Role of the Spleen and Effect of Splenectomy in Sickle Cell Disease

By C. C. Sprague and J. C. S. Paterson

The differential agglutination method of determining the life-span of the erythrocyte has been applied to the study of sickle cell anemia, sickle-cell/Hb-C disease and pure (homozygous) hemoglobin-C disease. In this way the survival time of sickle cells was found to be shortened whether transfused to normal recipients, to recipients with sickle cell trait, or to recipients with sickle cell anemia, whereas normal and sickle cell trait cells exhibited normal survival times when transfused to recipients with sickle cell anemia. Singer concluded from these cross-determination studies that the shortened survival time of sickle cells was due essentially to the removal from the circulating blood of cells which were abnormal by reason of an intracorpuscular defect. The findings in sickle-cell/Hb-C disease and in pure hemoglobin-C disease were of a like nature.

The Ashby method permits determination of the survival time of erythrocytes transfused to recipients of suitable blood group, whereas the labeling of erythrocytes with radioactive isotopes permits determination of the survival time of erythrocytes within their peculiar blood stream.

Weinstein et al. determined the survival time in their parent circulations of the erythrocytes of patients suffering a variety of abnormal hemoglobin syndromes by the use of radioactive sodium chromate, and found for this method good agreement with the survival times suggested from cross-determination studies by the Ashby method. By the N\textsuperscript{15}-glycine method of labeling erythrocytes in vivo, the half-life time of sickle cells has been computed in one instance to be 29 days, and in another, 11 days. James and Abbott suggested that this difference in the survival times of sickle cells, containing only “S” type hemoglobin (together with a small amount of fetal hemoglobin), might be attributed to the influence of extracorpuscular factors, but recognized that no substantial evidence for the presence of such factors had been reported. It should be taken into account, however, that whereas the sickle cells were stated to contain 100 per cent “S” type hemoglobin in the case of James and Abbott, this was not determined in the case of London et al. Cr\textsuperscript{51}-labeling also permits the simultaneous determination of the survival times of abnormal cells in the donor’s own circulation and in that of the recipient.
of any compatible recipient. In the present investigation this method has been employed to determine the survival times of sickle cells and sickle-cell/Hb-C cells, and the report concerns the role of the spleen in the hemolytic process.

METHODS

The diagnosis of sickle cell anemia or sickle-cell/Hb-C disease was established, unless otherwise specified, by paper electrophoresis using a veronal buffer (pH 8.6, ionic strength 0.05); all runs were made for a period of approximately four hours at 22 ma. Family studies provided supporting data for the appropriate diagnosis in each instance.

Erythrocyte survival was determined by the radioactive chromium method. Sodium radiochromate (Na₂, Cr⁶⁺ O₄) was added to 50 ml. fresh venous blood that had been collected in 10 ml. low dextrose-ACD solution.* This mixture was incubated at 37 C. for 30 minutes. Aliquots were then injected intravenously into the patient and a compatible recipient; for adult recipients the dose of administered sodium radiochromate was approximately 125 μc., and for children 30-70 μc. depending on body weight. Compatibility was determined by a negative indirect antiglobulin (Coombs') test in addition to negative saline and protein cross-matching. Ten hours following the injection of the tagged erythrocytes a sample of venous blood was obtained without stasis; this sample served as the reference standard with which all future samples were compared. The period of four hours was chosen in order to allow the plasma to be cleared of any appreciable radioactivity. In our experience the plasma is essentially free from radioactivity by this time and this technic is preferred to the addition of ascorbic acid to the cell suspension prior to injection. Additional samples were obtained from the recipient at 24 and 48 hours following injection of the tagged erythrocytes, and twice weekly thereafter. The radioactivity of 2 ml. whole blood was determined by a gamma-sensitive sodium iodide-thallium, scintillation, well-type, crystal. The initial four-hour reference standard sample was always counted at the same time that subsequent samples were counted. This was done in order to obviate a mathematical correction for physical decay and any error that might be introduced by day to day variation in the efficiency of the counter. The radioactivity of each sample drawn subsequently to the initial four-hour sample was expressed as a percentage of that of the initial sample. No correction was made for the rate of elution of chromium from the erythrocytes. In our laboratory the half-life time (T½ value) for normal erythrocytes in normal recipients is 30 ± 3 days.

SELECTION OF PATIENTS. All patients included in this study were from Charity Hospital, New Orleans, Louisiana. The majority have been followed by the authors for the entire period of observation reported.

