PRIMARY NONFAMILIAL HEMOLYTIC ANEMIA

By J. M. Stickney, M.D., and Frank J. Heck, M.D.

ALTHOUGH patients with hemolytic anemia are not numerous, they continue to be a problem of special interest and great difficulty. In the majority of cases the disease is of the familial or congenital type. The commonly accepted criteria for the diagnosis of congenital hemolytic anemia include the presence of a microspherocytic blood picture with an increase in signs of regenerative activity, increased fragility of the erythrocytes in varying concentrations of hypotonic saline solution, splenomegaly, an elevated value for indirect serum bilirubin with an increased excretion of fecal urobilinogen, and a history of anemia, icterus, splenomegaly or increased fragility of erythrocytes in other members of the patient’s family.

In the differential diagnosis of the different types of hemolytic anemia, the question not infrequently arises as to whether an individual instance of the disease should be regarded as belonging to the congenital or familial type or to the acquired type. As Watson pointed out, there has been a tendency to regard all instances of 'primary hemolytic jaundice as of familial or congenital type.' There are, however, no clear-cut criteria to which all writers on the subject agree. In some cases in which the family history is negative but other criteria are present, the disease is classified as acquired. It must be admitted that a negative family history is not a definite indication that the disease is of the acquired type since actual investigation of close relatives may reveal such changes as increased fragility of the erythrocytes in the absence of other findings.

In the years 1942 through 1946, at the Mayo Clinic, splenectomy was performed in 22 cases of hemolytic anemia in which no positive family history could be obtained. These 22 cases are the object of our special interest.* As far as could be determined, the hemolytic syndrome in these cases was not secondary to any toxic, infectious or poisonous agent and was not symptomatic and part of a primary disease such as lymphoblastoma, leukemia or hepatic cirrhosis.

We have divided these cases into two groups which happen to be equal in number. In the first group, either microspherocytosis or increased fragility of the erythrocytes or both were found. In the second group, such evidence was not present. The groups are summarized in tables 1 and 2.

REPORT OF SELECTED CASES

Case 3. The patient was a married woman, aged 35. There was no family history of anemia, jaundice or splenomegaly. In November, 1940 she complained of weakness and malaise. She was yellowish and was found to be anemic. On March 10, 1941, the erythrocytes numbered 790,000 and the leukocytes numbered 77,750 per cubic millimeter of blood. Many transfusions were given over a period of one month with moderate benefit. Physical examination disclosed that the spleen was enlarged and extended about 1½ inches below the costal margin.

From the Division of Medicine, Mayo Clinic, Rochester, Minnesota.

*In the years 1942 through 1946, a diagnosis of congenital hemolytic icterus was made in 115 cases at the Mayo Clinic. Splenectomy was performed in approximately 90 of these cases.
When she was admitted to the hospital on May 1, 1941, the hemoglobin value was 11.05 Gm. per 100 cc., the erythrocyte count was 3,140,000, and the reticulocytes numbered 17.6 per cent. Examination of a blood smear showed the picture of congenital hemolytic icterus (microspherocytosis). The serum bilirubin value (indirect reaction) was 0.9 mg. per 100 cc. of serum. The bromsulfalein test for liver function did not show any retention of the dye. The fragility of the erythrocytes was normal; initial hemolysis occurred at a concentration of sodium chloride of 0.44 per cent with complete hemolysis at 0.32 per cent. Splenectomy was performed May 5, 1941; the spleen weighed 310 Gm. The patient had a stormy convalescence but was dismissed June 11, 1941, without having been given any transfusion. At that time, the hemoglobin value was 10.6 Gm. and the erythrocyte count was 3,700,000.

