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β-Thalassemia Disease Prevention: Genetic Medicine Applied

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SUMMARY

We report here an evaluation of a program for thalassemia-disease prevention, comprising education, population screening for heterozygotes, and reproductive counseling; the evaluation includes cost analysis. A preprogram survey in 1978 of 3,247 citizens in the high-risk communities (85% were high-school students) showed that 88% favored a program but that only 31% considered fetal diagnosis as an acceptable option. Screening in high school or before marriage was preferred by 56%. In a 25-month period (December 1979–December 1982), we screened 6,748 persons, including 5,117 senior high-school students, using MCV/HbA_2 indices. The participation rate was 80% in the high-school group. The frequency for β-thalassemia heterozygosity was 4.7% with 10-fold variation among ethnic groups at risk; the overall frequency for all variants found was 5.4%. We surveyed 60 carriers and 120 noncarriers after screening high-school students (response rate 77%): most carriers told parents (95%) and friends (67%) the test result; and 38% of the carriers' parents (vs. 18% of the noncarriers' parents) were also screened. Carriers would ascertain their spouses' genotype (91%) and approved uniformly (95%) the high-school screening experience and its goal. We performed 11 fetal diagnoses in a 25-month interval (> 75% participation in target population) either by fetoscopy and globin-chain analysis or by amniocentesis and genomic DNA analysis; two of three affected fetuses were aborted at parental request, there was one spontaneous abortion (after fetoscopy), and seven live births. The at-risk couples claimed pregnancy

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would not be contemplated without the fetal-diagnosis option. We analyzed economic costs of the program: cost per case prevented is ≈$6,700, slightly less than cost-per-patient-treatment-year or about 4% of undiscounted treatment cost incurred in the first 25 years of life for an affected individual. These findings indicate: collective acceptance of the program, appropriate attitudes among carriers, general acceptance and efficacy of fetal diagnosis, and global cost-effectiveness.

INTRODUCTION

β-Thalassemia is one of the most prevalent lethal inherited diseases in the world. It is the homozygous or compound manifestation of several mutations, polymorphic in the aggregate, at the β-globin locus on chromosome 11 [1, 2]. Pathogenesis of disease manifestations begins with deficient production of normal hemoglobin; impaired development, fertility, and longevity are the major consequences of the mutant phenotype in affected persons. At present, there is no cure for the disease, and the available treatment only partially reduces its manifestations. Accordingly, to prevent the impact of β-thalassemia mutations in the population and in families, one is still dependent on carrier detection, genetic counseling, and fetal diagnosis.

The Quebec Network of Genetic Medicine [3] has implemented several programs whose common goal is prediction and prevention of particular Mendelian or multifactorial diseases in the population of the province. One of the Network programs is concerned with β-thalassemia. Whereas the provincial health-care system provides treatment for thalassemia patients, the government and citizens have chosen to give equal priority to prevention of the disease. We report here how that program was implemented. We also document: an evaluation of the screening component of the program; evidence for acceptance of screening by the high-school students who are its principal participants; acceptance and outcome of fetal diagnosis by carrier-couples; and costs of the program. The program reflects recent advances in our knowledge of thalassemia; its impact reflects applications of that knowledge.

MATERIALS AND METHODS

Consultation with Community

The communities at highest risk for thalassemia in Quebec are: Italian (population 225,000); Greek (population 70,000); Asian and Oriental (population ≈40,000), many of its members being very recent immigrants; and a French Canadian deme in which the thalassemia gene, but not the disease, is also present [4]. We consulted two of these communities (Greek and Italian) before implementing the program.

A federal grant (Local Initiative Projects) was obtained and advertised in 1977 to implement the preprogram survey. With persons self-selected from the communities at large, representatives of social and community agencies, and families involved with patients, we designed and implemented an inquiry about: (1) knowledge of thalassemia, its cause, and impact; (2) attitudes toward screening for carriers of the mutation(s); and (3) acceptability of fetal diagnosis in the counseling program. The survey was administered by one of us

(M. B.) to 465 adults and 2,782 high-school students. An audiovisual presentation about the cause, pathogenesis, and natural history of thalassemia preceded a discussion of facts and attitudes; the questionnaire was administered immediately thereafter.