1. Sickle cell anemia: (a) Five patients with sickle cell anemia and splenomegaly were studied prior to and following splenectomy. The duration of the period of observation following splenectomy was from 18 to 36 months.

Two additional sickle cell anemia patients with splenomegaly were studied. One has had splenectomy, but postsplenectomy erythrocyte survival studies have not been done.

(b) Seven patients with sickle cell anemia who had undergone splenectomy were either washed with saline or had ascorbic acid added prior to injection into the recipient circulation. However, there was no significant difference between the results achieved with such treatment as compared with the injection of the untreated Cr⁶⁺-tagged cells.
Splenectomy in Sickle Cell Disease

Splenectomy some years earlier are included in this study. Although only follow-up observation of these patients was possible, it was considered that this provided an opportunity to assess better the long-term effects of splenectomy in sickle cell anemia.

(c) Data from seven sickle cell anemia patients whose spleens were not palpable are also presented. Their ages ranged from 10 to 26 years with a mean age of 16.5 years.

2. Sickle-cell/Hb-C disease: Seven patients, in two of whom splenectomy has been performed, have been studied.

Results

1 (a). Sickle cell anemia with splenomegaly: There were seven patients in this group, ranging in ages from 18 months to 7 years. The average age of the seven patients is 3.9 years. Data for this group of patients are presented in Table 1. In six of these patients splenectomy was performed. The spleens varied in weight from 120 Gm. to 503 Gm. with an average weight of 277 Gm. The average of all hemoglobin determinations made prior to splenectomy was 5.6 Gm. per 100 ml., and the average postsplenectomy value (all determinations reported were done after an interval of at least four months following splenectomy and/or blood transfusion) in five patients was 8.3 Gm. per 100 ml. Prior to splenectomy the average reticulocyte count in the seven patients was 28.7 per cent; in the five patients following splenectomy, and in whom counts have been made, the average reticulocyte count was 16.3 per cent.

Table 1.—Hematologic Data on Patients with Sickle Cell Anemia and Splenomegaly

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Splenomegaly</th>
<th>RBC Survival</th>
<th>Hemoglobin (Gm. per 100 ml.)</th>
<th>Reticulocytes (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.J. 4 6</td>
<td>188</td>
<td>5 11 7.0 8.3 17 13.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.G. 4 7</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.P. 7 10</td>
<td>333</td>
<td>2 8 4.5 8.0 28 13</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>A.F. 2 5</td>
<td>120</td>
<td>5 16 8.5 8.5 38 17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.I. 4½ 5½</td>
<td>503</td>
<td>3 10 5.5 8.5 51 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.W. 11/12 1½</td>
<td>211</td>
<td>2 5.0 22 13</td>
<td>4 5.0 30 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Refers to finger-breadths below costal margin.
†Hemoglobin levels and reticulocyte counts before splenectomy are the averages of all determinations recorded whether the patient was in crisis or not. The postsplenectomy values are the averages of all determinations made after an interval of four months following splenectomy and/or blood transfusion.
The $T_{1/2}$ value for erythrocyte survival for the entire group ranged between two days and five days with an average of 3.7 days. In the five patients in whom comparison is possible the $T_{1/2}$ value prior to splenectomy was 4.0 days, whereas after splenectomy it was 11.4 days. A less objective but nonetheless important way in which the value of splenectomy may be assessed is to compare the number of admissions to the hospital for crisis prior to splenectomy with the number following splenectomy. The six patients had a total of 26 admissions in 191/2 patient-years prior to splenectomy and two admissions in 121/2 patient-years following splenectomy. The parents were unanimous in the opinion that their children had benefitted from the operation. Additional information concerning these patients is recorded below:

Case 1: L.J., born September 30, 1950. Mother has sickle cell trait; father lives elsewhere and is stated to have been in hospital for sickle cell disease. Patient admitted to hospital 3 times for "painful" crises during the year prior to splenectomy. Average of five Hb determinations during this time was 7.0 Gm. per 100 ml. Transfused with 750 ml. whole blood prior to splenectomy on February 17, 1955. Has been admitted to hospital on 2 occasions for bronchopneumonia since operation. Average of 6 Hb determinations since splenectomy is 8.3 Gm. per 100 ml. Reticulocyte count, 38 per cent following one episode of bronchopneumonia, and 13.6 per cent on November 18, 1957.

