Prolonged Survival in Paroxysmal Nocturnal Hemoglobinuria

By SAMUEL CHARACHE

ALTHOUGH paroxysmal nocturnal hemoglobinuria (PNH) is a chronic disease, most patients survive less than ten years after diagnosis.9,18 Occasional patients survive for much longer periods of time.

Two of the earliest cases identified in the United States were reported from the Johns Hopkins Hospital in 1936 by Hamburger and Bernstein.13 Their paper was the first in the English language in which the disease was specifically recognized. One of their patients, a man, died of uremia in 1949, with kidneys appearing like the terminal stage of glomerulonephritis.14 Their other patient died in 1968 at the age of 60 of carcinoma of the breast. Forty-three years after the onset of PNH, she was no longer anemic, but evidence of PNH was still detectable by laboratory tests. Her longevity, and apparent “remission” of her disease, raised the question whether all patients who survive for more than 20 years also exhibit apparent “cure” of PNH.

CASE REPORTS

Case 1 (JHH #17 02 77) (Fig. 1a). This patient’s early history has been described in detail by Hamburger and Bernstein,13 and summarized by Wagley.23 At Christmas time in 1925 an 18 year old high school student had a sudden episode of abdominal pain and dark urine. Her physician subsequently found her to be pale, although her urine was no longer dark. He followed her course during the spring and summer of the next year; she fatigued easily, and her urine became dark on several occasions. By September she was jaundiced; hospitalization was required for the first time in December 1926. The urinary pigment was assumed to be hemoglobin, and diagnoses of paroxysmal cold and exertional hemoglobinuria were considered. The Wasserman reaction and the Donath-Landsteiner test were consistently negative, however, and paroxysms of hemoglobinuria continued while she was kept at bed rest. At the time of discharge, her hemoglobin was 7.2 Gm./100 ml.; she was advised to wear warm underwear and go to a warmer climate during the winter months.

Paroxysmal hemoglobinuria and anemia continued until the winter of 1930, but then remitted until June 1934 when fever, jaundice, and severe anemia developed. The paroxysm cleared in three days, and she felt well until September 1935 when she became seriously ill with a urinary tract infection. Pancytopenia was present; the hematocrit value was 18 per cent. Hemoglobinemia and hemosiderinuria were detected, but hemoglobinuria was not present and never recurred. Her condition slowly improved, but it was not until February 1936 that her hemoglobin had risen to 8.7 Gm./100 ml. During this period of critical illness the patient’s brother, a medical student, searched the European literature for some clue to the nature of his sister’s illness. It was he who called the attention of her physicians to descriptions of “paroxysmal nocturnal hemoglobinuria,” and his sister’s case was reported several months later.

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Over the next 20 years, anemia gradually subsided and did not recur during the subsequent ten years. The patient had two children, one in 1939 and one in 1941. She underwent a radical mastectomy in 1943, and she was seriously injured in an automobile accident in 1963, but she neither required transfusions nor showed evidence of hemolysis at those times. Hemosiderinuria was still present in 1957, and autohemolysis during sterile incubation was increased, but the patient was not anemic and the acid hemolysis test was negative. In 1967 a mass was discovered in her remaining breast. Her reticulocyte count was slightly increased (2.6 per cent), but she was not anemic. Serum bilirubin concentration, red cell cholinesterase activity, urine hemosiderin, and fecal urobilinogen were normal. The acid hemolysis, heat resistance, and autohemolysis tests were negative, but sucrose hemolysis was increased (2.6 per cent hemolysis; normal < 1 per cent), and serum haptoglobin was decreased (electrophoretic assay < 50 mgm./100 ml. hemoglobin binding capacity; immunoassay positive in 1:2 dilution (normal > 1:16)). A second
radical mastectomy was performed, but the carcinoma recurred, and the patient died in February 1968.

