Appendix B
Case Studies of Other Carrier Screening Programs

Carrier screening programs have historically been focused within a particular group---e.g., Tay-Sachs among Ashkenazic Jews and sickle cell anemia among African Americans. With cystic fibrosis (CF), the potential target population is larger and less defined, which may introduce both technical and organizational complexity not present in past carrier screening. This appendix describes past carrier screening programs for Tay-Sachs, sickle cell anemia, and ß-thalassemia. It also delineates the similarities and differences of these programs to reveal considerations for CF carrier screening.

SCREENING FOR TAY-SACHS DISEASE

Tay-Sachs is a lethal genetic disorder that predominantly affects Jews of Eastern and Central European descent (Ashkenazic Jews) and populations in the United States and Canada descended from French Canadian ancestors; it also occurs infrequently in the general population. The disorder affects the central nervous system, resulting in mental retardation and death within the first 3 to 6 years of life. Unlike for CF, the means to screen for Tay-Sachs carrier and affected status have existed for more than two decades.

Shortly after accurate tests were developed, a number of large-scale carrier screening programs were initiated, first in the United States, and then throughout the world. Carrier screening programs for Tay-Sachs are frequently considered models for other genetic screening endeavors (54,64,66). While some of the experiences can be generalized to other genetic disorders, other facets of Tay-Sachs carrier screening programs derive from specific aspects of the condition and the populations targeted.

The Disease

TaY-Sachs (also called G_{M2} gangliosidosis, Type I) is a progressive, degenerative disorder of the central nervous system. Due to the absence of a particular enzyme, hexosaminidase A (Hex A), fatty substances-specifically G_{M2} gangliosides—accumulate in cells throughout the central nervous system, eventually destroying them. The process begins prenatally, though the infant can appear normal for the first months of life. Symptoms usually begin between 4 and 12 months with an exaggerated startle response, followed by increasing motor weakness. Blindness, seizures, and continual decline into a vegetative state ensue until the child dies. No cure exists (19).

Genetics of Tay-Sachs Disease

Like CF, Tay-Sachs is a single gene disorder inherited in an autosomal recessive pattern; that is, only a child receiving a defective copy of the gene from each parent will be affected; carriers have no clinical symptoms. Among the general population, Tay-Sachs mutations are rare, occurring with a carrier frequency of 1 in 167, giving rise to 1 in 112,000 affected births, The disease is significantly more common, however, among Ashkenazic Jews: the carrier frequency is 1 in 31 and birth incidence is 1 in 3,900 (77). Prevalence in Ashkenazic Jews is a function of ethnic background, and is unrelated to religious practice, Elevated incidence of variant alleles are also found among Moroccan Jews (97), French-Canadians (l), and a distinct population of Louisiana French Acadians (41).

In 1969, scientists identified the lack of Hex A as the underlying metabolic defect in Tay-Sachs disease (60). A year later, an enzymatic assay was developed to measure Hex A activity. Application of this test to known carriers revealed intermediate activity of the enzyme in these individuals, which led to the assay for carrier identification among those without family histories (59).

Tay-Sachs carrier screening is performed on blood serum, although for pregnant women, women using oral contraceptives, and persons with liver disease, the blood serum test does not yield accurate results. Instead, white blood cells, platelets, or tears are used; such methods are more time-consuming and costly. The biochemical assay also can be used to detect affected fetuses through either amniocentesis *(79)* or chorionic villus sampling. This assay has had significant false positive carrier rates but lower false negative rates (80).

In the mid-1980s, characterization of the Hex A gene structure and mutations led to the possibility of DNA-based Tay-Sachs screening and diagnosis. Three distinct mutations account for 90 to 98 percent of Tay-Sachs chromosomes in this population (28,62,94); one—a 4 base pair insertion-is present in over 70 percent of Tay-Sachs Ashkenazic alleles. In contrast, among non-Ashkenazic carriers, the three mutations comprise about 20 percent of defective mutations (28,62,94). For Moroccan Jews, a single base pair deletion predominates (56), while in French-Canadians, multiple mutations are present (29). Preliminary results in the Imuisiana French Acadian population indicate the presence of two alterations correlated with Ashkenazic carrier alleles (50). Additionally, one of the prevalent Ashkenazic mutations results in an “adult-onset” form of the disease (94).

DNA analysis is useful in confirmatory and family studies and is being tested as a carrier screening method in some centers. Currently, DNA assays allow confirmation of diagnosis, reducing levels of both false positives and false negatives (62,94). In the future they might replace the enzymatic assay.

Screening Programs

Initial awareness of Tay-Sachs centered in Jewish communities; hence, screening programs (using biochemical assays) for carrier status originated there. After these efforts were launched, similar programs spread to areas where French-Canadians clustered and, most recently, to parts of Louisiana, The almost immediate implementation of carrier screening programs among Ashkenazic Jews was facilitated by a number of factors:

- occurrence of the disease is concentrated in a defined population;
- determination of the carrier state is easy and relatively inexpensive;
- at-risk pregnancies can be monitored through prenatal diagnosis of the disease (34); and
- public funding or subsidies were available-e. g., through the National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs, and Genetic Diseases Act (Public Law 94-278).

Tay-Sachs Carrier Screening Programs

Tay-Sachs carrier screening began in 1971 in the Baltimore, MD-Washington, DC Jewish populations at the behest of the Jewish communities (34). The pilot program involved community outreach: 14 months of organizational planning, technical preparation, and education of medical and religious leaders preceded massive public education campaigns. Every aspect was carried out within the community, from planning to sample collections, which were held in synagogues, high school gymnasiums, and Jewish community centers (34). Eighteen hundred people showed up in one day for the first screening; in under a year, 5,600 individuals were screened, and 245 carriers identified (34,35).

Following the success of this effort, Jewish communities throughout the United States and Canada implemented similar endeavors. By 1976, 52 cities in the United States, and others in Canada, England, Israel, South Africa, and Japan were conducting carrier screening programs (34). Many centers followed the initial protocol, adapting specifics to individual locations. Most changes were made in the target population group and in

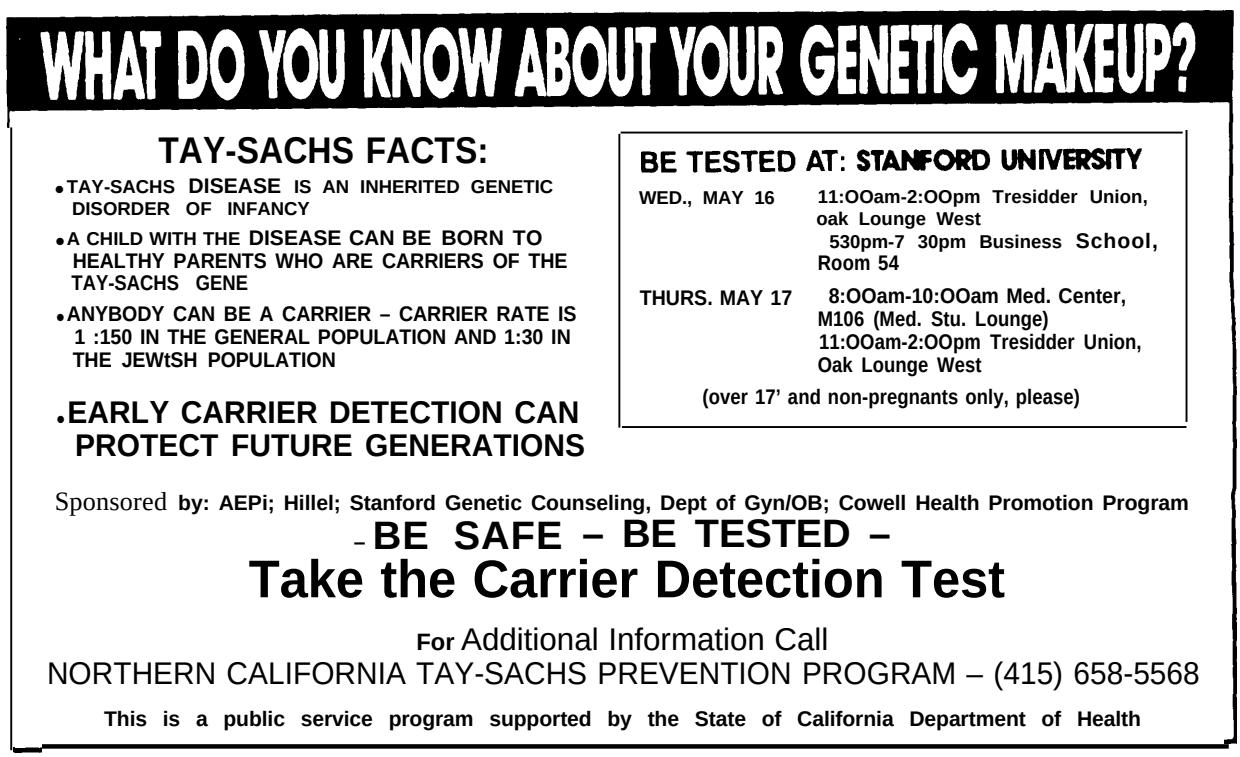


Photo credit: Alpha Epsilon Pi

An advertisement for Tay-Sachs carrier screening.

emphasis on public or physician education. Three main approaches evolved:

- educating and screening the entire community (mass screening);
- targeting couples of reproductive age, usually with the involvement of physicians; and
- screening high school and college students.

Mass Screening. Mass screening programs essentially followed the prototype of the Baltimore, MD-Washington, DC endeavor. In a south Florida area with a high concentration of Ashkenazic Jews, for example, a program involving leaders of the local community, parents of children with Tay-Sachs, and the Department of Pediatrics at the University of Miami School of Medicine was organized in 1973. In 1974, the steering committee overseeing the Florida effort decided to reemphasize mass screening sessions, and established small, local clinics (including synagogues and colleges) where screening sessions could be coordinated with local blood banks' visits to the community. Though screening was available to all individuals, young, single persons were counseled that it might be more effective to delay screening until after marriage, when reproductive decisions would be more pertinent (93).

Couples of Reproductive Age. In 1977, clinical chemists in Akron, OH designed a program that focused on educating family physicians and minimizing public education (63). Information was disseminated to rabbis and Jewish community centers advising them to refer married couples, either pregnant or planning a pregnancy, to physicians for screening. In 1983, a unique program, Chevra Dor Yeshorirn, in New York City's Orthodox Jewish population began screening people prior to arranged marriages to ensure that no marriages would occur between carriers (box B-l).

Students. A different approach was launched in Montreal, Canada in 1974. -A school-based screening program, operated by physicians and paramedical personnel, garnered participation of 75 percent (48). An 8-year followup study indicated that Canadians screened in high school had largely positive attitudes toward genetic screening long after the experience, and made appropriate use of the results (82,83,106). Others criticize the followup study for underestimating the forgetfulness of the adolescents screened (91). Though voluntary genetic screening of high school students is considered acceptable and successful by many in the Montreal community (83), some outside the community accuse the program of coercion (30).

Tay-Sachs Screening Today

Through 1987, 600,000 people had been screened through voluntary programs in the United States (55). Almost 22,000 heterozygotes had been identified, and more than 1,400 pregnancies were monitored. Over 200 affected fetuses were detected and more than 1,000 healthy babies were born from at-risk pregnancies (55).

Box B-1-Chevra Dor Yeshorim Tay-Sachs Program

Chevra Dor Yeshorim, which originated in New York City's OrthCdox Jewish community, is a unique Tay-Sachs screening program. The elevated incidence of Tay-Sachs in this population, combined with religious beliefs opposing abortion and contraception, led community leaders to conclude that preventing Tay-Sachs was possible only by avoiding reproduction between carriers (52). Such reproduction could be avoided because this Orthodox Jewish community arranges marriages through matchmakers.

In 1983, the Committee for Prevention of Jewish Genetic Diseases formed Chevra Dor Yeshorim, which still operates today. All marriageable people are assigned a number and screened for Tay-Sachs carrier status at a local center (52). No one is informed of his or her result, which is filed by `numik` only. When a marriage is proposed, the matchmaker calls the center with the prospective couple's numbers and is informed whether the proposed match involves two Tay-Sachs carriers; if the match does not, marriage plans proceed. If the match involves two carriers, the matchmaker tells the two families to contact the center, where the families are informed that both children are carriers and referred to counseling. Carriers thus learn their status only if they match with another carrier families can report the match has failed for other reasons and look for new matches. This system of anonymity is employed because of historical stigmatization of carriers (52).

Chevra Dor Yeshorim has eventually become an adolescent rite of passage. Similar programs have been developed in California, Tennessee, Michigan, Florida, Maryland, Massachusetts, Illinois, Montreal, Israel, Europe, and other communities (45). By 1992, more than 30,000 people have been screened through such programs. More than 7,000 inquiries have been made and 47 prospective matches between Tay-Sachs carriers identified and halted (45).

SOURCE: OffIce of Technology Assessment, 1992.

Today, the focus has changed somewhat from the early mass education and screening approach, with over 100 hospitals and clinics nationwide offering screening on a continual basis. According to the National Tay-Sachs and Allied Diseases Association (NTSAD), a major aim "continues to be the promotion of genetic screening programs nationally through affiliated hospitals and medical centers, and through [NTSAD'S] local chapters and community organizations" (55).

A program in Toronto, Canada illustrates some general trends in Tay-Sachs carrier screening. Begun in 1972 as a community outreach program along the lines of the Baltimore, MD-Washington, DC prototype, it faced lagging community attendance by the end of the decade. By 1978, the orientation changed from mass screening to one of case finding, where physicians referred patients for screening on an individual basis (14,15,47). In this manner, 600 to 700 individuals are screened each year. Nearly two-thirds are pregnant at the time of screening, suggesting that determination of carrier status is being viewed as part of prenatal care rather than preconception planning.

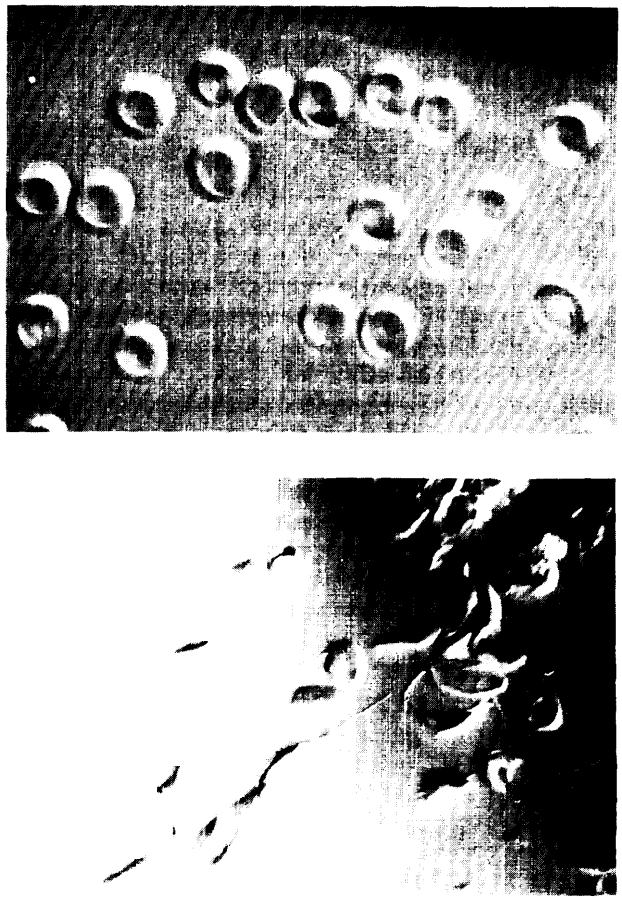
Though outreach efforts are directed beyond the Jewish community, knowledge of Tay-Sachs is generally confined to this population. When multiple cases of Tay - Sachs surfaced in a rural, Catholic community in Louisiana, NTSAD and Tulane University organized a mass education and screening program (41). NTSAD continues public education efforts through nationwide mailings to community and religious organizations and to college, high school, and grammar school libraries.

SCREENING FOR SICKLE CELL ANEMIA

If Tay-Sachs screening is often held as an example of a successful screening campaign, early sickle ceil screening efforts are frequently cited as ''screening gone wrong. Like Tay-Sachs, sickle cell anemia is an autosomal recessive condition generally affecting a particular population—for sickle cell anemia, people of African descent. Sickle cell anemia impairs red blood cell flow through the circulatory system, causing complications in organ systems throughout the body.

As for Tay-Sachs, massive screening programs for sickle cell were undertaken in the United States in the 1970s. Sickle cell programs, however, differed immensely from the Tay-Sachs program in a variety of ways. Screening was mandatory in some States, and there was neither treatment nor prenatal diagnosis. Early programs also suffered from misinformation and discrimination against carriers.

Figure B-l—Normal and Sickled Red Blood Cells



In sickle cell anemia, many red blood cells are distorted from their normal round shape (top), into the shape of a crescent or sickle (bottom). These distorted cells can obstruct smaller blood vessels or be removed too rapidly by the spleen.

SOURCE: M. Murayama, National Institute of Arthritis, Musculoskeletal, and Skin **Diseases, National Institutes of Health, Bethesda,** MD, 1992.

The Disease

The sickle cell mutation affects hemoglobin (Hb), the oxygen-carrying molecule in the blood stream. Hb is found in the red blood cells and can be of a variety of types. Fib A is found in healthy red blood cells; Hb S occurs in the red blood cells of sickle cell anemia patients. Hb S causes the cells to become deformed and sickle shaped (figure B-l). Sickled red blood cells become trapped, decreasing red blood cell survival and, therefore, oxygen transport. Individuals with sickle cell anemia are susceptible to episodes of extreme pain in the limbs, back abdomen, or chest, which are thought to be caused by blockages of the deformed red blood cells in the circulatory system, These crises occur as often as once a month to once every other year and can last from 3 days to more than 3 weeks. Lack of oxygen in the spleen,

kidneys, bones, and joints can also damage these organs and tissues. Eight to 30 percent of children with sickle cell anemia die in the first years of life from complications of severe bacterial infection (25). However, intensive antibiotic treatment-if begun early enough-imparts some resistance to these conditions (25). No cure exists for sickle cell anemia. Unlike Tay-Sachs, sickle cell anemia does not involve mental retardation.

Genetics of Sickle Cell Anemia

Like CF and Tay-Sachs, sickle cell anemia is a genetic disorder inherited in an autosomal recessive pattern. A person with two copies of the sickle cell mutation is homozygous and has sickle cell anemia. A person with a single copy is heterozygous and is said to be a sickle cell carrier or to have sickle cell trait. The red blood cells of people with the sickle cell trait contain both Hb A and Hb S. These individuals do not have sickle cell anemia and are considered to be healthy with a normal life expectancy (88,101). Some clinical abnormalities have been found in people with sickle cell trait including defects in urine concentrating ability and occasional bouts of blood in the urine (88), Under extremely low-oxygen, high-exertion conditions, minimal sickling of red blood cell can occur (36).