Case 2. R.G., born February 8, 1949. Both parents, mother's half-brother, and one sibling have sickle cell trait. Patient well until June 1952 when there occurred an episode of questionable hematuria. First admission to hospital, October 1952, in crisis; Hb 3.0 Gm. per 100 ml., spleen palpable 3 cm. below costal margin; transfusion of 1000 ml. whole blood. Second admission, February 11, 1952 for bronchopneumonia; Hb 8.5 Gm. per 100 ml. Third admission, June 1953, in crisis; Hb 4.0 Gm. per 100 ml.; transfusion of 500 ml. whole blood. Fourth admission, July 1953, in crisis; Hb 6.5 Gm. per 100 ml., spleen palpable at level of umbilicus; transfusion of 500 ml. whole blood. Fifth admission, August 1953, in crisis; Hb 2.5 Gm. per 100 ml., spleen palpable five-finger breadths below costal margin; transfusion of 1000 ml. whole blood. Sixth admission, November 1953, in crisis; Hb 3.5 Gm. per 100 ml., reticulocytes 15 per cent, spleen palpable at level of umbilicus. Two days prior to this admission patient had been seen in clinic; Hb 6.0 Gm. per 100 ml., reticulocytes 10 per cent. There seemed little doubt that this fall over the period of two days represented an example of hyperhemolytic crisis. Received transfusion of 1000 ml. whole blood on this admission. Seventh admission, February 1954, with Hb less than 2.0 per 100 ml.; she received transfusions amounting to 1250 ml. whole blood and splenectomy was performed on March 21, 1954. She has been admitted to the hospital on one occasion following splenectomy. This occurred two years after operation when she developed fever and chest and abdominal pains. Sputum contained staph. aureus and a diagnosis of bronchopneumonia was made; Hb 7.0 Gm. per 100 ml., P.C.V. 19 per cent. Treated with penicillin and achromycin; no blood transfusion was given. One month later Hb was 8.0 Gm. per 100 ml. and reticulocytes 1.3 per cent. The findings suggested aplastic crisis. The patient has not been seen since this episode occurred and we have been unable to trace her family.

Case 3. M.P., born February 11, 1946. The mother was the only member of the family available for study. She has sickle cell trait and was not anemic. First admission to hospital, April 1948, following the ingestion of kerosene; no hematologic values reported. Second admission, February 1949, for cellulitis of right forearm; Hb 9.5 Gm. per 100 ml., P.C.V. 31 per cent. Third admission, August 1950, with fever, vomiting, and pain in wrists and fingers; Hb 6.5 Gm. per 100 ml., P.C.V. 25 per cent, spleen, 4-finger breadths below costal margin;
received transfusion of 200 ml. whole blood. Fourth admission, November 1950, with fever and pains in wrists and hands; Hb 8.7 Gm. per 100 ml., spleen palpable just below costal margin. Fifth admission, December 1950, with upper respiratory tract infection: Hb 4.5 Gm. per 100 ml., spleen palpable at level of umbilicus; transfusion of 500 ml. whole blood. During the following two years the child was frequently ill with nose bleeds, headaches, and cramping abdominal pains, occurring every 2 to 3 weeks. Sixth admission, October 1952, with fever, headaches, and convulsions; Hb 2.5 Gm. per 100 ml., P.C.V. 12 per cent, spleen palpable 12 cm. below costal margin; transfusion of 550 ml. whole blood. Seventh admission, January 1953, with fever, headache, and vomiting; Hb 3.5 Gm. per 100 ml.; transfusion of 500 ml. whole blood. Eighth admission, December 1953, in crisis; Hb less than 3.0 Gm. per 100 ml., spleen palpable at level of pelvic brim; transfusion of 350 ml. packed red cells. Ninth admission, February 1954, in crisis; Hb 2.5 Gm. per 100 ml.; transfusion of 250 ml. packed cells. Tenth admission, March 1954, with Hb 3.5 Gm. per 100 ml.; received a transfusion of 500 ml. whole blood. Further transfusions of 250 ml. whole blood and 600 ml. packed red cells were given prior to splenectomy on July 2, 1954. He has been essentially free from symptoms and has not required admission to the hospital during the 3½ years since splenectomy; average Hb value has been 8.0 Gm. per 100 ml. during this time compared with 4.5 Gm. per 100 ml. before splenectomy.