A group of interested citizens comprising parents of patients, adolescents, and young adults with thalassemia disease, health-care personnel, and geneticists organized and legally incorporated the Thalassemia Society of Quebec in 1979. The Society assumed responsibility for initiating the screening and educational components of the program. Technical support for screening, phenotype diagnosis, and fetal diagnosis was implemented by the Quebec Network of Genetic Medicine and hospitals affiliated with McGill University. Treatment of affected patients was provided at the principal pediatric-care centers in the province (Montreal Children's and Ste. Justine Hospitals).

Implementation of the Disease Prevention Program

The program comprised: (1) educational activities, (2) screening for potential carriers (heterozygotes), (3) diagnostic procedures, (4) counseling resources, (5) procedures for fetal diagnosis, (6) outcome evaluation of components (2) and (5), and (6) cost analysis. Community leaders (lay and religious), officials from the School Commissions of Montreal, parents, patients, and organizers met to define the specific objectives, process, and structure of the total program. No initiatives were taken without approval and involvement of representatives from the communities at risk.

Educational materials (letters, pamphlets, and posters) were prepared in five languages (English, French, Greek, Italian, and Chinese); prescreening instructional sessions were offered in the appropriate language to potential participants.

Screening was offered to the communities at large and performed at neighborhood health centers (Centre Local pour de Services Communautaires) beginning in 1979; and, later, focused in high schools (for students 16–17 years of age) beginning in January 1981 (parental consent is not required by students under Quebec Bill 30, Article 36). The screening component of the program was administered from the Montreal Children's Hospital (Medical Genetics Service). All samples were analyzed by standard procedures (see below). Results were recorded on file cards containing pertinent demographic and medical facts submitted by the participants at the time of screening. Diagnostic tests for follow-up investigation of possible iron deficiency or variant hemoglobin phenotype were performed in the hematology laboratories of the Royal Victoria Hospital and the Montreal Children's Hospital.

The result of the screening test was reported to participants by letter in their preferred language in a self-addressed envelope. Results indicating a heterozygous phenotype for β-thalassemia (or other hemoglobinopathy) were interpreted in a covering letter signed by the coordinator and director; this material was the final product of three field trials. Additional explanation was offered, by telephone, 2 weeks later to all carriers. Persons with evidence of iron deficiency or α-thalassemia heterozygosity (mean corpuscular volume [MCV] < 78 femtolitres [fl], HbA_2 3%) were encouraged to seek further diagnostic studies.

Eleven couples in which both partners were heterozygous (carrier couples) received specific counseling about reproductive options; they all requested fetal diagnosis. The latter was performed, by a single team, by amniocentesis at about the 16th week for restriction endonuclease analysis of genomic DNA in cultured amniocytes or by fetoscopy at about the 18th week of pregnancy to obtain a fetal blood sample for analysis of globin chains.

Post-Screening Survey

Evaluation of knowledge and attitudes of high-school students was performed after the screening experience in 1982; we used a questionnaire mailed to 180 persons (60 carriers, 120 noncarriers). We also surveyed the 11 couples who had pursued fetal diagnosis to determine their opinions after the procedure.

Cost Analysis

Costs of thalassemia-prevention services were analyzed and compared with corresponding costs of treatment. Costs were measured in 1981 constant Canadian dollars, using market prices for supplies, equipment, and nonphysician labor and prices set by the Quebec Health Insurance Board for physician services, hospitalization, and diagnostic tests. The identification and measurement of costs followed principles described [5–7].

Analytical Methods

The screening test for β-thalassemia heterozygosity was performed on EDTA-treated blood samples (2–5 ml) obtained by venipuncture from an antecubital vein under minimal stasis. Red blood cell sizing for MCV was performed with a Coulter Counter (Model ZF). Samples with MCV < 78 fl were analyzed further for HbA_2 content on DEAE cellulose columns (Mandel, Montreal); persons with low MCV and $> 3\%$ HbA_2 were classified as β-thalassemia heterozygotes [8]. Persons with a low MCV value and $HbA_2 < 3\%$ were investigated further for iron deficiency or α-thalassemia heterozygosity.

Fetal diagnosis was performed on reticulocytes or amniocytes of the fetus. Reticulocytes were analyzed for γ/β-globin-chain ratio by the method of Congote [9]. Amniocytes were cultured and the genomic DNA isolated and subjected to restriction endonuclease digestion in families with informative DNA polymorphisms. DNA analysis was performed, as described by Boehm et al. [10], in the laboratory of Dr. H. Kazazian, Jr., at Johns Hopkins Hospital, Baltimore.