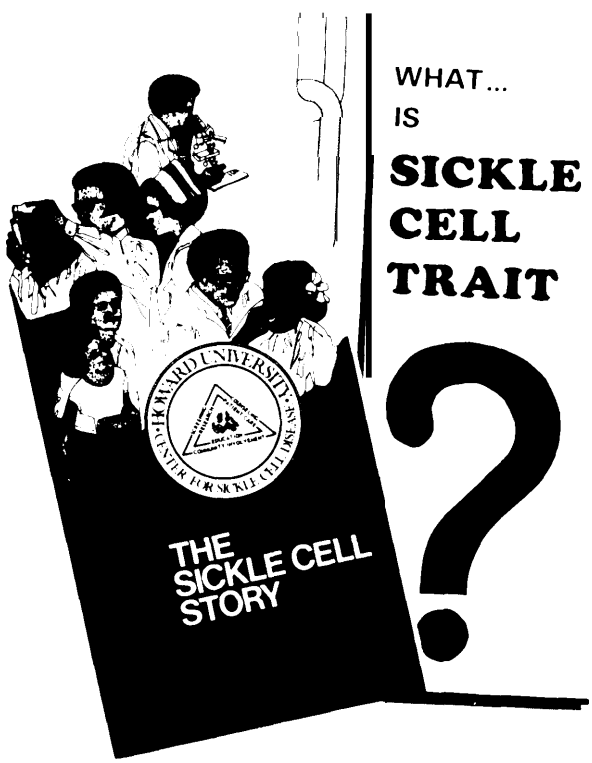


Photo creadit: Howard University

Patient education brochures describing sickle cell anemia and sickle cell trait.

The precise difference between Hb A and Hb S was elucidated in 1956 (57); since then, the specific mutation causing these mutations has been found. The genetic basis of sickle cell is rare: One base change accounts for all cases of the disorder (57). Abase change of an adenine for a thymine in the ß-globin gene produces a single amino acid difference of the 146 amino acids in the ß-chain—one of the two protein components of Hb.

Although the incidence of the sickle cell mutation is high in Greeks, Italians (particularly Sicilians), Eti-Turks, Arabs, southern Iranians, and Asian Indians, the highest frequency occurs in Africans and their descendants (7). One in 400 African American newborns has sickle cell anemia (32), and 1 in 10 or 11 has sickle cell trait (3,57,96).

Diagnostic procedures for sickle cell anemia evolved as knowledge of the biochemistry of Hb increased. Discovery of the differential electrophoretic mobility of Hb S and Hb A permitted testing of blood samples. The presence of only Hb A indicated noncarrier status, only Hb S indicated sickle cell anemia, and the combination of Hb A and Hb S in an individual indicated sickle cell trait. Restriction fragment length polymorphism analysis has had an important impact on diagnosis of sickle cell disease and trait, especially in the prenatal diagnosis of affected fetuses by amniocentesis and chorionic villus sampling. In the early 1980s, a restriction enzyme, Mst II, that recognizes a sequence at the site of the sickle cell mutation itself was found (61). Since 1982, researchers have performed this procedure with 100 percent informativeness and rare errors (39). Diagnosis no longer depends on having informative family members. DNA diagnosis to detect sickle cell has been shown to be 100 percent informative and 99 percent reliable (43). Additionally, polymerase chain reaction can now be used with nonradioactive, enzyme-labeled, allele-specific oligonucleotide probes in dot-blot format (76).

Screening Programs

In the early 1970s, 16 States and the District of Columbia enacted laws to identify people with sickle cell trait and sickle cell anemia so that carrier couples could be informed of their risks of having affected children. Most laws were drafted and promoted by African American legislators at the height of the civil rights movement. At first glance, they offered an inexpensive benefit to African American citizens (65). Depending on the States, screening was mandated for newborns, preschool children, pregnant women, couples applying for marriage licenses, inmates of State institutions, or some combination of these groups. Some States mandated that tests be offered, while others mandated screening.

Many aspects of State sickle cell screening laws generated public critique. Statutes consistently contained

blatant medical and scientific errors including calling for immunization for sickle cell anemia. Some States classified sickle cell carrier status with having sexually transmissible diseases on marriage licenses; others called it a communicable disease (65). Almost every State law failed to insist on using the most sensitive assay available. Controversy also focused on the racial distribution of sickle cell mutations and the target screening population. Sickle cell anemia was considered a "Black Disease" (32). The laws were seen by many citizens as racist eugenic measures aimed at reducing the number of marriages between carriers and decreasing the number of pregnancies at risk for affected children of a minority population. The fact that the programs were largely designed and operated by Caucasians fueled proclamations of genocide.

Most State laws failed to provide adequate education and counseling for persons with sickle cell anemia and trait. The most common error conferred disease status on those who were carriers. Those diagnosed with sickle cell trait were often told they could not have children, that childbirth would be hazardous, or other untruths. Only 4 of 13 programs mentioned counseling of any sort. People were often confused about which condition they had—sickle cell disease or sickle cell trait—which led to increased anxiety.

State laws also failed to provide public education to guard against discrimination and stigmatization. By 1972, for example, at least one flight attendant had been grounded (32). Stories of job and insurance discrimination multiplied as screening programs proliferated. Additionally, too little concern was expressed over confidentiality of results, Some States required that positive test results be filed with the State's public health entity.

National Legislation

In 1971, President Nixon spoke of the problem of sickle cell anemia and the need for more research and education. The 1972 National Sickle Cell Anemia Control Act authorized $85 million over 3 years for the ''establishment and operation of voluntary sickle cell anemia screening and counseling programs, ' and to ''develop information and educational materials relating to sickle cell anemia and to disseminate such information and materials to persons providing health care and to the public generally" (Public Law 92-294). Some $30 million was allocated for research on the disease and for development of educational, screening, and counseling programs. Applicants for Federal funds were required to meet certain standards and to ensure confidentiality of all medical and counseling records. The law also promised community participation: African Americans delivering the service to African Americans.

Sickle Cell Screening Today

By 1973, laws in eight States had been repealed (57). By 1977, more than one-third of States had enacted laws under the National Sickle Cell Anemia Ccntrol Act (65). Mandatory screening was eliminated, and the need for adequate genetic counseling, public education, and confidentiality of test results was recognized (65). Nevertheless, discrepancy between the ideal and actual practice existed, as criticism focused, in the late 1970s, on a continued lack of ''community participation' and accusations of Federal money granted disproportionately to white institutions (65),

Today, sickle cell screening is often done routinely on pregnant women as part of routine blood workup and on newborns (3,23). Prenatal sickle cell screening infrequently results in selective pregnancy termination (103). Forty States screen newborns for sickle cell anemia (103), detecting babies with sickle cell anemia and babies who are carriers, Some States screen all newborns, some target a particular population, and some have voluntary screening that varies from hospital to hospital (103). Some newborn screening is done without informed consent, but with counseling of the parents if carrier status is detected (3).

SCREENING FOR ß-THALASSEMIA

ß-thalassemia, also known as Cooley's anemia, thalassemia major, target cell anemia, and Mediterranean anemia, is an autosomal recessive condition for which carrier screening has been undertaken. ß-thalassemia clusters in particular ethnic groups—people of Mediterranean, Middle Eastern, Asian Indian, Chinese, Southeast Asian, and African descent (7). Legislative action concerning ß-thalassemia has occurred both in the United States and abroad. Screening for a-thalassemia, a related disorder, was first introduced in 1975 and continues today in some parts of the world (box B-2). Many European programs emphasize hemoglobinopathy screening encompassing all clinically significant a and ß alleles and their combinations (103).

The Disease

ß-thalassemia is one of the most common genetic disorders in the world (92). Like sickle cell anemia, the condition affects the Hb of red blood cells. In ß-thalassemia, the amount of Hb is diminished, causing red blood cells to be smaller and have a' 'target" appearance. Severe anemia, frequent infections, spleen enlargement, growth retardation, and marrow hypertrophy are all characteristics of the disorder (57). Death usually results from iron toxicity, most often in childhood. Therapy for ß-halassemia includes transfusions, folic acid supplementation, and intensive treatment of infections. Transfu-

Box B-2---a-Thalassemia

a-thalassemia is another genetic condition often included in carrier screening programs. Like ß-thalassemi~ it is an autosomal recessive disorder affecting hemoglobin (Hb) production. The level of a-globin, a component of Hb, is decreased, resulting in abnormal Hb molecules: Hb H and Hb Bart. It is the most common genetic disease in some Chinese provinces and is found throughout Southeast Asia and the Mediterranean. According to the World Health Organization, 10,000 babies are born with a-thalassemia each year in Asia (42). a-thalassernia also affects people of African descent (7).

a-thalassemia results from mutations in the a-globin genes (87). While there is one ß-globin gene in the human genome, there are two a-globin genes. The most severe type of a-thalassemia is caused by homozygous deletion of both a-globin genes. This condition, called hemoglobin Bart's hydrops fetalis, generally leads to intrauterine death (57,98) and is the primary cause of stillbirth in Southeast Asia (57). Three to five percent of African Americans are heterozygous carriers of mutations for both a-thalassemia genes, and about 26 percent are heterozygous carriers for mutations in one of the a-thalassemia genes (6).

