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Invited Editorial: Prenatal Screening for Hemoglobinopathies

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The papers by Rowley and co-workers (Loader et al. 1991; Rowley et al. 1991*a*, 1991*b*) in this issue of the *Journal* investigated the feasibility of prenatal education, testing, and counseling of pregnant women for hemoglobinopathies in blacks, whites, Asians, and other ethnic groups. In order to place the papers in perspective, I will first review hemoglobinopathy testing in the United States. The papers by Rowley and co-workers will then be analyzed. Next, social factors which may complicate prenatal genetic screening in the United States will be considered. Finally, by comparison, some prenatal thalassemia screening programs in Canada, Italy, and Greece will be mentioned.

Sickle hemoglobin testing was initiated in the early 1970s following the commercialization of a solubility test for sickle hemoglobin by a major pharmaceutical company (Bowman 1977). Although widely advertised as such, this test did not delineate sickle cell trait from sickle cell disease. Most educational brochures implied that sickle cell anemia is confined to blacks, even though sickle hemoglobin is also quite prevalent in populations other than Africans and their descendants, such as Greeks, southern Italians, Arabs, southern Iranians, and Asian Indians. Educational brochures—some even emanating from the National Institutes of Health—were replete with misinformation, the most inveterate of which was the equation of sickle cell trait with sickle cell disease (Bowman 1977). For example, in *HEW NEWS* (National Heart and Lung Institute, National Institutes of Health 1971), the then National Heart and Lung Institute, in a news release entitled "Background Information—Sickle Cell Disease," claimed that sickle cell disease is the most common inherited disorder in the United States and is present in more than 2 million black U.S. citizens.

At least 12 states passed mandatory sickle hemoglobin screening laws, usually under pressure from black community organizations. Many laws were restricted to the testing of blacks and specified preschool children, schoolchildren, and couples before marriage; and, oddly, one law included inmates of mental and correctional institutions. Major corporations began selectively screening blacks. Black flight attendants—who had just been admitted to these jobs—were screened for sickle hemoglobin, and those who tested positive were discharged. A majority of the major life insurance companies raised rates as high as 25% on persons with sickle cell trait, even though the life expectancy of individuals with sickle cell trait is the same as that of those who do not have sickle hemoglobin. Sickle cell organizations proliferated and vied with each other for funds; many of them replicated misinformation in the black community (Bowman 1977, Reilly 1977).

Community pressure and, allegedly, politics resulted in the passage of the National Sickle Cell Anemia Control Act (1972), which was later modified to the Omnibus Genetics Bill (1976) and then to the Health Services Amendments (1978). The title "National Sickle Cell Anemia Control Act" was unfortunate because the "control" of sickle cell anemia is only possible with eugenics practices reminiscent of Nazi Germany. Sickle hemoglobin misinformation even infiltrated the first line of the Sickle Cell Anemia Control Act, which stated that more than 2 million blacks in the United States have sickle cell *anemia,* when sickle cell *trait* should have been used. Federal legislation inaugurated a National Sickle Cell Disease Program with support of community education, testing, and counseling programs; comprehensive sickle centers with education, testing, counseling, and research components; and program projects, which were limited to research. Federal guidelines for education, testing, and counseling programs were developed. The equa-

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tion of sickle cell trait with sickle cell disease was rebutted. The National Sickle Cell Disease Program and the Hematology Section of the Centers for Disease Control also set standards for appropriate hemoglobin testing by various electrophoresis techniques and discouraged the use of a solubility test as the *primary* screening device (Schmidt and Brosius 1972).

The federally supported screening and education clinics were directed, unfortunately, to mass population screening of as many as 20,000 subjects/year, an unrealistic goal because the personnel to appropriately care for the educational, counseling, and psychosocial needs of the target populations were not available. Ostensibly, the major objective of these programs was to enable the community to make informed decisions about reproduction. Counseling was allegedly nondirective—a standard caveat in genetic screening programs, including Rowley's. But what were the options before the advent of prenatal diagnosis? They were all somewhat distasteful: abstinence, artificial insemination, genetic roulette, or abortion. But since these programs were initiated before the 1973 Roe v. Wade decision, legal abortion was available in only a few states.

