2. THE ROLE OF GENES IN HEALTH AND DISEASE

Canadians are leading longer lives than ever before. Many of the diseases that were devastating to previous generations are no longer a major threat. One hundred years ago tuberculosis and pneumonia were the leading causes of death, and the infectious diseases of childhood made reaching puberty a highly uncertain proposition.[22] Today, tuberculosis and many of the formerly lethal ailments of childhood are largely under control, at least in the developed world. Even though viral diseases, including the common cold, remain a health problem requiring attention, their contribution to mortality in Canada is low. Infectious diseases, with the conspicuous exception of acquired immune deficiency syndrome (AIDS), have largely been tamed through effective public health measures.

The common diseases of today are different from the diseases of 100 years ago.

The major Canadian health problems now include diseases of the heart and circulatory system, cancer, and the common chronic diseases of middle and old age.[23] Effective strategies to deal with these problems are not yet available.

Heart and circulatory diseases, cancer, and the diseases of old age now predominate.

Before the middle of the 19th century doctors could set bones, lance boils, alleviate symptoms, and offer comfort; what they could not do very often was cure disease. Social changes, public health measures, vaccines, and new medical technologies, including surgical and pharmaceutical interventions, have all been responsible for the increasing average life expectancy and reduced mortality of Canadians. Controls on workplace contaminants and some reduction of environmental pollutants have also led to improvements in health.

Social changes, public health measures, and new medical technologies have increased life expectancy.

However, despite tangible successes, modern medicine is still limited in its capabilities. Although medical advances and more effective drugs and operations appear continually, we have reached what seems to be a plateau in health status. The ability to prevent and treat disease remains limited in part by lack of understanding of the underlying cause and processes of most diseases, and scarcity of the tools to predict, diagnose, and treat them. The emerging information on genes and their role in health and disease is helping to provide such tools.

Modern medicine is still limited in its capabilities, but understanding the role of genes in health and disease is providing new tools.

Achieving Health

Most current definitions of health involve more than the absence of disease, although that remains the core component of the concept of good health. Accordingly, much of our health care effort is directed toward identifying and dealing with any deviations from the balance that constitutes good health. The causes of such deviations may be external (such as infection or injury) or internal and innate to the biology of the individual (such as the genes for Tay-Sachs disease or cystic fibrosis, classic metabolic disorders). It is becoming apparent that most diseases are multifactorial: they result from a combination of internal and external factors.[24] Their occurrence reflects both the predisposition of the individual to the specific disease, and the external environmental factors that may stimulate onset of the disease. The patient is not simply the host of a specific disease, but an individual with complex, interrelated requirements that must be met to maintain health. Understanding the causes of a disease is key to developing ways to prevent or delay onset, or to treat the disease when prevention is not possible.

Most diseases are multifactorial — they result from a combination of internal and external factors.

Box 2
Examples of Single-Gene Disorders: Frequency and Severity

Adult Polycystic Kidney Disease (APKD)
One in every 1000 newborns will eventually develop APKD.

The early signs of the disease include pain, blood in the urine, frequent kidney infections, and high blood pressure. The average age at onset of the disease is 41 years. Between 5 and 10 per cent of people with APKD develop end-stage renal disease. APKD is now a major reason for renal dialysis. Enlargements (aneurysms) of the cerebral arteries are found in 10 to 30 per cent of cases. About 3 per cent of people who die from ruptured cerebral aneurysms have APKD.

Cystic Fibrosis (CF)
About one in 2000 Caucasian newborns develops CF. Approximately one in 20 Caucasians carries a copy of the gene that causes CF if present in a double dose.

CF affects the glands that secrete tears, sweat, saliva, and mucus. Excess production of sticky mucus in the lungs makes breathing difficult and results in progressive lung and heart damage. The lungs of a person with CF are an ideal environment for infections to develop. The abnormal mucus level prevents adequate flow of pancreatic enzymes, limiting the effectiveness of the digestive system. The severity of these symptoms varies considerably. Treatment of CF symptoms has improved significantly in recent years. Approximately 50 per cent of people with this illness now survive to about 24 years of age. In the 1960s the 50 per cent survival rate occurred at age four.

Canadian geneticists identified the CF gene in 1989. There are a number of different forms of the gene that can result in CF. At present, about 70 per cent of persons carrying a mutant CF gene can be identified.

Duchenne Muscular Dystrophy (DMD)
About one in every 3500 males is born with the gene that causes DMD. The disease is extremely rare in females.

The disease is characterized by progressive and eventually fatal muscular weakness and wasting. The symptoms usually begin before the age of five. Death due to respiratory infection or heart failure usually occurs by the third decade of life.

Familial Hypercholesterolaemia (FH)
One in every 500 people in North America has one copy of the gene that causes FH. One in a million newborns has two copies of the gene. The incidence is two times higher in French Canadian populations.

FH affects cholesterol levels. People with two copies of the gene have extremely high blood cholesterol levels, which usually induce death from coronary heart disease by the age of 30. People with one copy of the FH gene also have abnormally high cholesterol levels. About 50 per cent of men with one copy of the gene have symptoms of coronary heart disease by 50 years of age. The corresponding proportion for women is about 33 per cent.

Haemochromatosis
About 10 per cent of the Canadian population carries one copy of the gene that causes the disease when present in a double dose. Carriers may have some symptoms. Two to three people in every 1000 have haemochromatosis.

The gene for haemochromatosis causes excessive and damaging accumulation of iron in organs such as the liver, heart, and pancreas. Iron accumulation can produce enlargement of the liver, diabetes, and heart disease. If left untreated, haemochromatosis can be fatal.

(continued on page 20)

It is now generally accepted that human health is dependent on the interaction of four major factors in what a milestone Canadian report called the "health field concept."[25] The factors are: human biology, the external environment, lifestyle, and health care organization. It makes sense that all four elements must be continually addressed in an integrated and balanced manner if we are to achieve a healthy population. However, there will be instances when one or another of these factors will offer a particular opportunity to address specific health problems or improve general health status. The growing knowledge of the role of genes in health and disease is providing such an opportunity now.[26]

Human health is dependent on four factors: human biology, external environment, lifestyle, and health care.

Genetic Disease

The general public, most patients, and many health care professionals tend to think of genetic disease as the relatively rare, single-gene diseases such as haemophilia, Huntington disease, or cystic fibrosis (see Box 2). However, the impact that genetic make-up has on health is much more far-reaching. Genes, by virtue of their essential role in the structure and function of cells, are probably implicated in most diseases.

The effects of genetic make-up on health are far-reaching, but still only partly understood.

Each individual has a unique genetic inheritance. For most disorders, the links between that inheritance and the occurrence of disease are complex and still incompletely understood. However, the technology to characterize or "see" genes is being refined and is resulting in a growing understanding of the role of genes in health and disease. Information implicating genes in specific diseases is emerging at an accelerating rate. To date, nearly 5000 disorders and traits with classic inheritance patterns have been identified, and their number continues to grow (see Box 3).

Nearly 5000 disorders and traits with classic inheritance patterns have been identified.

It is now clear that genes play an important role, as predisposing agents, in a much wider spectrum of diseases than originally suspected. The influence of genes is recognized in such common serious disorders as hypertension, many forms of cancer, psychiatric disorders, and circulatory and heart disease.[27] Information on the occurrence and current understanding of the role of genes in some common diseases is provided in Boxes 4 and 5. Genes are also implicated in many diseases not traditionally thought of as genetic, including infectious diseases[28] such as tuberculosis and polio (see Box 6). Infectious diseases must have a susceptible host, and genes are one of the factors influencing susceptibility.

Genes also play an important role, as predisposing agents, in a wide spectrum of diseases.

As primarily nongenetic diseases are better controlled through public health, social policies, and medical technologies, the proportion of gene-related disease is growing.[29] Polio is an example of an infectious disease controlled in Canada through immunization programs and better sanitation; as a result, genetic forms of chronic musculo-skeletal disability have become more prominent.[30] Rickets is an example of a disease in which the genetic causes became more significant when the other contributing causes were controlled (see Box 7).[31]

The relative significance of disorders with genetic causes is increasing.

The concept of genetic predisposition to disease is not new. In 1931 Sir Archibald Garrod brought this already old issue to the attention of his medical contemporaries in his book *Inborn Factors of Disease*.[32] Garrod was ahead of his time and the significance of the concept was not widely accepted. The medical community of the day was preoccupied with more immediate health problems; infectious diseases such as diphtheria, polio, and tuberculosis had not

The concept of genetic disease is not new, but most of the diagnostic technologies are.

Box 2 (continued)

Haemophilia A and Von Willebrand Disease

Usually only males develop haemophilia A. The disease affects one in every 10 000 newborn males. Von Willebrand disease affects as many as one in 200 people (male and female).

Both haemophilia A and Von Willebrand disease result from a deficiency in factor VIII, a substance involved in blood clotting. The basic feature underlying both diseases is the tendency to bleed. The symptoms of the two conditions vary considerably in severity. Mild cases of both diseases involve excessive bleeding only in response to serious trauma such as surgery. In severe cases of haemophilia A, bleeding in the joints without any external cause may start by six months of age. The average life span of someone with haemophilia A is about 40 years.

Huntington Disease

One in every 10 000 Caucasians has Huntington disease. For every person with the disease, there are an average of five to eight relatives at risk. Usually the disease is transmitted to offspring before it is diagnosed in the parent.

The disease involves degeneration of a specific region of the brain. This produces symptoms that include movement disorder, intellectual dysfunction, and personality changes. Huntington disease is progressive and eventually fatal, usually 15 to 20 years after onset. In most cases its symptoms begin to appear between 30 and 45 years of age.

Persons inheriting the gene from their father tend to experience earlier onset of the disease than those inheriting it from their mother.

Sickle Cell Anaemia

This disease occurs most often in black populations.

Two copies of the gene result in sickle cell anaemia, which can be fatal. The disease produces an abnormal form of haemoglobin which interferes with blood circulation. Individuals with only one copy of the gene are carriers and may themselves show mild symptoms of the disease.

People who have only one copy of the gene are resistant to falciparum malaria infection. This resistance is a "selective advantage" and has favoured maintenance of the sickle cell gene in the population. Among U.S. blacks, one in every 625 newborns has sickle cell anaemia and 8 per cent are carriers. In some areas of Africa carrier frequency is up to 30 per cent because of the protection against falciparum malaria. With improved public health measures and medicine to prevent and treat malaria, the advantage of the sickle cell gene is declining in importance.

yet yielded to public health solutions. Moreover, the diagnostic technologies that would identify individuals genetically predisposed to disease had not yet been developed. Today, appropriate diagnostic tests are increasingly available.

Occurrence of Genetic Disease

Diseases with a genetic component affect many Canadians.

Common diseases with a genetic component affect many Canadians. In addition, there are more than 3600 known single-gene diseases that collectively affect a significant number of individuals even though each is relatively rare. Since genetic diseases are often characterized by early onset,[33] the resulting years of ill health, the years of life lost, and the subsequent social, emotional, and financial costs are high.[34] The costs of one disease — cystic fibrosis — are outlined in Box 8.

Current figures underestimate the occurrence of genetic disease during the course of life.

Some 60 per cent of the population will experience a disease with a genetic component to its cause.

At present, we cannot quantify the contribution of genetic disease to sickness and death in Canada. For many diseases an understanding of the role of genes is only now emerging. To understand the importance of genetics in the health and sickness of Canadians will require better knowledge of the causes of disease, more emphasis on genetic epidemiology, and better methods of classifying disease and processing health data. Available figures tend to underestimate the occurrence of genetic disease. Nevertheless, existing estimates show that genetic disease significantly contributes to disease and affects the quality of life and health. It is estimated that during their lifetime 60 per cent of the population will experience a disease that in some cases has a genetic component to its cause.[35] Genes are implicated in health status and in disease at all stages of life.

From Conception to Birth

Genetic aberrations are a major factor in failed pregnancies.

More than half the pregnancies of healthy women fail to produce liveborn babies.[36] Genetic aberrations are a major factor in failed pregnancies, particularly those occurring during the first three months after conception. Chromosomal abnormalities are detected in 50 per cent to 60 per cent of early, recognizable spontaneous abortions.[37]

From Infancy to Young Adulthood

Available data show that disorders with a genetic cause are common in infancy and young adulthood.

Data from the British Columbia Health Surveillance Registry show that at least 5.3 per cent of the province's population under 25 years of age has a handicapping condition that is wholly or partly genetic (see Box 9). The specific handicapping conditions differ in severity but all affect the quality of life and call for health care services.

Mortality rates and hospital utilization statistics also provide a partial indication of the relative significance of genetic factors. In Canada and the United States at the turn of the century, the infant mortality rate was approximately 150 per 1000 live births, with 5 deaths per 1000 due to clearly genetic causes. Today the infant mortality rate is only a tenth of what it was in 1900, but the number of infant deaths related to genetic causes has remained constant at about 5 per 1000 live births.[38]

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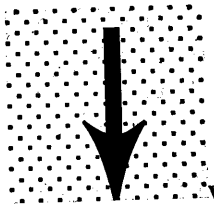
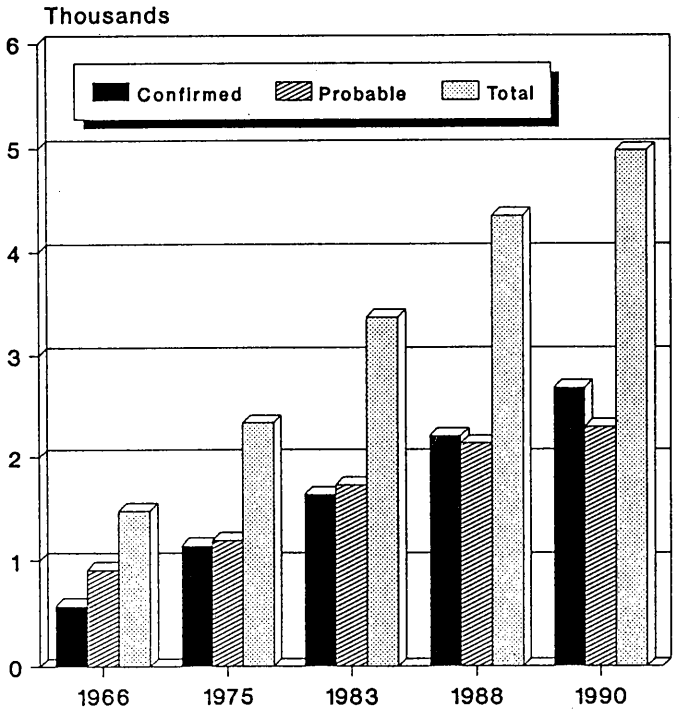


Box 3
Number of Disorders and Traits Associated with Specific Mutations



Box 4
Examples of the Genetic Contribution to Multifactorial Disease

Multifactorial disease results from a complex interaction of genetic and environmental influences. We are just beginning to understand the ways in which genes contribute to multifactorial disease. In many cases the sequence of events that initiates, promotes, and triggers the symptoms of disease has not yet been identified.

Alzheimer Disease (AD)

Two to three per cent of Canadians over 60 years of age have AD. The proportion increases to about 20 per cent in people over 80. The disease progresses from forgetfulness to complete inability to care for oneself. It is estimated that AD contributes to the death of at least 10 000 Canadians every year.

The proportion of cases of AD with a genetic basis has not been established but estimates range from 10 to 100 per cent. In some families the disease is inherited as an autosomal dominant (see Box 10). Genetic markers for familial AD have been identified on chromosome 21 but the gene thought to produce AD has not yet been identified. Other genetic and environmental factors probably modify the gene's impact, for instance by influencing the age at which symptoms of the disease appear.

Coronary Heart Disease (CHD)

The death rate in 1987 from heart disease (208.5 per 100 000 population) was greater than from all cancers (175.5 per 100 000 population). Heart disease is also a major cause of premature death, accounting for 17.2 per cent of all potential years of life lost in 1985.

A family history of CHD occurring by 55 years of age is the strongest risk factor for CHD. Several other risk factors with genetic involvement have also been identified, including high cholesterol levels, high blood pressure, and diabetes.

(continued on page 24)

Up to 50 per cent of children in Canadian paediatric hospitals have disorders that are known to be strongly influenced by genetic factors.[39] For example, 57 per cent of childhood cases of musculo-skeletal disease admitted to hospitals are gene-related.[40]

In Adulthood

Our knowledge about the effects of genetic factors on the health of individuals beyond 25 years of age is limited. There are, however, indications that genes play a significant role. In the 1970s, it was estimated that 12.5 per cent of hospitalized adults had genetically influenced disorders.[41] Data indicate that of individuals considered severely mentally retarded, approximately 15 per cent have disorders that are inherited through a single gene and 45 per cent have disorders that are in some way genetically influenced.[42]

Genes also play a significant role in the health of adults.

Genetic Material, Variation, and Mutation

The phenomenon of heredity — the transmittal of characteristics from one generation to the next — has been recognized for hundreds of years. However, the genetic mechanisms of heredity are only now being clarified. We now realize that genes we inherit from our ancestors control many of the processes essential to normal biological function and health.

Genes control many of the processes essential to normal biological functions and health.

Genetic material serves as an internal blueprint for the detailed function of the human body. The genetic information is carried on molecules of deoxyribonucleic acid (DNA) found in all cells. (Appendix 1 provides basic information on DNA, genes, and chromosomes.) Information is currently accumulating almost daily on human DNA sequences, the biological processes they encode, and the diseases they cause (or inhibit).

Information is accumulating rapidly on DNA sequences, the processes they encode, and related diseases.

An important feature of genes is their ability to be reproduced identically and transmitted from generation to generation. But genes can also be altered: the specific sequences of nucleotides along a DNA molecule are susceptible to change through a process known as mutation. Mutations can happen in a number of ways:[43]

- through rearrangement of genetic material (DNA strands) during the process of cell division to produce eggs or sperm;
- through exposure to specific environmental factors (called mutagens);
- through a failure of the DNA repair mechanism; or
- as a consequence of spontaneous change.

The process of mutation results in genetic variation, which enables species to adapt to changing conditions. However, what is good for the survival of the species is not always healthy for the individual. In most cases, a random change in a complex, specialized DNA sequence will not be advantageous to the individual organism.

The process of mutation results in genetic variation. Although mutations fuel evolution, they usually impair health.

Because of the combination of genetic inheritance and new mutations, each of us has a susceptibility or resistance to various diseases. An understanding of genetic variability helps to explain why only certain individuals develop specific diseases, and why those diseases vary in their severity and prognosis among individuals.

Box 4 (continued)

The cholesterol levels of genetically related individuals tend to be more similar than the levels of unrelated individuals sharing the same household. Between 2 per cent and 4 per cent of the population has a known single-gene disorder (familial hypercholesterolaemia) that leads to CHD. There is also a genetic trait (hyperalphalipoproteinaemia) that appears to protect against CHD.

Blood pressure levels of family members also tend to be more alike than those of genetically unrelated individuals sharing the same household. One-quarter of all people with hypertension (high blood pressure) are under 60 years of age and also have one or more siblings with the same condition. Many from this group also have lipid abnormalities (e.g., abnormal cholesterol levels).

CHD often affects people with diabetes mellitus. There are many different types of diabetes, and there is evidence for genetic involvement in many of them.

There are other genetic conditions that contribute to the overall incidence of CHD. For example, homocystinuria is a relatively uncommon recessively inherited disorder. However, between 0.5 and 1.4 per cent of the population carries one copy of the gene that causes the disease when present in a double dose. People with one copy of the gene have a much greater chance than average of early onset of arterial disease.

Lung Cancer

In 1989 about 11 700 Canadian men were diagnosed as having lung cancer. The corresponding number for women was 5100. The total number of deaths from lung cancer in that year was approximately 13 500. This disease is also a leading cause of premature death: it accounted for 32 per cent of all potential years of life lost to cancer in 1986. Damage to chromosome 3 has been associated with all the major forms of lung cancer. In some cases this damage may involve an inherited component. Lung cancer is more common in some families than others, even when smoking is taken into account. Smoking is more likely to cause lung cancer when there is a family history of the disease. A genetically influenced biochemical response to cigarette smoke has been identified that is associated with 20 to 40 times the average risk of one type of lung cancer. About 10 per cent of the population shows this particular response.

Schizophrenia

The risk of having schizophrenia at some time during one's life is about 1 per cent. More than 40 per cent of all days spent in Canadian psychiatric hospitals are due to schizophrenia. There are many different types of this disease. Symptoms may include hallucinations, disordered thought, delusions, and disorganized behaviour.

The risk of developing schizophrenia varies with the closeness of one's genetic relationship to a person with the disease and the number of affected people in the family. For example, the brother or sister of a schizophrenic has between a 40 per cent and 60 per cent chance of developing schizophrenia if both parents are also affected. This risk falls to about 15 per cent if one parent is affected and to 10 per cent if neither parent is affected. If one member of a pair of identical twins is schizophrenic, there is a 55 per cent chance the other twin will also develop the disease. In non-identical twins of the same sex the risk is about 18 per cent.

Evidence for genetic involvement in schizophrenia also comes from studies of adopted children. Individuals adopted early in life share genetic characteristics with their biological parents but share environmental experiences with their adoptive parents. Adoptees are about three times more likely to develop schizophrenia if their biological parents have the disease than if their adoptive parents are affected.

Schizophrenia may in some (but not all) cases be associated with a particular region of chromosome 5. Studies indicate that there may be different genes involved in different families.

The effect of mutations on the organism can range from the insignificant to the catastrophic. If the variation in a specific nucleotide sequence results in the failure of the gene to perform its functions successfully, the consequence can be disease, malformation, or death.[44]

The effect of mutations may range from the insignificant to the catastrophic.

Some genetic disorders are inherited, resulting from mutations in DNA passed on from parents. Other genetic disease results from mutations in the body cells of an individual; the resulting disorder may or may not be transmitted to offspring. There are several ways in which mutant genes can be involved in the cause of disease (see Box 10). The presence of a specific mutant gene can result in the development of a specific disease. For example, the presence of a Tay-Sachs mutation leads invariably to onset of the disease, with death occurring in childhood. In other disorders, the presence of the mutated gene alone is not enough to cause manifestation of the disease; other biological factors or environmental factors are also required. These are multifactorial diseases. In such cases the genes only make the individual susceptible to the disease. Polygenic diseases, a category of multifactorial disease, require more than one mutant gene to start the pathological process.

Mutant genes may be involved in disease in a number of ways...

...in some cases a specific gene results in a specific disease; in other cases a gene may confer only susceptibility.

The same clinical manifestations (symptoms) can result from a variety of causes. For example, over 50 different mutations can cause the hereditary anaemia called ß-thalassaemia.[45] Several different mutations, all in the same gene, have also been linked to familial hypercholesterolaemia.[46] Knowledge of the specific mutation has implications for diagnosis and for treatment of the related disease.

Improved knowledge of genes and their relationship to disease will help answer the following questions:

- Are mutations an important underlying cause of the disease?
- Which mutations result in disease or susceptibility to disease?
- What causes the mutation and can it be prevented?
- What are the cellular and molecular effects of the mutation?
- How does a mutation produce the clinical signs and symptoms of a disease?
- Do different mutations cause the same clinical manifestation?
- Does the mutation always result in the disease?
- What other factors are required for onset of the disease?
- Is there a delay between the occurrence of a mutation in an individual and the clinical expression of the resulting disease?
- Is diagnosis of the defect possible before the onset of the clinical signs of the disease?

Our accumulating genetic knowledge will help answer many questions about the cause and development of disease.

A number of methods exist to identify disease-mutation links. The methods are based on the study of natural variation in DNA sequences and the association between specific DNA sequences and clinical disorders.[47] Recombinant DNA technologies provided the technical breakthrough that allows the isolation and analysis of genes, and enables the search for the genetic basis of disease to occur directly at the DNA level. The technologies involve taking samples of the complete DNA complement of an individual from accessible tissues, and breaking the DNA molecules down into smaller, more manageable fragments.

Recombinant DNA technologies enable the search for the genetic basis of disease to occur directly at the DNA level.

Box 5
Cancer:
A Genetic Disease

Cancer results from changes in genetic material that produce abnormal, accelerated cell growth. The processes that produce cancer are varied and complex. Most cancers are the result of interaction between an individual's genetic make-up and the environment. Cancer-causing genetic changes fall into two broad classes.

- Some cancers result from mutations that involve loss of specific chromosomal regions. Loss or inactivation of genes that have an "anti-cancer" function can begin the cancer process.
- Mutations can also induce particular genes to gain cancer-causing abilities. Prior to mutation, these genes are called proto-oncogenes and are thought to play a role in regulation of cell growth. Once a specific genetic alteration has occurred, proto-oncogenes are converted to oncogene status and uncontrolled cell growth follows.

Different groups in society have different risks of developing cancer. There will always be some cases of cancer because genetic material mutates spontaneously. People who are exposed to agents that induce mutation (e.g., certain viruses and chemicals, radiation) have a higher risk than people who are not similarly exposed. An estimated 20 per cent of cancer cases involve DNA viruses; these cases may be avoidable using vaccines against the infecting viruses.

Some individuals possess characteristics that favour spontaneous or induced mutations. For example, people who have a defective DNA repair surveillance and repair system (which corrects spontaneous or induced mutations in the normal situation) are at higher than average risk for cancer.

Another risk category includes people with an inherited susceptibility to particular cancers. A number of events have to occur before a malignant tumour is produced. People born with a susceptibility are already at stage one of the process. If the other necessary events occur, which may include environmental exposure, such people will develop cancer.

For example, retinoblastoma affects one in 14 000 newborns and is usually manifest in children by the age of seven. Retinoblastoma produces tumours that may necessitate eye removal unless detected very early. The disease can be inherited or occur in a family with no previous history of the disease. Those with a predisposition to retinoblastoma inherit a specific mutation at conception from one of their parents. The mutation is present on one of the two copies of chromosome 13. Retinoblastoma develops if a similar mutation is acquired on the other copy of chromosome 13. Cases occurring in families with no previous history of the disease follow a similar route except both mutations must be acquired. The basic genetic alteration is thought to be the same in both inherited and non-inherited cases.

Evidence is emerging that genetic predisposition may be involved in a significant proportion of cases of the more common cancers. For example, more than 50 per cent of cases of colon cancer may involve genetic susceptibility and about 9 per cent of breast cancer cases are associated with a particular inherited genetic mutation.

A better understanding of inherited cancers will help in unscrambling the contributions of genes and the environment to common cancers, and increase the chances of intervening effectively at the most appropriate time. Possibilities for more effective preventive and therapeutic interventions include a more accurate assault on cancer-causing environmental hazards; avoidance (particularly by genetically susceptible people) of cancer-causing agents that cannot feasibly be eliminated from the environment; and application of therapies that replace or mimic the effects of "anti-cancer" genes.

The technologies can be used to identify whether a gene with a known gene product is responsible for a specific disease; to locate and identify genes responsible for single-gene disorders, but whose function is still unknown; and also to identify genes responsible for multifactorial disorders. (Some basic information on recombinant DNA technologies and their applications is provided in Appendix 2.)

