dies. Such patients presumably benefit from seeing a doctor because he listens sympathetically to their words and then consoles and reassures them. This exercise of what might be called the art of medicine has probably not improved since 1912; indeed, social changes and the ascendancy of technology have probably impaired it. Hence, one's evaluation of Henderson's maxim depends to a considerable extent on one's definition of "benefit." If the whole spectrum of medical care is included, ranging from a pat on the back to transplantation of the heart, it is doubtful that the benefit-harm ratio of personalized medical care has changed appreciably over the last 100 years. If, however, attention is focused on certain serious organic diseases—infectious, metabolic, and even malignant—then the contribution of science and technology to modern medicine have been truly wondrous. If the patient of 1978 has the right disease, and consults the right physician with the right scientific knowledge and the right technical skills, there can be no doubt that his chances for improvement by far exceed those of a similar patient two-thirds of a century ago.

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Genetics and Medicine: An Evolving Relationship

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Mendel identified the factors we know as genes and Darwin realized the biological importance of natural selection in biological evolution, but it was the physician A. E. Garrod who revealed the relevance of their concepts for our view of health and disease (*1*). Garrod was the first to describe Mendelian inheritance of a human disease (*2*), and he introduced the term "inborn error of metabolism" to encompass the now well-established generalization that a gene exerts its effect upon a component of metabolism by directing the synthesis of the enzyme that controls it. Garrod also believed that the inborn errors were only extreme examples of a pervasive human biochemical individuality, and he recognized not only the likelihood of "private" susceptibility for a particular illness in specific individuals but also the implications for treatment and prevention offered by this concept.

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Extent of Human Genetic Variation

Along with the exponential growth in knowledge of the inborn errors of metabolism since Garrod's time (*3*) has come the realization that each human gene locus brought to our attention by such disorders possesses a variety of mutant alleles, or alternate forms of the gene (*4*). Nowhere has this been made more apparent than in the case of the α- and β-globin genes (*5*). Such knowledge is of great practical relevance for the physician and medical geneticist because it implies that medical treatment of individual patients with such Mendelian disorders must be titrated to the requirements set upon them by their particular mutations. By analogy with the hemoglobinopathies and the inborn errors of metabolism, mutational heterogeneity should exist in most if not all other human genes, and, indeed, that is the case. Surveys in human populations of 104 genes coding for enzyme structure reveal that 32 percent are polymorphic in one or more major ethnic groups (*6*). From the observed prevalence of polymorphic genes, it is estimated that the average heterozygosity per human gene locus is at least 6.3 percent; that is to say any single person is likely to be heterozygous at no less than 6 percent of his or her structural genes. This means that, with the exception of monozygotic twins, no two individuals are alike in their metabolic machinery. Each person is adjusted in a different manner to the universal environment. Everyone has a different and relative state of health.

Genetic Versus Medical Paradigms of Health and Disease

Familiarity with the extent of human genetic variability encourages one to propose a genetic paradigm of health and disease (*7, 8*) such that health is viewed as a state of equilibrium and disease as disequilibrium in the relationship between organism and environment (Fig. 1). Any biological function involves both matter and energy for which it is ultimately dependent on the environment; the interaction between environment and function is controlled by a gene product. The interaction is normally in equilibrium; disequilibrium results either when the environmental component is changed significantly or when the gene product is modified by mutation. The genetic paradigm recognizes the role of intrinsic (genetic) factors for individual homeostasis and susceptibility or resistance to disease; the medical paradigm emphasizes the importance of extrinsic (environmental) factors in the etiology of disease. Because individuals have their own genetic signature, it follows from the genetic paradigm that each person is at his or her own specific risk for a particular disease. This is quite different from the medical paradigm which views all persons as if they were at equivalent risk.

The genetic paradigm also views disease as a spectrum (Fig. 2). The position

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of a particular illness on the spectrum is relevant in the planning of its prevention and treatment. At one end are conditions in which the effects of the mutation are always apparent in the universal environment. The symptomatic chromosomal mutations and a great many of the Mendelian disorders fall in this region of the spectrum (*9*). Toward the middle are diseases in which the expression of a particular gene, or genes, in a specific environment is responsible for illness. The pharmacogenetic disorders and the so-called multifactorial diseases have this character. At the other end of the spectrum are diseases whose origins lie in the interaction of specific environment with universal genotype.