Case 2 (JHH #23 15 82) (Fig. 1b). A 36 year old woman began to have attacks of abdominal pain in December 1938 and was found to be anemic in 1939. In 1941 the hematocrit value was 20.7 per cent, reticulocyte count 8.6 per cent, and the white blood cell count was 2400/mm³. Plasma hemoglobin was increased, but results of an acid hemolysis test were equivocal. Attacks of abdominal pain continued at two-month intervals until 1946, and the patient noted dark red urine after many of them. Her hemoglobin level was "25-50 per cent" during that period. In 1949 hemosiderin was found in her urine, and the acid hemolysis test was positive, but dark urine was noted only rarely. The hematocrit value began to rise, but platelets fell from normal levels to 50,000/mm³ in 1954. Since 1955 the hematocrit value has been normal, although reticulocyte counts have varied between 1.5 and 4.2 per cent. Red cell cholinesterase was 5.2 mEq./min./cc. Red cells in 1965 (normal 6–8); the neutrophil alkaline phosphatase score was normal, the acid hemolysis test was negative, and hemosiderin could not be demonstrated in the urine. The patient is now 66 years old; a mild bruising tendency persists. Her spleen extends 3 cm. below the left costal margin. The hematocrit value is 47.3 per cent, white blood count 3,400/mm³, and platelet counts vary between 56,000–62,000/mm³. Red cell cholinesterase activity is now normal (0.8–4 pH/hr; normal 0.50–1.05).

Case 3 (JHH #26 79 29) (Fig 1c). A 34 year old woman complained of severe weakness, and bleeding from the gums and vagina, in 1941. Her hemoglobin level was 24 per cent, and treatment with oral and intramuscular liver extract was started. In September 1942 the hemoglobin concentration was 2.4 Gm./100 ml., hematocrit value 7 per cent, white blood cell count 1,100/mm³, and platelets 1500/mm³. A bone marrow aspirate was hypocellular, and she was considered to have aplastic anemia, although the reticulocyte count was 4.6 per cent. Initially, she was transfused at weekly intervals. By 1948 the interval between transfusions had increased to two months. Red urine was noted after transfusions, and after upper respiratory infections. Hemosiderin was found in the urine, the acid hemolysis test was positive, and a bone marrow biopsy then showed erythroid hyperplasia. Her transfusion requirement continued to decrease, and in May 1959 she had had no transfusion in 13 months. Pancytopenia was present, and the reticulocyte count was 6.6 per cent. In 1963 she developed encephalitis, and her transfusion requirement increased. One year later her hematocrit value was 18.4 per cent, reticulocyte count was 29 per cent, white cell count 1000/mm³, and platelet count was 43,000/mm³. When she was seen in 1968 at the age of 66, there had been no change, aside from development of a chronic urinary tract infection. During hospitalization the hematocrit value fell to 15 per cent; white count was 3,200/mm³ and platelet count was 114,000/mm³. Serum urea nitrogen was 18 mgm. per cent, sucrose hemolysis was 11 per cent (normal < 1 per cent), neutrophil alkaline phosphatase score was 8 (control 64), the urine contained hemosiderin, and it varied in color from yellow to deep red.

**DISCUSSION**

Observation of the patients reported here prompted a survey of several large clinics interested in PNH. Through the cooperation of many investigators, eight other patients who had survived for more than twenty years were located. Six additional cases were found in the literature (Table 1). It is clear that remission of the disease is not necessary for prolonged survival.

