Genetic Aspects of Sickle Cell Anemia and Microdrepanocytic Disease

By E. Silvestroni, M.D. and I. Bianco, M.D.

SICKLE CELL ANEMIA is a severe chronic disease usually confined to the Negro race but occasionally found in individuals of the white race mostly of Southern Italian or Greek stock. Clinically there is chronic hemolytic anemia with crises, osteo-muscular pains, bouts of severe abdominal pain and ulcerations of the legs. Hematologically, the disease is characterized by the ability of the red cells to assume an elongated and curved shape ("sickling") when blood is sealed under a cover slip and kept at 37°C for a few hours. The disease occurs in families, all of whom present sickling, although sickle cell anemia is present in only a few. Since, moreover, sickle cell anemia affects consecutive generations, there is no doubt that the disease and the trait have a genetic basis. It has been thought that the ability of the red cell to sickle was due to a single dominant factor, which is responsible for the transmission of all types of the disease, from the simple, asymptomatic sickleemia to the severe sickle cell anemia. This theory, although generally accepted, is not in agreement with the clinical observation that sickle cell anemia occurs almost exclusively among those individuals in whom both parents present the sickle cell trait.

In 1947, Neel presented a genetic theory for sickle cell anemia analogous to that postulated for Mediterranean anemia, and suggested "that there is present in the colored population a certain factor which, when heterozygous may have no discernible effects, but usually results in sickling and, when homozygous, tends to result in sickle cell anemia." In 1949, Neel tested this hypothesis by studying 42 parents of 29 patients with sickle cell anemia and found that the blood of all the individuals tested sickled. Beet working with a Bantu tribe in Africa, confirmed these results, and showed further that while only 55 per cent of the offspring of 32 families of sickle cell trait Negroes presented sickling, the sickle cell trait was always present in both parents of patients with sickle cell anemia.

In the course of an investigation on microcythemia (Mediterranean anemia, Thalassemia), we were able to study families of healthy individuals with drepanocytemia (sickle cell trait), and of patients with sickle cell anemia, all of Sicilian or Central and Southern Italian stock. The study of two families of healthy individuals showing the sickling trait indicated that the sickle cell trait in the white as well as in the Negro behaves as a Mendelian dominant transmitted in consecutive generations (fig. 2, families 4 and 5). Asymptomatic individuals are heterozygous carriers and their offspring are either normal or carriers of the sickling trait. Three families of patients with sickle cell anemia were studied (fig. 1) and in all, both parents of the individuals with the active disease were found to have the sickle cell trait. In Family 3, the father, a carrier who was suffering

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from carcinoma of the lung was studied by us\textsuperscript{12} while the mother (also a carrier) and other relatives were studied in the United States by Guyton and Heinle.\textsuperscript{3} Our observations agree with Neel's hypothesis, since they confirm the finding that sickling depends on an hereditary factor which results in the asymptomatic sickle cell trait when heterozygous and sickle cell anemia when homozygous.

There are reports in the early literature concerning cases in which sickling...
could not be demonstrated in one or both parents of a patient with sickle cell anemia. Neel believes that these discrepancies are almost always due to unfamiliarity with the techniques employed to demonstrate sickling. Moreover it is pointed out that admission is not certain proof of paternity and it is conceivable that, in some cases at least, incomplete penetrance of the trait-carrying gene might be responsible for the apparent absence of sickling. Our studies have moreover shown that especially in the white race, certain cases of apparent sickle cell anemia may actually be another condition which we have called "microdrepanocytic disease." In this condition one of the parents of the patient has the sickle cell trait and the other that of microcythemia (or Mediterranean anemia).

According to our studies, microdrepanocytic disease has many of the clinical and hematologic features of sickle cell anemia, from which however, it may be distinguished on the basis of hematologic and genetic characteristics. The patient presents chronic hemolytic anemia with moderate jaundice, hepato- and splenomegaly, chronic ulcerations of the leg, recurrent bouts of fever with osteoarticular pains and crises of severe abdominal pain. Although many patients reach adult life, the disease is a serious and fatal one. Death usually ensues in the wake of frequent infections, particularly of the respiratory tract.

Hematologically, microdrepanocytic disease differs from sickle cell anemia in several characteristics, indicating that the two anomalies, sickleemia and microcythemia, are present simultaneously. In microdrepanocyte disease there are hypochromic anemia, sickleemia, decreased red cell fragility, microcytosis and marked abnormalities in the morphology of the erythrocytes (anisocytosis, poikilocytosis, marked hypochromia, presence of target cells, fig. 3). In sickle cell anemia, on the contrary, the anemia is normochromic and macrocytic, and the poikilocytosis is moderate and inconstant; target cells are also present (fig. 4).

Characteristically, the patients with microdrepanocytic disease have the gene of both sickleemia and microcythemia alike, the parents having transmitted one or the other of the two genes. In 7 of the 11 families studied (fig. 2), one parent exhibited the sickle cell and the other the microcythemic (Mediterranean) trait; in one family the father was himself suffering from microdrepanocyte disease and the mother was a microcythemia carrier. In the 3 remaining families, one of the parents showed the sickle cell trait; the other parent had died, but microcythemia was found in some of his relatives or children. It appears then, that while sickle cell anemia appears in families in which both parents exhibit the sickle trait, microdrepanocytic disease occurs when one of the parents possesses the sickle cell and the other the microcythemic trait.