The traditional medical paradigm is effective in preventing and curing disease when the environment plays the primary role in pathogenesis. Thus, nutritional deficiency and infections have been controlled by combating the cause (public health) or by mobilizing a cure (therapeutics). As a consequence, diseases in which a genetic component is prominent are now on the ascendancy, and their control will require a different approach.

Summary. The rapid expansion of knowledge in human and medical genetics has revealed at least 6 percent average heterozygosity per structural gene locus, in excess of 2300 Mendelian (single gene) variants and several hundred chromosomal variants in man. This means that with the exception of monozygous twins, no two individuals are alike in their phenotype. Therefore, each person has a relative state of health, and genetic factors contribute significantly to disease. The ubiquity of genetic diversity requires the development of services for genetic screening, diagnosis,and counseling to prevent and treat a major portion of disease in modern society. Specific programs in Quebec and Canada illustrate how individuals and populations can be served by such services. Better education of citizens and health professionals in human genetics is essential for the further improvement of genetics services in society.

Prevalence of Genetic Disease

Human disease with a genetic component is now quite prevalent in developed countries. Frequency varies with geographic region and ethnic group, but the following general estimates are not unreasonable. Chromosomal mutations occur in about five of every ten spontaneously aborted fetuses, in about 5 percent of stillbirths and of infants dying within 7 days of birth, in about 5 per 1000 surviving live births (*10*); about 10 percent of live-born infants have some form of genetic variation that could be responsible for handicap during the person's lifetime (*11*); approximately 12 percent of pediatric hospital admissions are for single gene, chromosomal or multifactorial disease; another 18 percent are for multifactorial congenital malformation (*12*); and at least 12 percent of adult hospital admissions reflect disease with a significant genetic component (*13*). Among those with severe mental retardation, 15 percent of diagnoses are Mendelian and 45 percent reflect a genetic component (*14*).

Because of founder effects, selection, or genetic drift, particular Mendelian conditions may occur at unusually high frequency in specific ethnic groups (*15*) —for example, porphyria variegata (Afrikaaner), hereditary tyrosinemia (French Canadian), sickle cell anemia (West African Negro), β-thalassemia (Greek and Italian), cystic fibrosis (West European), Tay-Sachs disease (Ashkenazi Jew), congenital nephrosis (Finn), Ellis-Van Creveld syndrome (Amish), and α-thalassemia and glucose-6-phosphate dehydrogenase deficiency (Oriental). Multifactorial congenital malformations also show variation in regional and ethnic frequency (*15*). Age may also confer increased risk for chromosomal nondisjunction in older women and new dominant mutations in older men.

Rationale for Genetics Services

Whereas in the aggregate, disease with a genetic component can form a large portion of the medical care burden, individual patients with specific genetic diagnoses are not numerous in office practice. Of the medical problems seen by the typical American family practitioner, one-half falls under 22 diagnostic headings, and, among those, the genetic problems likely to be encountered are of the complex, multifactorial nature (*16*). That about 550 other diagnoses constitute the balance of the family practitioner's experience, means that close encounters with Mendelian and chromosomal conditions are likely to be infrequent. The prevailing nature of medical practice further hampers provision of appropriate genetic counseling because (i) it is traditionally problem-oriented and episodic and does not encourage development of an extensive family history or of preventive regimens; (ii) the proprietary nature of practice makes it difficult to initiate medical investigation of collateral relatives under the care of other practitioners; and (iii) the prevalent specialization among practitioners constrains the broad view of genetic problems that, by their nature, cut across typological boundaries (*8*).

