Nucleated Red Blood Cells in Congestive Heart Failure

By Abraham M. Frumin, M.D., Theodore H. Mendell, M.D., Solomon S. Mintz, M.D., Paul Novack, M.D., and Arthur T. Faulk, M.D.

NUCLEATED red cells may be discovered in the peripheral blood of patients with congestive heart failure. This phenomenon and its connotation of poor prognosis has not been generally recognized. Only a few reports, restricted primarily to the hematologic literature, have stressed these findings. Because of the prognostic importance of peripheral nucleated red cells in congestive heart failure we are describing 5 cases with this finding (table 1) admitted to the Albert Einstein Medical Center, Southern Division, in a 6-year period. The previously reported cases are reviewed and analyzed.

REPORT OF CASES

Case 1. A 62-year-old white man, was admitted on December 2, 1951, with the chief complaint of cough, shortness of breath, and abdominal discomfort of 1 day's duration. A 1-year history of exertional dyspnea was obtained.

The blood pressure was 108/70, and the pulse was 190. The lips and nailbeds were cyanotic and there were signs of fluid retention in the lungs, liver, and legs. The heart was enlarged to the anterior axillary line, the sounds were of poor quality, and a gallop rhythm was present. The patient, was given oxygen, digitalis, meperidine, quinidine, penicillin, and meperidine. His condition deteriorated, anuria and jaundice developed, and he died in 3 days.

At autopsy the heart weighed 550 Gm. The chambers were markedly dilated and the left ventricle was hypertrophied. On gross and microscopic examination numerous old infarcts were seen in the left ventricular myocardium, and fresh soft infarcts were noted in the anterior apical and the posterior basal regions. The coronary vessels were severely sclerotic, and the left anterior descending and left circumflex arteries were occluded by old thrombi.

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Case 2. A 63-year-old white woman, was admitted on March 3, 1952, because of edema of the legs and chest pain on effort. She was apparently well until 1949, when she experienced an episode of precordial pain associated with dyspnea, which subsequently increased and was followed by pedal edema. A questionable history of rheumatic fever in childhood was elicited.

Physical examination revealed cyanosis, dyspnea, and icterus. The blood pressure was 170/88. The heart was enlarged. A diastolic thrill was felt in the aortic area, and loud aortic and mitral systolic murmurs and a soft mitral diastolic murmur were heard. The liver was enlarged and there was pitting edema of the lower extremities. A diagnosis of rheumatic disease with mitral stenosis and insufficiency and aortic stenosis was made. X-rays of the chest revealed fluid in both pleural cavities and enlargement of all cardiac chambers. The electrocardiograph showed right heart strain. The patient became progressively more decompensated in spite of usual cardiac therapy, jaundice increased, her blood pressure gradually fell, and she died in 8 days.

Autopsy revealed atherosclerosis of the aorta and major branches. The lungs were edematous and there was advanced pulmonary atherosclerosis. The right ventricle was markedly hypertrophied and dilated and the right atrium was dilated. The left ventricle was minimally hypertrophied. There was no evidence of rheumatic valvular disease. The liver and spleen were congested and edematous and the kidneys exhibited focal pyelonephritis.

Case 3. A 77-year-old white man, was admitted on October 28, 1950, with a history of sudden onset of right upper quadrant abdominal pain and shortness of breath. There was no previous history of cardiac disease. The blood pressure was 150/80 and the pulse was 84 and irregular due to atrial fibrillation. There were rales in the lung bases bilaterally and the heart was enlarged to the left. The apical ventricular rate was 100. A grade-II aortic systolic murmur with radiation to the apex was heard. The liver was enlarged 5 cm. below the right costal border and the legs were edematous. A chest x-ray showed cardiomegaly with mild pulmonary congestion. The electrocar-
diagrams revealed left ventricular strain but no signs of acute myocardial infarction. The patient was digitalized with good clinical response and was discharged in 4 days. The patient was readmitted on March 23, 1952, in acute pulmonary edema. He had suffered several episodes of acute pulmonary edema in the intervening 15 months. He died in 2 hours, despite therapy.

At autopsy there was moderate atherosclerosis of the aorta and major branches. There were bilateral pleural effusions, pulmonary edema and congestion, and areas of emphysema. The left ventricle was hypertrophied and all of the cardiac chambers were dilated. A thrombus was present in the left atrial appendage. Moderate coronary sclerosis and a fresh posterior myocardial infarction were noted. The spleen was congested and the liver showed congestion, fatty degeneration, and cirrhosis. The kidneys contained fresh and old infarcts.

