MOST PATIENTS with abnormal hemoglobin diseases have a lower than normal red cell mass and the anemia is hemolytic in nature. The majority of the measurements of red cell life span that have been done in such patients have used radioactive chromium as the red cell tag. During such survival studies there is a small but significant loss or elution of chromium from the red cells. This elution rate unfortunately is not the same from one patient to another and may not even be the same from time to time in the same patient. Furthermore, the site of chromium binding to the red cell is the beta chain of the hemoglobin molecule. Yet few studies have been performed to study the rate of chromium loss from red cells bearing abnormal beta chains such as those of hemoglobin S or hemoglobin C. This study was planned to compare the red cell survival curves obtained using the chromium tag with those using a $^{32}$DFP tag. The latter has been shown to give true survival data.

MATERIAL AND METHODS

Clinical data from the patients studied are in Tables 1 and 2. There were 7 patients with normal hemoglobin, although none were completely free from disease. Seventeen patients had sickle hemoglobin either as sickle cell trait, sickle cell anemia, sickle cell-thalassemia disease (high $A_2$ type) or sickle cell-hemoglobin C disease. Six individuals had hemoglobin C: one with C trait, three with homozygous hemoglobin C disease and two with sickle cell-hemoglobin C disease.

Standard technics were used to measure red cell autosurvival with $^{51}$Cr. Ascorbic acid was not added to block further chromium binding after injection and blood volume samples taken 15-40 minutes after injection of chromated cells were not used in the estimation of red cell survival. In the determination of blood volume, appropriate corrections were made for plasma $^{51}$Cr. Except where indicated in the Table, 60-80 mc. (300-450 mc./mg.) $^{32}$DFP was injected intravenously 30-40 minutes after the reinjection of $^{51}$Cr-tagged red cells and the removal of blood specimens to measure the red cell volume. Samples were then taken every 2-4 days for 2-6 weeks to determine residual erythrocyte radioactivity. $^{51}$Cr radioactivity was measured in a well-type scintillation counter equipped with a single channel radiation analyzer and an automatic sample changer. Preliminary studies showed that no significant $^{32}$P radioactivity was detected when this instrument was set to span the $^{51}$Cr photopeak with a 100 Kev window. To determine residual red cell $^{32}$DFP, erythrocytes were washed, plancheted and counted in duplicate in a gas flow counter using Geiger.

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*Nuclear-Chicago Corporation, Des Plaines, Ill.
Table 1