Prior to DNA analysis, diagnosis relied on assaying the presence of Hb Bart in cord blood of babies suspected to have dmlassemia. Identifying carriers by determination of mean corpuscular volume (MCV) and globin chain electrophoresis was inexact. Today, DNA technologies have increased the speed and efficacy of prenatal and carrier screening for a-thalassemia (44).

Carrier screening for a-thalassemia occurs worldwide (100). One program is currently undenvay in Hong Kong, where 98 percent of the population are ethnic Chinese from South China, with a carrier frequency of 3 percent (12). Public education, and formal organization of screening, counseling, and referral were required to make the program successful (12). Today, both carrier screening and prenatal diagnosis appear to be well accepted in Hong Kong (12). A similar effort is advancing in Guangdong Province in southern China (107), where the carrier frequency is about 5 percent.

a-thalassemia carrier screening has also been conducted in the United States. In the 1980s, researchers in southern California educated a Southeast Asian population about screening through the community's churches. Thalassemia screening was performed on a cross-section of the population and on newborns using MCV indices and Hb electrophoresis. Approximately 8 percent of more than 600 individuals were found to be carriers. Today—although the program is no longer operating because Federal funding expired-overall awareness of a-thalassemia appears to have been maintained among physicians, and screening now targets pregnant women in obstetricians' offices (21).

One study in Hawaii assessed consumer attitudes towards thalassemia screening (105). As part of the Hawaii Hereditary Anemia Project, 862 ***a-*** and ß-thalassemia carriers who were identified through the project were surveyed about feelings of stigmatization and attitudes toward knowledge gained. Researchers concluded that learning carrier status provoked little anxiety (except in less educated populations) and provided meaningful benefits (105). Researchers in Rochester, NY have found that the percentages of people seeking an explanation of the test result, having the partner screened, and undergoing prenatal diagnosis are all higher among Southeast Asians than non-Southeast Asians (72).

SOURCE: Office of Technology Assessment 1992.

sions, however, can result in hemochromatosis (iron overload), which can be improved slightly by using chelating agents to reduce excess iron. Splenectomy—removal of the spleen—is indicated if signs of hypersplenism exist and is performed preferably after age 5 (57),

Genetics of ß- Thalassemia

Like sickle cell, ß-thalassem.ia is an autosomal recessive disease caused by mutations in the ß-globin gene. Unlike sickle cell, however, several mutations lead to ß-thalassemia (37). Depending on the number and type of mutations, symptoms range from mild to severe (9). Some mutations in the β-globin gene render the β-globin gene product useless and lead to severe β-thalassemia. Other mutations reduce the output of β-globin, but have relatively little clinical effect.

Each ethnic group has a unique distribution of β-thalassemia mutations (37). At least 91 β-globin mutations leading to β-thalassemia have been characterized, and common mutations exist in a variety of ethnic groups including Mediterranean, African American, Southeast Asian, Indian, and Middle-Eastern populations (38).

The advent of DNA technology has enhanced diagnostic testing for β-thalassemia and β-thalassemia trait. Prior to DNA assays, numerous methods were used to diagnose β-thalassemia (72). Biochemical assays continue to be adequate for carrier screening, but DNA assays allow for mutation identification and improved prenatal diagnosis (5,8,10,76). β-thalassemia diagnosis using DNA analysis is 95 percent informative and 99 percent reliable, comparing favorably to Hb electrophoresis and other biochemical methods (43).

Screening Programs

β-thalassemia is considered a major world health problem, and a number of carrier screening programs have been established both within the United States and abroad. Each program has distinct characteristics and serves specific populations within its society.

United States

β-thalassemia occurs most often in Mediterranean American, African American, and Asian American populations (69). Though 4 percent of the Italian American population has β-thalassemia (70), most Americans have never heard of the condition (75). In the late 1970s and early 1980s, adults in a health maintenance organization (HMO) in Rochester, NY were screened for β-thalassemia trait as part of general health care or multiphasic screening. There was no informed consent, and screening was done by Hb electrophoresis. Patients identified as β-thalassemia carriers received genetic counseling by a physician or watched a videotape that presented basic information about the disorder and the meaning of carrier status. Both methods of providing information were shown to be equally effective (24). Compared to noncarriers (who were not counseled), carriers demonstrated increased knowledge about β-thalassemia and its genetics (70), which was retained at 2 and 10 months postcounseling (71).

β-thalassemia was also incorporated in a 5-year comprehensive prenatal hemoglobinopathies (genetic disorders of Hb) carrier screening program in Rochester, NY, in the early 1980s (74). Pregnant women were screened for β-thalassemia and other hemoglobinopathies as part of routine prenatal screening (73). Every blood sample drawn was screened with no separate informed consent, since providers felt they had their patients' implicit consent for relevant diagnostic blood tests (74). Screening included examining red cells to determine mean corpuscular volume (MCV) and Hb A_2 determination.

In this study, 18,907 pregnant women were screened—about 35 percent of pregnancies in the Rochester metropolitan area. Over 800 women were identified as carriers or as homozygous for a hemoglobinopathy, of whom 92 were β-thalassemia carriers (73,74). Twenty-two percent of these β-thalassemia carriers were not Mediterranean American, African American, or Asian American (74), those populations generally considered at high risk. This finding argues in favor of screening all pregnant women, not only those usually regarded as at elevated risk based on ethnicity or race. Eighty-six percent of women who were counseled about their hemoglobinopathy carrier status said they wanted their partners screened, 55 percent had their partners screened, and 47 percent of carrier couples identified underwent prenatal diagnosis. Thus, unselected patients in a primary care setting in the Rochester region, even though pregnant, were receptive to and utilized genetic information (74). The researchers concluded that genetic screening in such a setting has many advantages over that in non-health-care settings, including comprehensive coverage of the population, screening at a time appropriate or relevant for the individual, and increased likelihood of appropriate medical followup (69).

The Federal Government has also been involved with ß-thalassemia screening. In 1972, the National Cooley's Anemia Control Act (Public Law 92-414) was introduced and sponsored by legislators of Mediterranean heritage. It authorized $3 million for ß-thalassemia screening, treatment, and counseling programs, $3 million for public education, and $5.1 million for disease research over a 3-year period (65).

Canada

A program for ß-thalassemia prevention comprising education, population screening for carriers, and reproductive counseling has been carried out in Canada (81). In a 25-month period (1979-81), 6,748 persons, including 5,117 high school students, were screened for ß-thalassemia trait using MCV indices; the participation rate was 80 percent(81). Researchers surveyed 60 carriers and 120 noncarriers among the high school student population, and most carriers told parents (95 percent) and friends (67 percent) the test result. Most carriers (91 percent) reported they would ascertain their spouses' genotype; 95 percent approved of the screening effort (81).

Sardinia

ß-thalassemia is a significant health problem. One couple in 80 is a carrier couple—i.e., at 1 in 4 risk of an affected pregnancy. Prior to screening, 1 in 250 live births had ß-thalassemia. Most ß-thalassemia cases in Sardinia are severe-i. e., ß-globin chains are absent. About 96 percent of the ß-thalassemia mutations in this population are of a single type, and another mutation accounts for 2.1 percent of the remaining mutations (1 1).

In 1976, the region's Department of Public Health initiated a voluntary program to control ß-thalassemia in Sardinia based on carrier screening, genetic counseling, and prenatal diagnosis. General practitioners, obstetri-

cians, and paramedics were trained at specific educational meetings about the philosophical and technical aspects of the program. The program was targeted toward young unmarried men and women, married couples, and pregnant women. When a carrier was identified, the professionals urged that other family members also consider testing (1 1).

Prior to implementing the program, a mass media educational campaign geared to the general public was launched. About 47 percent of couples and 65 percent of singles screened said they learned of the program through this campaign. Screening was performed first on one member of a couple. If that individual was positive, his or her partner was screened. Prenatal diagnosis was also performed (1 1).

To date, 24 percent of Sardinia's population has been screened, and 85 percent of the theoretical number of carrier couples (+/+) in the population have been identified. In large part, this high efficiency results from followup screening of carriers' family members (1 1). Sixty-five percent of those screened in 1980 were pregnant women. By 1990, only 30 percent were pregnant, demonstrating a trend in increased knowledge--i. e., individuals came in for screening prior to conception. The incidence of ß-thalassemia in Sardinia has declined from 1 in 250 live births in 1974 to 1 in 1,200 in 1991, an effective prevention of 90 percent of predicted cases (11). Of babies born with ß-thalassemia, 67 percent were born to parents who were unaware of the disease and of carrier screening, 20 percent were to parents who, for ethical reasons, decided against abortion after prenatal diagnosis, and 13 percent were cases of false paternity (1 1).

An important early result of the program was the impact on carriers. Many had difficulty finding jobs, chiefly because the national army is the predominant employer in Sardinia and refuses to employ ß-thalassemia carriers due to a misunderstanding about carrier status. Ongoing efforts to educate the army appear likely to reverse this practice in the near future (1 1). ß-thalassemia screening in Sardinia is currently moving to encompass the school-aged population (1 1).

Cyprus

In Cyprus, 1 in 7 individuals is a carrier, and 1 in 1,000 Cypriots is a patient under treatment for ß-thalassemia (2). In the early 1970s, the realization that demand for treating this single disease could outstrip resources for all health care led to the development of a national carrier screening effort. Undertaken with World Health Organization support, the program consisted of public education, population screening for carriers, genetic counseling for carrier couples, prenatal diagnosis, and premarital screening (2).