Case 4. A.F., born February 13, 1952. Both parents have sickle cell trait and are not anemic. First admission, April 1954, because of screaming attacks, loss of appetite, and listlessness; Hb 10 Gm. per 100 ml. (This value seems unduly high in view of his subsequent course and may reflect either shrinkage of the plasma volume in association with a "painful" crisis or, perhaps, a laboratory error.) Second admission, May 1954; Hb 3.5 Gm. per 100 ml., spleen palpable 3-finger breadths below costal margin; an unspecified amount of blood was transfused to raise the hematocrit level from 15 per cent to 24 per cent. Third and fourth admissions, July and November 1954, with "painful" crises. Fifth admission in a period of 18 months, November 1955, with abdominal pain, headache, cramps in the legs; Hb 8.0 Gm. per 100 ml.; transfused with whole blood to bring his hematocrit to a level of 39.5 per cent prior to splenectomy on December 13, 1955. He has been essentially free from symptoms and has not been admitted to the hospital during the 2½ months since splenectomy; average postsplenectomy Hb level is 8.5 Gm. per 100 ml.

Case 5. B.I., born September 19, 1951. Patient's mother has sickle cell trait; father deserted the family and was not available for study; one sibling has only normal adult hemoglobin on electrophoresis; a maternal aunt has been told that she has sickle cell anemia. The patient was well until September, 1955 when she became ill with fever, pains in the arms and legs, lassitude, and jaundice; she was not seen by a physician at this time. First admission to the hospital, December 1955, in crisis; Hb 3.3 Gm. per 100 ml., reticulocytes 18.8 per cent, spleen palpable 6 cm. below costal margin; received transfusion of 425 ml. packed red cells. For the next year she suffered intermittent abdominal pain and pains in the arms and legs but was not taken to a physician. Second admission, January 1957, in crisis; Hb 5.0 Gm. per 100 ml., reticulocytes 62 per cent, spleen palpable at the level of the umbilicus; transfused to a hemoglobin level of 10 Gm. per 100 ml. and splenectomy was performed on February 8, 1957. The patient has been symptom-free since operation and when seen last on November 4, 1957 the Hb level was 8.0 Gm. per 100 ml. and reticulocyte count 22 per cent.

Case 6. D.W., born November 27, 1955. One sibling died of sickle cell disease at 3 years of age. There are six living siblings, three having sickle cell trait and three being completely normal hematologically. First admission, November 1956, with fever and convulsions; Hb less than 3.5 Gm. per 100 ml., spleen palpable 4 cm. below costal margin; transfusion of 200 ml. packed red cells. Second admission, January 1957, for
vomiting and diarrhea; Hb 8.5 Gm. per 100 ml. and reticulocytes 25 per cent. Third admission, February 1957, with bronchopneumonia and crisis; Hb 4.0 Gm. per 100 ml., reticulocytes 45 per cent, spleen palpable 9 cm. below costal margin. Fourth admission, March 1957, in crisis; Hb 4.4 Gm. per 100 ml.; transfusion of 140 ml. whole blood. Fifth admission, March 29, 1957, eight days after discharge from hospital. This was the fifth admission in five months and the patient was again in crisis with a hemoglobin level of 5.1 Gm. per 100 ml. and reticulocytes 21.6 per cent. Transfused with 150 ml. whole blood, and splenectomy was carried out April 4, 1957. Patient has been asymptomatic and has not been admitted to the hospital since splenectomy.

Case 7. L.W., born June 24, 1952. Father and three siblings all have sickle cell trait; the mother was not available for study. First admission, September 1954, for hydrocele; Hb 12.0 Gm. per 100 ml. Second admission, November 1954, in crisis; Hb 3.8 Gm. per 100 ml., reticulocytes 15.6 per cent, spleen palpable 7 cm. below costal margin; transfusion of an amount not specified. On January 13, 1955 the hemoglobin level was 8.2 Gm. per 100 ml. and reticulocyte count 8 per cent. Two weeks later (January 27) the hemoglobin level was down to 3.7 Gm. per 100 ml. and the reticulocyte count had risen to 21.2 per cent. The spleen was palpable 6 cm. below the costal margin. He received transfusion of 250 ml. whole blood. During the ensuing six months he was admitted to the hospital five times. On three occasions he suffered crises with hemoglobin levels on admission below 4.0 Gm. per 100 ml. Two admissions were for "painful" crises. On each occasion the spleen was found palpable 3 to 6 cm. below the costal margin. The patient was last seen on November 7, 1957 when he had a hemoglobin level of 4.7 Gm. per 100 ml. and P.C.V. of 18 per cent. Splenectomy has been recommended, but the parents have not consented to the operation.

