SIGNIFICANCE OF NUCLEATED RED BLOOD CELLS IN PERIPHERAL BLOOD

ANALYSIS OF 1,496 CASES

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Under normal conditions, nucleated red blood cells are found only in the circulating blood of the fetus and the newborn infant. Beyond that period the presence of nucleated red blood cells in the peripheral blood indicates disorder in the blood-producing mechanism. Because nucleated red blood cells are immature cells, they do not enter the blood normally. No totally satisfactory explanation is available of the precise mechanism that maintains a "barrier" that normally prevents primitive cells of the marrow from reaching the peripheral circulation. Evidence suggests at least two mechanisms: one chemical, primarily influenced by anoxia; the other physical, dependent at least in part on the syncytial arrangement of primitive cells. The violation of this "barrier" and the escape of nucleated red blood cells signal the presence of a stimulus that is allowing the release of these cells, before they have passed through the intermediate reticulocyte stage, to become adult red blood cells ready for the circulation. An abnormal demand for red blood cells produces an outpouring into the peripheral blood of all cellular elements, because there is a certain amount of nonspecific stimulation that will increase the white blood cells with a concomitant increase in primitive white blood cells. The specific stimulation will bring an increase in young red blood cells and the reticulocytes and, in the severe case, an increase in nucleated red blood cells, which is the point of interest here.

Stimuli sufficient to cause nucleated red blood cells to cross the barrier between the marrow and the general circulation are (1) hemorrhage, (2) hemolysis, (3) pernicious anemia, (4) marrow displacement, which may be intrinsic or extrinsic, (5) anoxia from other causes, and (6) a diverse miscellaneous group of conditions that will be listed specifically later. Our interest in the significance of nucleated red blood cells in the peripheral blood was aroused by the remarkably high incidence of death that was noticed in a group of patients in whom this phenomenon had been observed. The present study, which revealed a mortality of almost 50% among patients in whom nucleated red blood cells appeared in the peripheral blood, confirmed this correlation.

EARLIER OBSERVATIONS

It was not until the end of the last century that nucleated red blood cells were observed to be present in the peripheral blood in certain diseases: Von Noorden, quoted by Da Costa,1 in 1891 emphasized the presence of showers of nucleated red blood cells in cases of chlorosis. Da Costa interpreted these blood crises as a favorable sign indicating regeneration of blood and therefore indicating an increase in red blood cells and the hemoglobin level. Bramwell2 saw nucleated blood cells in the peripheral blood as being indicative of an excessive or imperfect blood formation, an effort on the part of nature to compensate for increased corpuscular destruction. He cited experimental work in which nucleated red blood cells were made to appear in the peripheral blood of animals by bleeding them. In 1904 Cabot3 noted that nucleated red blood cells occur in patients with severe infections and cited a fatal case of pneumonia with empyema in which the patient had a red blood cell count of 4,500,000. Cabot also noted that these nucleated cells were frequently present in cases of carcinoma even though an adequate red blood cell count and amount of hemoglobin were present. We now generally tend to think first of erythroblastosis fetalis, of Mediterranean anemia, and the other hemolytic anemias in connection with nucleated red blood cells in the peripheral blood. Diamond4 had pointed out, however, that infectious diseases such as syphilis must be ruled out when erythroblastosis is suggested, before a diagnosis is made. In 1948 Groen and Godfried5 observed that the prognosis is poor when nucleated red blood cells occur in the peripheral blood in congestive heart failure. In all the cases mentioned by these men, thrombi were found in the lungs, and cyanosis was a prominent clinical sign. Our studies confirm Groen and Godfried's observation with regard to prognosis.