The larger objective of all genetic services is to reduce the burden and cost of genetic disease both in the individual and in society (*15, 17*). To reach this goal an organizational structure that serves several specific objectives is required (Fig. 3). In their simplest terms, the components of the program are genetic screening; patient retrieval; diagnosis; and counseling, treatment, and follow-up. Intake of patients into the program will occur by two routes: through organized programs of genetic screening (*18, 19*) and through individual referrals for medical diagnosis and genetic counseling (*20*). Genetic screening has three major objectives (*18, 19*): (i) to provide opportunities for medical intervention (treatment), (ii) to provide opportunities for counseling about reproductive options, and (iii) to collect research data pertinent to public health policy and basic knowledge. Genetic counseling (*20*) is a communication process that attempts to help an individual or family to comprehend medical facts, to appreciate how heredity contributes to the disorder, to understand the options for dealing with recurrence risks, to act upon these options in a manner appropriate for the counselee, and to make the best possible adjustment to the presence or risk of the disorder in themselves, their offspring, or other family members.

There is no single program now in existence that achieves all the goals of "genetic medicine." Moreover, it has been observed that the success of the screening component of genetic services is related to the prevailing health care system (*18, 19*). In that context, we now describe some of the Canadian experiences with genetic services and its attempts to prevent and modify the expression of potentially harmful mutations among citizens in our society.

The Canadian Experience: Overview

Canada, a nation of about 24 million persons in 3.8 million square miles, has a federal parliamentary system of govern-

ment replicated at the level of its ten provinces. Canada also has universal health care insurance. Health care is a provincial responsibility (except in the Northwest Territories), whose costs are shared by federal and provincial governments.

Government-sponsored resources exist in Canada for screening, diagnosis, counseling, and treatment of hereditary metabolic disease in particular, and genetic disease in general (*18, 21*). These programs have emphasized hereditary metabolic disease—because it was a practical activity with which to begin the development of genetic services programs—and they must be viewed only as a model experience for the much greater effort that will be required to cope with the full spectrum of genetically influenced disease.

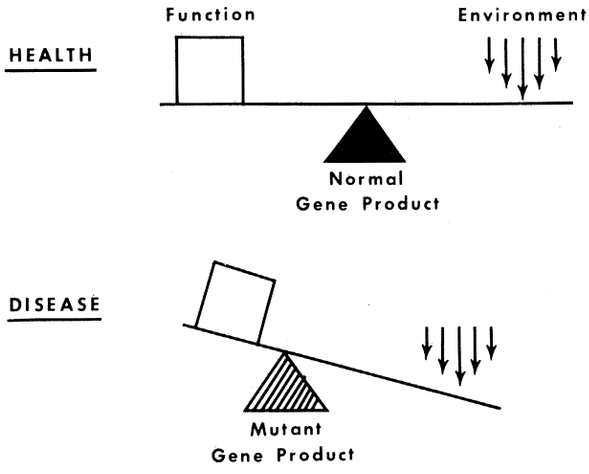

Fig. 1. Health seen as a state of equilibrium between organism and environment; and disease, as disequilibrium. The "fulcrum" for interaction between environmental events and a particular biological function is a gene product (for example, an enzyme). Mutation can modify the enzyme ("fulcrum") and thus the interaction.

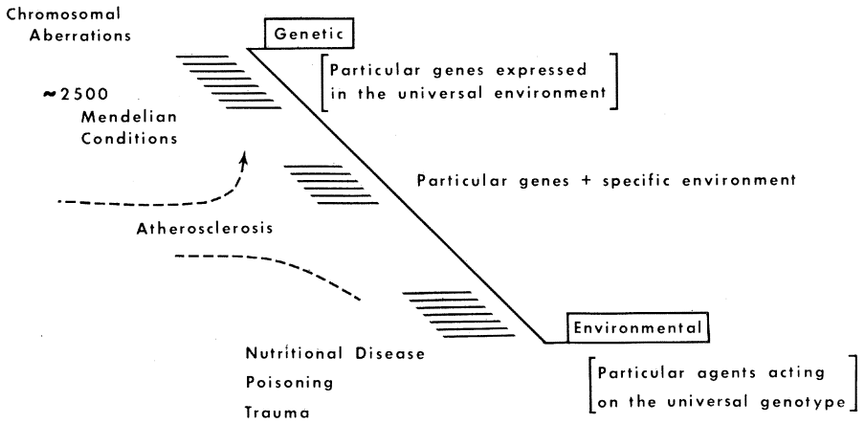

Fig. 2. A spectrum of diseases—from those in which genetic (intrinsic) factors are more important in their pathogenesis to those in which environmental (extrinsic) factors are more important. When intrinsic and extrinsic factors coexist more or less equally (midspectrum), the multifactorial "common" diseases are usually encountered.