RESULTS

Pre-Program Survey

The survey was answered voluntarily by people attending information sessions at local community centers and in high schools. Participants (no. = 3,247) supported the concept of a voluntary disease-prevention program: 88% agreed that it should begin as soon as possible; only 5% rejected the proposal. Patients (adolescents and young adults, no. = 6) with thalassemia disease, and their parents, were also consulted; they unanimously supported the concept of a program involving screening, counseling, and fetal diagnosis. One of the patients has participated, subsequently, as an advocate in the high-school screening clinics.

We asked 465 adults (surveyed before the information seminars) whether they were familiar with thalassemia and its significance for health: 61% had never heard of the disease, 30% admitted casual familiarity, and the remainder did not reply. After the information seminars, 90% of respondents (no. = 3,247) appreciated that thalassemia major is a heritable disease associated with severe anemia; 82% were aware that thalassemia minor is of no direct consequence to their own health. The majority of participants (53% of students, 65% of adults) considered the 25% occurrence risk for thalassemia disease in offspring of carrier couples to be "high"; a minority (22% and 4%, respectively) considered it "low." Among the various options proposed for the preferred time of screening, 34% specified the newborn period, 56% preferred the senior high-school years or before marriage, and 6% replied "when ready to have children." The great majority (84%) indicated that they would seek counseling and medical advice if they and their intended spouse were both carriers of the β-thalassemia gene. Fetal diagnosis, with abortion of an affected fetus, was acceptable to 31% and unacceptable to 32%; 30% were uncertain, and the remainder did not reply. Nonetheless, 63%

of all respondents recommended that the intended program should include fetal diagnosis; the remainder would exclude it.

Results of Screening

The voluntary screening component of the program became operative in neighborhood health clinics on December 1, 1979, and in high schools in January 1981. All senior high-school students received a general information session in school hours; in-school screening clinics followed within 1–5 days. Participation rates were below 10% among reproductive-age adults, and 80% or higher for students in the high-risk ethnic groups. Pilot studies preceded the full program [8]. The 25-month period prior to December 31, 1982, was selected to evaluate the outcome of screening.

Ethnic origins of participants, frequencies of heterozygosity, and variant globin phenotypes identified are shown in table 1. The overall frequency of confirmed variants in the screened population (no. = 6,748) was 5.4%; β-thalassemia minor was the major phenotype (4.7%), but heterozygosity for α-thalassemia (0.5%) and other mutations (0.16%) was also found. The major source of participants was the high-school program (table 2); community clinics were much less efficient relative to high schools despite extensive preclinic publicity and apparent awareness of the program in the communities at risk.

A small number of participants (740 or 10.9% of the total) were screened by appointment in our laboratory. Because these persons were not randomly ascertained, we requested the reason for referral. Many were sent by their physician (fig. 1); two other important sources of referral were relatives and the fetal-diagnosis program of the Quebec Network of Genetic Medicine [8]. Among the 139 persons (18.9%) with a variant phenotype identified from these referrals, 32

TABLE 1

FINDINGS IN SCREENING COMPONENT OF THALASSEMIA DISEASE PREVENTION PROGRAM

GEOGRAPHICAL ORIGIN OF PARTICIPANTS OR THEIR FAMILIES	No. PARTICIPANTS	VARIANT PHENOTYPES β-Thal no. (%)	α-Thal no. (%)	Other no. (%)	All no. (%)
Greece	2,447	166 (6.8)	14 (0.6)	7 (0.3)*	187 (7.6)
Italy	3,401	133 (3.9)	7 (0.2)	3 (0.1)†	143 (4.1)
India	71	4 (5.6)	1 (1.4)	· · ·	5 (7.0)
Far-East	171	6 (3.5)	7 (4.3)	1 (0.6)‡	14 (7.6)
Middle East	109	1 (0.9)	3 (2.7)	· · ·	4 (3.7)
Western Europe§	31	1 (3.2)	3 (9.7)	· · ·	4 (12.9)
Portugal	161	1 (0.6)	· · ·	· · ·	1 (0.6)
Spain	62	1 (1.6)	· · ·	· · ·	1 (1.6)
Quebec (French Canada)	68	2 (2.9)	· · ·	· · ·	2 (2.9)
Other	227	5 (2.2)	· · ·	· · ·	5 (2.2)
Total	6,748	320 (4.7)	35 (0.5)	11 (0.16)	366 (5.4)

NOTE: Findings are for the interval December 1, 1979 to December 31, 1982.
* S/C compound (no. = 4); Lepore (no. = 2); δ-β-thalassemia (no. = 1).
† Lepore (no. = 2); δ-β-thalassemia (no. = 1).
‡ Hemoglobin H (no. = 1).
§ Non-Mediterranean European countries.