### Table 1.—Hemolytic Anemia with Significant Microspherocytosis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Hemoglobin, Gm. per 100 cc.</th>
<th>Erythrocytes, No. per cu. mm.</th>
<th>Fragility†</th>
<th>Reticulocytes</th>
<th>Gallstones</th>
<th>Time followed</th>
<th>Hemoglobin, Gm. per 100 cc.</th>
<th>Erythrocytes, No. per cu. mm.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>F</td>
<td>3.9</td>
<td>1,390,000</td>
<td>0.46-0.38</td>
<td>25</td>
<td>0</td>
<td>13</td>
<td>4.100,000</td>
<td>0.40-0.36</td>
<td>Improvement</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>F</td>
<td>6.0</td>
<td>1,530,000</td>
<td>0.50-0.38</td>
<td>62</td>
<td>0</td>
<td>30</td>
<td>4.000,000</td>
<td>0.38-0.34</td>
<td>Excellent</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>F</td>
<td>11.0</td>
<td>3,140,000</td>
<td>0.44-0.32</td>
<td>18</td>
<td>+</td>
<td>12</td>
<td>8.3 Gm.</td>
<td>2.740,000</td>
<td>Poor†</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>8.4</td>
<td>2,530,000</td>
<td>0.50-0.38</td>
<td>51</td>
<td>+</td>
<td>9</td>
<td>84%</td>
<td>3,537,000</td>
<td>Excellent</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>F</td>
<td>8.3</td>
<td>2,710,000</td>
<td>0.46-0.31</td>
<td>32</td>
<td>0</td>
<td>9</td>
<td>84%</td>
<td>3,537,000</td>
<td>Excellent</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>F</td>
<td>8.4</td>
<td>2,900,000</td>
<td>0.46-0.36</td>
<td>44</td>
<td>+</td>
<td>16</td>
<td>88%</td>
<td>5,000,000</td>
<td>Excellent</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>F</td>
<td>6.3</td>
<td>3,850,000</td>
<td>0.48-0.36</td>
<td>3</td>
<td>0</td>
<td>12</td>
<td>12.5 Gm.</td>
<td>3,850,000</td>
<td>Excellent</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>M</td>
<td>6.8</td>
<td>2,000,000</td>
<td>0.50-0.34</td>
<td>37</td>
<td>0</td>
<td>14</td>
<td>90%</td>
<td>5,000,000</td>
<td>Excellent</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>F</td>
<td>4.9</td>
<td>1,640,000</td>
<td>0.66-0.40</td>
<td>40</td>
<td>0</td>
<td>4</td>
<td>13.6 Gm.</td>
<td>3,760,000</td>
<td>Excellent†</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>F</td>
<td>6.0</td>
<td>1,520,000</td>
<td>0.50-0.36</td>
<td>17</td>
<td>0</td>
<td>14</td>
<td>60%</td>
<td>2,800,000</td>
<td>Fair</td>
</tr>
</tbody>
</table>

* In hypotonic solution of sodium chloride.
† Reported in detail in text.

When the patient returned to the clinic on August 11, 1941, the hemoglobin value was 10.6 Gm., the erythrocyte count was 3,450,000 and the reticulocytes numbered 6.5 per cent. On September 19, 1941, the hemoglobin value was 10 Gm., the erythrocyte count was 2,610,000 and the reticulocytes numbered 24.3 per cent. The fragility of the erythrocytes had increased; initial hemolysis occurred at 0.5 per cent and was complete at 0.36 per cent. On May 9, 1942, the hemoglobin value was 8.3 Gm., the erythrocyte count was 2,740,000 and the reticulocytes numbered 18.8 per cent. The value for the indirect serum bilirubin was 1.8 mg. Examination of blood smears revealed typical microspherocytosis and increased regeneration of erythrocytes.

In a letter dated February 7, 1945, the patient stated that her hematologic picture was about the same as it had been before splenectomy was performed.

Case 3 illustrates the failure of splenectomy to relieve the anemia. Of interest in this case are the presence of normal fragility prior to splenectomy and an increase in fragility after removal of the spleen. Despite the absence of a family history of hemolytic anemia in this case, the blood picture was considered 'typically that of hemolytic icterus' by several observers.
Case 9. A married woman, aged 61, came to the clinic on December 3, 1946. She had been perfectly well until the previous summer, when she had noted a loss of strength and loss of appetite. In the fall of 1946, she had become very thirsty. On October 31, she had been admitted to a hospital because of diabetic coma. The blood sugar value was 310 mg. per 100 cc. The presence of diabetes had not been recognized previously. Hematologic examination had disclosed severe anemia; the hemoglobin value had been found to be 5.6 Gm. She had not been jaundiced previously and there was no family history of anemia, jaundice or splenomegaly. The diabetes had been controlled by dietary measures and by the administration of insulin. She had received eight transfusions of blood, 500 cc. at each transfusion. The last transfusion had been administered on November 29. Despite the lack of clinical evidence of transfusion reactions, the anemia had not improved.

