An Unusual Type of Hemoglobinopathy Resembling Sickle Cell-Thalassemia Disease in a Jamaican Family

By L. N. Went and J. E. MacIver

In a previous communication1 cases of sickle cell-thalassemia disease seen in Jamaica were described. The family which is the subject of this report was mentioned briefly in that paper, but in view of the unusual findings we feel that fuller description is merited.

Methods

Standard hematologic methods were used.2 In vitro sickling tests were carried out using the method of Daland and Castle.3 Fetal hemoglobin was estimated by the alkali denaturation technic of Singer, Chernoff and Singer.4 Filter-paper electrophoresis of hemoglobin was performed in a horizontal tank using barbitone buffer pH 8.6 and ionic strength about 0.02. The technic is described in detail elsewhere.5 A clear separation between hemoglobins A, F and S can be made by this method. In figure 1 the pattern of the mother (whose blood contains 24% of fetal hemoglobin) is significantly different from that of the normal control (AA) whose blood contains less than 1% of fetal hemoglobin. A difference can also be seen between the patterns of the son (hemoglobin S + 24% of hemoglobin F) and that of a case of sickle cell anemia (SS) whose blood contains only 10% of hemoglobin F.

Results

A family tree is given in figure 2, and the main hematologic and biochemical findings are presented in table 1.

The index case (II-2 Lucia B.) is a 26-year-old female of African descent. She was discovered during an investigation of women attending the ante-natal clinic at the University College Hospital undertaken to determine the incidence of the genes responsible for abnormal hemoglobins.6 Her hemoglobin gave a pattern on filter-paper electrophoresis which was indistinguishable from that found in sickle cell anemia except for an unusually high fetal fraction. She was five months pregnant when first seen and was perfectly well. She had had four normal pregnancies, and her children were alive and apparently well. Her past history was completely negative. On physical examination no abnormality was found, and she was not anemic. Throughout pregnancy her hemoglobin level—average 12.5 Gm.%—was consistently above the mean (11.2 Gm.% for the 1000 pregnant women studied.7 On further laboratory investigation her blood sickled, but not so readily as would be expected in sickle cell anemia. The appearances of a stained blood film (fig. 3) and the osmotic fragility of her red cells (fig. 4) were normal. The reticulocyte count was slightly raised (3%). A high level of fetal hemoglobin was found (27%). As it seemed unlikely that she did in fact have sickle cell anemia a study of her family was carried out.

From the Department of Pathology, University College of the West Indies, Jamaica. The authors are indebted to Dr. T. H. J. Huisman of Groningen (Netherlands) for his kindness in investigating a blood sample and for his permission to include the results in this paper; and to Dr. K. Standard for his assistance in collecting some of the blood specimens from the remoter parts of Jamaica.

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Fig. 1.—Paper electrophoresis patterns of some members of the family (Father I-1, Mother I-2, and Son II-6) compared with normal cord blood and bloods from cases of sickle cell anemia and homozygous hemoglobin C disease.

The father (I-1) was healthy. His blood sickled, but was otherwise hematologically normal. Electrophoresis gave an A + S pattern. Fetal hemoglobin was 1%.

The mother (I-2) was also healthy. Her blood did not sickle, but a stained blood film showed slight hypochromia and occasional target cells. No basophil stippling was seen. The film appearances were not typical of thalassemia minor. The osmotic fragility was normal on one occasion and slightly decreased on another. Electrophoresis gave an A + F pattern and 24% of fetal hemoglobin was found on alkali denaturation.

There are seven children of this marriage, all living.

II-1 was found to have slight anemia (hemoglobin 11.7 Gm./100 ml.) but otherwise no abnormality could be demonstrated. The film appearances did not suggest thalassemia minor.

II-3 was anemic (hemoglobin 9.6 Gm./100 ml.), her blood sickled, and electrophoresis gave an A + S pattern. Fetal hemoglobin was 1%. Her anemia could be explained as she had only left the hospital three weeks previously, following an abortion.

II-4 and II-5 had the sickle cell trait.

II-6 (son of fig. 1) gave a history of being easily tired, and on examination his con-
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Fig. 2.—Family tree. The arabic numerals to the right of the symbols refer to the levels of fetal hemoglobin found. Follow-up studies show that III-5 has, in fact, the genotype AS.

Fig. 3.—Photomicrographs of blood smears from the index case (Lucia B. II-2), her brother, II-6, and two of her children, III-2 and III-4.

Junctivae were pale and slightly icteric. On laboratory examination he was found to be anemic (hemoglobin 10.2 Gm./100 ml.). His blood sickled in vitro, and the appearances of a stained blood film were very abnormal (fig. 3). Osmotic fragility was grossly decreased (fig. 4). The reticulocyte count was 4%. Electrophoresis gave an S + F pattern, and 24% of fetal hemoglobin was found on alkali denaturation.

II-7 was healthy and his blood was completely normal on examination. Electrophoresis
### Table 1.—Hematologic Findings

<table>
<thead>
<tr>
<th>Designation in Family Tree</th>
<th>Age</th>
<th>Hb Gm./100 ml.</th>
<th>RBC 10^6 mm.</th>
<th>PCV %</th>
<th>MCV μ</th>
<th>MCHC %</th>
<th>Retic.</th>
<th>Hypochromia</th>
<th>Film appearances</th>
<th>Target cells</th>
<th>Sickled cells</th>
<th>Fragility</th>
<th>Sickling</th>
<th>Electroforetic phenotype</th>
<th>Fetal Hb %</th>
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<tbody>
<tr>
<td>I-1 (Father)</td>
<td>60</td>
<td>15.6</td>
<td>6.0</td>
<td>48</td>
<td>80</td>
<td>33</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>normal</td>
<td>+</td>
<td>A + S</td>
<td>1</td>
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<tr>
<td>I-2 (Mother)</td>
<td>53</td>
<td>15.0</td>
<td>5.0</td>
<td>45</td>
<td>90</td>
<td>33</td>
<td>1</td>
<td>sl.</td>
<td>occ.</td>
<td>—</td>
<td>normal</td>
<td>—</td>
<td>—</td>
<td>A + F</td>
<td>24</td>
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<tr>
<td></td>
<td>12.6</td>
<td>5.0</td>
<td>39</td>
<td>78</td>
<td>32</td>
<td>2</td>
<td>sl.</td>
<td>occ.</td>
<td>—</td>
<td>sl. decreased</td>
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<td>—</td>
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<td>26</td>
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<tr>
<td>II-1</td>
<td>31</td>
<td>11.7</td>
<td>—</td>
<td>37</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>normal</td>
<td>—</td>
<td>A</td>
<td>2</td>
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<td>II-2 (Lucia B) *</td>
<td>26</td>
<td>12.5</td>
<td>4.9</td>
<td>38</td>
<td>77</td>
<td>33</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>normal</td>
<td>+</td>
<td>S + F</td>
<td>27</td>
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<tr>
<td>II-3</td>
<td>6</td>
<td>13.0</td>
<td>—</td>
<td>41</td>
<td>—</td>
<td>32</td>
<td>2</td>
<td>sl.</td>
<td>—</td>
<td>—</td>
<td>normal</td>
<td>—</td>
<td>+</td>
<td>A + S</td>
<td>2</td>
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<tr>
<td>III-1</td>
<td>6</td>
<td>13.0</td>
<td>—</td>
<td>41</td>
<td>—</td>
<td>32</td>
<td>1</td>
<td>sl.</td>
<td>—</td>
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<td>normal</td>
<td>—</td>
<td>—</td>
<td>A + F</td>
<td>16</td>
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<tr>
<td>III-2</td>
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<td>9.1</td>
<td>—</td>
<td>28</td>
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<td>32</td>
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<td>+</td>
<td>+</td>
<td>+†</td>
<td>grossly decreased</td>
<td>+</td>
<td>A + S</td>
<td>10</td>
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<tr>
<td>III-3</td>
<td>3</td>
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<td>—</td>
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<td>+</td>
<td>A + S</td>
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<td>—</td>
<td>23</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>grossly decreased</td>
<td>+</td>
<td>S + F</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>III-5 (cord blood)</td>
<td></td>
<td>12.6</td>
<td>—</td>
<td>38</td>
<td>—</td>
<td>33</td>
<td>11</td>
<td>sl.</td>
<td>occ.</td>
<td>—</td>
<td>—</td>
<td>decreased</td>
<td>—</td>
<td>F (+A)</td>
<td>60</td>
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<tr>
<td>III-5 (25 weeks old)</td>
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<td>12.2</td>
<td>4.0</td>
<td>38</td>
<td>95</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>A + S</td>
<td>3</td>
</tr>
<tr>
<td>II-3</td>
<td>23</td>
<td>9.6</td>
<td>—</td>
<td>30</td>
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<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>sl. decreased</td>
<td>+</td>
<td>A + S</td>
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<tr>
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<td>—</td>
<td>8</td>
<td>—</td>
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<td>+</td>
<td>+</td>
<td>grossly decreased</td>
<td>+</td>
<td>S</td>
<td>3</td>
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<tr>
<td>II-4</td>
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<td>15.6</td>
<td>5.0</td>
<td>45</td>
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<td>A + S</td>
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<tr>
<td>II-5</td>
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<td>14.2</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>normal</td>
<td>—</td>
<td>A + S</td>
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<tr>
<td>II-6 (son)</td>
<td>16</td>
<td>10.2</td>
<td>4.7</td>
<td>32</td>
<td>68</td>
<td>32</td>
<td>4</td>
<td>+</td>
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<td>A + S</td>
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<td>43</td>
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<td>—</td>
<td>normal</td>
<td>—</td>
<td>A + F</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

*Index case.
†Occasional nucleated red cells in film.
sl. = slight; occ. = occasional.
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Fig. 4.—Osmotic fragility curves of the index case (Lucia B. II-2), her brother II-6, and two of her children III-2 and III-4.

showed an A + F pattern, and 26% of fetal hemoglobin was found on alkali denaturation. II-8 (Lucia B's husband) was healthy. Hematologically no abnormality was found apart from a slight decrease in the osmotic fragility and a positive sickling test. Electrophoresis showed an A + S pattern. Fetal hemoglobin was 2%.

The children of Lucia B (II-2) were all studied.

III-1 was well, and no hematologic abnormality was found apart from slight hypochromia in the stained film. No basophil stippling was seen. However, electrophoresis showed an A + F pattern, and fetal hemoglobin was 16%.

III-2 and III-4, although clinically well and without relevant history, were anemic. Both had positive sickling tests, reticulocytosis, and decreased osmotic fragility (fig. 4). The electrophoretic pattern showed hemoglobin S only in both cases. Fetal hemoglobin levels of 10% and 12%, respectively, were found. The stained blood film of III-2 contained numerous sickled cells whereas that of III-4 contained none. Hypochromia and target cells were well marked in both (fig. 3).

III-3 was healthy, and hematologically normal apart from a positive sickling test. Electrophoresis gave an A + S pattern and fetal hemoglobin was 2%.

III-5, the last child of Lucia B, was born on 1 6 57. Examination of the cord blood revealed that about 50% of the cells sickled in vitro, and many of these were of the filamentous type (fig. 5). Electrophoresis showed the normal pattern for cord bloods, no hemoglobin S being demonstrable, and alkali denaturation gave a value of 60% fetal hemoglobin. The blood film showed slight hypochromia and occasional target cells. The child was admitted to the hospital when 20 weeks old with bronchopneumonia following on whooping cough. At this time, examination of the blood showed anemia, but electrophoresis gave an A + S pattern and only 4.5% fetal hemoglobin was found (table 2). Five weeks later, when the child had completely recovered, the hematologic findings were essentially normal, apart from 95% sickling (table 1). Fetal hemoglobin had decreased to 3%.

III-6, the only child of II-3, had a spastic quadriplegia of unknown cause which apparently developed suddenly when the child was one year old. Laboratory examination revealed typical sickle cell anemia. The stained blood film contained numerous sickled cells, electrophoresis revealed hemoglobin S only, and 3% of fetal hemoglobin was found on alkali denaturation. The father was not available for study.
DISCUSSION

The index case (Lucia B.) in this family apparently suffers no disability and has successfully given birth to five children despite an $S + F$ hemoglobin pattern. Her brother (II-6) has the same pattern, but although he has never been ill (complaining only of some tiredness at the end of the day) examination of his blood revealed a mild hemolytic anemia. Her mother (I-2), brother (II-7) and one son (III-1) all showed high levels of hemoglobin F in their red cells unassociated with any definite hematologic abnormality. The amount of hemoglobin F found was much in excess of that seen in thalassemia minor, in which condition normal or slightly raised values are usually found. Edington and Lehmann have reported a similar condition in a family in Africa in which the index case was a man, without symptoms of anemia, who gave on electrophoresis a pattern indistinguishable from that found in sickle cell anemia but with 26 per cent hemoglobin F. A child was found to have 24 per cent hemoglobin F, no hemoglobin S and a normal blood film. They regarded this as a case of thalassemia minor. We have not found any other report of a similar nature.

The gene which gives rise to these high levels of fetal hemoglobin, as noted in a woman of African extraction and which we found in 3 generations of her family, we have labeled "F" in figure 2. When cases I-2 and II-7, both of whom have inherited the "F" gene alone ($A + F$ pattern), are compared with cases II-2 and II-6 who have also inherited the $S$ gene ($S + F$ pattern), a remarkable constancy in the percentage of fetal hemoglobin is seen. The "F" gene appears to control the fetal hemoglobin level regardless of which other hemoglobin types are present. The precise rela-
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The relationship between this gene and the thalassemia gene is uncertain, but in combination with the S gene it also produces suppression of hemoglobin A formation in the phenotype. It is stated by Zuelzer et al. that there may be several thalassemia loci, and it is possible that this “F” gene represents another variant of thalassemia. It might be, as postulated by Singer et al., that we are here dealing not with a single gene but with a combination of a thalassemia gene and a modifying gene which are together responsible for the high levels of fetal hemoglobin. We feel that this possibility is unlikely in our family. The likelihood of two independent genes being inherited simultaneously in at least five members of this family is small.

In the third generation, in case III-1, the presence of the “F” gene alone is certain, but in cases III-2 and III-4 the problem is more difficult. We had hoped that a study of Lucia B. and her five children would throw light on the mode of inheritance of the S and “F” genes. They could be alleles like the S and C genes or, as is thought to be the case with the thalassemia gene, could be situated at different loci and inherited independently. However, the unexpected occurred and Lucia B’s husband (II-8) was found to have the sickle cell trait. In the light of this finding, cases III-2 and III-4 might either have the genotype SS (S from father and S from mother), they might have the genotype S “F” (S from father and “F” from mother) or they might be S “F” (both genes from mother). It is not possible to decide between these last two combinations and a choice between the first one and the other two can only be made by inference. The relatively low levels of hemoglobin F present in cases III-2 and III-4 (10 per cent and 12 per cent respectively) might be somewhat more in favor of true sickle cell anemia, since in those members of the family who certainly have an “F” gene the level of hemoglobin F is much higher. It cannot, however, be excluded that the percentage of hemoglobin F in III-2 and III-4 may rise with age. In this connection III-1, who has the same genetic condition as I-2 and II-7, but is much younger, has a somewhat lower percentage of hemoglobin F. Against sickle cell anemia in both cases it can be argued that they have had no complaints whatsoever related to their genetic condition up to the present time. In general, sickle cell anemia gives definite symptoms in the first years of life, but on the other hand we have seen some undoubted cases of sickle cell anemia in whom the symptoms first appeared in adult life. In figure 2 we have labeled III-2 SS and III-4 S “F” on the basis of the hematologic findings. In the first place sickled cells are numerous in the blood film of III-2, whereas they are completely absent in that of III-4 (fig. 3). Although occasional sickled cells may be seen in cases of sickle cell–thalassemia disease, in our experience they are not numerous. Secondly the reticulocyte count in III-2 is higher than in III-4, indicating a more active hemolytic process. Finally, the mean corpuscular hemoglobin concentration is normal in III-2, whereas it is low in III-4. However, the genotype in these two children cannot with certainty be defined on the basis of these differences.

The last child of Lucia B. (III-5) was born on 1/6/57. On paper electro-
TABLE 2.—Results of Serial Studies on the Youngest Child (III-5) of Lucia B.

<table>
<thead>
<tr>
<th>Age</th>
<th>Hb/Gm./100 ml</th>
<th>Fetal Hb %</th>
<th>Electrophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>cord blood</td>
<td>12.6</td>
<td>60</td>
<td>F (+A)</td>
</tr>
<tr>
<td>6 days</td>
<td>14.4</td>
<td>50</td>
<td>F (+A)</td>
</tr>
<tr>
<td>7 weeks</td>
<td>10.9</td>
<td>25</td>
<td>F + A (+S)</td>
</tr>
<tr>
<td>20 weeks</td>
<td>9.9</td>
<td>4½</td>
<td>A + S</td>
</tr>
<tr>
<td>25 weeks</td>
<td>12.2</td>
<td>3</td>
<td>A + S</td>
</tr>
</tbody>
</table>

Electrophoresis of the cord blood the hemoglobin showed the same pattern as other cord bloods: a large amount of hemoglobin F and a small amount of hemoglobin with a mobility the same as hemoglobin A. In addition fetal hemoglobin estimations gave consistently figures around 60 per cent. There was definitely no hemoglobin discernible in the S position. Notwithstanding this, about 50 per cent of the child's red cells sickled (fig. 5), whilst in some preparations (we put up 18 in all) up to 90 per cent of the cells sickled. In quite a number of the cells which did not sickle a definite sickling tendency could be seen.

A specimen of blood taken when the child was six days old was sent to Dr. Huisman in Groningen. His findings were as follows:

1. Alkali denaturation gave a value of 48 per cent hemoglobin F (we found on this specimen 50 per cent).

2. Column chromatography identified three bands in the F, A, and S positions. Dr. Huisman approximated their concentrations at 50 per cent, 30 per cent and 20 per cent respectively.