TABLE 2

THALASSEMIA SCREENING: PARTICIPATION AND FREQUENCY OF VARIANT PHENOTYPES RELATED TO COMPONENT OF PROGRAM

	High-school clinic	Community clinic	Tested at program laboratory	Total
No. participants	5,117	891	740	6,748
No. clinics	44	31	Continuous	75*
Participants per clinic (average)	116	28	...	80†
Carriers identified:				
No.	192	34	140	366
% of screened	3.7	3.8	18.9	5.4

NOTE: For the interval December 1, 1979 to December 31, 1982.
* Total excludes referred persons screened at laboratory.
† Average for clinics only: excludes referrals to laboratory.

stated that they were screened because they had a relative with thalassemia disease or heterozygosity, and 79 persons among the 740 referrals stated that they came for this reason. The revised frequency of variant phenotypes (15.2%), corrected for this referral bias, is still higher than in the general program in high schools and neighborhood clinics (3.8%).

Post-Screening Survey

A questionnaire was distributed by mail to 180 screened Italian and Greek high-school students (60 carriers, 120 noncarriers, equal numbers of males and females in both groups). We selected the student group because of its high rate of participation (80%) in the screening component and the demographic homogeneity relative to other participating groups. We received 139 replies (participation

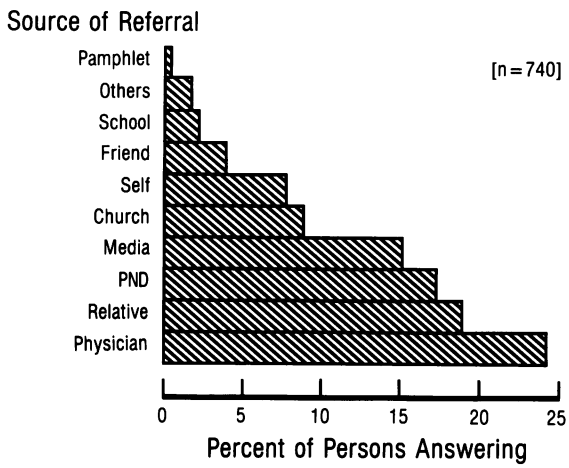

FIG. 1.—Distribution of referral sources indicated by 740 consultands responding to an inquiry about why they came for a screening test at the Medical Center responsible for the thalassemia program. *PND* means referral from prenatal-diagnosis program of the Quebec Network of Genetic Medicine.

rate 77%: males/females, 63/75; rate for carriers: 75%; males/females, 18/25; rate for noncarriers: 78%; males/females, 45/51). Elapsed time between the test experience and reply to the survey was 2–11 months; mean interval 8 months.

Ninety-five percent of carriers and noncarriers alike approved the high-school testing experience (table 3). Carriers were more worried initially by their test result and tended to remain worried relative to noncarriers. Nearly all respondents (95%), both carriers and noncarriers, had discussed the test result with their parents; only 67% of carriers discussed it with friends, whereas 88% of noncarriers did so.

Among the carriers, 89% described no change in self-image, 9% said it was diminished, and 2% said it was improved. Among noncarriers, self-image was unchanged in 75% and increased in 5%; 20% did not reply. About a third of the parents of carriers had been tested (as recommended in the initial letter sent with the test result), whereas only one-sixth of the parents of noncarriers had been tested.

In regard to applying the knowledge gained from the test, 91% of carriers and noncarriers alike would want to know the genotype of their future spouses. Awareness of the medical and genetic significance of heterozygosity was different in carriers and noncarriers. Only a fifth of carriers, but almost half of noncarriers, believed thalassemia minor affected health; the respondents were unsure whether the impact was physical or emotional. Carriers and noncarriers were both ill-informed of the Mendelian probabilities of having an affected child.