When the patient came to the clinic on December 3, the hemoglobin value was 4.9 Gm., the erythrocyte count was 2,640,000 and the leukocyte count was 11,200. Examination disclosed moderate icterus. The spleen was greatly enlarged and extended downward to the crest of the ilium. Examination of blood smears disclosed marked microspherocytosis, very active regeneration of erythrocytes, and 40 per cent reticulocytes. The serum bilirubin values were 1.4 mg. direct and 3.9 mg. indirect. A fragility test showed initial hemolysis at 0.66 per cent and complete hemolysis at 0.36 per cent. The bromsulfalein test for liver function did not disclose any dye retention. During the first forty-eight hours in the hospital, the average amount of fecal urobilinogen excreted each twenty-four hours was 4,800 mg.; during the next forty-eight hours, this averaged 1,220 mg. No irregular agglutinins were demonstrable.

The diabetes was carefully controlled. Splenectomy was performed on December 13. The spleen

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Before splenectomy</th>
<th>After splenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hemo-</td>
<td>Erythrocytes</td>
</tr>
<tr>
<td></td>
<td>yrs.</td>
<td></td>
<td>globin,</td>
<td>No. per cu.</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>F</td>
<td>8.1</td>
<td>1,770,000</td>
</tr>
<tr>
<td>13</td>
<td>13</td>
<td>M</td>
<td>10.3</td>
<td>3,270,000</td>
</tr>
<tr>
<td>14</td>
<td>19</td>
<td>F</td>
<td>4.3</td>
<td>800,000</td>
</tr>
<tr>
<td>15</td>
<td>21</td>
<td>F</td>
<td>8.8</td>
<td>2,520,000</td>
</tr>
<tr>
<td>16</td>
<td>24</td>
<td>F</td>
<td>11.9</td>
<td>4,100,000</td>
</tr>
<tr>
<td>17</td>
<td>33</td>
<td>M</td>
<td>6.3</td>
<td>3,240,000</td>
</tr>
<tr>
<td>18</td>
<td>34</td>
<td>F</td>
<td>11.6</td>
<td>3,350,000</td>
</tr>
<tr>
<td>19</td>
<td>40</td>
<td>F</td>
<td>4.9</td>
<td>1,560,000</td>
</tr>
<tr>
<td>20</td>
<td>46</td>
<td>F</td>
<td>8.1</td>
<td>3,850,000</td>
</tr>
<tr>
<td>21</td>
<td>54</td>
<td>F</td>
<td>5.7</td>
<td>1,340,000</td>
</tr>
<tr>
<td>22</td>
<td>59</td>
<td>F</td>
<td>4.7</td>
<td>1,530,000</td>
</tr>
</tbody>
</table>

* In hypotonic solution of sodium chloride.
† Reported in detail in text.
‡ Course following splenectomy reported through courtesy of Dr. C. J. Watson.
PRIMARY NONFAMILIAL HEMOLYTIC ANEMIA

Weighed 1,570 Gm. The postoperative convalescence was uneventful and no transfusion of blood was administered. The amounts of urobilinogen excreted in the feces were as follows: on December 17 and 18, 230 mg. per twenty-four hours; on December 19 and 20, 85 mg. per twenty-four hours; on December 21 and 22, 45.5 mg. per twenty-four hours.

On December 23, the value for the indirect serum bilirubin was 0.6 mg. When the patient was dismissed on January 4, 1947, the hemoglobin value was 8.7 Gm. and the erythrocytes numbered 2,900,000.

In a letter dated March 17, 1947, the patient stated that her blood picture had improved. The hemoglobin value was 13.6 Gm., the erythrocyte count was 3,760,000 and the leukocyte count was 11,600.

In case 9, which belongs to the microspherocytic group, the result has been excellent. In this group, the results of splenectomy as a whole were considered good. In 9 of the 11 cases, the patients were women. There was one death in this group and in one case (case 3) the patient was not improved. In case 11 the patient was improved but did not obtain an excellent result.

Case 13. A boy, aged 11, came to the clinic July 31, 1942. He had had intermittent attacks of jaundice since the age of 2, when he had had a febrile illness which had been diagnosed as Malta fever. The ordinary contagious diseases of childhood, such as whooping cough, measles and scarlet fever, each had been followed by jaundice. The jaundice also had occurred after an infection of the upper part of the respiratory tract.

When the patient was examined at the clinic, he was slightly icteric and the spleen could be palpated 2 inches below the costal margin. The hemoglobin value was 10.5 Gm., the erythrocyte count was 3,270,000 with 10 per cent reticulocytes, and the leukocyte count was 5,400. Examination of a blood smear disclosed active regeneration of the erythrocytes but no microspherocytosis. The indirect serum bilirubin value was 2.2 mg. and the bromsulfalein test for liver function disclosed no dye retention. The fragility of the erythrocytes was normal. It was felt that the patient had hemolytic anemia of an acquired type.