3. To his surprise no poorly soluble reduced hemoglobin could be demonstrated in the sample using the salting-out technic of Derrien. He states that this method is excellent for identifying hemoglobin S.

These findings are difficult to explain. Watson studied 19 cord bloods which sickled in vitro. A carefully controlled investigation showed that the proportion of cells which sickled varied from one to 29 per cent (mean 11 per cent). Eleven cases which were followed up showed a progressive increase in sickling reaching an average of 90 per cent at the age of four months. Schneider et al. studied seven cord bloods in which from 3 to 15 per cent of the erythrocytes sickled in vitro. Hemoglobin S, measured by moving-boundary electrophoresis, was not demonstrable in one case and constituted from 12 to 21 per cent in three other cases. It rose to 40 to 50 per cent at seven months, by which time 95 to 100 per cent of the erythrocytes sickled in vitro. We recently had the opportunity to examine the cord blood from the child of a woman with proven sickle cell anemia. In this specimen only very occasional cells could be made to sickle in vitro (less than 5 per cent). Our finding of about 50 per cent sickling (and in some preparations even more) in the cord blood of III-5, associated with such a low level of hemoglobin S, and 60 per cent hemoglobin F is surprising. It could be explained, were one to suppose, that the hemoglobin which behaves as hemoglobin F on paper electrophoresis, alkali denaturation and column
chromatography also gives rise to the sickling phenomenon. In this connection it is interesting that Huisman could not identify hemoglobin S in this specimen using the sensitive salting-out technic of Derrien.

Follow-up studies on this child are summarized in table 2. By the time the child was 25 weeks old a normal A + S pattern could be demonstrated. The fetal hemoglobin was observed to decrease asymptotically from 60 per cent in the cord blood to 3 per cent at 25 weeks.

It is tempting in the case of Lucia B. to suggest that the high level of hemoglobin F in her red cells may account for the lack of clinical and hematologic abnormalities. If we suppose that the distribution of hemoglobin is uniform throughout the red cell population (which according to Allison\textsuperscript{12} is not always the case) then the hemoglobin content of each cell will consist of 75 per cent of the relatively insoluble hemoglobin S, and 25 per cent of the very soluble hemoglobin F. Her red cells will therefore require a much lower oxygen tension to produce crystallization of the hemoglobin i.e., sickling) than would be the case with lower concentrations of hemoglobin F. This might explain why her red cells sickle relatively slowly in vitro and why they probably do not sickle in vivo. Thus high levels of hemoglobin F may exert a protective effect. However, it is not usually held that the level of fetal hemoglobin influences the clinical severity of sickle cell anemia. Such a protective effect would have to be variable, as is clear when the clinical and hematologic features of cases II-2 and II-6, which must have the same genotype, are compared.

**Summary**

Three generations of a Jamaican family of African extraction are described, in several members of which an abnormal gene is carried. This gene produces high levels of fetal hemoglobin unassociated with the usual stigmata of thalassemia. It is found in all three generations of the family associated with hemoglobin A only and is also found in at least two members of the family interacting with hemoglobin S. In the latter combination little or no disability results.

The mode of inheritance of this abnormal gene is discussed, and reasons are put forward for a possible protective effect of high fetal hemoglobin levels due to inhibition of sickling.

The findings in the cord blood of the youngest child, including an unusually high percentage of sickling, are discussed, together with follow-up studies to the age of 25 weeks.

**Summario in Interlingua**

Es describite tres generationes de un familia jamaican de ancestría african, incluse plure membros qui es portatores de un gen anormal. Iste gen produce alte nivellos de hemoglobina fetal non associate con le stigmas usual de thalassemia. Illo es trovate in omne le tres generationes del familia in association exclusive con hemoglobina A. In al minus duo membros del familia illo etiam occurre in interaction con hemoglobina S. In iste ultime combination, nulle o pauc invaliditate resulta.
Le modo de hereditage de iste anormal gen es discutite. Es presentate rationes que attribuerea un possibile effecto protectori a alte nivellos de hemoglobina fetal, gratias a un potentia de lor parte de inhibir le falciformation.

Es discutite le constatationes in le sanguine de cordon del plus juvene patiente. Iste constatationes includeva un inusualmente alte procentage de falciformation. Es presentate le resultatos de studios consecutori usque al etate de 25 septimeas.

REFERENCES
An Unusual Type of Hemoglobinopathy Resembling Sickle Cell-Thalassemia Disease in a Jamaican Family

L. N. WENT and J. E. MACIVER