TABLE 3

EVALUATION OF SCREENING IMPACT BY POST-SCREENING SURVEY

Information requested*	Carriers (%)†	Noncarriers (%)†
1. Approve high-school screening program?	95	95
2. Worried by test results?		
a. Initially	63	10
b. Now	56	10
3. Discussed result with:		
a. Parents	95	93
b. Friends	67	88
4. Self-image after test result was:		
Unchanged	89	75
Decreased	9	0
Increased	2	5
5. Parents have been tested?		
Fathers	33	18
Mothers	37	18
6. Would want spouse tested?	91	91
7. Thalassemia minor is a disease?	20	47
8. Knowledge of Mendelian probability for disease occurrence was correct?	33	18

* Overall response rate to survey sent after distribution of test results was 77%: comprising 43 carriers (75% response) and 96 noncarriers (78% response); overall sex ratio was 63:75 (M:F) without significant change in subgroups.

† Affirmative answer expected: data in last two columns indicate % of carriers and noncarriers answering affirmatively.

TABLE 4

THALASSEMIA FETAL DIAGNOSIS

1. Participation*: Predicted for region	10–12 couples		
Experience	9 (+2 external) couples		
% of predicted for region	75%–90%		
2. Would you have another pregnancy in absence of fetal diagnosis?†			
	(No.)	Yes	No
a. Carrier couples with affected child	(3)	0	3
b. Carrier couples without affected child	(4)	0	4
c. Naïve couples identified by screening after referral from fetal diagnosis program‡	(1)	0	1
Total	(8)	0	8

* Predicted participation calculated from known carrier frequencies and endogamy rates in high-risk communities.

† Retrospective survey (by mail) after fetal diagnosis: eight of 11 couples replied; the couple with an affected fetus, which did not terminate the pregnancy, did not reply. Respondents are classified according to their awareness of thalassemia.

‡ Referrals were made by the Quebec Network's fetal-diagnosis program [3] for screening of any person at high risk for thalassemia heterozygosity (viz., fig. 1). One carrier couple was identified by this means.

Results of Fetal Diagnosis and Counseling

Population screening began only when fetal diagnosis for thalassemia was available in Quebec. Information about prenatal diagnosis and access to it had been widely disseminated in the educational component of the program. Accordingly, there were referrals for reproductive counseling of carrier couples from the outset of the program—even though Canadian demographic data and vital statistics indicate that carriers of high-school age will generate referrals for family planning only 7 years (mean interval) after they have been screened. The corresponding data for frequency of endogamous marriages and expected fertility of heterozygotes per generation indicate that five or six pregnancies per year are at risk for a fetus affected by thalassemia disease in the referring population(s).

Eleven couples came for fetal diagnosis in the 25-month period reviewed here; two of the 11 couples came from outside the province. Participation in the primary referral region (nine couples from Quebec) was 75%–90% of that anticipated. One additional couple was counseled but did not proceed to fetal diagnosis because of spontaneous abortion in the 10th week.

We evaluated retrospectively the impact of reproductive counseling and fetal diagnosis on behavior and knowledge. A questionnaire was sent to the 11 couples; eight replied. All respondents indicated that their pregnancy was possible and encouraged because prenatal diagnosis was known to be available (table 4).

All couples who had sought counseling accepted, in advance, the voluntary option of fetal diagnosis; outcomes of the procedures and the pregnancies are summarized in figure 2. Three affected fetuses were diagnosed (one by globin analysis; two by genomic DNA analysis). Two of the affected pregnancies were terminated by request of the parents and confirmed by appropriate tests. One couple decided to continue the pregnancy; the infant, born at term, was unavailable