1 (b). Seven sickle cell anemia patients underwent splenectomy several years ago with effects which can best be presented by a brief résumé of the medical histories:

Case 1. W.D., born March 19, 1943. Splenectomy, March 24, 1944. The spleen weighed 105 Gm. The patient did reasonably well following splenectomy, being admitted to the hospital 6 times during the period of 11 years between splenectomy and his removal to another state. His most recent admission to the hospital was in 1952 for a pulmonary infarction at which time his hemoglobin was 7.5 Gm. per 100 ml. An aunt who lives in New Orleans states that the boy is well at present.

Case 2. S.F., born August 21, 1949. Admitted in crisis on four occasions prior to splenectomy in 1952. The spleen weighed 93 Gm. There have been two admissions since splenectomy, the most recent being on May 6, 1957 when he was admitted with symptoms of abdominal pain and fever. His hemoglobin at that time was 8.0 Gm. per 100 ml.

Case 3. L.R., born July 17, 1948. Brought up by an aunt who was unable to remember anything about his earlier history other than that he suffered from fever. Admitted, supposedly in crisis, at the age of 9 months when splenectomy was done. The spleen weighed 60 Gm. His hemoglobin level at the time of admission was 3.6 Gm. per 100 ml. The average of 10 subsequent hemoglobin determinations is 7.5 Gm. per 100 ml. The child has had no joint pains at any time since splenectomy and abdominal pain on only one occasion. He has required no blood transfusions during the 8 years following splenectomy.

Case 4. R.M.B., born November 25, 1948. She was first noted to have severe abdominal pain at one year of age; this recurred at short intervals (approximately once per month). She was admitted in crisis and was given blood transfusions at approximately two-month
intervals during her second year of life. Splenectomy was carried out at the age of two years, the spleen weighing 320 Gm. She has complained of abdominal pain and fever only once in the ensuing 6 years and has required no transfusions during this period. During the year prior to splenectomy her average hemoglobin level on five occasions was 7.0 Gm. per 100 ml. The average of 7 hemoglobin determinations since splenectomy was performed is 9.6 Gm. per 100 ml.

Case 5. W.H., born July 14, 1939. This patient first experienced abdominal pain at the age of two years; this recurred at very frequent intervals during the next two years, requiring admission to the hospital and blood transfusions. Splenectomy was carried out at the age of four years, in 1943. He has had no joint or abdominal pain during the subsequent 14 years and at present is asymptomatic. The average of nine hemoglobin determinations during the postsplenectomy period is 7.2 Gm. per 100 ml.

Case 6. M.B., born July 20, 1940. This patient had a splenectomy performed at 7 years of age because of recurrent crises. Only one hemoglobin determination prior to splenectomy is available and that was 4.0 Gm. per 100 ml. The spleen weighed 460 Gm. The average hemoglobin value of five determinations during the 8 years following splenectomy is 8.7 Gm. per 100 ml. There is no record of the patient for the past two years.

Case 7. A.C., born March 14, 1949. This boy was admitted on 6 occasions for crises during the 3 years prior to splenectomy on March 18, 1952. His average hemoglobin during this period was 6.5 Gm. per 100 ml. He has not been admitted to the hospital since splenectomy and has been asymptomatic for the entire period. The average of 6 hemoglobin determinations during this five-year period is 7.8 Gm. per 100 ml.

The data in this series of cases are obviously incomplete but enough to suggest that the course of the disease was significantly affected by splenectomy. Admissions to the hospital for crisis were fewer, hemoglobin levels higher, and blood transfusions were no longer needed. In one of the patients (case 4) the data suggest that the survival of transfused cells was diminished before operation, but there is no evidence to suggest that this obtains for all the patients.

