The Inheritance of Sickle Cell Anemia

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If a drop of blood is collected from each member of a randomly assembled series of American Negroes and sealed under a cover slip with vaseline, to be observed at intervals up to 72 hours, in the case of about 8 percent of the individuals composing the series a high proportion of the erythrocytes will be observed to assume various bizarre oat, sickle, or holly leaf shapes. This ability of the erythrocytes to “sickle,” as the phenomenon is commonly described, appears to be attended by no pathological consequences in the majority of these individuals, and they are spoken of as having sickleemia, or the sickle cell trait. However, a certain proportion of the individuals who sickle are the victims of a severe, chronic, hemolytic type of anemia known as sickle cell anemia. This proportion has been variously estimated at between 1:1.4 (8) and 1:40 (4). The essential difference between sickleemia and sickle cell anemia appears at present to depend at least in part upon the relative ease with which sickling takes place. In sickle cell anemia the erythrocytes may frequently sickle under the conditions encountered in the circulating blood, whereas in sickleemia sickling does not usually occur under these conditions (12). This difference has been attributed to a greater tendency of the erythrocytes of sickle cell anemia to sickle when the O$_2$-tension is reduced, although recently this viewpoint has been challenged (13). Perhaps because of this difference—although there may be other factors involved, such as the aniso- and poikilocytosis to be observed in some individuals with the disease, and a greater resistance to hemolysis of trait cells when sickled than sickle cell anemia cells when sickled—the erythrocytes of a patient with sickle cell anemia have a greatly shortened life span, both in the individuals with the disease and in normal persons who have been transfused with the cells of sickle cell anemia patients, whereas sicklemia erythrocytes have an normal life span (3, 14).

The ability of the red cells to sickle was observed to have a genetic basis not long after sickle cell anemia was recognized as a clinical entity (5). On the basis of a study of one large family, Taliaferro and Huck (15) postulated that the ability to sickle was due to a single dominant gene. At that time the clinical distinction between sicklemia and sickle cell anemia had not been clearly drawn, and the inference was that this gene was more strongly expressed in some individuals (sickle cell anemia) than in others (sicklemia). This has remained the accepted hypothesis up to the present time. Several years ago the author, in a review on the clinical detection of the genetic carriers of inherited disease (9), was led to suggest an alternative hypothesis—namely, that there existed in Negro populations a gene which in heterozygous condition results in sicklemia, and in homozygous condition in sickle cell anemia. This hypothesis has a counterpart in the relationship which has been demonstrated to exist between thalassemia major and minor (10, 16). Recently the opportunity has arisen to give this hypothesis a thorough test.

There exist a number of arguments permitting a critical decision between the two hypotheses. The present preliminary note will consider only one of these arguments. If the homozygous-heterozygous hypothesis is correct, then both the parents of any patient with sickle cell anemia should always sickle (barring the occasional role of mutation; see below). If, on the other hand, the disease is due to a dominant gene with variable expression, only one parent need sickle, although occasionally, due to the chance marriage of two sicklers, both parents may sickle. In calculating the exact proportion of sicklemia to be expected among the parents of individuals with sickle cell anemia according to the dominant hypothesis, certain assumptions must be made. To the best of the author’s knowledge, the question of the phenotype of the homozygote has never been raised by those who have accepted the variable dominant hypothesis of sickle cell anemia. For purposes of calculation we shall assume that under the variable dominant hypothesis all homozygotes have sickle cell anemia—alternative assumptions, such as intra-uterine lethality, are possible. We shall further assume that one in fifty heterozygotes also develops sickle cell anemia. Finally, we shall assume on the basis of the clinical data that the fertility of those with sickle cell anemia approximates 20 percent of normal, with the result that only a few individuals with this disease—so few

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that they may be disregarded in so rough a calculation—have one or both parents who are likewise affected. With these assumptions we may calculate, as shown in Table 1, that the proportion of sickling among the parents of individuals with sickle cell anemia should be 0.765. If one assumes that more than one in fifty of the heterozygotes develop sickle cell anemia, or that the homozygote is lethal, then the proportion of sickling parents should be even lower.

Thus far we have tested 42 parents of 29 patients with sickle cell anemia for the occurrence of sickling. In 13 instances both parents were studied and in 16, only one. Tests have been conducted in a variety of ways; especial reliance has been placed on a combination of the techniques described by S. H. Waugh (11) and Hansen-Pruss (7), whereby a tourniquet is applied to a finger for 3-5 minutes, and then a drop of static blood from the finger is placed on a slide to which a small amount of Janus green or methylene blue has been added, and it is quickly covered with a cover slip which is sealed with vaseline. Observations are made at intervals up to 72 hours. Five preparations have been made for each individual. Every parent tested to date has sickled. This is the result expected from the homzygous-heterozygous hypothesis outlined above. On the other hand, the probability of the occurrence of such a number of positive parents under the variable dominant hypothesis is (0.765)42, or 0.000013.

Table 1 shows the frequency of sickling among individuals with sickle cell anemia.

<table>
<thead>
<tr>
<th>Type of marriage</th>
<th>Frequency of marriage</th>
<th>Frequency of offspring of the indicated genotype</th>
<th>Proportion in general population</th>
<th>Proportion among total anemia patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>One sickler parent</td>
<td>2 × 0.08 × 0.92 = 0.1472</td>
<td>0.0673 0.0736 0.0376</td>
<td>0.0736 0.0673 0.0376</td>
<td>0.02 × 0.0736 + 0.01472</td>
</tr>
<tr>
<td>Two sickler parents</td>
<td>0.08 × 0.08 = 0.0064</td>
<td>0.0016 0.0032 0.0016</td>
<td>0.0016 + 0.0032</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

The approximate frequency of the gene responsible for sickling in the American Negro (p) may be determined from the equation: 2p (1 - p) = 0.08. Solution of this equation yields a p value of 0.042, from which the incidence at birth of the disease, disabling, and fatal disease among Negroes may be placed at 0.042² = 1.8 per 1000. The ratio among Negro births in the United States of those with sickle cell anemia is approximately 80:1.8 = 44:1; in the Negro population as a whole the ratio of sickle cell anemia is significantly higher because of the greater occurrence among those with sickle cell anemia. In Africa, the incidence of sickling has been reported to vary from approximately 12 percent in Northern Rhodesia (1) to 21 percent in the Gold Coast Negroes and 19 percent in natives of Nigeria and the Camaroons (6). This would correspond to a gene frequency of approximately 0.064-0.106, and a frequency of the homozygote of 4.1-11.2/1000. The complex and fascinating problems in gene dynamics raised by frequencies of this order will be dealt with in another paper.

In a genetic situation such as the one here, where the heterozygote, who may be termed the genetic carrier of the disease, may be readily distin-
guished from normal and from the homozygote, it is possible to predict with a high degree of accuracy which marriages should result in homozygous individuals—in this case, children with sickle cell anemia. Since (homozygous) individuals with sickle cell anemia either die young or, if they reach maturity, have a greatly lowered fertility, the vast majority of cases of the disease are the issue of marriages between two
(homozygous) persons with the sickle cell trait. In the absence of marriage between individuals whose erythrocytes exhibit the sickling phenomenon, the frequency of the homozygote would greatly decrease, and sickle cell anemia would tend to disappear, with only a very rare case arising as a result of mutation in a normal individual married to a person homozygous or heterozygous for the sickling gene.

References