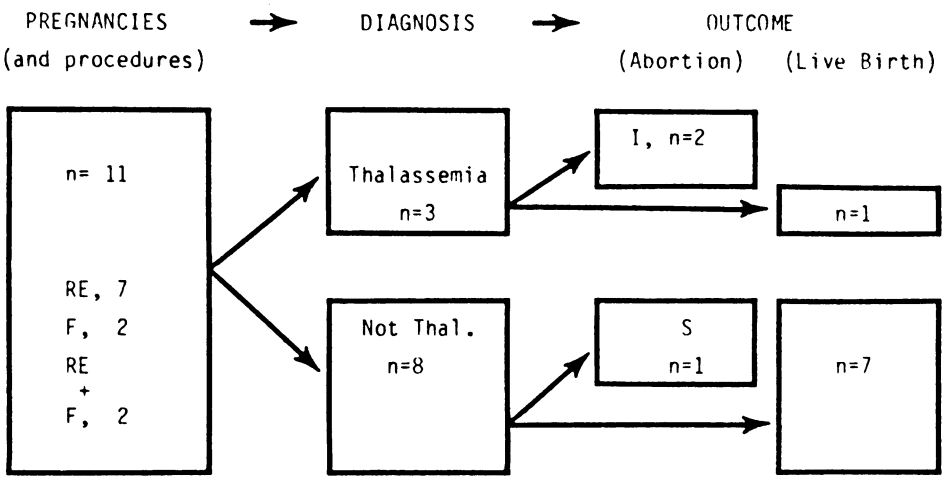

FIG. 2.—A description of activity in the fetal-diagnosis component of the thalassemia-disease prevention program. Abbreviations: *RE*, restriction endonuclease analysis of genomic DNA obtained by amniocentesis; *F*, fetoscopy followed by analysis of globin chains in fetal reticulocytes; *I*, induced abortion; *S*, spontaneous abortion.

for follow-up evaluation. Of the remaining eight pregnancies, one ended in miscarriage after fetoscopy with diagnosis of a nonaffected fetus; the other seven pregnancies, in which fetal diagnosis indicated absence of thalassemia disease, have gone to term with the birth of a healthy infant (no. = 7). One offspring is known to be a carrier, one is not, and the remainder await classification; none has thalassemia disease.

Cost-Analysis of Program

The formal economic analysis of the program is described in detail in [11]. We summarize here the comparative costs of heterozygote screening, fetal diagnosis, and treatment of thalassemia disease (table 5). Since the thalassemia program is offered within the pre-existing services of the Quebec Network of Genetic Medicine and the health-care system, it incurs fewer costs for equipment and labor than if it had been implemented independently. We measured only the costs of the extra demand put on existing facilities resulting from the additional services for thalassemia prevention and treatment.

The costs of carrier screening, based on a sample of 3,550 persons, were measured in 1981. The annual cost for screening was $26,648. Assuming an overall heterozygote frequency of 5.4% (viz., table 1), the cost per carrier identified is $139.

Costs for fetal diagnosis by fetoscopy with globin analysis or by amniocentesis with DNA analysis were analyzed separately (table 5). Costs for fetal diagnosis by DNA analysis were calculated for the fetus at risk, meaning that all costs of studying the family to demonstrate Mendelian segregation of an informative restriction fragment length polymorphism were included. Diagnosis by fetoscopy and globin analysis or by amniocentesis and DNA analysis were comparable in

cost. We assumed that four pregnancies are monitored (on average) per case of thalassemia identified and that the two carrier parents were identified by screening. Accordingly, the total cost per case prevented was $6,754 when fetal diagnosis required fetoscopy with globin analysis, and $6,638 with amniocentesis and DNA analysis; the difference in comparative costs per case prevented is trivial.

Costs for treatment of thalassemia were also measured (table 5); 42 patients are enrolled in the program at the time. Cost data include all medical examinations, diagnostic and surveillance tests, transfusions, and chelation therapy. The cost per case prevented is slightly less than the average cost of a single year of treatment for individuals with homozygous thalassemia; or about 4% of the undiscounted total treatment costs incurred in the first 25 years of life for an affected individual.

DISCUSSION

Cause and pathogenesis of β-thalassemia are now known in detail [1, 2, 12, 13]. Yet, its clinical manifestations persist despite substantive improvements in therapy [1, 12]: there is persistent impairment of β-globin synthesis, disability attached to deficient hemoglobin function, and severe handicap to patients because of the inability to attain normal lifestyle or life expectancy. Accordingly, efforts to prevent the disease have become equal in importance to advances in treatment in populations where thalassemia is prevalent [13].

TABLE 5

COST ANALYSIS (1981 CANADIAN DOLLARS)

1. Screening:	
a. Supplies	4,076
b. Education	623
c. Labor	21,909
Annual total	26,648
Cost per carrier found	139
2. Fetal Diagnosis (cost per case)*:	
a. Fetoscopy/globin analysis	1,619
b. Amniocentesis/DNA analysis	1,590
Average cost per fetal case found:	
Method a	6,754
Method b	6,638
3. Treatment:	
a. Nonrecurrent (initial diagnosis, pump, etc.)	4,600
b. Maintenance (transfusion, chelation, etc.)	7,057
c. 25-year costs [a + (b × 25)]	176,426
4. Cost effectiveness:	
Annual—per case prevented	≈ 1-yr treatment
Lifetime—per case prevented	≈ 4% lifetime costs†

* Includes costs per carrier found (both parents) and costs for monitoring four pregnancies assuming one in four occurrence rate for an affected fetus.