Although individual investigators thought particular means of therapy were efficacious, survival could not clearly be attributed to any particular therapeutic regimen. Some patients (S. A., W. P., A. H.) showed no evidence of PNH when last studied; our Case 1 showed slight laboratory abnormalities, Case 2 has persistent thrombocytopenia, and other patients show flagrant evidence of the disease. Dacie has stressed that laboratory signs of PNH may
Table 1.—Prolonged Survival in Paroxysmal Nocturnal Hemoglobinuria
Results of Most Recent Studies

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Sex</th>
<th>Source</th>
<th>Date of Study</th>
<th>Duration (years)</th>
<th>Age at Onset (years)</th>
<th>Requires Transfusion</th>
<th>Hct. %</th>
<th>Hb. Gm./100 ml.</th>
<th>Retic. %</th>
<th>Improvement</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.W.</td>
<td>F</td>
<td>JHH Case 1,23</td>
<td>1967</td>
<td>43</td>
<td>18</td>
<td>no</td>
<td>40</td>
<td>2.6</td>
<td></td>
<td>gradual</td>
<td>Abnormal sucrose hemolysis, haptoglobin</td>
</tr>
<tr>
<td>D.M.</td>
<td>M</td>
<td>Rosenthal21</td>
<td>1930</td>
<td>33</td>
<td>19</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Died after splenectomy in 1930.</td>
</tr>
<tr>
<td>R.B.</td>
<td>M</td>
<td>Crosby5,5</td>
<td>1968</td>
<td>29</td>
<td>42</td>
<td>no</td>
<td>52</td>
<td>1-4.3</td>
<td></td>
<td>gradual</td>
<td>Hct. 50% for past 10 years. Dark urine during recent attack of pneumonia. Platelets. WBC normal.</td>
</tr>
<tr>
<td>H.R.</td>
<td>F</td>
<td>JHH Case 2</td>
<td>1968</td>
<td>29</td>
<td>37</td>
<td>no</td>
<td>47</td>
<td>1.8</td>
<td></td>
<td>gradual</td>
<td>WBC 3400; platelets 84,000.</td>
</tr>
<tr>
<td>K.F.</td>
<td>F</td>
<td>Crosby5,11</td>
<td>1968</td>
<td>28</td>
<td>18</td>
<td>yes</td>
<td>20</td>
<td>7.0</td>
<td>&lt;3.0</td>
<td>no</td>
<td>2 brief remissions during pregnancy and after marrow infusion from twin. Probably has myeloid metaplasia. Platelets 25,000; WBC 2,000.</td>
</tr>
<tr>
<td>S.A.</td>
<td>F</td>
<td>Laforet10</td>
<td>1967</td>
<td>28</td>
<td>39</td>
<td>no</td>
<td>14.3</td>
<td>2.2</td>
<td>yes</td>
<td></td>
<td>No laboratory evidence of PNH.</td>
</tr>
<tr>
<td>O.C.</td>
<td>M</td>
<td>Melkild &amp; Möstad&lt;sup&gt;10,24&lt;/sup&gt;</td>
<td>1963</td>
<td>28</td>
<td>16</td>
<td>no</td>
<td>7.9</td>
<td>yes</td>
<td>Remission after splenectomy age 20; again after second splenectomy age 42. NPN 45. “In excellent health” in 1968.</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>K.M.</td>
<td>F</td>
<td>JHH Case 3</td>
<td>1968</td>
<td>27</td>
<td>33</td>
<td>yes</td>
<td>17</td>
<td>26.0</td>
<td>no</td>
<td>WBC 3200; platelets 114,000.</td>
<td></td>
</tr>
<tr>
<td>A.H.</td>
<td>M</td>
<td>Dacie&lt;sup&gt;6,7,10&lt;/sup&gt;</td>
<td>1968</td>
<td>26</td>
<td>18</td>
<td>no</td>
<td>nl</td>
<td>16.5</td>
<td>2.2</td>
<td>yes</td>
<td>No laboratory evidence of PNH.</td>
</tr>
<tr>
<td>M.P.</td>
<td>M</td>
<td>Castle&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1968</td>
<td>25</td>
<td>38</td>
<td>yes</td>
<td></td>
<td></td>
<td>no</td>
<td>Limited renal function.</td>
<td></td>
</tr>
<tr>
<td>W.P.</td>
<td>M</td>
<td>Dacie&lt;sup&gt;6,7,10&lt;/sup&gt;</td>
<td>1956</td>
<td>24</td>
<td>38</td>
<td>no</td>
<td>nl</td>
<td>16.5</td>
<td>2.3</td>
<td>yes</td>
<td>Died 1956; superior mesenteric artery thrombosis; no evidence of PNH in 1952.</td>
</tr>
<tr>
<td>A.A.</td>
<td>M</td>
<td>Gardner&lt;sup&gt;12&lt;/sup&gt;</td>
<td>1960</td>
<td>24</td>
<td>9</td>
<td>yes</td>
<td>16–27</td>
<td>7.5</td>
<td>6.6</td>
<td>some</td>
<td>Anemia responded to androgen therapy; obstruction inferior vena cava 1960; died 1961 from liver failure.</td>
</tr>
<tr>
<td>#1</td>
<td></td>
<td>Stats et al.&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1948</td>
<td>21</td>
<td>24</td>
<td></td>
<td></td>
<td>32–70%</td>
<td>3–8</td>
<td>Occasional hemoglobinuria.</td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td></td>
<td>Stats et al.&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1948</td>
<td>21</td>
<td>21</td>
<td></td>
<td></td>
<td>34–75%</td>
<td>.5–9</td>
<td>Rare hemoglobinuria.</td>
<td></td>
</tr>
<tr>
<td>M.Y.</td>
<td>F</td>
<td>Jenkins &amp; Hartman&lt;sup&gt;15&lt;/sup&gt;</td>
<td>1968</td>
<td>20±</td>
<td>36</td>
<td>no</td>
<td>38</td>
<td>4.0</td>
<td>yes</td>
<td>Rare hemoglobinuria.</td>
<td></td>
</tr>
</tbody>
</table>
persist long after cessation of overt hemolysis. A small proportion of the red cells of Case 1 hemolyzed in isotonc sucrose solution, and hemolysis was somewhat more evident in reticulocyte-rich fractions of her blood. In some patients, in whom hemolysis lessened, other abnormalities persisted. It has been suggested that PNH is produced by a somatic mutation, with emergence of a clone of abnormal cells during a period of bone marrow hypoplasia. The postulated aberrant clone is at a disadvantage because of its increased susceptibility to hemolysis, and presumably emerges only because the normal cell line is inhibited, in much the same fashion that antibiotic-resistant bacteria with “disadvantageous” growth patterns emerge during exposure to antibiotics. If remission of the disease is to be equated with repopulation of the bone marrow by normal hemopoietic elements, the data reported here suggest that the disadvantages of some descendants of the aberrant clone may be mild enough to permit their survival for many years.