Splenectomy was advised.

The patient returned to the clinic May 25, 1944. In August, 1943, he had had an attack of epigastric pain. He had been markedly jaundiced and his temperature had reached 103°F. After ten days he had made a rapid recovery. Examination disclosed hematologic findings as they were at the time of the patient's first visit to the clinic with the exception that the indirect serum bilirubin value was 3.5 mg. Splenectomy was performed on May 29. The spleen weighed 266 Gm. When the patient was dismissed, the value for the hemoglobin and the erythrocyte and leukocyte counts were the same as they had been when the patient came to the clinic but the indirect serum bilirubin value had dropped to 0.5 mg.

He returned to the clinic July 19, 1944, because of an attack of pain in the upper part of the abdomen and jaundice. At this time, the hemoglobin value was 12.3 Gm., the erythrocyte count was 3,880,000 and the leukocyte count was 11,800. Macrocytosis of the erythrocytes was observed for the first time. No change in the hematologic findings was observed when the patient was seen again on August 8, 1946. Attacks of jaundice had continued to occur. The patient's growth has continued in an apparently normal manner.

Case 15. A married woman, aged 21, came to the clinic April 20, 1945. In January, 1944, she had had a miscarriage at the fourth month of pregnancy. During the pregnancy, her parents had thought that she had appeared yellow. After the miscarriage, she had lost weight and had become very weak. She had been treated for anemia. There was no family history of hemolytic anemia. Serologic tests for syphilis on both the blood and spinal fluid had been strongly positive, and antisyphilitic treatment had been administered intramuscularly. There was no personal or family history of syphilis and the patient denied the possibility of contact infection. Between March 27 and April 12, 1945, she was given a total of 2,500 cc. of blood in nine transfusions. She had been told that her hemoglobin value was lower after these transfusions than it had been previously.

When she was examined at the clinic, the hemoglobin value was 8.8 Gm., the erythrocyte count was 2,520,000 and the leukocyte count was 8,200. Examination of a blood smear revealed a marked increase in the regeneration of the erythrocytes and a regenerative macrocytosis. There was abundant myeloid
immaturity but no evidence of microspherocytosis. The indirect serum bilirubin value was 1.6 mg. The fragility test revealed that hemolysis began at 0.44 per cent and was complete at 0.34 per cent. The bromsulfalein test disclosed no dye retention. The Kline, Kahn, Hinton and Kolmer serologic tests for syphilis were negative.

On May 1, the hemoglobin value was 4.5 Gm., the erythrocyte count was 1,470,000 with 32.2 per cent reticulocytes, and the leukocyte count was 7,500. The amounts of urobilinogen excreted in the feces were as follows: On May 1 and 2, 834 mg. per twenty-four hours; on May 3 and 4, 641 mg. per twenty-four hours. A transfusion of 500 cc. of blood was administered on three occasions between May 3 and May 9. Splenectomy was performed on May 9. The spleen weighed 670 Gm. Another transfusion of blood was given on May 11.

The patient was greatly improved when she returned to the clinic for examination on October 24, 1945. The hemoglobin value was 12.7 Gm., the erythrocyte count was 4,620,000 with 8.6 per cent reticulocytes and, the leukocyte count was 12,900. In the blood smear there was active regeneration of the erythrocytes with many macrocytes. The amount of urobilinogen excreted in the feces was determined for a period of four days. The average amount was 147 mg. per twenty-four hours. The indirect serum bilirubin value was 0.45 mg.

On March 15, 1947, the patient's family physician informed us that the hemoglobin value was 78 per cent and that the erythrocyte count was 4,120,000.

In the group of cases without significant microspherocytosis, females again predominated. The higher incidence of this disease among females has also been noted by Fowler. In this group, the results have not been as good as they were in the microspherocytic group although the number of cases is not large enough to draw definite conclusions. However, the results are encouraging enough to warrant further trial of splenectomy. A longer period of observation is desirable to determine how frequently hemolytic episodes may occur after operation.

**Comment**

In recent years several excellent reviews dealing with hemolytic anemia have appeared. Watson has classified the hemolytic anemias as microcytic (familial or congenital) and macrocytic (secondary or acquired). He stated that in all cases of the acquired type of the disease the erythrocytes are at least slightly larger and often much larger than the normal. Dameshek and Schwartz and Singer and Dameshek, pointed out that in some cases of acquired hemolytic anemia, spherocytosis and increased hypotonic fragility are present, although a "pseudomacrocytic" blood picture may be seen. Fowler found that spherocytosis was not consistently present in a group of cases of acquired hemolytic anemia and that macrocytosis was more frequently encountered.