The development of techniques for newborn screening and for the prenatal diagnosis of sickle cell disease ushered in a new phase of hemoglobin screening. Newborn screening was important because morbidity and mortality in infants with sickle cell disease was reduced by penicillin prophylaxis to prevent infections, particularly those of pneumococcal origin (Gaston et al. 1986). This was a major accomplishment of the National Sickle Cell Disease Program. Unfortunately, important issues raised by newborn screening can only be alluded to here, because a proper discussion of the myriad problems of newborn hemoglobinopathy screening would divert the discussion from prenatal diagnosis.

The National Association for Sickle Cell Disease (1990), with Dr. Charles F. Whitten as president, developed a position on the prenatal diagnosis of sickle cell anemia. On the first prenatal visit all black mothers should be tested to determine whether they are carriers of the sickle gene. (Whitten's program emphasizes sickle hemoglobin, not hemoglobinopathies, and only black pregnant women are screened.) Second, each mother who is a carrier should be counseled that the father should be tested to determine whether he is also a carrier and that, if both are carriers, prenatal tests can determine whether the fetus has sickle cell anemia. If the partners elect to continue the pregnancy, their decision must be supported. Postabortion counseling should also be offered. No mention was made of options if the father refuses testing or is unavailable. Let us now go to the program of Rowley and co-workers.

Providers of prenatal care—from obstetricians in private offices, to public health care providers, to health maintenance organizations—were enlisted. All pregnant women were screened for hemoglobinopathies at the first visit. The provider was given the option of obtaining informed consent for hemoglobinopathy screening; however, obstetricians in only one of 19 centers elected to inform their patients. The others asserted that they had implied consent for diagnostic tests. Patients who tested positive were notified by telephone or by certified mail with return receipt required. The letter informed the patients who were carriers that their health would not be affected but that the fetus could have a serious disorder should the partner be a carrier. The method of contacting those who had a hemoglobin disease was not mentioned. Counseling was given by three genetic associates. Counseling and all laboratory services were given without charge. Women who had a positive result were offered counseling, but prenatal diagnosis was offered *only* to those women whose partners agreed to be tested and were found to be positive and if the couples agreed to learn the risks and their options. The cost of amniocentesis, however, was not borne by the program.

Four major goals of the investigation were specified: (1) Does a woman make a special visit to receive an explanation of her test results? (2) Does she want her partner tested? (3) Does the partner come for testing? (4) Do couples at risk choose prenatal diagnosis?

Of those coming for counseling, 50% were not living with the putative father, and 62% were single. It is significant that 75% of pregnancies were <18 wk duration. Of 453 women counseled during their first screened pregnancy, 86% wanted their partners tested; but only 55% had their partners tested. In 77 pregnancies at risk, 12 women were too late in their pregnancy to be offered prenatal diagnosis; in another 12 pregnancies the condition for which the fetus was at risk was considered too mild to require the offer of prenatal diagnosis. Prenatal diagnosis was offered in the remaining 53 pregnancies but was accepted by only 25 couples.

Important issues were uncovered by Rowley's studies. First, should programs for prenatal testing for hemoglobinopathies include only populations at high risk, such as blacks, peoples of Mediterranean origin, Middle Easterners, Asians, or Southeast Asians? Ap-

parently not. At least 7% of the subjects with sickle cell trait were not black, and 22% of individuals with β-thalassemia trait were not Mediterranean, black, or Asian. The authors concluded that *all* women—rather than only those of high-risk groups—should have prenatal hemoglobinopathy screening. Additional support for the screening of all women in a prenatal hemoglobinopathy testing program is that individual racial identification—not ancestry—has a social rather than a biological or genetic basis (Bowman and Murray 1990). Some states, such as Georgia, that selectively screen only those identified as African-American in newborn hemoglobinopathy screening programs, may wish to take note of Rowley and co-workers' findings.