SUMMARY

Some patients with paroxysmal nocturnal hemoglobinuria survive for many years. Three such patients are reported with survivals of 43, 29, and 27 years. Their histories, and those of 14 other patients who survived for more than 20 years, suggest that prolonged survival is not necessarily related to amelioration of the disease. In some patients with apparent “remission” of the disease, laboratory abnormalities persisted for many years.

SUMMARIO IN INTERLINGUA

Certe patientes con paroxysmic hemoglobinuria nocturne superviveva durante multe annos. Es reportate le casos de tres tal patientes qui superviveva 43, 29, e 27 annos, respective-mente. Le historias clinic de iste patientes, insimul con le historias clinic de 14 altere patientes con periodos de superviventia de plus que 20 annos, suggestiona que le superviventia prolongate non es necessarimente relationate con un amelioration del morbo. In certes de iste patientes con apparente “remission” del morbo, le anormalitates laboratorial persisteva durante multe annos.

ACKNOWLEDGMENTS

Many physicians cooperated in collection of the data reported here. Drs. Alan Bernstein and Philip Wagley furnished records of Case 1, and Dr. C. L. Conley furnished records of Cases 2 and 3. Drs. Frank Gardner and M. C. Brain provided valuable assistance and information concerning other patients described in Table 1. Dr. J. R. Gaintner assisted in the laboratory evaluation of Case 1.

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