The association of microcythemia and sickleemia genes in patients with microdrepanocytic disease is also clearly suggested by other findings. Twenty-two cases of microdrepanocytic disease were discovered among 63 individuals belonging to 9 of the 11 families we studied (table 1). Their rate of occurrence is in good agreement with the frequency to be expected (22.5%) according to Weinberg's formula of correction. Our data were analyzed with Weinberg's method since his formula takes into account the proband in the total number of affected indi-
FIG. 3.—Photomicrographs of blood smears of 4 patients with microdrepanocytic disease. Note extreme degrees of poikilocytosis, hypochromia and many target cells.

FIG. 4.—Photomicrographs of blood smears of 2 patients with sickle cell anemia. Note relatively slight degree of poikilocytosis and hypochromia.
viduals, and the proband in this case was represented by the child with microdrepanocytic disease. Two of the 11 families encountered were discarded since, in one, the patient with microdrepanocytic anemia was the only child and in the other the father himself had microdrepanocytic disease. The analysis of our data clearly stresses the fact that the occurrence of microdrepanocytic disease is strictly related to the occurrence of the heterozygous genes of sickleemia and microcythemia. Finally in a case reported by Powell, Rodarte and Neel (1950), the first case of microdrepanocytic disease observed in the United States, two children of the patient had microcythemia; this is the crucial genetic evidence that individuals with microdrepanocytic disease possess the genes for both microcythemia and sickleemia.

Powell et al. have advanced a number of explanations for the genetic patho-

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<th>Number of children from family</th>
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(63 children)

Standard error = ±3.18

genesis of microdrepanocytic disease: (1) The two genes (microcythemic and sicklemic) are inherited independently and are located on different chromosomes (interaction of non-allelic factors); (2) the disease is an extreme variant of either microcythemia or sickleemia, the other gene being present but without etiologic role; (3) genes for microcythemia and sickleemia are members of a series of multiple allelomorphs.

Since individuals suffering from microdrepanocytic disease represent about one-fourth of the entire number of offspring, the second hypothesis is probably not correct. It would be difficult to explain this constant one-fourth ratio if either gene had no etiologic significance.

Our findings appear to support Powell’s first hypothesis. Children resulting from the mating of a patient with microdrepanocytic disease and a normal individual should, if Powell’s first hypothesis is correct, be in equal numbers, normal, microcythemic, drepanocytic and suffering from microdrepanocytic disease. Should the third hypothesis be correct, one-half of the offspring should show
microcythemia and one-half sicklemia. In our Family 9 (fig. 2), among the children of a patient of microdrepansocytic disease and a microcythemic wife, one was normal, one exhibited the sickle cell trait and a third suffered from Mediterranean anemia. In Family 6 (fig. 2), described incompletely in a previous communication, the child of a man with microdrepansocytic disease and a normal mother showed typical microcythemia and sicklemia. It appears evident that the offspring of an individual with microdrepansocytic disease and a normal partner may be normal, microcythemic, sicklemic or be affected by microdrepansocytic disease. This conclusion upholds Powell's first hypothesis, although more complete genetic observations are obviously necessary.

The genetics of Family 9 (fig. 2) are open to some interesting speculations. Examination of the possibilities in this family indicate that the offspring might be (1) normal; (2) asymptomatic carriers of heterozygous gene for microcythemia or sicklemia; (3) patients with Cooley's anemia (homozygous for microcythemia); (4) patients with microdrepansocytic disease (heterozygous for the genes of both microcythemia and sicklemia); and (5) children heterozygous for sickle cell trait and homozygous for microcythemia. The latter would probably resemble clinically patients with Cooley's anemia and with microdrepansocytic disease. It is possible that children from this family diagnosed as cases of Cooley's anemia were in effect suffering from microdrepansocytic disease or from microdrepansocytic disease and Cooley's anemia simultaneously.

**SUMMARY**

1. A brief review is presented of the genetic theories of sickle cell anemia and the sickle cell trait.
2. The genetic data on 2 families of asymptomatic individuals with the sickle cell trait and of 3 families of patients with sickle cell anemia are reported. These data confirm the heterozygous-homozygous theory of Neel.
3. The possibility is considered that many of the cases of sickle cell anemia described in the white race are actually examples of "microdrepansocytic disease."
4. Microdrepansocytic disease is a new syndrome, first described by the authors from Italy. It has some of the characteristics of both sickle cell anemia and Mediterranean anemia. On the basis of studies in 11 families, the presence of the sickle cell trait in one parent and of microcythemia (Mediterranean anemia trait) in the other, results in microdrepansocytic disease in some of the offspring. Hematologic studies in these patients indicate the simultaneous presence of both sickle cell and microcythemic genes.
5. Genetic studies of these families suggest that the genes for microcythemia and for sicklemia are located on different chromosomes and are inherited independently of each other. On the other hand, their simultaneous presence leads to a disease of a moderate degree of severity having many of the features of sickle cell anemia.

**REFERENCES**

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