1c. Sickle cell anemia without splenomegaly: It has long been recognized that as the patient with sickle cell anemia grows older the spleen becomes smaller. It is very common for the spleen to be palpable during infancy and early childhood, and by the time the child reaches the age of six or seven years the spleen is seldom palpable, and only occasionally during crisis. There is a progressive shrinkage in the size of the spleen and it is not uncommon in the adult to find a small fibrotic mass at the site of the spleen. It is also known that crises are more severe and occur with greater frequency during infancy and childhood than in adult life. Hence clinical observation suggests that erythrocyte survival may be greater in patients whose spleens are not palpable. In order to confirm or refute this suggestion, erythrocyte survival was determined in seven patients with sickle cell anemia whose spleens were not palpable. The findings are recorded in table 2. The average age of this group was 16.5 years and the average survival time (T1/2) was found to be 10 days. This survival time is quite similar to the postsplenectomy finding, 11.4 days, for the Group 1(a) patients. Blood from five of the sickle cell anemia patients without splenomegaly was transfused
TABLE 2.—Sickle Cell Anemia Without Splenomegaly; Erythrocyte Survival (T_{1/2}) in Parent Circulations and in Circulations of Normal Recipients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Parent Circulation</th>
<th>Circulation of Normal Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.B.</td>
<td>15</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>R.B.</td>
<td>15</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>D.B.</td>
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<td>5</td>
<td>6</td>
</tr>
<tr>
<td>I.B.</td>
<td>18</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>L.K.</td>
<td>16</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>J.J.</td>
<td>16</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>A.W.</td>
<td>18</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Average</td>
<td>16.5</td>
<td>10.0</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Into normal recipients to determine whether there might be an extracorpuscular hemolytic factor introduced by the normal splenic circulation. In four of the five, the erythrocyte survival time was found to be shorter in the normal recipients than in the patients. For the erythrocytes of these five patients the average T_{1/2} value in their own circulation was 9.2 days, and in the circulation of normal recipients 4.4 days. This latter value, 4.4 days, is comparable with that observed for the sickle cells of patients with splenomegaly, 3.7 days. Exploratory laparatomy was not carried out in any of the Group 1(c) patients so that the actual size of the spleen is unknown; it is assumed that in the majority the spleens were considerably decreased in size.

2. Sickle-cell/Hb-C disease: Results from seven patients having a combination of hemoglobins S and C are presented in table 3. Three of the seven had palpable spleens, and of these three, two had splenectomy. In one the pre- and postsplenectomy survival times were the same, the T_{1/2} value being 13 days. In the second patient the presplenectomy T_{1/2} value was 15 days and the postsplenectomy value, 21 days. The average erythrocyte T_{1/2} value for the whole group was 15.7 days.

Blood from three of these patients was transfused into normal recipients

TABLE 3.—Sickle-Cell/Hb-C Disease; Erythrocyte Survival (T_{1/2}) Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Spleen size and weight (Gm.)</th>
<th>Parent Circulation prior to Splenectomy</th>
<th>Parent Circulation post-Splenectomy</th>
<th>Circulations of Normal Recipients</th>
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</thead>
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<td>C.M.</td>
<td>6</td>
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<td>13</td>
<td>13</td>
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<tr>
<td>E.St.M.</td>
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</tr>
<tr>
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<td>11</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>J.H.</td>
<td>22</td>
<td>***</td>
<td>13</td>
<td>—</td>
<td>9</td>
</tr>
<tr>
<td>E.D.</td>
<td>6</td>
<td>0</td>
<td>23</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>W.S.</td>
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<td>—</td>
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<tr>
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<tr>
<td>Average</td>
<td>18.4</td>
<td>15.7</td>
<td>17</td>
<td>7.0</td>
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</table>

*Refers to finger-breadths below costal margin.
and it was found that the cells survived for a shorter period of time in the normals (average T½, 7 days) than in the patients (average T½, 12.3 days). This was somewhat surprising in view of the fact that two of the patients had splenomegaly. The data, which accord with the findings of Chernoff et al., are suggestive but too few to permit a certain conclusion concerning the effect of a spleen upon the hemolytic process in sickle-cell/Hb-C disease.

**DISCUSSION**

The validity of the findings reported in this paper is no greater than that of the method employed to determine the erythrocyte survival. Ebaugh and his colleagues found that the radioactive sodium chromate method was of definite value in following short-term variations in erythrocyte survival, and Weinstein and Leroy concluded that the method was entirely satisfactory for the study of hemolytic processes. The latter also concluded that although an absolute value for the rate of red cell destruction could not be obtained, except by extrapolation, the relative rate of hemolysis with respect to normal subjects, or before and after therapy in the same subject, could be determined readily and reliably. Strumia and his colleagues, however, pointed out that when determining the erythrocyte survival, corrections must be made for variations in the volume of red cells caused by changes in the rate of new red cell production during the period of observation. These authors suggested that determination of the red cell volume at the beginning and end of the period of observation, with frequent determinations of the venous hematocrit on the intervening days, provided the data for satisfactory correction. With these findings Turnbull, Hope and Verel were in general agreement but drew attention to the effect of changes in the plasma volume, namely, that plasma volume changes tend to offset changes in the red cell volume. Thus in the two cases of hemolytic anemia studied by Turnbull et al. it was found that the uncorrected survival data were remarkably close to the survival data corrected for changes in red cell and plasma volumes, whereas correction for the hematocrit changes alone gave rise to unpredictable errors. In future studies of the survival of sickle cells in vivo it is clear that corrections for red cell and plasma volume changes should be applied as suggested by Turnbull et al. In the present study plasma volumes were not estimated, and for the reasons given above uncorrected survival data are reported. It appears likely that these uncorrected data derived from short periods of observation and with the subjects in a state of clinical remission, provide a reliable index of the life-span of the erythrocytes.