An unusual compliance mechanism is one facet of the Cyprus program. The Greek Orthodox Church recognized the problems of the high incidence of ß-thalassemia births, but was reluctant to endorse pregnancy termination to prevent such births. In 1983, however, the Church agreed that, before the Church would bless a marriage or engagement, a couple would be required to present a certificate proving they had been screened and had received genetic counseling. With the Church's cooperation, the number of people screened skyrocketed from 1,785 in 1977 to 18,202 in 1983. Today, 10,000 to 11,000 people are screened annually. Since most couples of reproductive age have been screened, attention now focuses on single people. Since 1985, a 20 percent fall in the expected proportion of +/+ couples has been noted, perhaps indicating that carriers are avoiding marriage to other carriers (2).

As in Sardinia, the number of newborns with ß-thalassemia has fallen dramatically. In 1974,53 of 8,594 births were affected: From 1986 through 1990, there were five, for a prevention rate of 97 percent. Ninety percent of the 69 affected babies born between 1978 and 1980 resulted from lack of knowledge among the public and the medical profession about the Cyprus carrier screening effort. Two births were due to refusal of prenatal diagnosis on religious grounds, two were laboratory errors, and one was parental choice after positive prenatal diagnosis.

The program's success is attributed to several factors, including extensive and continuous public education, small population size, and homogeneity of the population (2). Time spent on counseling is much less today than when the program was initiated-a direct result of increased public education. A newer program is under way in Turkish Cyprus.

Other ß-thalassemia Screening Programs

Screening programs for ß-thalassemia in the United Kingdom (58) incorporate treatment and prevention into general health care. Primary health care, peripheral centers, and reference centers coordinate the program's efforts. Individuals learn about the screening through schools and public information posters. Community involvement, particularly through parents' and patients' associations is an important component, and a detailed education program provides effective information about genetic risks and services. Fewer ß-thalassemia births have been avoided in the United Kingdom than in Cyprus or Sardinia, chiefly because of the large population size, the occurrence of ß-thalassernia in ethnic minorities scattered throughout an indigenous population, and the beliefs of many of those at risk that prenatal diagnosis and abortion are socially and religiously unacceptable (58). Southeast Asia, Hong Kong, East Mediterranean coun-

tries, and South China have ß-thalassemia carrier screening programs (12,46,107).

LESSONS FOR CYSTIC FIBROSIS CARRIER SCREENING

The Tay-Sachs, sickle cell anemia, ß-thalassemia, and ß-thalassemia experiences offer lessons that might be applicable to routine carrier screening for CF. These lessons involve five principal aspects of the programs described in this appendix:

- nature of participation,
- setting and fiscal support,
- target population,
- public education, and
- counseling carriers and at-risk couples.

Nature of Paticipation

Participation in the programs described in this appendix was voluntary or mandatory. The Tay-Sachs expedience offers a model of voluntary participation, which contributed to its efficacy and success—both in reducing disease and in avoiding stigmatization (54,66). It is noteworthy, nonetheless, that one survey found that nearly half of participants in one Tay-Sachs program felt screening should be mandatory, although the breakdown of carriers and noncarriers expressing those opinions was not measured (13).

The sickle cell experience, on the other hand, included some mandatory State screening of people in schools or correctional institutions, or of couples applying for marriage licenses. Such mandatory participation was viewed as a contributing factor in the widespread failure of these efforts (65,66). ß-thalassemia programs in the United States and abroad have used the voluntary approach and have been generally successful (2,11,74,105). ß-thalassemia programs in the Mediterranean that use a quasi-mandatory approach through the involvement of the Greek Orthodox Church also have been successful in reducing disease. Although stigmatization appeared to be an issue initially, it seems to now be obviated (2). The success of these mandatory programs, however, can be attributed mainly to the cultures of Cyprus and Sardinia and is likely not applicable to carrier screening in the United States.

Thus, success of voluntary initiatives and the failure of mandatory programs (excluding the Cyprus example) lead many to conclude that voluntary participation for CF carrier screening is essential. The National Institutes of Health (NIH) Workshop on Population Screening for the Cystic Fibrosis Gene recommended that screening be voluntary (4).

Setting and Fiscal Support

The environment in which a genetic screening program is administered also affects its success and acceptance. Tay-Sachs carrier screening was community-based. Leaders within the Jewish community became leaders of the screening programs, which were offered through synagogues, storefronts, and community centers. The community was involved in all aspects of the program. For CF, however, the target population is larger and more diffuse, with a wide range of religious beliefs. Thus, it would be an ill fit to organize CF carrier screening solely through religious centers.

In stark contrast, the sickle cell anemia programs were run largely by the State and Federal governments, their contractors, and grant recipients. During a time of tension over civil rights, Caucasians from outside of the community generally controlled screening, which was viewed extremely negatively by the African American community. The resulting lack of support by the targeted population doomed sickle cell screening programs to failure.

ß-thalassemia programs in the United States have been more diverse, involving primary care physicians in neighborhood health centers, a large HMO, hospital prenatal clinics, a family medicine program, and private practice. The particular setting seems less important to success than other factors, (e.g., patient and provider education> although a primary care clinical setting is desirable (69)—and likely will prove most appropriate to CF carrier screening. (ß-thalassemia experiences in Europe revolve around national health care systems, making it difficult to compare setting and funding to U.S. experiences.)

Beyond the particular setting is the issue of funding for organizing and maintaining the effort. Historical perspectives probably apply least in this area. Most efforts launched in the 1970s and 1980s involved some degree of public funding. With respect to routine CF carrier screening in the United States, the funding issue is complex, but direct funding in the manner of Tay-Sachs, sickle cell, or the thalassemias is unlikely to materialize beyond the current NIH pilot projects (ch. 6). Thus, to the extent that direct public subsidy contributed to the success of past screening, routine CF carrier screening will unlikely realize such a benefit.

Target Population

Tay-Sachs programs targeted a narrow slice of the U.S. population. The population was easily identifiable, largely urban, educated, and receptive to screening and reproductive options; all are population characteristics often cited as beneficial to a program's success (34). Sickle cell programs targeted African American communities at the

height of the civil rights movement, causing considerable controversy about segregation, discrimination, and stigmatization. Racial tensions created by singling out a population already historically discriminated against stress the importance of prior awareness of the implications of focusing on members of a particular group and their potential reactions to screening.

The age and sex of the screened population also have implications for CF carrier screening. With the ability to perform prenatal diagnosis, much attention focuses on screening pregnant women (95). Some argue that screening during pregnancy offers the advantages of immediate interest in knowledge of genetic information and comprehensive coverage of the population (75). Disadvantages of screening during pregnancy include eliminating the option to avoid conception, so that prenatal fetal testing might be perceived as necessary. Or, it might be too late in a pregnancy for prenatal diagnosis even if desired. Some also believe that carrier identification can be too anxiety-producing during pregnancy to be efficacious. Others argue that screening women first can be perceived as eugenic screening for breeding fitness (102).

Many studies have attempted to ascertain the optimal group for carrier screening: newborns, students, primary care recipients, pregnant women, couples planning to marry, or married couples (13,16,17,99,106). The studies often conflict: Each group offers advantages and disadvantages that vary by disease, available technology, and manifestations of the disease (ch. 6). Thus, the optimal population for CF carrier screening remains a topic of debate. Additionally, while CF mutations have a high prevalence in one racial group-Caucasians-the ethnic diversity of this population in the United States poses a challenge that did not exist for previous screening efforts. Beyond diversity per se, many Americans do not know specifics of their ethnic backgrounds, knowledge which might assist in more precisely assigning risks (96). Further, CF also occurs, albeit less frequently, in Asian Americans and African Americans. The extent to which routine screening within these two groups is appropriate is also an issue.

Public Education

Consumer knowledge--both about medical aspects of the specific genetic condition and the meaning of carrier status—is key. Conditions that affect mental function, such as Tay-Sachs, appear to have a greater acceptance of carrier screening and prenatal diagnosis (20,22,26). The high acceptability of screening that resulted from public education for Tay-Sachs might be less informative for routine CF carrier screening, for example, although the mechanism of providing the education could be illustrative. Likewise, CF carrier screening might not serve as a good indicator of future screening for disorders such as fragile X syndrome (box B-3).

Stigmatization of carriers, widely cited as a negative outcome of genetic screening (27,30,67), is largely attributed to ignorance within both the community being screened and the general population. In contrast to acceptability, lessons about the importance of public education to avoid stigmatization can be gleaned from history. With Tay-Sachs screening, a concerted effort was made to educate community and religious leaders, who then helped educate the public through outreach, mailings, media, and word of mouth before any screening took place. Educational efforts were adjusted over time, and in general, data indicate the majority of carriers believe they were not stigmatized, although a small percentage of noncarriers expressed attitudes of superiority (13,40), Similarly, the Mediterranean ß-thalassemiaprograrn demonstrates the effectiveness of massive public education through the local media, although some contend the massive public education bordered on propaganda and coercion (31). The sickle cell experience demonstrates how poor public outreach and lack of knowledge among professionals in the program lead to failure (54,66).

Regardless of the precise mechanism through which education is achieved, implementation of CF carrier screening can benefit from the knowledge that public education has had a positive effect on previous screening experiences. Lessons learned from Tay-Sachs, sickle cell, and ß-thalassemia efforts can be applied to CF carrier screening to increase public knowledge and decrease stigmatization.