**Case 4.** A 43-year-old white woman was admitted February 1, 1954, with dyspnea, hemoptysis, fever, and feeling of pressure in her chest of a few days' duration. There was no previous history of heart disease or rheumatic fever.

Physical examination revealed a thin, acutely ill patient with cyanotic lips and fingernails. The blood pressure was 120/70, and the temperature was 102 F. There were areas of dullness in the left base and in the right lung, and many rales throughout the chest. The heart was greatly enlarged. Atrial fibrillation was present, with a ventricular rate of almost 250 and a pulse rate of 160 per minute; murmurs were not heard. The liver was enlarged 4 cm. below the right costal margin. Chest x-rays showed cardiomegaly with straightening of the left heart border suggestive of mitral stenosis; there were multiple densities throughout both lungs due to possible pulmonary infarctions. Electrocardiograms revealed atrial fibrillation and right and left ventricular hypertrophy. Large amounts of digitalis were required to control the rapid ventricular rate. Anticoagulants, oxygen, mercurials, and antibiotics were also administered. The patient had a very stormy course with fever, cyanosis, and hemoptysis for a week. Rales were heard for 3 weeks. When the ventricular rate became slower a low-pitched, mid-to-late diastolic murmur was heard at the apex. After 4 weeks the cardiac rhythm was converted to

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**Table 1.—Blood Studies in Five Cases**

<table>
<thead>
<tr>
<th>Case No. and date</th>
<th>1</th>
<th>2/2</th>
<th>2/3</th>
<th>2/19</th>
<th>2/20</th>
<th>2/21</th>
<th>2/22</th>
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<tbody>
<tr>
<td>Red blood cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(million per mm.²)</td>
<td>4.1</td>
<td>4.95</td>
<td>4.5</td>
<td>4.5</td>
<td>5.21</td>
<td>3.56</td>
<td>4.39</td>
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<tr>
<td>Hemoglobin (Gm. %)</td>
<td>12.6</td>
<td>17.2</td>
<td>16.0</td>
<td>17.6</td>
<td>15.0</td>
<td>17.6</td>
<td>11.7</td>
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<td>Hematocrit (%)</td>
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<td>54</td>
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<tr>
<td>Mean corpuscular volume (μ)</td>
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<td>95</td>
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<tr>
<td>Color index</td>
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<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
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<tr>
<td>Reticulocytes (%)</td>
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<td>1</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Nucleated red cells (per 100 white cells)</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>White blood cells</td>
<td>(per mm.²)</td>
<td>12,900</td>
<td>16,900</td>
<td>11,600</td>
<td>26,450</td>
<td>13,600</td>
<td>10,200</td>
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<td>Polymorphonuclear cells (%)</td>
<td>71</td>
<td>82</td>
<td>70</td>
<td>82</td>
<td>74</td>
<td>53</td>
<td>59</td>
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<td>Lymphocytes (%)</td>
<td>17</td>
<td>17</td>
<td>30</td>
<td>18</td>
<td>22</td>
<td>29</td>
<td>33</td>
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<td>Eosinophils (%)</td>
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<td>14</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Monocytes (%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Platelets</td>
<td>(per mm.²)</td>
<td>160,000</td>
<td>160,000</td>
<td>160,000</td>
<td>160,000</td>
<td>160,000</td>
<td>160,000</td>
</tr>
<tr>
<td>Myelocytes (%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Metamyelocytes (%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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</table>

*Serum bilirubin 2.6 mg. % (direct 1.6, indirect 1.0).*
NUCLEATED CELLS IN CONGESTIVE FAILURE

normal sinus rhythm with quinidine sulfate. The patient is well at present.

Case 5. A 72-year-old man, was admitted on November 15, 1957, because of cough, shortness of breath, and chest pain of recent onset. He had been treated with digitalis for 15 years because of hypertensive cardiovascular disease. The blood pressure was 120/100, and the pulse was 80. Bilateral basal rales, poor heart sounds, thready pulse, enlarged liver 6 cm. below the right costal margin, and slight bilateral pedal edema were present. The electrocardiogram showed a supraventricular tachycardia with intraventricular block. He was given lanatoside C, mercurials, oxygen, and narcotics, but he died the following day. The arterial oxygen saturation was 100 per cent (patient was receiving nasal oxygen at the time).