† Since the life expectancy of homozygotes is uncertain, the cost of treatment for only the first 25 years of life is measured. This assumed a minimum estimate of the lifetime treatment cost, since chelation therapy, started early in life, is improving the survival of individuals with transfusion-dependent beta-thalassemia [12].

Explanations of cause (inherited mutation) lead to a concern about the probability of an individual being a carrier for the thalassemia allele(s) and the risk that carrier-couples will have an affected child. Genetic screening (for carriers) converts the probability statement (the infant has x% chance of being a carrier) into a statement of fact that the person is a carrier, or is not; fetal diagnosis (for carrier-couples) converts a probability statement (the couple has a 25% chance of having an outcome of thalassemia disease with each pregnancy) into a statement of fact that the fetus has the disease, or it does not.

One goal of genetic screening is to counsel persons about their reproductive options so that they can avoid the consequences of passing on a harmful mutation [14]. Thalassemia screening identifies asymptomatic heterozygotes so that carrier couples can be counseled. Screening of populations at increased risk for thalassemia disease is feasible when voluntary options for fetal diagnosis and selective abortion of an affected fetus are available. A beneficial effect of carrier screening and fetal diagnosis on the incidence of thalassemia disease in the population and on the fertility of carrier couples has been documented for homogeneous European/Mediterranean communities in which β-thalassemia is one of the most common diseases in prereproductive life [13]. We introduced our program for thalassemia disease prevention to a large cosmopolitan North American community where ethnic subgroups at high risk were identifiable. We show here that such a program can be supported in the appropriate milieu of medical care, is accepted by the populations at risk, and is effective in reducing the disease burden at a cost advantage.

Motulsky [15] outlined pitfalls and defined goals of thalassemia screening. To avert the potential criticism that our program was imposed upon the communities at risk, consultation with a large sample of its members was held first and representative community leaders and affected families were then involved in planning the program. This aspect of the program's development is described in some detail, because, in a society that provides universal medical care, as is the case in Quebec, it may seem that health care is dictated by the agency (government) that pays the cost. Our approach recognized that disease content (character) defines need and thus the structure of health care [16]; it was with the aid of citizens that we defined the need and developed the structure to meet that need.

The primary objective of the screening component in our program was to identify carriers of β-thalassemia alleles. The screening method is conventional [12], and it has a low error rate (≈ 0.001) in classification of individuals [8]. Diagnostic services were integrated with the screening process to confirm variant phenotypes. Specific knowledge of allele frequencies permitted estimates of thalassemia-disease incidence in our community, when adjusted for demographic factors. This allowed us to plan resources to cope with counseling and fetal diagnosis and to carry out a cost analysis on the impact of the program. The organizational structure of our program accommodates recommendations on genetic screening offered by the National Academy of Science [14].

Our program emphasizes screening of senior high-school students. A precedent for this preference is found both in a recommendation by Motulsky [15] and in

our parallel experience with Tay-Sachs screening in Quebec. Outcome evaluations of the latter program near the time of screening [17] and again 8 years later [18] both clearly indicated that high-school students tolerate and approve of the screening experience. Participation rates in the screening component of the thalassemia program were much higher in the high-school population relative to the global community (table 2), as was the case in the Tay-Sachs program [17–19]. Accordingly, the efficiency of screening was improved by focusing this component on high-school students.

About 11% of the screened consultands in the thalassemia program were seen by direct referral to our medical center. This novel group of participants have no counterpart in the parallel Tay-Sachs program. In the latter, we observed a low rate of referral by physicians in the early days of the program [19]; this phenomenon persists still. On the other hand, physicians are a significant source of referrals to the thalassemia program (fig. 1). We have not yet discerned why this is the case. Our approach to the communities at risk and their medical practitioners has been similar in both programs.