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Sex</th>
<th>Hemoglobin</th>
<th>Hct</th>
<th>MCV</th>
<th>T-45</th>
<th>T-144</th>
<th>MCL</th>
<th>M = DFP</th>
<th>K =</th>
<th>Mean Reticulocytes</th>
<th>Predicted Index</th>
<th>Diagnosis and Remarks</th>
<th>Type of DFP Curve</th>
</tr>
</thead>
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<tr>
<td>4588</td>
<td>22</td>
<td>M</td>
<td>27.0</td>
<td>21.4</td>
<td>7.1</td>
<td>9.7</td>
<td>14.0</td>
<td>*</td>
<td>11.1</td>
<td>6.4</td>
<td></td>
<td></td>
<td>SS Arithmetic Curve</td>
<td>F</td>
</tr>
<tr>
<td>7490</td>
<td>20</td>
<td>F</td>
<td>21.0</td>
<td>15.8</td>
<td>6.9</td>
<td>8.9</td>
<td>12.7</td>
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<td>11.9</td>
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<td>Exponential Curve</td>
<td>F‡</td>
</tr>
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<td>7.6</td>
<td>9.6</td>
<td>13.9</td>
<td>*</td>
<td>13.6</td>
<td>6.7</td>
<td></td>
<td></td>
<td>SS</td>
<td>R‡</td>
</tr>
<tr>
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<td>21.0</td>
<td>17.2</td>
<td>8.5</td>
<td>12.3</td>
<td>17.8</td>
<td>2.6</td>
<td>15.2</td>
<td>4.0</td>
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<td>24.4</td>
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<td>3.0</td>
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<td></td>
<td>SS</td>
<td>R‡</td>
</tr>
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<td>1.8</td>
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<td>0.1</td>
<td>2.6</td>
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<td>SS</td>
<td>R‡</td>
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<td>12.0</td>
<td>*</td>
<td>16.9</td>
<td>6.4</td>
<td></td>
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<td>R‡</td>
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<td>1.5</td>
<td>0.7</td>
<td></td>
<td>S-β Thalassemia</td>
<td></td>
<td>F</td>
<td></td>
</tr>
<tr>
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<td>35.0</td>
<td>21.5</td>
<td>24.9</td>
<td>37.0</td>
<td>53.5</td>
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<td>1.7</td>
<td>S-β Thalassemia</td>
<td></td>
<td>R</td>
<td></td>
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<tr>
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<td>39.0</td>
<td>17.5</td>
<td>15.3</td>
<td>16.0</td>
<td>23.6</td>
<td>0.3</td>
<td>2.6</td>
<td>3.1</td>
<td>S-C Disease; Cr 51 study begun 2 weeks prior to start of 32DFP test.</td>
<td></td>
<td>R‡</td>
<td></td>
</tr>
<tr>
<td>8654</td>
<td>26</td>
<td>M</td>
<td>39.0</td>
<td>23.5</td>
<td>16.5</td>
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<td>28.6</td>
<td>0.7</td>
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<td></td>
<td>S-C Disease</td>
<td>R‡</td>
</tr>
<tr>
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<td>F</td>
<td>32.5</td>
<td>20.4</td>
<td>18.7</td>
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<td>38.5</td>
<td>1.1</td>
<td>2.2</td>
<td>2.2</td>
<td></td>
<td></td>
<td>C-C</td>
<td>R‡</td>
</tr>
<tr>
<td>1224</td>
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<td>F</td>
<td>30.5</td>
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<td>24.3</td>
<td>35.1</td>
<td>0.9</td>
<td>2.4</td>
<td>2.0</td>
<td></td>
<td></td>
<td>C-C</td>
<td>R</td>
</tr>
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<td>7673</td>
<td>16</td>
<td>F</td>
<td>15.5</td>
<td>10.3</td>
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<td>8.9</td>
<td>0.5</td>
<td>5.8</td>
<td>4.8</td>
<td></td>
<td></td>
<td>C-C, acute leukemia, bleeding</td>
<td>R</td>
</tr>
<tr>
<td>3717</td>
<td>38</td>
<td>F</td>
<td>33.0</td>
<td>19.5</td>
<td>32.3</td>
<td>164</td>
<td>1.5</td>
<td>0.7</td>
<td>0.5</td>
<td></td>
<td>AS, ? α Thalassemia</td>
<td></td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>3789</td>
<td>23</td>
<td>F</td>
<td>37.0</td>
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<td>30.1</td>
<td>92.4</td>
<td>1.0</td>
<td>0.9</td>
<td>0.7</td>
<td></td>
<td>AS, elliptocytosis</td>
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<td>F</td>
<td></td>
</tr>
<tr>
<td>3902</td>
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<td>AS, elliptocytosis</td>
<td></td>
<td>F‡</td>
<td></td>
</tr>
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<td>8929</td>
<td>46</td>
<td>F</td>
<td>37.0</td>
<td>18.5</td>
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<td>94.2</td>
<td>1.4</td>
<td>1.3</td>
<td>0.8</td>
<td></td>
<td>AS, elliptocytosis (Mother of 3789 and 3902)</td>
<td></td>
<td>F‡</td>
<td></td>
</tr>
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</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Sex</th>
<th>Mean Hematocrit</th>
<th>BCC Ml./Kg.</th>
<th>Tg Cr</th>
<th>Tg DFF</th>
<th>MCL =DFF</th>
<th>k</th>
<th>Mean Metahbocytes</th>
<th>Preoning Index =DFF</th>
<th>Diagnosis and Remarks</th>
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</thead>
<tbody>
<tr>
<td>7101</td>
<td>43</td>
<td>M</td>
<td>29.5</td>
<td>13.0</td>
<td>27.7</td>
<td>57.1</td>
<td>0.6</td>
<td>0.9</td>
<td>0.9</td>
<td>AC, Tuberculosis</td>
<td>F</td>
</tr>
</tbody>
</table>

* 2 exponent fit better; see Table 3.
† Significant at 5 per cent level or less for arithmetic (F) or exponential (R) curve.
I Eye fit; too few points for computer fit.
Sibling pairs bracketed.

Table 2.---Summary of Data from Patients with Normal Hemoglobin

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Sex</th>
<th>Mean Hematocrit</th>
<th>BCC Ml./Kg.</th>
<th>Tg Cr</th>
<th>Tg DFF</th>
<th>MCL =DFF</th>
<th>k</th>
<th>Mean Metahbocytes</th>
<th>Preoning Index =DFF</th>
<th>Diagnosis and Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>4684</td>
<td>41</td>
<td>F</td>
<td>31.5</td>
<td>16.3</td>
<td>25.7</td>
<td>80.2</td>
<td>1.2</td>
<td>2.9</td>
<td>0.8</td>
<td>Intermittent bleeding</td>
<td>F</td>
</tr>
<tr>
<td>7327</td>
<td>55</td>
<td>M</td>
<td>32.0</td>
<td>20.2</td>
<td>22.7</td>
<td>39.9</td>
<td>52.3</td>
<td>1.1</td>
<td>4.2</td>
<td>Rheumatoid arthritis</td>
<td>R</td>
</tr>
<tr>
<td>2915</td>
<td>19</td>
<td>F</td>
<td>37.0</td>
<td>22.9</td>
<td>25.5</td>
<td>95.6</td>
<td>1.5</td>
<td>0.4</td>
<td>1.0</td>
<td>Elliptocytosis</td>
<td>F</td>
</tr>
<tr>
<td>8876</td>
<td>26</td>
<td>M</td>
<td>45.0</td>
<td>22.1</td>
<td>23.3</td>
<td>85.3</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
<td>Elliptocytosis</td>
<td>F</td>
</tr>
<tr>
<td>3926</td>
<td>22</td>
<td>F</td>
<td>38.5</td>
<td>20.9</td>
<td>27.7</td>
<td>102.5</td>
<td>1.4</td>
<td>1.3</td>
<td>0.9</td>
<td>Elliptocytosis (Sister of 3902 and 3789)</td>
<td>F</td>
</tr>
<tr>
<td>9209</td>
<td>31</td>
<td>M</td>
<td>42.5</td>
<td>22.4</td>
<td>23.0</td>
<td>49.8</td>
<td>71.8</td>
<td>1.6</td>
<td>0.6</td>
<td>Mild hemolysis, cause unknown</td>
<td>R</td>
</tr>
<tr>
<td>2054</td>
<td>29</td>
<td>F</td>
<td>33.5</td>
<td>16.4</td>
<td>12.6</td>
<td>14.8</td>
<td>21.4</td>
<td>0.7</td>
<td>4.2</td>
<td>Hereditary spherocytosis</td>
<td>R</td>
</tr>
</tbody>
</table>

* Significant at 5 per cent level for arithmetic (F) or exponential (R) curve, using an F ratio of the sum of the squares of the residuals.
gas. Usually 1 ml aliquots were used. Activity was expressed as counts per minute/ml. red cells as calculated using the hematocrit reading of the washed cells. Preliminary studies also indicated no need to correct for self-absorption with the volume used. Specimens obtained before the injection of \(^{32}\)DFP but after injection of \(^{51}\)Cr-tagged cells were counted in most cases and the later \(^{32}\)DFP counts were corrected for the counting of about 1 per cent of the \(^{51}\)Cr counts registered by the well system. All samples were counted together to avoid the need to correct for radioactive decay. Samples were counted with the help of an automatic sample changer to a total of 5,000–10,000 preset counts, giving a counting error of significantly less than 3 per cent in all instances.

The resulting \(^{32}\)DFP curves were analyzed by computer\(^*\) for least squares fit to exponential or linear equations. The \(^{51}\)Cr curves were fitted by computer to 1 or more exponential curves.

The sums of the squares of residuals of these curves were appropriately compared using an F ratio to determine whether the linear or the exponential fit was significantly better at the 5 per cent level or less. When the curve is linear, the mean cell life (MCL) is the point of intercept with the X (horizontal or time) axis. When the curve is exponential, the exponent (or slope on semi-logarithmic paper) is the decimal daily red cell loss. The MCL is...

\[
\text{MCL} = \frac{100}{\text{daily red cell loss}}
\]

The standard error of the estimate (SEE) determined in the computer program is \(\sqrt{\frac{\text{SSR}}{n}}\) where SSR = sum of the squares of residuals and \(n\) = the number of points on the curve. When the \(^{32}\)DFP curve clearly fitted an exponential line, the \(^{51}\)Cr elution rate was determined from the difference between the \(^{51}\)Cr slope and the \(^{32}\)DFP slope.\(^5\)

The \(^{51}\)Cr elution rate when red cell life span is finite is the slope of \(\ln \frac{\text{cpm} \ ^{51}\text{Cr}}{\text{cpm} \ ^{32}\text{DFP}}\) plotted against time.\(^5\)

\textbf{Results}

The results of the studies are summarized in Tables 1 and 2. As expected all \(^{51}\)Cr curves fit exponential equations. Unexpectedly the curves obtained from 4 patients fitted 2 exponential lines better than 1 alone. In 2 others, the eye fit suggested 2 exponents, but mathematically, 2 were not significantly better than 1. This apparently was caused by 2 different rates of \(^{51}\)Cr elution which will be discussed further below. These data are summarized in Table 3. The \(^{32}\)DFP lines of all but 1 of the patients with sickle cell anemia were clearly exponential. Inexplicably, one seemed to fit a linear curve better. Only in the cases of 4 patients with elliptocytosis (2 with and 2 without sickle cell trait) was the curve clearly arithmetic, indicating a finite cell life. In 5 other patients a finite life span was suggested, but the F ratio was not significant at the 5 per cent level. None of the \(^{32}\)DFP curves had more than one component. Illustrative curves are seen in Figures 1 and 2.

The mean red cell life span (MCL) was calculated from the \(^{32}\)DFP data. For the 9 patients with sickle cell anemia the average MCL was 17.2 days (range of 12.0–24.4). The other patients had varied MCL's as one would expect from their varied clinical problems (Tables 1 and 2). One patient (\#3717) is exceptional and unexplained. By hemoglobin electrophoretic and family studies, she has sickle cell trait although the simultaneous presence of \(\alpha\) thalassemia trait cannot be excluded (one newborn infant was found not

\*Courtesy of Dr. Herbert Maizel, Computation Center, Georgetown University.
Table 3.—Double Exponential $^{51}$Cr Data for Six Patients

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Single Exp. mCr</th>
<th>Double Exp. #1 mCr</th>
<th>Double Exp. #2 mCr</th>
<th>$F$ Ratio and p Value</th>
<th>Half-life mCr</th>
<th>$K_{1}$</th>
<th>$K_{2}$</th>
<th>Diagnosis and Remarks</th>
</tr>
</thead>
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<tr>
<td>4588</td>
<td>0.0978</td>
<td>0.1126</td>
<td>0.0164</td>
<td>$F_{1.5}=80.99$; p&lt;0.01</td>
<td>0.0715</td>
<td>4.1</td>
<td>—</td>
<td>SS</td>
</tr>
<tr>
<td>7170</td>
<td>0.0915</td>
<td>0.1346</td>
<td>0.0350</td>
<td>$F_{6.4}=39.07$; p&lt;0.01</td>
<td>0.0720</td>
<td>6.3</td>
<td>—</td>
<td>SS</td>
</tr>
<tr>
<td>3043</td>
<td>0.0746</td>
<td>0.2550</td>
<td>0.0589</td>
<td>$F_{0.7}=4.06$; p&lt;0.05</td>
<td>0.0604</td>
<td>19.5</td>
<td>—</td>
<td>SS</td>
</tr>
<tr>
<td>64</td>
<td>0.1087</td>
<td>0.1589</td>
<td>0.0668</td>
<td>$F_{0.6}=24.12$; p&lt;0.05</td>
<td>0.0883</td>
<td>7.1</td>
<td>—</td>
<td>SS</td>
</tr>
<tr>
<td>3717</td>
<td>0.0215</td>
<td>0.0425</td>
<td>0.005</td>
<td>$F_{0.6}=2.87$; p&lt;0.05</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>AS; ? a Thalassemia; eye fit suggested double curve</td>
</tr>
</tbody>
</table>
to have any Bart's hemoglobin. Mild anemia is present and is not due to iron deficiency or other recognizable cause. The $^{32}$DFP curve fits a linear equation better than an exponential one but the difference is not statistically significant ($F_{8,8} = 1.14 \; p > 0.05$). In the equation $y = a + bx$, $a = 548.4$; $b = 3.34$; and SEE (of $y$) = 14.18. The data, therefore, are reasonably precise and the estimate of MCL = 164 days seems experimentally satisfactory but difficult to understand. For the exponential curve, the $^{32}$DFP $T_{1/2}$ is 99 days and the MCL 143 days.

The $^{51}$Cr elution rate ($K_e$) for 13 of the 17 patients with sickle cell hemoglobin had a single component curve with an average daily chromium loss of 1.4 per cent; the range was 0.1–2.7 per cent per day. Each of the other 4 patients had sickle cell anemia and had 2-component elution curves (Fig. 2). During the first part, which lasted 9–11 days, the $K_e$ was 4.1–19.5 per cent daily. The second component was so small as to be negligible. The $K_e$'s for patients with other than sickle hemoglobin are listed in the Table. For all patients with abnormal $\beta$ chains who had single component curves the mean $K_e$ was 1.2 per cent daily (range: 0.1–2.7). For the 7 studies done on patients with normal $\beta$ chains, the mean $K_e$ was 1.3 per cent per day (range: 0.7–1.6). These patients had a narrower range than did those with abnormal $\beta$ chains and all but one fell between 1.1 and 1.6 per cent daily.

Assuming a steady state, one can calculate red cell production from the
rate of red cell destruction. When this is related to normal erythropoiesis a production index can be calculated thus:

\[
\frac{1.00}{\text{MCL}} \times \text{RBC Vol (ml.kg)} = \text{Production index.}^1
\]

This is the multiple of the normal erythropoietic rate found in the patients studied. The production index for each patient is listed in the tables. Despite a severe anemia the patients with sickle cell anemia had a mean production index of only 4.3 (range: 2.7–6.7). Note that for 1 of the 2 patients with sickle-\(\beta\)-thalassemia disease the production index was less than 1 despite a nearly normal red cell life span.

**DISCUSSION**

In general the characteristics of the curves obtained were as expected from the studies of others, although few have measured the red cell life span in patients with sickle cell anemia by technics other than those using \(^{51}\text{Cr}\). Those that have been done with the Ashby technic\(^9\) or using tagged glycine\(^10\-^{12}\) have shown a random pattern of red cell destruction with a shortened mean cell life. The absolute values for MCL are similar to those obtained with \(^{32}\text{DFP}\) and reported above. The 2 patients with S-\(\beta\)-thalassemia had relatively mild disease. In one the red cells seemed to have a finite life span whereas in the other random loss of red cells seemed to occur. Few studies of red cell survival have been made in such patients and those had more severe anemia.
and hemolysis. This probably reflects the great variability in S-β-thalassemia disease although one of our subjects had a very high rate of chromium loss (2.4 per cent daily) which serves to shorten artefactually the T\(\frac{1}{2}\) \(^{51}\)Cr. Her fetal hemoglobin was 5.9 per cent (average of 4 determinations over 2 years) and \(A_2\), 6.3 per cent, which values probably do not account for the high \(K_e\). The other patient had nearly identical quantities for these 2 hemoglobins.

As expected, most of the \(^{51}\)Cr curves fit single exponential lines, at least for the first 3–4 weeks. Of interest is the occurrence of two different exponential curves in each of 4 patients with sickle cell anemia. This apparently caused by 2 different rates of chromium elution. Such a phenomenon has been reported by others in patients with normal hemoglobin. However, the second rate of elution is extremely low in the patients with sickle cell anemia, whereas in those reported by others the second component was still appreciable. The first and more rapid elution rate occurs while the first 50 per cent of the red cell radioactivity was disapppearing or during the period covered by a large number of red cell survival studies. Its affect on estimates of MCL from \(^{51}\)Cr data will be discussed below.

The \(K_e\) for all patients whose red cells contain abnormal beta chains and whose \(^{51}\)Cr curves had only 1 component varied over a 5-fold range from 0.5 to 2.7 per cent daily, except for one patient whose \(K_e\) was 0.1 per cent. The \(K_e\) for the 7 patients sporting normal beta chains varied less (0.7–1.7 per cent daily). With the small numbers in each series it is unlikely that the difference in degree of variation is significant. Certainly the mean figures are not different. The effect of this variable \(K_e\) on estimates of red cell survival can be ascertained by comparing mean cell life values obtained assuming the lowest \(K_e\) (0.5 per cent daily), the highest \(K_e\) (2.7 per cent daily) and an acceptable mean figure from the literature (1.5 per cent daily). The mean T\(\frac{1}{2}\) \(^{51}\)Cr for the 5 patients with sickle cell anemia who had single component curves is 11.2 days. Assuming a \(K_e\) of 2.7 per cent the MCL calculates to 28.6 days and assuming a \(K_e\) of 1.5 per cent the MCL calculates to 21.2 days. These errors are certainly appreciable though perhaps not clinically significant. Another illustration of errors introduced by the variable \(K_e\) is that 5 patients had a T\(\frac{1}{2}\) \(^{51}\)Cr of 26 days or more, values generally considered to be normal. Yet, the MCL \(^{32}\)DFP varied in these patients between 57.1 and 102.5 days. The \(^{51}\)Cr life span may be affected by differential labeling of cells of different ages, variable labeling of different hemoglobins (particularly \(F^\gamma\)) as well as by variable elution rates. In none of the patients with sickle cell anemia was there detected a tail of longer surviving red cells such as might be expected of those cells containing large amounts of hemoglobin \(^{15}\)F. Fetal hemoglobin concentration in the patients with sickle cell anemia was not very high (1.4–8.9 per cent; mean, 4.2 per cent; hence, a large and easily detectable tail might not have been present.

Assuming a steady state, which was present in each of the patients studied, the rates of red cell production can be determined from the rate of red cell loss and the results compared with normal. The patients with sickle cell anemia all had elevated production indices, but only 3 attained an erythropoietic rate of 6–8 times normal reported for patients with hereditary spherocytosis or
non-iron-deficient blood loss and presumably normal bone marrows.16,17 Four of the sickle cell anemia patients were producing red cells at 3 or less times normal. No apparent reason for or detrimental effect from this is apparent at present. The oldest patient had the second greatest production rate. Despite lowered red cell volumes and slightly lowered hematocrit values, one patient with S-β-thalassemia disease had a production index that was slightly below normal whereas the other had only slightly accelerated erythropoiesis. Similar relative defects in the ability of the bone marrow to compensate were seen in the patients with sickle cell-hemoglobin C disease and with homozygous hemoglobin C disease. These relative deficiencies of erythropoiesis could result from inadequate production of the abnormal hemoglobin or from inadequate stimulation. That greater stimulation can result in greater rates of erythropoiesis is suggested by the patient with both homozygous hemoglobin C disease and acute leukemia who achieved more than twice the hemoglobin production rate as did the other CC patients when she was more severely anemic. Inadequate stimulation of red cell production may occur if the hemoglobin oxygen dissociation curve is shifted to make oxygen more available to the tissues. Less hypoxia might stimulate less erythropoietin production and hence less erythropoiesis. Evidence for this latter hypothesis has recently been advanced by Bellingham and Huehns.18

Finally, 2 pairs of siblings with sickle cell anemia were included in the present study. The 2 brothers had relatively similar values (Fig. 1) but the sisters were quite widely divergent; one indeed had a 2-component 51Cr elution curve. Although it was later discovered that she had become pregnant during the study (and later miscarried) it seems unlikely that the 2-component curve was caused by the pregnancy. The other 3 patients with 2-component curves were males. It appears that the differences between siblings who presumably have the same pair of S hemoglobin genes are no less than between nonrelated patients with sickle cell anemia. This would suggest the importance of modifying genes or modifying environmental factors. The latter is somewhat less likely because one of the two brothers has had numerous complications including serum hepatitis, tuberculosis and traumatic fractures of the legs; yet his data are quite similar to those of his brother who has had little difficulty and few complications.

Summary

The red cell life span was measured simultaneously using 51Cr and 32DFP in 21 patients with abnormal hemoglobin β chains and in 7 patients with normal hemoglobin. The patients included 9 with sickle cell anemia, 2 with sickle-β-thalassemia disease, 2 with sickle cell-hemoglobin C disease, 3 with homozygous hemoglobin C disease, 4 with sickle cell trait and 1 with hemoglobin C trait. The 51Cr elution rate from red cells carrying abnormal β chains was 1.2 per cent daily (range: 0.1–2.7 per cent; 4 patients had 2-component elution curves, the first of which was quite rapid (4.1–19.5 per cent daily) and could lead to significant error in the 51Cr estimate of red cell survival. The 51Cr elution rate for red cells with normal β chains was 1.3 per cent daily (range: 0.7–1.6 per cent). In the steady state, production of red cells was
estimated from the \(^{32}\text{DFP}\) life span. Both figures varied with the disease process but erythropoiesis seldom obtained the 6–8 fold increase over normal that is considered to be the capability of normal bone marrow and hence a relative erythropoietic defect seems to be frequently present in patients with abnormal hemoglobin diseases. Two sibling pairs with sickle cell anemia were studied and were found to vary from each other as much as did the other patients with this disorder.

SUMMARIO IN INTERLINGUA

Le longevitate erythrocytic esseva mesurate simultaneemente con le uso de \(^{51}\text{Cr}\) e de \(^{32}\text{DFP}\) in 21 patientes con anormal catenas de hemoglobina \(\beta\) e in 7 patientes con hemoglobina normal. Le patientes includeva 9 con anemia a cellulas falciforme, 2 con morbo falciforme-thalassemic-\(\beta\), 2 con morbo falciforme-hemoglobina C, 3 con homozygot morbo a hemoglobina C, 4 con character de cellula falciforme, e 1 con character de hemoglobina C. Le intensitate del elution de \(^{51}\text{Cr}\) ab erythrocytos portatori de anormal catenas \(\beta\) esseva al media 1,2 pro cento per die (con valores extreme de 0,1 e 2,7). Quatro patientes habeva curvas de elution a duo componentes, incluse un que esseva sati rapida (\(ab 4,1\) ad 19,5 pro cento per die) e poteva resultar in errores significative in estimationes del superviventia erythrocytic con le use de \(^{51}\text{Cr}\). Le intensitate del elution de \(^{32}\text{DFP}\) ab erythrocytos con normal catenas \(\beta\) esseva al media 1,3 pro cento per die (con valores extreme de 0,7 e 1,6). In le stato stabile, le production de erythrocytos esseva estimate a base del longevitate a \(^{32}\text{DFP}\). Le duo cifras variava con le proceso pathologic, sed le erythropoiese rarmente attingeva le augmento sextuple o octuple relative at norma que es considerate como le limite del capacitate de normal medulla ossee. Isto suggere un relative defecto erythropoietico como characteristica frequente in patientes con morbos a hemoglobina anormal. Duo pares de confratemos con anemia a cellulas falciforme esseva studiate, e il esseva trovate que le differentias inter illes non esseva minus significative que le differentias inter le altere patientes con le mesme disordine.

REFERENCES

1. McCurdy, P. R.: Erythrokinetics in ab-
normal hemoglobin syndromes. Blood 20:

2. Malamos, B., Belcher, E. H., Gyftaki,
E., and Binopoulos, D.: Simultaneous radio-
active tracer studies of erythropoiesis and
red cell destruction in sickle-cell disease and
sickle-cell haemoglobin/thalasaemia. Brit.
J. Haemat. 9:467, 1963.

3. Weinstein, I. M., Spurling, C. I., Klein,
H., and Necheles, T. F.: Radioactive sodium
chromate for the study of survival of red
blood cells. III. The abnormal hemoglobin

4. Erlandson, M. E., Schulman, I., and
Smith, C. H.: Studies on congenital hemolyti-
cic syndromes. III. Rates of destruction and
production of erythrocytes in sickle cell

5. Cline, M. J., and Berlin, N. I.: The red
cell chromium elution rate in patients with
some hematologic diseases. Blood 21:83,
1963.


7. Pearson, H. A.: The binding of \(^{51}\text{Cr}\) to
hemoglobin. II. In vivo elution rates of
\(^{51}\text{Cr}\) from Hb CC, Hb CS and placental

8. Cline, M. J., and Berlin, N. I.: An evalua-
tion of \(^{32}\text{DFP}\) and \(^{51}\text{Cr}\) as methods of
measuring red cell life span in man. Blood

9. Singer, K., Motulsky, A. G., and Wile,
S. A.: Aplastic crisis in sickle cell anemia:
A study of its mechanism and its relation-
ship to other types of hemolytic crises. J.

10. Moon, J. H., Abbott, L. D., Jr., and
James, G. Watson III: Simultaneous \(^{51}\text{Cr}\)
and \(^{15}\text{N}-\text{glycine erythrocyte survival times.}

11. James, G. W. III, and Abbott, L. D.
Jr.: Erythrocyte destruction in sickle cell
anemia: Simultaneous \(^{15}\text{N}\) Hemin and \(^{15}\text{N}\)


32DFP and 51Cr for Measurement of Red Cell Life Span in Abnormal Hemoglobin Syndromes

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