Extracorpuscular hemolytic factors are usually considered to exist when normal erythrocytes fail to exhibit a normal survival time following transfusion to the recipient suffering from hemolytic anemia. There are only a few reports of accelerated destruction of transfused normal erythrocytes in sickle cell anemia, and extracorpuscular hemolysis, as defined, does not ordinarily account for the shortened survival time of the sickle cell. In the present study it is evident in the first place that the survival times of sickle erythrocytes are shortened in the presence of a spleen and lengthened (though still much below normal survival times) after splenectomy. In the
second place, the erythrocytes of adult sicklers, whose spleens may be presumed to be atrophic, have a shorter survival time in the circulations of normal recipients whose spleens are intact. It may then be asked how the spleen—even a normal spleen—influences the survival times of these erythrocytes without affecting the survival of normal erythrocytes.

In a study of the splenic circulation Björkman concluded that, although erythrocytes may pass through the fenestrated walls of the splenic sinus, the main function of the sinus wall is to allow plasma to be filtered from the red cells. These become stagnant for a varying period of time and so altered that finally they undergo hemolysis. In particular Björkman found that spherocytic cells (produced by saponin injection in the rabbit) did not readily pass the sinus wall filter. Whipple et al., on the other hand, have suggested that blood from the splenic arterioles and capillaries flows into the pulp spaces which are irregular in conformation and in which blood may stagnate, the direction of its flow varying with pressure differences within the intercommunicating system. Dacie and Young et al. considered that in hereditary spherocytosis the spherocytes were more readily trapped in the spleen pulp because their abnormal shape renders it more difficult for them to pass through the slit-like openings into the sinusoids. This view was accepted by Emerson et al., who emphasized the increase in osmotic and mechanical fragilities brought about by this period of stagnation and noted that this mechanism, promoting hemolysis, might be considered a normal function of the spleen. In analogous fashion it is not unreasonable to postulate that the rigidity of the sickled cells interferes with their passage from the splenic pulp, rendering them even more subject to stagnation and eventually to destruction. Tomlinson found pooling of blood in the pulp cords to be the characteristic splenic lesion in sickle cell anemia.

Harris et al. have demonstrated that homozygous (SS) sickle cells undergo sickling within the physiologic range of oxygen tension, and that upon sickling the cells lose their plasticity and the viscosity of the blood increases. These authors considered that the increase in viscosity leads to stasis, which, together with a lowered pH and continuing tissue utilization of oxygen, further augments the sickling and stasis. Harris and his colleagues found that after prolonged stasis a proportion of the erythrocytes were irreversibly sickled; the osmotic and mechanical fragilities of these cells were increased. Watson et al. found a higher proportion of irreversibly sickled cells in the splenic aspirate than in the peripheral blood of patients in whom sickle cell anemia was accompanied by splenomegaly. Weisman et al. found that sickle cell anemia erythrocytes transfused to a nonsickling recipient before splenectomy were sequestered in the spleen and showed an increase in osmotic fragility.

This sequence of events leading to the hemolysis of sickled erythrocytes is ultimately dependent upon the proportion of S-type hemoglobin contained within the erythrocytes and upon the lowering of the oxygen tension of the blood. The latter occurs wherever the blood flow becomes stagnant, and particularly in the spleen which is constructed so that stagnation of blood within its pulp spaces is a normal occurrence. It may be concluded that the
Spleen plays a relatively passive role in sickle cell anemia, the effect of its presence being to accelerate the hemolytic process.

In sickle cell anemia, therefore, splenectomy would be expected to effect the removal of only one organ in which sickle cells tend to stagnate, albeit a principal organ, and thereby to effect only a mitigation of the hemolytic process. From the clinical standpoint it is important to determine whether this limited improvement is enough to warrant splenectomy. Shotton et al. collected together earlier reports of splenectomy in sickle cell anemia and found better results where the spleen was large. Splenectomy has been recommended for patients in whom the spleen is large and true extracorpuscular hemolysis demonstrated or suspected. Conley et al. reported that five of their six children, in whom splenectomy was carried out because of recurrent crises, have been entirely well, without crises and without the need for transfusions, following operation. Our own experience is in accord with that of Conley et al. and the findings reported suggest that where no true extracorpuscular hemolysis is present splenectomy may be of considerable benefit to children with sickle cell anemia because of the greater longevity of the sickle cells. This experience concerned children, commonly under four years of age, in whom painful and hemolytic crises occurred with undue frequency and necessitated admission to the hospital and treatment by means of blood transfusions. Where the apparent erythrocyte survival determined by the radioactive chromium method was markedly shortened (T\textsubscript{1/2} less than 6 days) splenectomy appears to have been a justifiable procedure.