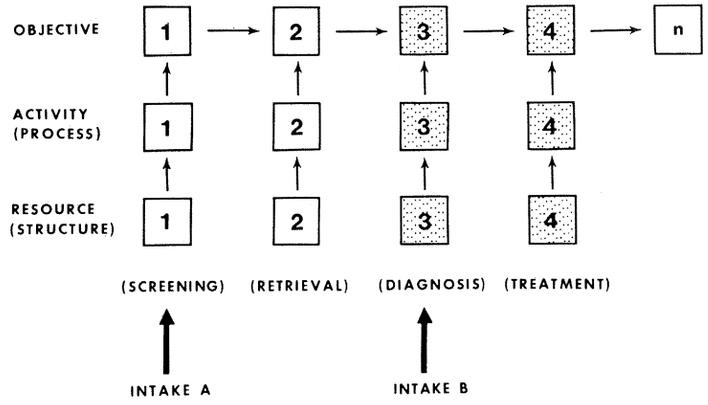

Fig. 3. Organization of health care services whose objective is to reduce cost and burden of genetic disease among individuals or populations. Intakes A and B indicate the entry of patients through genetic screening (with follow-up) or counseling (with diagnosis). Stippling indicates objectives performed customarily at medical genetics centers.

Of the ten provinces, all but one have mass screening programs to detect inherited metabolic disease in the newborn for purposes of medical intervention. The testing procedure is customarily centralized within a single regional laboratory, but 25 percent of screening tests in one densely populated region of the country (Ontario) are carried out at local institutions. In most provinces, the programs are directed toward finding of cases of hyperphenylalaninemia; some programs provide multiphasic screening, sometimes at several postnatal ages. The average compliance rate in the provincial programs for the screening of the newborn is 94.9 percent, with a range of 83 percent to more than 99 percent. Participation in all programs is voluntary.

Only two provinces officially sponsor heterozygote screening for the purpose of reproductive counseling; these programs are for Tay-Sachs carrier detection. Prenatal diagnosis is nonetheless offered at several genetic centers across the country. Evaluation of the risks and benefits has been performed through an interprovincial cooperative study including all centers, under the administrative sponsorship of a federal committee (*22*).

All provinces have regional facilities for confirmatory diagnosis of patients detected by screening (Fig. 3, intake A) and for those referred for specific genetic counseling (Fig. 3, intake B). These are largely located at 16 medical centers across the nation.

Genetic counseling resources are of two types: (i) individuals skilled in the full spectrum of medical genetic counseling, and (ii) persons who, by experience or by preference, restrict their efforts to specific subgroups of genetic disease. In some regions of the country, there is an additional systematized program in which trained allied health personnel are used under the authority of the regional genetic referral center. No province meets the World Health Organization recommendation of at least five professional genetic counselors per million population (*15*).

Services for treatment are less uniformly established than those for screening. Only one province (Quebec) has a broadly structured treatment program with emphasis on ambulatory care for patients; others limit their support to the provision of a low-phenylalanine diet

product for treatment of phenylketonuria. Two provinces (Alberta and British Columbia) maintain registries of handicapping disease, and these registries serve as resources for the planning of services for patients with genetic disease of all types (*23*).

Special interprovincial activities include (i) typing of blood groups and mutational variants of enzyme activity (*24*), (ii) banking of mutant somatic cell lines, and (iii) banking of specific treatment products for the management of hereditary metabolic diseases.

Quebec Network for Genetic Medicine

The Quebec program provides genetic screening, diagnosis, counseling, and treatment for a number of the conditions, about 30, that fall at the "genetic" end of the disease spectrum (Fig. 2). The organization of the program is consistent with the concept that a series of structures is required to serve the various objectives (Fig. 3).