Second, will prenatal programs for pregnant women in black communities result in a significant number of abortions of affected fetuses? Or is abortion such an anathema in the black community that prenatal diagnosis for sickle cell disease will frequently be rejected? Are there population differences in the acceptance of abortion? Rowley and co-workers concluded that black women often would not terminate a pregnancy for any reason but that Southeast Asians frequently accepted abortion. Black women's attitude toward abortion was similar to that seen in a survey of prenatal diagnostic services for sickle cell disease at 12 centers in the United States (Rowley 1989). The induced abortion rate for fetuses with sickle cell anemia in the centers was 39%, and it was 23% for fetuses with hemoglobin SC disease. It is interesting, however, that in the United States induced abortion has been consistently far more frequent among blacks than among whites (National Center for Health Statistics Health United States 1990). In the white population there were, per 100 live births, 17.5 abortions in 1973 and 30.0 in 1987. Blacks were classified in an "all other" group and undoubtedly constituted the vast majority. In this population there were, per 100 live births, 28.9 abortions in 1973 and 55.7 in 1987. These figures are intriguing, because it would be odd if black women abort unaffected fetuses at a higher rate than do white women but forgo aborting fetuses with sickle cell disease.

Should women whose partners either refuse testing or are unavailable be offered prenatal diagnosis? The National Association for Sickle Cell Disease did not address this issue, but *partner* decision making was emphasized in that program, as in Rowley and co-workers' study. Admittedly, there is no unanimity on this issue, but I offer another perspective. Of 463 black women who were counseled during pregnancy, the partner was not tested in 209 instances; and prenatal diagnosis was not offered. Nevertheless, if a black woman has sickle cell trait and if her partner is black, the odds are about 1:40 that she will have a child with sickle cell disease—more commonly sickle cell anemia (hemoglobin SS), hemoglobin SC, or hemoglobin S/β-thalassemia. A recalcitrant or unavailable partner in Rowley and co-workers' program subjects a woman to a high risk of having a child with sickle cell disease even though she may not want such a child, even though prenatal diagnosis is routinely offered for many disorders that have much lower odds of resulting in an affected child. Should not the pregnant woman be allowed to make a choice? Yes. Is her autonomy compromised? Yes. Should a genetic counseling program *conceal* important reproductive options? No. The choice was evidently between autonomy and paternalism. Here, paternalism adversely affected those who could least afford it.

Along these lines, an editorial in the *New York Times* (1988) stated that the Department of Health and Human Services issued regulations banning federal funds to clinics that offer abortion counseling. It was pointed out that, should these rules take effect, 4 million women—mainly poor women—who depend on federally supported family-planning clinics would be denied access not only to abortion but also to medical information that would keep them from becoming pregnant. The editorial asked the question, How can a physician, forbidden under the regulations even to mention the word "abortion," help a woman make an informed choice about family planning. "And how cruel that a poor woman can't be told that an abortion is a legal option—and given a referral if she requests one—compared with the woman who can afford a private doctor." The editorial concluded that in the United States there are two kinds of family-planning counseling: one for the affluent and one for the poor. Selective counseling—with its consequential denial of access—places Rowley and co-workers' prenatal screening program, as well as other centers that restrict prenatal counseling to couples, in the same category as do the Department of Health and Human Services's regulations.

Is informed consent practical when pregnancy testing is moved from the genetics center to the obstetrician's office? Holtzman (1989) found that obstetricians, like those in Rowley's program, often performed tests on pregnant women without obtaining the latter's consent. The obstetricians in Holtzman's study defended this practice with the premise that tests will be normal in the vast majority of instances, so why alarm the patient needlessly. In a study of alpha-fetoprotein (AFP) screening, Holtzman found little justification for the

obstetrician's alibi. Women who were informed about AFP tests were no more alarmed than those who were not.