The post-screening survey of students in the thalassemia program (table 3) was modeled after an earlier survey of students in the Tay-Sachs program [17]. In both programs, we discerned more initial anxiety among persons classified as carriers relative to noncarriers of the mutant allele; screening also had some impact on self-image. There is an opinion that anxiety among heterozygotes is an unacceptable cost of screening. On the other hand, follow-up studies in the parallel Tay-Sachs program [18] show that the anxiety of carriers dissipates with time, and the information gained by screening is applied in a positive manner to deal with the risk of having an affected child.

There is some evidence that carrier-students possess more accurate knowledge about the medical and genetic facts of thalassemia than do noncarriers. But in this program, as in the Tay-Sachs program, it is also apparent that the screening experience was not, in itself, a universal source of knowledge. All one can say is that both programs are more effective than any earlier attempts in our community to educate some young people on some health-related issues of human genetics and that continued and greater efforts directed at the high-school cohort in the population could enhance public awareness of the larger issues and may reduce the inappropriate stigma attached to genetic heterozygosity [20].

The high participation rate in the screening program (80% for high-school students) would not be laudable if the consequences of carrier ascertainment were disadaptive to these persons. Rowley et al. [21] found that the act of being screened and counseled significantly increased learning by carriers about thalassemia and had beneficial effects on their behavior. Mounzouras et al. [22] also found that screening leads to awareness of thalassemia and increases knowledge. Barrai and Vullo [23] showed that knowledge of status does not modify random marriage patterns in Italians. Lastly, Silvestroni et al. [24] found that high-school screening was acceptable to Italians and reached about 75% of those eligible. In our follow-up study in the parallel Tay-Sachs program [18], we found no evidence for disadaptive behavior in couples when one or both partners were heterozygous.

We have no corresponding long-term follow-up study of thalassemia heterozygotes, but we do have information on 11 carrier couples counseled in our program.

Our calculations indicate that the program is also reaching 75% or more of the couples in the population at risk for having offspring with thalassemia diseases. Such efficiency at identifying carrier couples might preclude the need for population screening, as is the case in some other thalassemia programs in homogeneous populations [12, 13, 25, 26]; however, because we are working with a cosmopolitan community, we would not abandon population screening.

With regard to the couples who sought reproductive counseling and fetal diagnosis, four facts emerge (table 4; fig. 2): first, the availability of fetal diagnosis was a stimulus for these couples to have children; second, all participating couples took the option of fetal diagnosis even though the pre-program survey implied that fewer than two-thirds might do so; third, access to fetal diagnosis reduced the incidence of thalassemia disease; and fourth, one couple with an affected fetus did not terminate the pregnancy, indicating that consultands can practice voluntary choice. Our findings corroborate other studies documenting the beneficial effects of access to fetal diagnosis on fertility in couples at risk for thalassemia [27, 28], and on the incidence of thalassemia disease in the population [26–29].

The manner by which the fetal phenotype was ascertained in our program is of interest. In nine of the 11 couples, there was an informative DNA polymorphism permitting amniocentesis as opposed to fetoscopy. This frequency of DNA polymorphism at the β-globin locus (82%) is similar to that reported by Boehm et al. [10] in other North American thalassemic populations. On the other hand, fetoscopy was actually required in four pregnancies in our program: in two for lack of an informative DNA polymorphism and in two as a back-up procedure because of delay in the DNA analysis. This experience indicates that thalassemia programs are likely to have a continuing need for fetoscopy until direct analysis of DNA can uniformly reveal thalassemia mutations in the genome of amniocytes or chorionic villus cells.

We did not attempt a cost-benefit analysis of the program [7]; we compared only the costs of disease prevention by screening and fetal diagnosis with the corresponding costs for treatment of disease (cost-effectiveness analysis). Our thalassemia-disease prevention program is cost effective. Cost-effectiveness is an important determinant of what programs are implemented (or continued) in the health-care system of Quebec. Accordingly, sensitivity analysis [7] of cost data is important to indicate their true meaning. This analysis was performed [11] at various rates of endogamy, fertility, and discounting for economic inflation. We found an unfavorable (< 1.0) cost ratio (avoided:incurred) only at a very high discount rate (8% per annum) and at lower levels of endogamy and fertility than is the case now.

Diagnosis and treatment of affected patients have not been neglected in the program. Both continue; only the goals have changed. We recognize that, in time, thalassemia-disease prevention could be incorporated into primary health care [30]. In the meantime, the community has decided to implement prevention as a parallel activity; in time, frequency (all cases) and costs of thalassemia disease will fall as incidence (new cases) declines.

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