The network (*17, 18, 19, 25*) is operated by four university medical schools (Laval, McGill, Montreal, and Sherbrooke) on behalf of the provincial Ministry of Social Affairs (equivalent to the Ministry of Health and Welfare). A working committee with two representatives from the government and two from each university directs this program. An annual inclusive budget is awarded to the network by the Ministry.

The network has three working principles. The participation by the citizens is voluntary; communication between regional centers, the network laboratories patients, and their physicians is encouraged; and ongoing research and development (pilot studies) precedes the development of new services and is also used to evaluate those components of the program that should be maintained or altered.

The program came into being in 1969 as a demonstration project at the request of the heads of the four pediatric departments of the respective universities. While it is significant that the universities and the government were in accord on this plan, it is also important to recognize that the actual events came about through the actions of a few individuals who were determined that a genetic program would materialize and be cost-effective (*25*). The demonstration project utilized information obtained from a feasibility study that involved 40,000 families in screening of the newborns for medical intervention (*26*).

Special problems were then selected for research and development while the mass screening component of the program was being initiated and evaluated; they were hereditary tyrosinemia among French Canadians (*27*) and the role of allied health personnel in the ambulatory care of patients with hereditary metabolic disease (*28*). The outcome of the demonstration project and research and development activities encouraged the Minister to create the Quebec Network of Genetic Medicine in 1972. While the insight and wisdom of Claude Castonguay, the Minister of Social Affairs at the time, were crucial factors in this new development, subsequent ministers have continued to give their strong support to the network.

Several important structural components characterize the network (*17, 25*).

1) All biochemical testing for mass screening is centralized at two laboratories located at the University Medical Centers—one for screening of blood spots collected on filter paper, the other for screening of urine collected on filter paper. Statistical methods to evaluate secular trends in quantitative phenotype distributions are used (for example, seasonal variation in phenylalanine content of blood spots) so that maximum specificity and sensitivity are maintained in the screening process. Centralization is particularly important in the component of the program screening for congenital hypothyroidism (*29*).

2) Rapid follow-up of positive screening tests was made possible by a negotiated arrangement between the network and the Professional Corporation of Physicians. It was agreed that the central laboratories would communicate directly with patients through the regional centers; as a result, delay in follow-up is minimal and retrieval efficiency approaches 100 percent.

3) Confirmation of positive screening tests and interpretation of diagnostic tests are confined to the four regional centers.

4) Counseling and treatment, if indicated, is carried out at the regional centers in consultation with the patients' physicians, who maintain the responsibility for all other medical acts performed on their patients. The costs of treatment and monitoring are covered by the network.

The acceptability of these arrangements is reflected in performance and attitudes. A survey of mothers revealed virtually unanimous approval for preventive screening as it is practiced in the program. Urine screening, which requires collection of a sample by the mother from the infant on the 14th day of life in the home, is carried out in 85 percent of the 95,000 annual births. Physician support of the program is positive and widespread.

The design of the Quebec program has allowed flexibility in its operation. For example, the original programs for screening the newborn provided for assays of phenylalanine and tyrosine on filter-paper blood samples; to this panel of tests, blood galactose screening was later added at marginal cost. However, when galactosemia screening proved to be inefficient (less than one case per 120,000 live births), this test was replaced by blood screening for low levels of thyroxine (T_4) after a pilot study of the network revealed the feasibility of this procedure. Screening for T_4, coupled to a backup assay for thyrotropin in the sample (*29*), is now yielding about one case per 5900 live births, and preliminary evidence that early diagnosis and treatment of the various forms of congenital hypothyroidism is highly beneficial.

The network has also initiated several high-risk screening projects to provide the opportunity for genetic counseling about reproductive options. Screening for Tay-Sachs carriers began as a pilot study in 1971 and became an official ongoing program soon afterward; it serves both the Ashkenazi (*30*) and French Canadian communities (*31*) in the province. Screening for Tay-Sachs carriers in the Jewish community has recently been shifted to the high schools (*32*) where the participation rate is 75 percent compared to 15 percent when the program was operated in the community at large (*30, 32*).

Prenatal diagnosis for a variety of metabolic and chromosomal abnormalities is provided by the network. The recommendations of the National Committee on Prenatal Diagnosis (*22*) are followed, and the facilities for the Quebec programs are confined to two of the regional centers. The provincial government is now defining a policy for expansion of this activity. In the meantime research and development of fetoscopy and analysis of β-globin chains in fetal reticulocytes is under way, so that the appropriate screening and counseling programs for β-thalassemia and sickle cell carriers can be offered to the Italian, Greek, and Black communities in the province. The development of reliable screening tests, in which two-test discrimination is used (*33*), for carriers of the Tay-Sachs and β-thalassemic genes was an outgrowth of network research activity.

The budget for the network is now $625,000 per year for a population of 6

million; blood and urine screening of the newborn, communications, computerized data storage and statistical analysis, diagnosis and treatment, and the high-risk screening activities are all included in the annual budget; a mutant cell repository and four traineeships in medical genetics are also supported from the budget. In contrast, salaries of the medical and genetic professionals are the responsibility of the universities, whereas regional health units that incidentally assist inpatient follow-up are funded separately by the Ministry.

Network Activities Outside the Province

Whereas the genetic services described above are an intraprovincial activity, three programs originating in the network have achieved a wider impact.

1) *The eastern Arctic program.* Surveillance by blood screening of the newborn Inuit in the eastern portion of the Canadian Arctic was initiated in 1970 by agreement with the Federal Department of Northern Affairs, and the highest recorded incidence of neonatal tyrosinemia in the world was discovered. The cause of Inuit neonatal tyrosinemia is still under investigation (*34*), but it is likely that the finding reflects an ethnic (hereditary) characteristic, possibly a polymorphism in the Eskimo.

2) *A national "food bank" for genetic patients.* Experience with dietary treatment and, in particular, with the distribution of special diets through its regional centers, led to the development of a National Food Distribution Center for the Management of Hereditary Metabolic Diseases in Canada (*35*). The national "food bank" was established in 1974 under the authority of the Federal Food and Drug Directorate by the following actions: (i) treatment diets were classified as foods by the Directorate; (ii) 16 regional treatment centers were appointed across the nation; (iii) a nonprofit distribution center was established in Montreal under the management of a patron with experience in food merchandising, and it assumed the responsibility for importation of diet products and their distribution to accredited centers. Operating costs of the center are shared by federal government and the patron. The food bank network of centers ensures regional availability of special diet products for the treatment of patients with any of many forms of hereditary metabolic disease. It has also encouraged rapid exchange and development of new information.

3) *A repository of mutant cell lines.* The proliferation of somatic cell culture methods has enhanced the diagnosis and investigation of many monogenic and chromosomal conditions of man. Early in the history of the Quebec network one of its centers began to bank mutant and normal cell lines during the investigation of biochemical mutants. Eventually this activity became formalized as a repository, with its own catalog of cell lines (*36*). Deposits and disbursements are carried on at local, national, and international levels and the "cell bank" is now one of two functional international services.

Professional and Expert Services in Canada

The Quebec experience depends on physicians, medical geneticists, and allied health personnel for implementation of its services. Because the network's focus is still constrained primarily to high-risk and mass screening activities for metabolic disorders, it has been possible to carry out the program effectively with the expertise available at the centers. However, Quebec is not different from any other region when it comes to the larger issues of multifactorial common disease and the great number of monogenic and chromosomal disorders that constitute the major case referrals in medical genetics. Here, as elsewhere, there is a dearth of professional expertise. Furthermore, services for high-risk heterozygote screening, genetic counseling, and prenatal diagnosis reach only a small fraction of those who would benefit from them. If the demand begins to approach the need, a major expansion in both laboratory facilities and trained personnel will be necessary (*15, 17*).

Medical geneticists now look forward to the time when the informed health planner will perceive that improved instruction and education in medical genetics in the curriculum of the health sciences will enhance medical services and health care (*37*). But increased familiarity with the daily commerce of medical genetics in the work of medical practitioners is unlikely to be realized in the near future, that is, until the genetic paradigm of health and disease is an integral part of the medical curriculum, and until license renewal is contingent on continuing education in medical genetics. Accordingly, improvement in the training of medical genetic professionals and allied health personnel is seen as the first step toward better medical genetics practices. A Canadian College of Medical Geneticists was incorporated in November 1975 for this purpose. The college would be unnecessary if any existing organization in Canada recognized medical genetics and geneticists in their own right; none does.

The objectives of the college are to formalize the training programs in which those calling themselves medical geneticists obtain their skills and knowledge, and to ensure the quality of laboratory and counseling services associated with medical genetic services (*38*). The college consists of and represents qualified Ph.D. and M.D. medical geneticists who provide services in Canada. Its various roles in establishing and maintaining professional standards of delivery of health care in the field of medical genetics are perceived as follows: (i) to define "medical genetic centers," (ii) to evaluate centers providing health care services, (iii) to advise governments at various levels on the role of medical geneticists in health care, (iv) to advise government at various levels on the nature and extent of medical services that should be provided, (v) to accredit medical geneticists in possession of the necessary qualifications, and (vi) to evaluate training programs for those professionals who will provide the medical genetic services.

The Canadian college is in its formative years, and the outcome of its activities cannot be evaluated now. It is of interest, though, that an analogous proposal was put forward in 1977 for discussion by the membership of the American Society of Human Genetics.

Public Concern for Medical Genetics

While improved medical genetic services arrive at a halting pace, the public may take matters into its own hands to urge the pace a bit. Malpractice suits will goad us. Public participation on commissions (*39*) will call for better services. But the most certain way to improve the genetic content of health services is to change the consumers' awareness of their own genetic dimensions and the role played by heredity in their own health and disease.

When our own experience in Tay-Sachs carrier screening took us to the high schools (*30, 32*), we became involved with students and their teachers. In the classroom, we found little emphasis on the teachings of Darwin, Mendel, Morgan, or their followers. We discovered that a course in biology is not a requirement for graduation from high school, and that those students who do take biology encounter little human genetics. A survey (*40*) of widely used biology textbooks in Canada reveals that

less than 10 percent of the average text is devoted to genetics and less than half of the examples used to illustrate basic genetic themes have human orientation. Nevertheless, Canadian student preferences clearly favor evolution, genetics, and human biology in contrast to the topics that receive major emphasis in the text and therefore in the classroom. Evaluation of student knowledge revealed surprising and important deficits, such as confusion or ignorance about the difference between a gene and a chromosome, the paternal origin of sex determination, Mendel's laws of inheritance, heritability of common traits, and ethnic diseases that are the subject of frequent media coverage in their own communities. Our students, however, have positive attitudes toward many of the genetic activities they perceive in their own society. They believe that genetic screening is important; they understand the value of prenatal diagnosis in relevant situations; they perceive that genetic heterozygosity could be an origin of disease. Yet, they do not appreciate the prevalence of heterozygosity—even when familiar with the hemoglobin S example—and they do not generally believe that they, as individuals, could possess alleles potentially harmful to themselves or their offspring. These observations have been corroborated, in general, among American students by the Biological Sciences Curriculum Study (BSCS) in another recent survey (*41*).

While our future citizens are not systematically educated in the rudiments of their own biological nature and there is a gap between their interest in, and knowledge of, the basic facts of human heredity, yet they hold very positive attitudes toward applied genetics in society. To respond to these needs, the BSCS group in collaboration with several medical and human geneticists has prepared a set of guidelines for human genetics education at all levels and has put forward an imaginative proposal to form a resource center for human and medical genetics education on the North American continent (*42*).

Conclusion

Science is an international human endeavor, and knowledge and learning belong on the agenda of every nation. At times in history, nations have placed extraordinary value on learning and on the application of knowledge to society. The era of the Great Instauration in England (1626–1660) was one such occasion (*43*). It was in those years that science assumed considerable significance in the affairs of the English nation, and extraordinary advances in medical sciences and their application were made that are with us even now. The present era could be another such occasion. Human dimensions are being perceived in genetic terms as never before, and the effects of genetic variation are being discovered as the root of many illnesses in modern society. Awareness of our own genetic dimensions through education, understanding of their significance in medical matters, and application of the knowledge through policy could improve health care today. A modest "instauration" of genetic knowledge in a small nation and in particular among its French-speaking citizens reveals what can be done in this winter of our discontent about health care.