MATERIAL AND RESULTS OF STUDY

The records of the Department of Hematology of the Cook County Hospital, Chicago, were reviewed for a 10 year period from 1941 to 1951. There were 1,496 cases in which nucleated red blood cells had been recorded during that time. In each of the 1,496 cases, the records showed whether the patient died while in the hospital or was discharged after therapy. Hemorrhage was the leading cause of nucleated red blood cells in the peripheral blood, and the most frequent lesion was a duodenal or gastric ulcer. Varices due to cirrhosis were next in order of frequency, and uterine bleeding was third. There were five cases of genitourinary bleeding of sufficient severity to produce

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nucleated red blood cells in the peripheral blood. Also included in this category were several cases of thrombo-cytopenic purpura and one case of Rendu-Osler-Weber disease. The gross mortality in this group was 36%. The second largest group exhibiting nucleated red blood cells in the peripheral blood were patients with pernicious anemia. It is notable that in this condition for which intensive treatment was employed and specific therapeutic agents were available, the mortality was still 29%. Patients with carcinoma comprised the third largest group, with an over-all mortality of 61%. This suggests that by the time nucleated red blood cells appear in the blood the carcinoma is well advanced, that is, it has led to either considerable anemia or extensive involvement of the marrow.

Among the cases of blood dyscrasias, acute and chronic myelogenous leukemia produced by far the largest number of nucleated red blood cells in peripheral blood. Of the 154 cases in this group, 90 were due to myelogenous leukemia and were equally divided between the acute and chronic forms. There were 21 cases of chronic lymphatic leukemia and the others were about equally distributed among lymphosarcoma, monocytic leukemia, reticulo-

Conditions in Which Nucleated Red Blood Cells Were Found in the Peripheral Blood

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Patients</th>
<th>No. Who Lived</th>
<th>No. Who Died</th>
<th>Percent of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>1,496</td>
<td>726</td>
<td>720</td>
<td>50</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>115</td>
<td>65</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>231</td>
<td>130</td>
<td>100</td>
<td>43</td>
</tr>
<tr>
<td>Cardiac conditions</td>
<td>195</td>
<td>120</td>
<td>75</td>
<td>38</td>
</tr>
<tr>
<td>Leukemia and related cases</td>
<td>154</td>
<td>117</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Infections</td>
<td>135</td>
<td>66</td>
<td>69</td>
<td>50</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>42</td>
<td>24</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>Miscellaneous (cerebral vascular accidents, diabetes, etc.)</td>
<td>42</td>
<td>24</td>
<td>18</td>
<td>43</td>
</tr>
</tbody>
</table>

The presence of nucleated red blood cells in the peripheral blood is generally a sign that the prognosis is poor, as evidenced by the appalling mortality rate of almost 50% in the present study. Our findings would indicate that this is also true in cases of cardiac disease and in infectious diseases, especially when anoxia is produced. It is worth repeating for emphasis that, of 93 patients with cardiac conditions in the selected group, 41% died, and in the total group of 195 patients, 66% did not survive when nucleated red blood cells appeared in the peripheral blood. The relatively large number of deaths in the infectious group, particularly from pneumonia, was unexpected. Of 115 cases in which infections comprised the principal cause of nucleated red blood cells in the peripheral blood, 57% were fatal, and, of the specially selected group of 42, 45% were fatal. Anoxia is evidently a dominant influence here as it is in the group of patients with cardiac conditions. Because of the nature of the underlying conditions, the prognosis is better in hemolytic anemia, hemorrhage, and pernicious anemia. The presence of cases in which bleeding was a consequence of cirrhosis of the liver raised the percentage of fatalities in the hemorrhagic group. The prognosis is least good in carcinomatosis and leukemia.

1835 W. Harrison St. (12) (Dr. Schwartz).

Boric Acid—It is incredible that a drug with such toxic properties and doubtful therapeutic value should continue to enjoy such popularity in the armamentarium of so many physicians and occupy such a prominent place in the home medicine cabinets. Perhaps the explanation of this paradox is that many topical agents survive as therapeutic agents, not so much in their power to do good, but in their failure to do harm. Apart from accidental poisoning with boric acid there should be greater awareness on the part of the medical profession and laity of the toxic effects of absorption of boric acid from broken skin surfaces and mucous membranes. Boric acid should be replaced in medical practice with more efficient and safer medication, and pharmaceutical houses should cooperate in an educational campaign to acquaint the public of its potential danger.—H. G. Poncher, M.D., Boric Acid, The Journal of Pediatrics, December, 1953.