But let us return to hemoglobinopathy testing. The screening of pregnant women will detect a significant number of individuals who do not know that they have sickle cell disease, and Rowley and co-workers found similarly unsuspecting patients. Accordingly, pregnancy screening for hemoglobinopathies may offer reproductive and medical information. Thus, if obstetricians do not screen for hemoglobinopathies, they could be at risk for medical malpractice if a pregnant woman with sickle cell disease is overlooked and has complications from the disease. Further, obstetricians and other health workers who fail to inform, counsel, or use improper techniques to detect genetic disorders in groups who are at high risk expose themselves to wrongful-birth suits (Capron 1979; Shaw 1984).

On the other hand, informed consent is inveterate in genetics programs and in present-day medical decision making. Genetic tests have the potential of invading not only the privacy of the individual but also that of the family. The door for the disclosure of nonpaternity is also opened, without prior warning—which could lead to the destruction of a stable family. Insurance companies may also take punitive measures, including restriction, denial, or termination of individual or family coverage (Holtzman 1989).

The papers by Rowley and co-workers are also significant because they raise issues that form a bridge between the era of testing for rare and selected high-frequency genetic disorders and future testing for literally hundreds of genetic markers. Kaback and O'Brien (1973) emphasized the importance of a period of community education *before* the institution of genetic screening programs. This approach became an integral part of the federally funded sickle cell disease programs: education, testing (with informed consent), and counseling were integrated into community screening programs. Perhaps genetics education in the schools may make individuals aware of genetic risks before they are confronted with genetics screening programs. If pregnant women are knowledgeable, they will question their obstetricians. Consequently, obstetricians will be forced to make their patients aware of tests that disclose genetic and economic risks.

Another complication—which is most evident in present-day newborn hemoglobinopathy screening programs—is that trained counselors are insufficient to care for the education, support, and psychosocial needs of the population. The availability of single-gene counselors, their training, and certification will be even more critical if community-wide cystic fibrosis screening programs ever come to pass. Limited counseling time in Rowley and co-workers' program was efficiently complemented by first showing at-risk women a video which contained most of the information needed to make a decision. All of the actors were black in the sickle-cell-trait tape, and all were white in the thalassemia-trait tape. (A minor point is in order here: the use of only black actors in the sickle hemoglobin tape and only white actors in the thalassemia tape leaves a hidden message that these hemoglobinopathies are restricted to these groups, which was certainly not the intent of the papers.) The tapes lasted about 20 min. The dramatization held interest, was complete, and saved professional time. The video was appropriately followed by a counseling session in which questions of a more individual nature were discussed. The women were then given educational materials to take home, and every effort was made to follow up.

The final paper by Rowley and co-workers (Rowley et al. 1991*b*) analyzes factors affecting decision making, with special attention to factors invoked by the Health Belief Model. The various levels of decision making have already been discussed. Three factors were predictors of the likelihood of the partner's cooperation in the program: living with the partner, gestational age at time of counseling (<18 wk), and the patient's belief that the partner was a carrier.

The papers by Rowley and co-workers open the door for a discussion of other ethical and legal issues. First, is a public policy *just* if it offers public support for newborn screening and prenatal diagnosis of hemoglobinopathies and other disorders and yet renounces public support for abortion of affected fetuses (Bowman 1983)? Such a public policy may not be just, but it is legal. The Supreme Court has repeatedly (Maher v. Roe 1973; Harris v. McRae 1980) upheld the denial of public support for abortion, if the state so chooses.

The Supreme Court in the case of Dandridge v. Williams (1970) also affirmed the legality of a maximum welfare grant imposed by the state of Maryland. This regulation restricted total state aid for dependent children to a maximum of $250.00/mo/family, no matter how large the family. If a limitation on public support for potentially healthy children is the law of the land, an even stronger case can be made to restrict public support for children with severe genetic disorders. There are many fanciful and theoretical back doors to eugenics, but Dandridge v. Williams is real.