Counseling Carriers and At-Risk Couples

CF carrier screening can be informed by the Tay-Sachs, sickle cell, and ß-thalassemia experiences with genetic counseling. Lessons about informing patients, counseling carriers, and counseling carrier couples can be applied to CF carrier screening. The sickle cell experience often omitted counseling, and so individuals with sickle cell trait became anxious, not only because they were given incorrect information, but also because they had received inadequate counseling.

Tay-Sachs programs considered informed consent, counseling of carriers, and counseling carrier couples to be high priorities. Such informed consent and counseling aided in the understanding and adjustment of individuals "who were identified as carriers. In contrast, with no apparent negative effect, ß-thalassemia carrier screening in one pilot involving pregnant women was done on every blood sample drawn, with no separate informed consent (since providers felt they had patients' implicit consent for relevant diagnostic blood tests) (74), As is acknowledged to be essential, carriers and carrier couples received post-test counseling.

Box B-3—Fragile X Syndrome

Recent advances elucidating the genetics of fragile X syndrome will have a great impact on future applications **to** screening. Fragile X syndrome is the most common form of inherited mental retardation. Its incidence is about 1 in 1,500 male and 1 in 2,500 female live births (58). It includes minor dysmorphic features such as an elongated Face, large ears, prominent jaw, and macroorchidism (78). The genetics of this disorder are different from the mtosomal recessive disorders of cystic fibrosis, Tay-Sachs disease, sickle cell anemia, and the thalassernias. Fragile X syndrome is an X-linked disorder-the gene for the disorder lies on the X chromosome, one of the two sex determining human chromosomes. (Females have two X chromosomes, while males have one X and one Y chromosome.)

Initially described in 1969, fragile X syndrome derives its name from the tendency for the tip of the X chromosome to break off or appear fragile (figure B-2) (49). Its mode of inheritance, however, is unlike other X-linked disorders such as hemophilia—it is neither recessive nor dominant. Unaffected men and women can transmit a fragile X chromosome without manifesting any symptoms of the syndrome or expressing the fragile site cytogenetically. Such transmitters, or carriers, can have children or grandchildren with fragile X syndrome (104). The mothers of all affected children are considered to be obligate carriers, and no affected offspring arise as a direct result of a new mutation (85). Among females, about half of the obligate carriers do not express the fragile X chromosome. About 50 percent of heterozygous females express the disorder to some extent, and 30 percent are mentally retarded. Approximately 20 percent of males who inherit the gene from their mothers are unaffected carriers. Furthermore, severity appears variable in different siblings even within the same family (58).

Physical signs of the disorder are neither specific nor constant, and generally appear after childhood, making diagnosis difficult. In the past, diagnosis generally occurred only after the birth of a second affected male (89), and involved expert, labor-intensive laboratory analysis (84). Once the X chromosome was shown to be fragile, linkage analysis of other family members could be performed, with prenatal tests also possible (33,86),

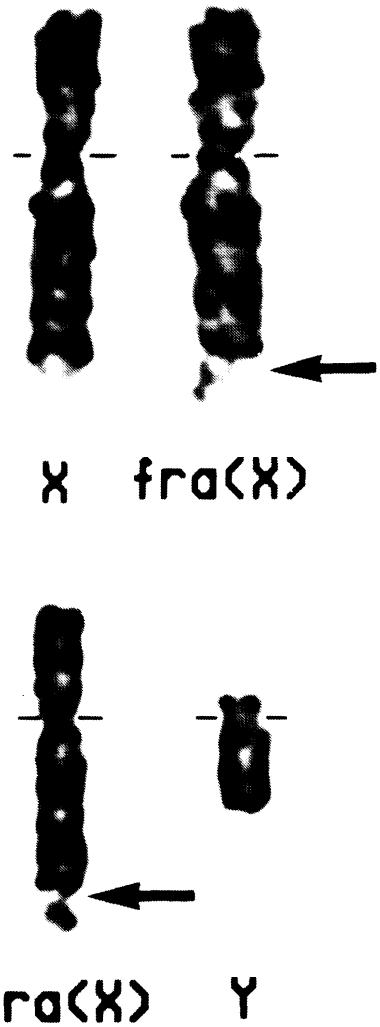
In 1991, researchers elucidated the uninique inheritance of fragile X syndrome and developed a DNA probe to detect the fragile X site (58,104). Reliable and specific detection of all male or female carriers of a fragile X site is now possible (58,68). Similarly, prenatal analysis can be performed (58,68,90). Moreover, results from DNA assays appear to correlate with disease severity, and so can be used to predict clinical outcome (58). Fragile X syndrome will likely be one of the first disorders for which the primary diagnosis is based on the direct analysis of a mutation at the DNA level (68,84)

The increased knowledge of the genetics of fragile X syndrome has applications to genetic screening. Most families with fragile X syndrome are presently unknown, because routine screening of the entire developmentally disabled population has not been practical and because fragile X syndrome historically has been poorly diagnosed (89). Given the high sensitivity and specificity of the new fragile X assay—and the value of early diagnosis for genetic counseling purposes-the next step to consider is selected population screening (18). Although such screening would initially focus on developmentally disabled males and females, if the frequency of normal transmitting males is as high as the frequency of affected males, as one hypothesis predicts, an argument can be made for general population screening, as has been proposed in the United Kingdom (18).

With respect to genetic counseling needs for fragile X syndrome, one study examined interest in prenatal diagnosis and attitudes towards termination of affected pregnancies (51). Surveyed prior to the advent of the DNA assay, 81 percent of women said they would seek prenatal diagnosis, and 28 percent indicated they would terminate an affected pregnancy. There was no significant difference in responses between women who had affected children and those who did not. Issues the subjects considered most important for discussion with a genetic counselor included the availability of treatment, risk for having an affected grandchild, and expectations for the future functioning of children with fragile X syndrome (51).

SOURCE: Office of Technology Assessment, 1992.

Figure B-2—Fragile X Chromosomes



The fragile X site appears as a break or separation at the distal end **of the long arm of X chromosomes (arrows). This computer-enhanced photomicrograph shows a carrier female (top) and an affected male (bottom),**
SOURCE: The Denver Children's Hospital, 1992.

APPENDIX B REFERENCES

1. Andermann, E., Scriver, C. R., Wolfe, L. S., et al., "Genetic Variants of Tay-Sachs Disease: Tay-Sachs Disease and Sandhoff's Disease in French Canadians, Juvenile Tay-Sachs Disease in Lebanese Canadians, and a Tay-Sachs Screening Program in the French Canadian Population, " *Tay-Sachs Disease: Screening and Prevention,* M.M. Kaback (cd.) (New York, NY: Alan R. Liss, Inc., 1977).
2. Angastiniotis, M., "Cyprus: Thalassaemia Prograrnme," *Lancet* 336:1 19-1120, 1990.
3. Benkendorf, J. L., Georgetown University Medical Center, Washington, DC, personal communication, December 1991.
4. Bernhardt, B. A., "Population Screening for the Cystic Fibrosis Gene," New *England Journal of Medicine* 324:61-62, 1991.
5. Boehm, C.D., Antonarakis, S.E., Phillips, J. A., et al., "Prenatal Diagnosis Using DNA Polymorphisms: Report on 95 Pregnancies at Risk for Sickle-Cell Disease or β-Thalassemia,'' New *England Journal of Medicine* 308:1054-1058, *1983.*
6. Bowman, J. E., Department of Pathology, University of Chicago, personal communication, April 1992.
7. Bowman, J. E., and Murray, R. F., Jr., *Genetic Variation and Disorders in Peoples of African Origin* (Baltimore, MD: The Johns Hopkins University Press, 1990).
8. Cai, S.-P., Chang, C. A., Zhang, J. Z., et al., "Rapid Prenatal Diagnosis of β-Thalassemia Using DNA Amplification and Nonradioactive Probes, " *Blood* 73:372-374, *1989.*
9. Cao, A., Gossens, M., and Pirastu, M., ''β-Thalassemia Mutations in Mediterranean Populations,' *British Journal of Haematology 71:309-312, 1989.*
10. Cao, A., Rosatelli, C., Galanello, R., et al., "Prenatal Diagnosis of Inherited Hemoglobinopathies, " *Indian Journal of Pediatrics* 56:707-717, *1989.*
11. Cao, A., Rosatelli, C., Galanello, R., et al., "The Prevention of Thalassemia in Sardinia," *Clinical Genetics* 36:277-285, *1989.*
12. Chan, V., Chan, T.K., and Todd, D., ''Thalassemia Screening and Prenatal Diagnosis in Hong Kong," *American Journal of Human* Genetics 49(Supp.):79, 1991.
13. Childs, B., "The Personal Impact of Tay-Sachs Carrier Screening," *Tay-Sachs Disease: Screening and Prevention,* M.M. Kaback (cd.) (New York, NY: Alan R. Liss, Inc., 1977).
14. Clarke, J.T., "Screening for Carriers of Tay-Sachs Disease: Two Approaches," *Canadian Medical Association Journal* 119:549-550, *1978.*
15. Clarke, J.T., Skomorowski, M.A., and Zuker, S., ''Tay-Sachs Disease Carrier Screening: Follow-Up of a Case-Finding Approach,' *American Journal of Medical Genetics* 34:601-605, *1989.*
16. Clew, C.L., and Scriver, C.R., "Knowledge and Attitudes Toward Genetic Screening Among High-School Students: The Tay-Sachs Experience,' *Pediatrics* 59:86-91, *1977.*
17. Clew, C.L., and Scriver, C.R., "The Adolescent Copes With Genetic Screening: A Study of Tay-Sachs Screening Among High-School Students," *Tay-Sachs Disease: Screening and Prevention,*

M.M. Kaback, (cd.) (New York, NY: Alan R. Liss, Inc., 1977).