All of our cases were examples of primary nonfamilial hemolytic anemia so far as we could determine. Microspherocytosis was not present in half of these cases but with one exception (case 13) we could not classify them as cases of macrocytic anemia. There was a considerable number of macrocytes in some of the smears but many of them were regenerative or polychromatophilic erythrocytes.

Agglutinins and hemolysins may be etiologic factors in a hemolytic syndrome. In two of our cases (cases 14 and 22) iso-agglutinins of an abnormal type were present. In each instance, the patient's serum agglutinated his own erythrocytes. In another case (case 4), an Rh negative patient had a high Rh antibody titer due to previous transfusions of Rh positive blood. Although the blood picture was micro-
spherocytic, it is possible that this antibody titer may have been the cause of the hemolytic anemia. In any event, improvement did not occur until splenectomy was done. At the present time, a more intensive search for irregular agglutinins and hemolysins is being carried out in certain cases of hemolytic anemia.  

Several authors have emphasized the dangers of severe hemolytic reactions following blood transfusion in hemolytic anemia. In one of our cases (case 10), death was probably due to a hemolytic transfusion reaction after operation. We have not noted any severe exacerbation of the hemolytic process in the other cases but we have been impressed with the failure of transfusion to benefit the patient, especially before splenectomy.

We have found it difficult to correlate the degree of anemia with the severity of the jaundice. In one case (case 4) as long as the patient was severely jaundiced the anemia was relatively mild. When the severity of the jaundice decreased, the concentration of hemoglobin decreased rapidly. This inverse relationship has been noted by Watson and Fowler.

In several of our cases bone marrow was examined. A definite hyperplasia of the normoblastic cells was seen in each instance. No megaloblasts were found.

Although not common, leukopenia and thrombocytopenia may accompany the anemia. Doan and Wright have recently reported this phenomenon as a panhematopenia. In case 14, the number of leukocytes ranged from 3,100 to 5,000 and the number of thrombocytes from 65,000 to 75,000 per cubic millimeter before splenectomy. Both were normal or increased in number after operation.

In a case not included in this series splenectomy was performed for what appeared to be a primary hemolytic anemia. The blood picture was subsequently that of chronic myelogenous leukemia. At the time of the original examination, there was not as much myeloid immaturity as there was in the blood of many of the patients in the present series. The sternal marrow was hyperplastic and could not be distinguished from nonleukemic hyperplastic marrow.

Splenectomy may be of definite benefit in symptomatic hemolytic anemia when the progress of the primary disease is not rapid. Recently, a woman who was 66 years of age came to the clinic because of weakness of six months' duration. The hemoglobin value was 8.3 Gm., the erythrocyte count was 2,250,000 with 15 per cent reticulocytes. A spleen which weighed 1,125 Gm. was removed and a diagnosis of follicular lymphoblastoma was made. There were no enlarged lymph nodes. One year later, the patient, who had regained her good health, returned because of enlarged axillary and inguinal lymph nodes. The hemoglobin value then was 11.7 Gm. and the erythrocyte count was 4,150,000. Biopsy of a lymph node confirmed the previous diagnosis and for the first time roentgen therapy was started. The splenectomy had relieved the weakness and anemia.

**SUMMARY**

In our experience, in half of the cases of primary hemolytic anemia in which there is no family history of anemia, jaundice or splenomegaly, examination of the blood disclosed microspherocytic erythrocytes and increased fragility of erythrocytes. The results of splenectomy in these cases are better than in those in which
microspherocytosis is absent. True macrocytosis was observed in only one instance. Females predominated in both groups of cases. Agglutinins and hemolysins have not appeared to play any significant role in the production of the hemolytic syndrome in our cases. We do not feel justified in expressing an opinion as to whether the microspherocytosis indicates a familial or congenital blood disorder. From a practical standpoint, it makes no great difference since splenectomy should be considered seriously in any case of chronic primary hemolytic anemia. It may be of value in some cases of secondary or symptomatic hemolytic anemia.

REFERENCES

5 Mathieson, D. R.: Personal communication to the authors.
PRIMARY NONFAMILIAL HEMOLYTIC ANEMIA

J. M. STICKNEY and FRANK J. HECK

Updated information and services can be found at:
http://www.bloodjournal.org/content/3/4/431.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml