Further Studies on Hemoglobin C

II. The Hematologic Effects of Hemoglobin C Alone and in Combination with Sickle Cell Hemoglobin

By Eugene Kaplan, M.D., Wolf W. Zuelzer, M.D., and James V. Neel, M.D., Ph.D.

In our original communication, we suggested that certain hematologic features might be characteristic of sickle cell-hemoglobin C disease and might serve to differentiate this condition from sickle cell anemia. The additional case material presented in the preceding article enabled us to extend our earlier observations and to confirm the validity of our first impressions. It seems possible now to define the hematologic picture and to delineate the diagnostic features of sickle cell-hemoglobin C disease. We are also reporting further studies on the asymptomatic hemoglobin C trait.

Sickle Cell-Hemoglobin C Disease

Our case material of sickle cell-hemoglobin C disease now consists of seven Negro children, three of whom were originally described in our first report and have since been followed for an additional period of continued observation. The four new cases have been described in the preceding paper.*

The anemia associated with this disease was chronic, with little tendency to fluctuation in the red cell counts or hemoglobin levels. Although in two of the seven patients the history indicated that the anemia had, for a short period, become severe, these episodes could not be evaluated since they occurred in association with acute infections, and the patients were not then under our observation. During the years since the patients came under our supervision, hemoglobin and red cell counts remained remarkably stable in these two children, as well as in the remainder of the group. The hematologic data are summarized in table 1.

The hemoglobin levels were in the neighborhood of 9 to 10 Gm. per cent and the red cell counts 3.5 to 4.5 million. The percentage of reticulocytes was frequently elevated, although never to a marked degree, 8 per cent being the maximum observed in any patient. Frequently, the reticulocyte count fell within the normal range. In each of the bone marrow specimens obtained from five of the patients, definite erythroid hyperplasia was noted. Like the reticulocytosis, this hyperplasia was not comparable in degree to that usually seen in sickle cell...
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Hemoglobin, Gm. %</th>
<th>RBC millions per cu. mm.</th>
<th>Reticulocytes, %</th>
<th>WBC per cu. mm.</th>
<th>Hema- tocrit</th>
<th>Mean corpuscular volume</th>
<th>Mean corpuscular hgb.</th>
<th>Mean corpuscular hgb. concentration</th>
<th>Target cells, average % stained film</th>
<th>Sickle cells, % in fixed smears</th>
<th>Siderocytes, % in fixed smears</th>
<th>Osmotic fragility, % saline</th>
<th>Mechanical fragility, in %, % hemolysis</th>
<th>Mechanical fragility in CO₂, % hemolysis</th>
<th>Serum bilirubin, mg.</th>
<th>Hemolytic index (fetal urobilinogen excretion)</th>
<th>Myeloid:erythrocyte ratio, bone marrow</th>
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<tr>
<td>J. Y.</td>
<td>8</td>
<td>M</td>
<td>8.6</td>
<td>7-9.6</td>
<td>3.4</td>
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<td>8-10.7</td>
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<td>3.1-4.6</td>
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<td>8</td>
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<td>70</td>
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<td>24</td>
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<td>P. A. C.</td>
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<td>F</td>
<td>9.2</td>
<td>6.8-10.6</td>
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<td>7,500</td>
<td>29</td>
<td>90</td>
<td>25</td>
<td>28</td>
<td>40</td>
<td>0.2</td>
<td>0.42-0.18</td>
<td>10</td>
<td>58</td>
<td>0.4</td>
<td>19</td>
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</table>
anemia. The myeloid-erythroid ratio was below 1:3 in each case. There was little, if any, leukocytosis.

The corpuscular constants indicated a definite microcytosis in all but one case. The mean corpuscular hemoglobin concentration was only slightly depressed, in contrast to the considerable depression of mean corpuscular volume and mean corpuscular hemoglobin. We assume this to be an expression of the occurrence of thin erythrocytes which are only slightly deficient in hemoglobin. The appearance of the red cells in ordinary fixed smears was in accord with this view. The erythrocytes were of remarkably uniform size and contour, in marked contrast with both thalassemia and sickle cell anemia. Sickled erythrocytes were either absent or

![Graph with data points](image)

**Fig. 1.**—A comparison of sickle cell-hemoglobin C disease and sickle cell anemia with respect to: (a) per cent sickled erythrocytes in blood smears; (b) per cent siderocytes in blood smears; and (c) hemolytic index (fecal urobilinogen excretion).

...found with some difficulty. A comparison of the frequency of sickled erythrocytes in blood smears of our patients and of children with sickle cell anemia is shown in figure 1a.

The striking feature of the erythrocytes of all our patients was the presence of target cells in large numbers (fig. 2a). Target cells were invariably present in serial examination of smears from all patients although in each individual the number of such cells showed minor variations. Considering the ease with which target cell formation on smears is influenced by technical factors, the percentage of target cells in consecutive specimens from each individual was found to be remarkably constant over a period of years. As shown in figure 3, the average percentage of target cells in these seven patients ranged from 40 to 85 per cent. Figure 3 represents a random sampling of the frequency of target cells in normal Negroes and whites and in individuals with sickle cell trait, sickle cell anemia,
thalassemia major and minor, the asymptomatic hemoglobin C trait, and sickle cell-hemoglobin C disease. It can be seen at a glance that in no other condition among those listed did the frequency of target cells tend to be as elevated as in

![Image of blood smears]

**Fig. 2.**—The appearance of smears of the peripheral blood in: (a) sickle cell-hemoglobin C disease; (b) hemoglobin C trait; (c) sickle cell anemia; and (d) thalassemia major.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Target Cell Frequency</th>
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<tbody>
<tr>
<td>Normal White</td>
<td>0-10</td>
</tr>
<tr>
<td>Normal Negro</td>
<td>0-10</td>
</tr>
<tr>
<td>Sickle Trait</td>
<td>10-30</td>
</tr>
<tr>
<td>HbC Trait</td>
<td>0-10</td>
</tr>
<tr>
<td>Sickle Cell Anemia</td>
<td>30-60</td>
</tr>
<tr>
<td>HbC Major</td>
<td>60-90</td>
</tr>
<tr>
<td>HbC Minor</td>
<td>0-10</td>
</tr>
</tbody>
</table>

**Fig. 3.**—The frequency of target cells in smears of the peripheral blood in a variety of conditions. Each dot represents the average target cell per cent for a single individual.

the combination of hemoglobin C and sickle hemoglobin. There was some overlapping with sickle cell anemia, in which the range was 7 to 40 per cent.

Siderocytes (erythrocytes with iron staining cytoplasmic granules when stained
with potassium ferrocyanide and dilute HCl) were not increased in the individuals with sickle cell-hemoglobin C disease, whereas, in our experience, they were commonly increased in sickle cell anemia. The siderocyte levels in our group compared with those found in a sampling of patients with sickle cell anemia are shown in figure 1b.

Erythrocyte sickling in sealed fresh preparations with sodium metabisulfite was rapid and complete and resulted in filamentous sickle forms. In this respect, the sickling resembled that seen in sickle cell anemia.

The osmotic resistance of erythrocytes was studied in six of our patients and was increased in every case. There was no increase in the fragility of the erythrocytes in these studies. The curve of percentage hemolysis at decreasing concentrations of saline from case J. Y. of family Y, showed a distinct right shift with complete hemolysis at 0.21 per cent saline (fig. 4). This increased resistance was to be expected in the presence of large numbers of target cells.

The mechanical fragility of erythrocytes was measured in three of these individuals. In an atmosphere of ordinary oxygen tension, the mechanical fragility was within normal limits. In an atmosphere saturated with carbon dioxide the mechanical fragility was significantly increased. As previously noted by us, this behavior appeared to be dependent upon the sickling phenomenon since it occurred as well in sickle cell anemia and the sickle cell trait, but not in the hemoglobin C trait.

The serum bilirubin was normal or occasionally very slightly increased in these patients. During the period of our observation, clinical jaundice was entirely absent.

![Fig. 4.—Erythrocyte fragility in hypotonic saline in a case of sickle cell-hemoglobin C disease. The broken line represents the values obtained for a control.](image-url)
HEMATOLOGIC EFFECTS OF HEMOGLOBIN C

The excretion of fecal urobilinogen was increased in each of the three children studied. The elevation of the hemolytic index was much less, however, than in children with sickle cell anemia. A comparison of the hemolytic indices in these two conditions is shown in figure 1c.

We have previously reported that the survival of erythrocytes from individuals with sickle cell-hemoglobin C disease transfused into normal recipients was greatly shortened, and that the survival of normal erythrocytes transfused into such patients was normal. An additional child with this disease has since been studied with identical results (fig. 5). Erythrocytes from case G. M. of family M, transfused into a normal recipient, were eliminated very rapidly, with a half-life of only ten days. There appeared to be a discrepancy between the rate with which these cells are eliminated when transfused and the relatively low hemolytic index in patients with this disease. Normal erythrocytes transfused into this child were eliminated at the normal rate. Normal survival was likewise observed when he was transfused with erythrocytes from the asymptomatic hemoglobin C trait.

THE HEMOGLOBIN C TRAIT

The hematologic data for 13 individuals with the hemoglobin C trait is summarized in table 2. The hemoglobin levels, red cell and reticulocyte counts, and corpuscular constants were entirely normal for the individual's age and sex. There was no erythrocyte sickling. The erythrocytes appeared normal in size and contour in ordinary smears and were well filled with hemoglobin. Siderocyte inclusions were not present.

As previously noted by us, the only significant morphologic abnormality of the erythrocytes in individuals with the combination of hemoglobin C and
normal hemoglobin was the presence of numerous target cells (fig. 2b). The frequency of target cells in this group, expressed as the average per cent for each individual, ranged from 3 to 33 per cent (fig. 3). There was less relative constancy in the target cell count on consecutive specimens taken from the same individual than was the case in sickle cell-hemoglobin C disease. Individuals whose maximum target cell count was 10 per cent occasionally had fewer than 2 per cent target cells. Individuals with counts above 20 per cent, however, were not observed to fall below a frequency of 15 per cent target cells. It was noteworthy that each of the three individuals in the latter group were members of family W. The percentage distribution of the hemoglobin components of three individuals with the hemoglobin C trait has been reported by Itano and Neel. The percentage of hemoglobin C was 30.5, 33.6, and 35.3 per cent and the average target cell frequency was 20, 3, and 10 per cent respectively, in these individuals. There was no apparent quantitative correlation between the percentage of hemoglobin C and the average number of target cells in this small sampling.

The incidence of target cells in individuals with the asymptomatic hemoglobin C trait is compared with that in normal individuals, both Negro and white, and individuals with other hematologic disturbances in figure 3. A considerable overlapping was to be noted with sickle cell trait and sickle cell anemia, thalassemia major and minor, and some apparently normal Negroes. The absence of sickling clearly differentiated the hemoglobin C trait from the sickle cell syn-

### Table 2—A Summary of the Hematologic Data for Individuals with the Hemoglobin-C Trait

<table>
<thead>
<tr>
<th>Family</th>
<th>Individual</th>
<th>Age</th>
<th>Sex</th>
<th>RBC millions per mm³</th>
<th>Hemoglobin, Gm. %</th>
<th>Reticulocytes, %</th>
<th>Hematocrit</th>
<th>Mean corpuscular hemoglobin volume</th>
<th>Mean corpuscular hemoglobin</th>
<th>Mean corpuscular hemoglobin concentration</th>
<th>Target cells, % on stained films</th>
<th>Osmotic fragility, % saline</th>
<th>Serum bilirubin, mg. %</th>
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</thead>
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<tr>
<td>W</td>
<td>H. W.</td>
<td>36</td>
<td>M</td>
<td>5.6</td>
<td>15.1</td>
<td>0</td>
<td>46</td>
<td>81</td>
<td>27</td>
<td>33</td>
<td>33</td>
<td>31–36</td>
<td>0.47–0.21</td>
</tr>
<tr>
<td>J. W.</td>
<td>34</td>
<td>M</td>
<td>5.6</td>
<td>14.9</td>
<td>1</td>
<td>45</td>
<td>81</td>
<td>27</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>16–25</td>
<td>0.40–0.18</td>
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<tr>
<td>Dv. W.</td>
<td>13</td>
<td>M</td>
<td>4.7</td>
<td>12.2</td>
<td>0.1</td>
<td>38</td>
<td>81</td>
<td>28</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>16–22</td>
<td>0.39–0.18</td>
</tr>
<tr>
<td>Dn. W.</td>
<td>10</td>
<td>M</td>
<td>4.5</td>
<td>11.8</td>
<td>0</td>
<td>35</td>
<td>77</td>
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<td>34</td>
<td>16–26</td>
<td>0.38–0.18</td>
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<tr>
<td>C</td>
<td>P. C.</td>
<td>30</td>
<td>M</td>
<td>5.2</td>
<td>15.9</td>
<td>0.8</td>
<td>48</td>
<td>92</td>
<td>30</td>
<td>33</td>
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<td>8–12</td>
<td>0.45–0.30</td>
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<tr>
<td>P. C.</td>
<td>7</td>
<td>M</td>
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<td>11.5</td>
<td>0.8</td>
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<td>93</td>
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<td>31</td>
<td>33</td>
<td>33</td>
<td>1.2–5</td>
<td>0.45–0.25</td>
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</table>

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The normal red cell size, shape, and contour distinguished it from thalassemia major and minor, with their characteristic microcytosis, hypochromasia, and variability in erythrocyte shape.

Figure 3 indicates that six of thirty-four apparently normal Negroes and eight of thirteen individuals with hemoglobin C trait showed 3 to 5 per cent target cells. The possibility existed that undiagnosed cases of the hemoglobin C trait may have accounted for some of the increase in target cells in this sampling of normal Negroes. The overlap between the two groups may not have been as great, therefore, as appeared at first glance. In three individuals with only normal hemoglobin demonstrable by electrophoresis, the target cell incidence was less than 1.5 per cent. The problem could not be settled in the absence of comparable electrophoretic studies in individuals with elevated target cell counts.

The erythrocyte osmotic fragility was studied in seven individuals with the hemoglobin C trait; increased resistance to hypotonic saline was observed in four. The average target cell frequency in the three individuals with normal osmotic fragility was 4, 10, and 12 per cent respectively. In the four individuals with increased osmotic resistance, the average number of target cells was 3, 20, 22, and 33 per cent. Erythrocyte mechanical fragility has been measured in one individual and found to be normal in both oxygen and carbon dioxide atmosphere.

Serum bilirubin levels were within the normal range for the age in the nine individuals examined. The fecal urobilinogen excretion and bone marrow aspirate was likewise normal in one case so studied.

In our previous communication, we reported that shortened erythrocyte survival was observed when blood from each of three donors with hemoglobin C trait
was transfused into normal recipients. No explanation could be offered for this phenomenon. To further test this experience, erythrocytes from two additional individuals with the hemoglobin C trait have since been transfused into normal recipients and the survival found to be normal (fig. 6). In one instance, the red cells were simultaneously transfused into the donor’s son (fig. 5), who has the combination of hemoglobin C and sickle hemoglobin. At the same time, this child received a transfusion of normal tagged erythrocytes, to serve as a control. In each of these studies the survival was entirely normal.

In view of these contradictory findings, one of the previously described hemoglobin C trait donors (J. W.), whose erythrocytes had been rapidly eliminated from a normal recipient, was again studied (fig. 7). On this occasion, a normal recipient was simultaneously transfused with erythrocytes from J. W. and with erythrocytes from a normal donor. The survival of the hemoglobin C trait erythrocytes was in this experiment just within the normal range in our experience with this method. The rate of elimination, however, was notably more rapid than that of the control normal erythrocytes simultaneously transfused.

At the time of our original observations, technical error seems to have been carefully excluded and no reasonable explanation could be made for the unexpectedly short survival of erythrocytes from individuals in whom no evidence for hemolytic activity could be demonstrated. In view of this conflicting evidence, these studies are being extended. For the present, it cannot be stated that abnormal erythrocyte survival is a characteristic of the uncomplicated hemoglobin C trait.
Hematologic Effects of Hemoglobin C

Discussion

The combination of hemoglobin C and sickle cell hemoglobin results in a hemolytic syndrome with distinctive clinical and hematologic features. As described in the preceding paper, the clinical course of sickle cell-hemoglobin C disease is mild and specific complaints are few, although we have seen at least one case (case J. Y., family Y) whose clinical severity approaches that of sickle cell anemia. There is little interference with normal activity, growth, and development. Attacks of musculoskeletal or abdominal pain are either absent or very infrequent. Moderate hepatosplenomegaly is present in early childhood, usually persists beyond the age of 5 years, and tends to subside completely. Cardiac enlargement and murmurs, and skeletal hypertrophy are virtually absent. The disorder is characterized hematologically by a mild chronic anemia whose essential features are erythrocyte sickling and target cells. The hemolytic disturbance is clearly due to an inherited intrinsic erythrocyte defect.

The clinical and hematologic characteristics of sickle cell-hemoglobin C disease form a distinctive profile which makes possible the differentiation of the syndrome from other hematologic conditions with which it may be confused and provides simple and valid criteria for the recognition of additional cases. A graphic representation of this and related profiles is shown in figure 8.

Sickle cell-hemoglobin C disease may be clearly distinguished from sickle cell anemia and the sickle cell trait, not only by its essential genetic and physicochemical differences, but also on the basis of its clinical and hematologic characteristics. Sickle cell anemia in children, although variably expressed in a large group of patients studied by us, is in general a severe hemolytic anemia with impaired nutrition, recurrent episodes of pain, cardiac enlargement, and splenomegaly which usually subsides by the third year of life or, if persistent, is associ-
ated with particularly severe manifestations. The anemia is severe and there is marked increase in reticulocytosis, marrow erythroid activity, and fecal urobilinogen excretion. Sickled erythrocytes, siderocytes, and target cells are frequent in blood films (fig. 2c). The target cells, however, are even more numerous in sickle cell-hemoglobin C disease, which helps to distinguish our cases from sickle cell anemia. In passing, it is noteworthy that there is a sharp distinction between the number of target cells in sickle cell anemia and the sickle cell trait. We have found this feature of the blood smear of great practical value in distinguishing these two conditions.

The clinical and hematologic profile of sickle cell-hemoglobin C disease is distinct from that of thalassemia major and minor. Thalassemia major is a chronic illness with persistent and marked splenomegaly. The anemia is often severe, requiring transfusions, and is characterized by extreme poikilocytosis and marked hypochromasia and microcytosis. Erythrocyte sickling and siderocytosis is absent. The incidence of target cells, in six cases examined by us, was found to be less than 10 per cent. In the only previously published report of actual target cell counts in this disease an incidence of 32 per cent, 2.4 per cent, and 1.2 per cent target cells was noted in three cases, while a fourth case was described as having “many”. Thalassemia minor, as seen in relatives of patients with the major form of the disease, is usually an asymptomatic trait with infrequent and slight splenomegaly. In our experience the erythrocyte changes, as seen in peripheral blood films, are often minimal, consisting of slight microcytosis, hypochromasia, and ovalocytosis. Siderocytes are not increased and there is no erythrocyte sickling. We found the incidence of target cells to be less than 10 per cent in 19 of 20 cases with this form of thalassemia, and increased to 26 per cent in the remaining case. Dameshek found fewer than 10 per cent target cells in each of approximately thirty cases of “hypochromic polycythemia”. It is our belief that target cells are not, as a rule, greatly increased in thalassemia. The marked increase in target cells in sickle cell-hemoglobin C disease (40 to 85 per cent) is therefore a significant point of distinction between these conditions. The distinctive electrophoretic behavior of hemoglobin C further differentiates thalassemia from sickle cell-hemoglobin C disease and the hemoglobin C trait.

Sickle cell-thalassemia disease is a rare syndrome resulting from the simultaneous inheritance of both the gene for sickling and that for thalassemia. The limited number of cases which have been studied in this country does not permit the construction of a clinical hematologic profile comparable to those presented in this paper for sickle cell anemia and sickle cell-hemoglobin C disease. In general, however, the condition appears more or less intermediate between the two.

**Conclusions**

It is now clear that there are several distinct hematologic disorders associated with the presence of the sickling gene and that it is essential, for prognostic purposes, to distinguish between the various forms. One of these syndromes, sickle cell-hemoglobin C disease, is due to the simultaneous presence in one individual of the genes responsible for sickle cell hemoglobin and hemoglobin C. Our studies have shown that this entity has its own characteristic diagnostic profile and can be differentiated from classical sickle cell anemia by simple hematologic methods.
Individuals heterozygous only for the hemoglobin C gene appear to be completely asymptomatic. An increase in target cells is the only consistent hematologic abnormality of the hemoglobin C trait, which is clearly differentiated from the sickle cell trait by the absence of sickling, and from thalassemia minor by the absence of microcytosis, hypochromasia, and abnormalities in erythrocyte contour.

The homozygous state with respect to hemoglobin C has not yet been recognized. Careful search should be made for this and the expected combinations of hemoglobin C with thalassemia, spherocytosis, and other inherited erythrocyte disorders.*

REFERENCES


2 —: Unpublished observations.


6 Neel, J. V., Itano, H. A., and Lawrence, J. S.: Two cases of sickle cell disease presumably due to the combination of the genes for thalassemia and sickle cell hemoglobin. Blood 8: 434–443, 1953.

* Since this paper was accepted for publication, homozygous hemoglobin C has been recognized by SpAET in a patient with mild hemolytic anemia (Pediatrics, in press). In addition, in a case to be reported, we have identified the combination of thalassemia and hemoglobin C in a Negro child.
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Hemoglobin C Alone and in Combination with Sickle Cell Hemoglobin

EUGENE KAPLAN, WOLF W. ZUELZER and JAMES V. NEEL