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44. We thank all of our colleagues who put human and medical genetics at the service of our fellow citizens. Supported by the Ministry of Social Affairs (Quebec), the Department of Health and Welfare (Ottawa, Division of Health Research Grants), the Medical Research Council of Canada, the National Genetics Foundation (New York) and special grants from Peter and Edward Bronfman and Arnold Steinberg. Address correspondence to C.R.S., deBelle Laboratory for Biochemical Genetics, Montreal Children's Hospital Research Institute, 2300 Tupper Street, Montreal, Quebec, Canada H3H 1P3.

Prenatal Diagnosis of Genetic Disorders

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Summary. Sampling of amniotic fluid, visualization of the fetus, fetal blood sampling, and screening of maternal blood represent successive approaches to the diagnosis of specific genetic disorders in the second trimester of pregnancy. Clinical and ethical concerns about the appropriateness, safety, and efficacy of the techniques have led to multidisciplinary assessments at an early stage. A major growth in demand for medical and educational genetic services can be anticipated.

A relatively simple procedure, amniocentesis, has revolutionized the practice of clinical genetics and genetic counseling. With this procedure, an increasing array of tests of chromosomes, enzymes, and other proteins can be applied to pregnant women at "high risk" of delivering infants with certain birth defects and other genetic disorders. Previously, the physician could offer only statistical estimates of the likelihood of occurrence or recurrence of these disorders; now prospective parents can learn whether the fetus is affected or not affected. It must be emphasized, however, that these tests cannot guarantee a "normal" baby, since there are many disorders for which no tests are available.

The two most common disorders that can be detected by this approach are Down syndrome (formerly called Mongolism) and neural tube closure defects. Down syndrome accounts for 10 percent of cases of severe mental retardation and can be diagnosed by examination of the fetal chromosomes. There are about 5000 new cases in the United States each year. Neural tube closure defects (open spine) include anencephaly, which is lethal, and meningomyelocele or spina bifida with paraplegia and incontinence and infectious complications. This birth defect, which affects 6000 to 8000 babies per year in this country, can be detected biochemically by the presence of a fetal protein in the amniotic fluid.

In my opinion, the development of the technologies for testing of fetuses during pregnancy represents a good example both of the progressive enhancement of technological capabilities and of the careful assessment of the safety and efficacy of the techniques. I have organized this article into five overlapping chronological stages in the development of techniques for prenatal diagnosis during the past decade and for the foreseeable future.

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Stage 1 Approach: Sampling of Amniotic Fluid and Cells

The procedure. Amniocentesis (*1*) should be performed by an obstetrician skilled in the technique only after the patient has received appropriate genetic counseling and has given her informed consent. Amniocentesis is a simple outpatient procedure for the woman at 15 to 17 weeks of pregnancy. After the overlying skin of the abdomen is anesthetized, a needle is inserted through the abdominal and uterine walls into the amniotic fluid sac surrounding the fetus. The timing is determined by the facts that the uterus enlarges beyond the pelvic bony structures only after about 12 weeks and that the volume of amniotic fluid is too small before 13 to 14 weeks. Figure 1 illustrates the procedure schematically, and Fig. 2 provides data on the actual volumes of fluid as a function of estimated gestational age. The amniotic fluid represents primarily fetal urine and contains cells sloughed from the skin, respiratory tract, and urinary tract. At least two different types of cells have been distinguished, epithelioid cells and fibroblastic cells. Chromosomal or biochemical studies usually require about 3 weeks to complete in the laboratory, and therefore the couple must wait until the 18th to the 20th week of pregnancy for the results. Further delay in performing the test would make termination of the pregnancy less safe, in the event that an affected fetus is detected and the parents elect to terminate the pregnancy.

Safety and efficacy. For the last several decades amniocenteses have been performed in the final 3 months of pregnancy; the procedure was used originally to inject radiopaque dye for fetal x-ray

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