18. Connor, J. M., ''Cloning of the Gene for the Fragile X Syndrome: Implications for the Clinical Geneticist, ' *Journal of Medical Genetics* 28:811-813, *1991.*
19. Desnick, R.J., and Goldberg, J. D., ''Tay-Sachs Disease: Prospects for Therapeutic Intervention, " *Tay-Sachs Disease: Screening and Prevention,* M.M. Kaback (cd.) (New York, NY: Alan R. Liss, Inc., 1977),
20. Drugan, A., Greb, A., Johnson, M, P., et al., ''Determinants of Parental Decisions to Abort for Chromosome Abnormalities," *Prenatal Diagnosis 10:483-490, 1990.*
21. Dumars, K., MediGene Facility, Inc., Fountain Valley, CA, personal communication, May 1992.
22. Faden, R.R., Chwalow, A. J., Quaid, K., et al., "Prenatal Screening and Pregnant Women's Attitudes Toward the Abortion of Defective Fetuses, " *American Journal of Public Health* 77:288-290, *1987.*
23. Fine, B. A., Northwestern University Medical School, Chicago, IL, personal communication, September 1991.
24. Fisher, L., Rowley, P.T., and Lipkin, M., Jr., "Genetic Counseling for β-Thalassemia Trait Following Health Screening in a Health Maintenance Organization: Comparison of Programmed and Conventional Counseling," *American Journal of Human Genetics* 33:987-994, 1981.
25. Githens, J. H., Lane, P. A., McCurdy, R. S., et al., "Newborn Screening for Hemoglobinopathies in Colorado: The First 10 Years," *American Journal of Diseases of Children* 144:466-470, *1990.*
26. Golbus, M. S., Loughman, W. D., Epstein, C. J., et al., ''Prenatal Diagnosis in 3,000 Amniocenteses," New *England Journal of Medicine* 300:157-163, *1979.*
27. Goodman, M, J., and Goodman, L. E., 'The Overselling of Genetic Anxiety,' *The Hastings Center Report* 12:20-27, *1982.*
28. Grebner, E. E., and Tomczak, J., "Distribution of Three et-Chain β-Hexosaminidase A Mutations Among Tay-Sachs Carriers,' *American Journal of Human Genetics* 48:604-607, 1991.
29. Hechtman, P., Kaplan, F., BayerIan, J., et al., 'More Than One Mutant Allele Cause Infantile Tay-Sachs Disease in French Canadians, " *American Journal of Human Genetics* 47:815-822, *1990.*
30. Holtzman, N. A., *Proceed With Caution: Predicting Genetic Risks in the Recombinant DNA Era* (Baltimore, MD: The Johns Hopkins University Press, 1989).
31. Holtzman, N. A., Johns Hopkins University Hospital, Baltimore, MD, personal communication, December 1991.
32. Hubbard, R., and Henifin, M. S., "Genetic Screening of Prospective Parents and of Workers: Some Scientific and Social Issues,' *International Journal of Health Services* 15:231-251, 1985.
33. Jenkins, E. C., Krawczun, M. S., Stark-Houck, S.L., et al., "Improved Prenatal Detection of fra(X) (q27.3): Methods for Prevention of False Negatives in Chorionic Villus and Amniotic Fluid Cell Cultures, *American Journal of Medical Genetics* 38:447-452, *1991.*
34. Kaback, M. M., Nathan, T.J., and Greenwald, S., ''Tay-Sachs Disease: Heterozygote Screening and Prenatal Diagnosis—U.S. Experience and World Perspective,' *Tay-Sachs Disease: Screening and Prevention,* M.M. Kaback (cd.) (New York, NY: Alan R. Liss, Inc., 1977).
35. Kaback, M. M., Zeiger, R. S., Reynolds, L. W., et al., "Approaches to the Control and Prevention of Tay-Sachs Disease,' *Progress in Medical Genetics* 10:103-134, *1974.*
36. Kark, J. A., Posey, D. M., Schumacher, H. R., et al., "Sickle-Cell Trait as a Risk Factor for Sudden Death in Physical Training,' New *England Journal of Medicine* 317:781-787, *1987.*
37. Kazazian, H. H., "Molecular Pathology of the β-Globin Gene Cluster," *Trends in Neuroscience* 8:192-200, 1985.
38. Kazazian, H. H., ''Thalassemia Syndrome: Molecular Basis and Prenatal Diagnosis in 1990," *Seminars in Hematology* 27:209-228, 1990.
39. Kazazian, H. H., Johns Hopkins University School of Medicine, Baltimore, MD, personal communication, December 1991.
40. Kenen, R.H., and Schmidt, R. M., "Stigmatization of Carrier Status: Social Implications of Heterozygote Genetic Screening Programs,' *American Journal of Public Health* 68:1 *16-1120, 1978.*
41. Kovner, A., The National Tay-Sachs and Allied Diseases Association, Inc., Brookline, MA, personal communication, August 1991.
42. Kuliev, A. M., ''The WHO Control Program for Hereditary Anemias,' *Birth Defects: Original Article Series 23(5 B):383-394,* March of Dimes Birth Defects Foundation, 1988.
43. Lebo, R. V., Cunningham, G., Simons, M. J., et al., "Defining DNA Diagnostic Tests Appropriate for Standard Clinical Care," *American Journal of Human Genetics* 47:583-590, *1990.*
44. Lebo, R. V., Saiki, R. K., Swanson, K., et al., "Prenatal Diagnosis of α-Thalassemia by Polymerase Chain Reaction and Dual Restriction Enzyme Analysis," *Human Genetics* 85:293-299, *1990.*

45. Lefkowitz, S., Chevra Dor Yeshorim, Center for the Prevention of Jewish Genetic Diseases, Brooklyn, NY, personal communication, March 1992,
46. Loukopoulos, D., "Screening for Thalassemia and HbS in the East Mediterranean,' *American Journal of Human Genetics 49(Supp.):79, 1991.*
47. Lowden, J. A., "Role of the Physician in Screening for Carriers of Tay-Sachs Disease," *Canadian Medical Association Journal* 119:575-578, *1978.*
48. Lowden, J. A., and Davidson, J., ''Tay-Sachs Screening and Prevention: The Canadian Experience, " *Tay-Sachs Disease: Screening and Prevention,* M.M. Kaback (cd.) (New York, NY: Alan R. Liss, Inc., 1977).
49. Lubs, H. A., "A Marker X Syndrome, " *American Journal of Human Genetics* 21:231-244,1969.
50. McDowell, G. A., Schultz, R. A., Schwartz, S., et al., "Presence of Both Ashkenazic Tay-Sachs Mutations in a Non-Jewish Inbred Population, " *American Journal of Human Genetics 45(* Supp.):A9, *1989.*
51. Meryash, D.L., and Abuelo, D., 'Counseling Needs and Attitudes Toward Prenatal Diagnosis and Abortion in Fragile X Families, " *Clinical Genetics* 33:349-355, *1988.*
52. Merz, B., "Matchmaking Scheme Solves Tay-Sachs Problem,' *Journal of the American Medical Association* 258:2636-2639, *1987.*
53. Modell, B., and Petrou, M., "Review of Control Programs and Future Trends in the United Kingdom," *Birth Defects: Original Article Series 23(5 B): 433-442,* March of Dimes Birth Defects Foundation, 1988.
54. National Research Council, Committee for the Study of Inborn Errors of Metabolism, *Genetic Screening: Programs, Principles, and Research* (Washington, DC: National Academy of Sciences, 1975).
55. National Tay-Sachs and Allied Disease Association, *Tay Sachs and the Allied Diseases: What Every Family Should Know,* brochure, 1987.
56. Navon, R., and Proia, R.L., ''Tay-Sachs Disease in Moroccan Jews: Deletion of a Phenylalanine in the a-Subunit of cx-Hexosaminidase, *American Journal of Human Genetics* 48:412-419,1991.
57. Nora, J, J., and Fraser, F. C., *Medical Genetics: Principles and Practice* (Philadelphia, PA: Lea & Febiger, 1989).
58. Oberle, I., Rousseau, F., Heitz, D., et al., "Instability of a 550-Base Pair DNA Segment Abnormal Methylation in Fragile X Syndrome, " *Science* 252:1097-1102, 1991.
59. O'Brien, J. S., Okada, S., Chen, A., et al., ''Tay-Sachs Disease: Detection of Heterozygotes and Homozygotes by Serum Hexosarninidase Assay," *New EnglandJournal of Medicine* 283: *15-20,1970.*
60. Okada, S., and O'Brien, J. S., ''Tay-Sachs Disease: Generalized Absence of a β-D-N-acetylhexosaminidase Component," *Science* 165:698-700, *1969.*
61. *Orkin,* S.H., Little, P.F., Kazazian, H.H., et al., "Improved Detection of the Sickle Mutation by DNA Analysis,' New *England Journal of Medicine* 307:32-36, *1982.*
62. Paw, B. H., Tieu, P. T., Kaback, M. M., et al., ''Frequency of Three *Hex A* Mutant Alleles among Jewish and Non-Jewish Carriers Identified in a Tay-Sachs Screening Program,' *American Journal of Human Genetics* 47:698-705, 1990.
63. Potter, J. L., and Robinson, H. B., Jr., "Screening for the Tay-Sachs Carrier: A Compromise Program, " *Clinical Chemistry* 27:523-525,1981.
64. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Screening and Counseling for Genetic Conditions: A Report on the Ethical, Social, and Legal Implications of Genetic Screening, Counseling, and Education Programs* (Washington, DC: U.S. Government Printing Office, 1983).
65. Reilly, P., *Genetics, Law and Social Policy* (Cambridge, MA: Harvard University Press, 1977).
66. Roberts, L., "One Worked: The Other Didn't (Genetic Screening programs for Tay-Sachs and Sickle Cell Anemia)," *Science* 247:18, *1990.*
67. Rosner, F., "ConfidentialTay-Sachs Carrier Screening,'' New *York State Journal of Medicine* 89:585, *1989.*
68. Rousseau, F., Heitz, D., Biancalana, V., et al., ''Direct Diagnosis by DNA Analysis of the Fragile X Syndrome of Mental Retardation,' New *England Journal of Medicine* 325:1673-1681, 1991.
69. Rowley, P.T., ''Prenatal Screening for Hemoglobinopathies,'' *American Journal of Human Genetics* 49:466-467, 1991.
70, Rowley, P.T., Fisher, L., and Lipkin, M., Jr., "Screening and Genetic Counseling for β-Thalassemia Trait in a Population Unselected for Interest: Effects on Knowledge and Mood," *American Journal of Human Genetics 31:718-730, 1979.*
71. Rowley, P.T., Lipkin, M., Jr., and Fisher, L., "Screening and Genetic Counseling for Beta-Thalassemia Trait in a Population Unselected for Interest: Comparison of Three Counseling Methods," *American Journal of Human Genetics 36:677-689, 1984.*
72. Rowley, P.T., Loader, S., Sutera, C. J., et al., ''prenatal Hemoglobinopathy Screening: Receptivity of Southeast Asian Refugees, ' *American Journal of Preventive Medicine* 3:317-322, *1987.*
73. Rowley, P.'I'l, Loader, S., Sutera, C.J., et al., "Do Pregnant Women Benefit From Hemoglobinopathy

Screening?," *Annals of the New York Academy of Sciences* 565:152-160, *1989.*

74. Rowley, P.T., Loader, S., Sutera, C. J., et al., ''Prenatal Screening for Hemoglobinopathies. I. A Prospective Regional Trial,' *American Journal of Human Genetics* 48:439-446, 1991.
75. Rowley, P.T., Loader, S., and Walden, M., "Toward Providing Parents the Option of Avoiding the Birth of the First Child With Cooley's Anemia: Response to Hemoglobinopathy Screening and Counseling During Pregnancy,' *Annals of the New York Academy of Sciences* 445:408-416, *1985.*
76. Saiki, R. K., Chang, C.-A., Levenson, C. H., et al., "Diagnosis of Sickle Cell and β-Thalassemia With Enzymatically Amplified DNA and Nonradioactive Allele-Specific Oligonucleotide Probes,' New *England Journal of Medicine* 319:537-541, *1988.*
77. Sandhoff, K., Conzelmann, E., Neufeld, E. F., et al., ''The G_{M2} Gangliosidoses" *The Metabolic Basis of Inherited Disease,* C.R. Scriver, A.L. Beaudet, W.S. Sly, et al. (eds.) (New York, NY: McGraw Hill, 1989).
78. Schepis, C., Palazzo, R., Ragusa, R. M., et al., ' 'Association of Cutis Verticis Gyrata With Fragile X Syndrome and Fragility of Chromosome 12," *Lancet* 2:279, 1989.
79. Schneck, L., Friedland, J., Valenti, C., et al., "Prenatal Diagnosis of Tay-Sachs Disease, " *Lancet* 1:582-583, *1970.*
80. Schulman, J. D., Genetics & IVF Institute, Fairfax, VA, personal communication, December, 1991.
81. Scriver, C. R., Bardanis, M., Cartier, L., et al., ''β-Thalassemia Disease Prevention: Genetic Medicine Applied, ' *American Journal of Human Genetics 36: 1024-1038, 1984.*
82. Scriver, C. R., and Clew, C. L., "Carrier Screening for Tay-Sachs Disease, " *Lancet* 335:856, 1990.
83. Scriver, C, R., and Clew, C. L., "Carrier Screening for Tay-Sachs Disease, " *Lancet* 336:191, 1990.
84. Shapiro, L. R., "The Fragile X Syndrome: A Peculiar Pattern of Inheritance, " *New England Journal of Medicine 325: 1736-1738, 1991.*
85. Shapiro, L. R., Wilmot, P. L., and Murphy, P.D., ''Prenatal Diagnosis of the Fragile X Syndrome: Possible End of the Experimental Phase for Amniotic Fluid, ' *American Journal of Medical* Genetics 38:453-455, 1991.
86. Shapiro, L. R., Wilmot, P. R., Shapiro, D. A., et al., "Cytogenetic Diagnosis of the Fragile X Syndrome: Efficiency, Utilization, and Trends, ' *American Journal of Medical Genetics* 38:408-410, *1991.*
87. Steinberg, M. H., and Embury, S. H., ' 'α-Thalassemia in Blacks: Interactions With the Sickle Hemoglobin Gene," *Birth Defects: Original Article Series 23* (5A):43-48, March of Dimes Birth Defects Foundation, 1988.
88. Sullivan, L. W., "Risks of Sickle-Cell Trait: Caution and Common Sense,' New *England Journal of Medicine* 317:830-831, *1987.*
89. Sutherland, G. R., 'Fragile Sites on Human Chromosomes: Demonstration of Their Dependence on the Type of Tissue Culture Medium," *Science 197:25-26, 1977.*
90. Sutherland, G. R., Gedeon, A., Kornman, L., et al., "Prenatal Diagnosis of Fragile X Syndrome by Direct Detection of the Unstable DNA Sequence," *New England Journal of Medicine* 325: *1720-1721, 1991.*
91. ten Kate, L. P., and Tijmstra, T., ''Carrier Screening for Tay-Sachs Disease and Cystic Fibrosis,' *Lancet* 336:1527-1528, 1990.
92. Thompson, J. S., and Thompson, M. W., *Genetics in Medicine* (Philadelphia, PA: W.B. Saunders Co., 1980).
93. Tocci, P. M., "Seven Years Experience With Tay-Sachs Screening in Florida,' *Journal of the Florida Medical Association* 68:24-29, 1981.
94. Triggs-Raine, B. L., Feigenbaum, A. S. J., Natowicz, M., et al., "Screening for Carriers of Tay-Sachs Disease Among Ashkenazic Jews: A Comparison of DNA-Based and Enzyme-Based Tests,' New *England Journal of Medicine* 323:6-12, 1990.
95. Tymstra, T., "Prenatal Diagnosis, Prenatal Screening, and the Rise of the Tentative Pregnancy, " *International Journal of Technology Assessment in Health Care* 7:509-516, *1991.*
96. Valverde, K. D., Cystic Fibrosis Center, St. Vincent Hospital and Medical Center, New York, NY, personal communication, December 1991.
97. Vecht, J., Zeigler, M., Segal, M., et al., "Tay-Sachs Disease Among Moroccan Jews,' *Israel Journal of Medical Science* 19:67-69, *1983.*
98. Wang, S., Wang, L., and Zhang, B., "A Survey of Hb Bart in Cord Blood and the α-Globin Gene in South China," *Birth Defects: Original Article Series 23 (5* A):23-30, March of Dimes Birth Defects Foundation, 1988.
99. Watson, E. K., Mayall, E., Chapple, J., et al., ''Screening for Carriers of Cystic Fibrosis Through Primary Health Care Services," *British Medical Journal* 303:504-507, *1991.*
100. Weatherall, D. J., "The Evolution of Thalassemia Screening, ' *American Journal of Human Genetics* 49(Supp.):79, *1991.*
101. Weatherall, D. J., Clegg, J. B., Higgs, D. R., et al., "The Hemoglobinopathies," *The Metabolic Basis*

of Inherited Disease, C.R. Scriver, A.L. Beaudet, W.S. Sly, et al. (eds.) (New York, NY: McGraw Hill, 1989).

102. Wilfond, B., University of Wisconsin Medical School, Madison, WI, personal communication, December 1991.
103. Willey, A. M., New York State Department of Health, Albany, NY, personal communications, January 1992, May 1992.
104. Yu, S., Pritchard, M., Kremer, E., et al., "Fragile X Genotype Characterized by an Unstable Region of DNA," *Science* 252:1179-1181, *1991.*
105. Yuen, J., and Hsia, YE., "Consumer Attitudes Toward Thalassemia Screening: Heterozygotes of Multi-Ethnic Origin," *American Journal of Human Genetics 49(* Supp.):331, *1991.*
106. Zeesman, S., Clew, C.L., Cartier, L., et al., "A Private View of Heterozygosity: Eight-Year Follow-Up Study on Carriers of the Tay-Sachs Gene Detected by High School Screening in Montreal," *American Journal of Medical Genetics* 18:769-778, *1984.*
107. Zhang, J, Z., Cai, S. P., and Kan, Y. W., "Thalassemia Screening and Prenatal Diagnosis in South China," *American Journal of Human Genetics* 49(Supp.):80, *1991.*