Further study in sickle-cell/Hb-C disease is required. Ranney et al. reported one such patient in whom splenectomy had been carried out without any marked effect upon the anemia.

**Summary**

The survival of sickle cell anemia and sickle-cell/Hb-C erythrocytes was determined by the radioactive chromium method, both in their parent circulations and in the circulations of compatible normal recipients.

In sickle cell anemia patients with splenomegaly the average erythrocyte survival time (T\textsubscript{1/2}) was found to be 3.7 days. After splenectomy T\textsubscript{1/2} increased to an average of 11.4 days.

In sickle cell anemia patients without splenomegaly the average T\textsubscript{1/2} was found to be 10 days. In five instances an average T\textsubscript{1/2} of 9.2 days was found, whereas the average T\textsubscript{1/2} for the same cells in the circulations of normal recipients was 4.4 days.

In sickle-cell/Hb-C disease the average T\textsubscript{1/2} was 15.7 days. Following splenectomy in two patients, T\textsubscript{1/2} was unchanged in one and increased in the second. T\textsubscript{1/2} was shortened in two of three instances when these cells were transfused into normal recipients, but the data are insufficient to permit conclusions to be drawn.

The role of the spleen in hemolysis is discussed briefly and it is concluded that the hemolytic process in sickle cell anemia is accelerated in the presence of a spleen. This finding is compatible with the diminution in the severity of sickle cell anemia frequently recognized in the adult patient whose spleen...
has atrophied, and in the child following splenectomy. The validity of the
chromate-tagging method for determining erythrocyte survival is discussed.
Splenectomy was performed in children in whom the erythrocyte survival
was shortened (T\(1/2\) less than 6 days).

**SUMMARIO IN INTERLINGUA**

Le methodo a chromo radioactive esseva usate pro determinar le tempore
de superviventia de erythrocytos de patientes con anemia a cellulas falciforme
e con morbo de cellulas falciforme e hemoglobina C, tanto in le circulation
native como etiam in le circulation de compatibile recipientes normal.

In patientes con anemia a cellulas falciforme e splenomegalia le tempore
medie del superviventia de erythrocytos (T\(1/2\)) esseva 3,7 dies. Post splenect-
oma le valor medie de T\(1/2\) cresceva a 11,4 dies.

In patientes con anemia a cellulas falciforme non accompaniate de spleno-
megalia le valor medie de T\(1/2\) esseva 10 dies. In cinque casos le valor medie
de T\(1/2\) esseva 9,2 dies, durante que le valor medie de T\(1/2\) pro le mesme
cellulas in le circulation de recipientes normal eseva 4,4 dies.

In morbo de cellulas falciforme e hemoglobina C le valor medie de T\(1/2\)
esseva 15,7 dies. Post splenectomia in duo patientes, le valor de T\(1/2\) se
monstrava inalterate in un caso e augmentate in le secunde. T\(1/2\) esseva
reducite in duo ex tres casos quando le cellulas esseva transfundite a re-
cipientes normal, sed iste datos non suffice pro le formulation de conclusiones.

Le rolo del splen in hemolyse es discutite brevemente. Es presentate le con-
clusion que le processo hemolytic in anemia a cellulas falciforme es accelerate
in le presentia del splen. Isti constatation es compatibile con le observation
que le severitate de morbo a cellulas falciforme recede frequentemente in
le patience adulte in qui le splen es atrophiate e in le patience juvenil in qui le
splen ha essite excidite. Es discutite le validitate del methodo a marcate
radioactive de chromatoto pro le determination del tempore de superviventia del
erythrocytos. Splenectomia esseva effectuate in patientes juvenil in qui le
tempore de superviventia del erythrocytos se monstrava reducite, i.e. in qui
T\(1/2\) esseva minus que 6 dies.

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SPLENECTOMY IN SICKLE CELL DISEASE


Role of the Spleen and Effect of Splenectomy in Sickle Cell Disease

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