the life span of neutrophils may be appreciably shorter than the value
obtained by isotope labeling; however, the major discrepancy between the
survival time of endogenous and exogenous cells has been related to the
sequestration of the injected cells by the lungs and to a lesser extent
by the liver and spleen. This was first elucidated in human beings by
Lanman, Bierman and Byron in 1950. Using leukemic cells, they noted the
marked decrease in the number of these cells in the arterial blood as compared
with the number in the venous blood of the right ventricle. This finding has
been confirmed by others using rats and rabbits and infusing P32-labeled
leukocytes. There is disagreement about whether the cells are destroyed
in the lung or merely stored and released later. Osgood considers the lung
to be a major part of the leukocyte regulating system, whereby cells are re-
leased when needed and stored when not. Unfortunately, the present experi-
ments shed no light on this interesting aspect of the problem, since we did not
extend the observations long enough to evaluate the possibility of re-entry
into the blood stream of sequestered cells.

The similarity of the curves obtained in the two experiments indicates that
the initial phase of intravascular survival of transfused normal and Pelger-
Huët cells is essentially the same. To date, no difference other than morpho-
logic between normal and Pelger-Huët cells has been demonstrated, and
the cause of this difference remains to be elucidated.

SUMMARY

1. Thirteen cases of Pelger-Huët anomaly occurring in three families are
presented and discussed. The second recorded case of the anomaly in Negroes
is included; the occurrence of familial hereditary elliptocytosis in this same
family and the possible relationship to the Pelger-Huët anomaly are discussed.

2. Certain less well-known facts about Pelger-Huët anomaly are considered
in relation to the cases presented.

3. The survival time of transfused neutrophils in the peripheral blood was
investigated using the anomaly as a tagging device. Most of the cells were
found to be absent from the peripheral blood stream in 6 to 8 hours, and
none was found after 49.5 hours.

SUMMARIO IN INTERLINGUA

1. Es presentate e discutite 13 casos del anomalia de Pelger-Huët, occurrente
in tres familias. Es includite in iste reporto le secunde caso publicate del
anomalia de Pelger-Huët in negros. Le occurrentia de elliptocytosis hereditari
familial in le mesme familia es signalate. Su relation possibile al anomalia de
Pelger-Huët es discutite.
2. Certe minus ben-cognoscite factos in re le anomalia de Pelger-Huët es considerate in relation al casos presentate.

3. Le tempore del superviventia de neutrophilos transfusionate in le sanguine peripheric esseva investigate con le utilisation del anomalia como medio de marcage. Esseva trovate que le plus grande parte del cellulas esseva absent ab le circulation peripheric post 6 a 8 horas. Nulle tal cellula esseva trovate post 49,5 horas.

REFERENCES
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The Pelger-Huët Anomaly in Three Families and Its Use in Determining the Disappearance of Transfused Neutrophils from the Peripheral Blood

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