It is lamentable that an escalating out-of-wedlock

birth rate in the black community is frequently ignored in federal and community programs and in state's premarital sickle hemoglobin testing mandates (Bowman 1983). Genetics programs are usually constructed on the basis of the classical description of the family. The testing of couples before marriage and of marriage partners is emphasized, but reality is ignored. (Wilson 1987) investigated family patterns and out-of-wedlock births in the black community. The proportion of women married and living with their husbands decreased from 52% in 1947 to only 34% in 1980. The jobless rate for black males is a major factor in the out-of-wedlock birth rate, because black women see little advantage in marrying a man who has little prospect for contributing to family support (Wilson 1987). The lessons are obvious. A genetics program that depends on the cooperation of putative fathers and partners who are readily available places the pregnant woman who does not wish to have a child with sickle cell disease in an untenable position and discounts the quandary of the majority of the target population. Recall that 62% of all women were single in Rowley's program and that their partners were usually uncooperative. Nationally, the out-of-wedlock black birth rate was 37.4% in 1970 and 62.2% in 1987 (National Center for Health Statistics 1990).

In contrast to Rowley's studies, prenatal thalassemia screening programs in Canada (Scriver et al. 1984), Italy (Tentori and Marinucci 1983), and Greece (Loukopoulos 1985) all had a high rate of acceptance of prenatal diagnosis and abortion. However, the populations were different; all were more homogeneous than that in Rowley and co-workers' study; all have some system of national health service; informed consent for testing was variable to nonexistent. Further, thalassemia major and sickle cell disease are not comparable disorders; thalassemia is more severe, and life expectancy is rarely past the third decade, without bone marrow transplantation. The morbidity and life expectancy in sickle cell anemia are variable and unpredictable, ranging from death at an early age to asymptomatic disease with a long life. In addition, systems of national health service usually are quite frank about reducing the incidence of genetic disorders.

The important investigations of Rowley and coworkers appear at a time when newborn screening for hemoglobinopathies has been instituted in at least 28 states (Illinois Department of Public Health 1990) and more are on the horizon. The time is near when pregnancy screening for hemoglobinopathies will like newborn screening, become routine—but I hope not mandatory. Though disturbing, it should be mentioned that arguments for mandated pregnancy screening for hemoglobinopathies could be more persuasive than mandated newborn screening. But even if pregnancy screening is not mandated, indirect coercion of pregnant women by the state, insurance companies, employers, the family, or friends may be just as effective.

The meticulous, interdisciplinary research of Rowley and co-workers is welcome. It introduces important models which address the complex task of transferring the exciting developments in the new genetic technology from academia to the community. Admittedly, it is difficult, but genetics programs should also take into account critical cultural, social, and economic attributes of the target populations and should modify them as needed to offer more equitable access.

Unfortunately, Rowley and co-workers' program reflects what may be a major challenge to the introduction of prenatal genetic screening on a large-scale basis in a heterogeneous community. In the ideal world of Kaback and O'Brien (1973), the women would have known of their options before they became pregnant, or they would have been able to query their obstetricians before testing. If funds had been adequate for an extensive period of community education before testing, the women in Rowley and co-workers' community would also have known that crucial decisions about pregnancy outcomes legally (and ethically) do not have to depend on the capricious whims of their partners. But Rowley is dealing with the real world, which will become evident to all of us as the number of genetic tests escalates.

Note added in proof: Since this editorial was submitted, an extensive nationwide sickle cell program in Cuba was reported, which involved education, detecting couples at risk, counseling, and prenatal diagnosis (Granda et al. 1991). As in the program of Rowley and co-workers, blood samples were obtained from mothers when they attended for prenatal care. If the mother was positive, *couples* were given an appointment at a genetics center, where fathers were tested and counseling provided. Although counseling was nondirective and decisions were made by the couples, the program reduced the number of newborns with sickle cell disease by 30% in 1989.

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