DISCUSSION

Our studies reemphasize the poor prognosis attached to the presence of nucleated red blood cells in the peripheral blood of patients with congestive heart failure. It will be noted that approximately 50 per cent of the patients died shortly after the discovery of the nucleated red cells. The cause of peripheral nucleated red cells in congestive failure is still controversial. The phenomenon was once thought to be due to anemia, but this theory was discarded when it was discovered in patients with normal red blood cell counts. Groen and Godfreid stated "decompensation alone does not seem to produce this phenomenon; it requires the presence of thrombi and/or infarcts in the lesser circulation. This is possibly why Waller et al. did not find normoblasts in their cases of congestive failure, as they excluded all cases with complications from their study. The presence of normoblasts in the peripheral blood in heart failure thus seems to indicate that the condition is complicated by a mural thrombosis in the heart or pulmonary artery, or by pulmonary emboli, or by a combination of these conditions. Hence it is easily understood why peripheral normoblastosis is a sign of poor prognosis." Two of our patients showed no evidence of thrombi in the heart or pulmonary circulation. This observation seems to negate this latter hypothesis.

Two of our patients were studied extensively, hematologically. There was no evidence for a hemolytic process, i.e., absent spherocytes, a negative Coombs test, and normal erythropoietic activity of the marrow. Antemortem marrow aspirations revealed that erythropoiesis was normoblastic in nature and occurred in normal numbers with a normal erythroid/myeloid ratio. The origin of these normoblasts is still unexplained. They do not appear to originate from areas of extramedullary hematopoiesis such as the liver or spleen. No such foci have been described and none was found in the microscopic sections of livers and spleens of our patients. We must therefore assume them to originate in the marrow. The probable stimulus for their production was anoxemia resulting from cardiac disease. The importance of local (marrow) anoxemia should be emphasized. The nucleated red cells in the peripheral blood may be due to the premature or abnormal release from the marrow due to local anoxia.

It was formerly believed that normoblasts occurred most frequently in heart failure due to rheumatic heart disease. This has been subsequently shown to be untrue, as in the Cook County Hospital series in which 2 patients had syphilis, 7 had cor pulmonale, and the rest were evenly divided among rheumatic, hypertensive, and coronary heart disease.

Reticulocytosis was undoubtedly of marrow origin and may have represented an attempt of the marrow to compensate for the arterial anoxemia. It should be remembered that reticulocytosis occurred in the presence of a normal red count and hemoglobin. Reticulocyte elevations of this magnitude, i.e., 5.8 and 8.4 per cent, are not found in the erythrocytoses due to arterial anoxemia. Some other cause should be ascribed to their presence in congestive failure. Possibly the acute onset of circulatory failure may be responsible for their presence.

The presence of jaundice in 3 of our patients is worthy of further comment. Although reported in previous cases, no hypothesis was
made to their possible etiology. The elevated direct serum bilirubin points to hepatocellular insufficiency rather than to a hemolytic process. Autopsy failed to reveal any significant gross or microscopic change in the liver; cardiac cirrhosis was not found. The bilirubinemia may therefore represent physiologic impairment of hepatic function resulting from arterial anoxemia or local anoxia.

Our findings and those reported in the literature reemphasize that the presence of nucleated red cells in the peripheral blood smear is of serious prognostic significance. It is difficult to draw specific conclusions because of the relatively few cases reported. Some of the cases had rheumatic heart disease with anemia, and subacute bacterial endocarditis was suspected. This anemia may have contributed to the production of nucleated red cells. In the patients with rheumatic heart disease with normal red cell and hemoglobin values, the nucleated red cells signified a poor prognosis with cardiac decompensation. The nucleated red cells may not be constant since they may temporarily disappear. Despite their disappearance these patients often succumbed within a short period of time.

**SUMMARY**

Five patients with congestive heart failure who had peripheral nucleated red cells are reported and the literature is reviewed.

We believe that bone marrow anoxia is the cause for the premature or abnormal release of nucleated red cells in congestive heart failure.

The presence of nucleated red cells in the peripheral blood of patients with congestive heart failure is suggestive of a poor prognosis.

**ACKNOWLEDGMENT**

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**SUMMARIO IN INTERLINGUA**

Es reportate le casos de cinque patientes con congestive disfallimento cardiac qui ha-beva erythrocytos nucleate in le circulation peripheric. Le litteratura es passate in revista.

Nos opinamos que anoxia in le medulla es le causa del liberation prematur o anormal de nucleate erythrocytos in congestive disfallimento cardiac.

Le presentia de erythrocytos nucleate in le sanguine peripheric de patientes con congestive disfallimento cardiac suggeste un prognosis pauc favorabile.

**REFERENCES**

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