Disease-mutation links can be identified by studying natural variation in DNA sequences, and correlating specific sequences with disorders.

The most direct approach to identifying a disease-causing mutation is to compare the nucleotide sequence of genes between affected and normal individuals. However, due to the sheer size of the human genetic complement or genome, this is not practical unless the location of the relevant DNA sequence is known. One successful approach to help focus on specific disease-causing mutations involves comparing specific landmark sequences within the total complement of DNA. These sequences are chosen because they are known to vary, to exist in different forms called alleles. By studying allelic differences between healthy individuals and individuals with a specific disease, it is possible to link many major genetic diseases to specific alleles. The discovery of such links then helps to focus the search for the specific mutation causing the disease. The cystic fibrosis gene was discovered in this way.

The concept that certain individuals are at particular risk for, or susceptible to, disease because of their genetic make-up underlies the new and growing field of genetic epidemiology, and helps to explain why some diseases cluster in families, ethnic groups, or geographical areas. For any specific clustering of disease, genetic epidemiology helps to determine the role of common environmental exposure, biologically inherited susceptibility, and culturally inherited risk factors such as behaviour or lifestyle.[48]

Twin and adoption studies are clarifying the relative contributions of genes and environment to certain diseases.

Twin and adoption studies are clarifying the relative contributions of genes and environment to certain diseases. Individuals adopted early in life share genetic characteristics with their biological parents but share environmental experiences with their adoptive parents. Such people offer insight into genetic and environmental influences on health and disease.[49] For example:

- Premature death: Genetic factors are significant contributors to premature, non-violent deaths. However, the relative importance of genetic and environmental factors appears to vary with the disorder.[50]

- Alcoholism: There is a substantial genetic component to alcoholism in some individuals. The frequency of alcoholism among adopted children of alcoholic biological parents is more than three times that of adoptees with non-alcoholic biological parents. Moreover, the frequency of alcoholism in the biological children of alcoholics is the same regardless of whether they are raised by their biological parents or adopted into another family.[51]

- Schizophrenia: The findings on schizophrenia are similar to those on alcoholism. The frequency of schizophrenia in the biological relatives of adopted schizophrenics is about three times the frequency in their adopted relatives. The biological children of schizophrenics have approximately the same chance of developing schizophrenia whether they are brought up by their biological or adoptive parents.[52]

Box 6
A Story the Brontë Sisters Didn't Tell Us

An old wives' tale says that tuberculosis runs in families. The conventional explanation is that the family member with active tuberculosis infects others in the family. The history of the Brontë family may tell another story: it takes two sets of genes to make an infection — the invader's and the host's.

The sisters, Emily, Charlotte, and Anne, are famous for their contribution to 19th century English literature. All died young, apparently of tuberculosis. Their mother died young too, some say of the same disease. The family — mother, father, three daughters, and one son — lived together in the parsonage at Haworth, Yorkshire. The father lived 84 years despite his heavy exposure to tuberculosis. The son died of something else.

A Canadian investigator (Emil Skamene) used an inbred mouse colony to discover a genetic factor in tuberculosis infection. A gene on mouse chromosome 1 confers resistance to tuberculosis infection; a variant of the gene confers susceptibility. Skamene then showed, by comparative gene mapping, that humans have a similar gene on chromosome 2.

Box 7
Rickets: An Example of the Increasing Significance of Genetic Cause

Rickets provides a good illustration of a disease where the genetic cause is becoming more significant as other causes are effectively prevented or treated. The history of rickets also shows how the most common route to disease can shift over time.

In the 19th and early 20th centuries rickets was common in industrialized Europe and the northern regions of North America. The principal cause was vitamin D deficiency as a result of poor diet and inadequate exposure to ultraviolet radiation. Following the discovery of vitamin D in the 1920s and the recognition of its dietary significance, food regulations were enacted to protect the population from dietary deficiencies. This led to a dramatic decline in the incidence of rickets. But rickets did not disappear entirely. Today patients still suffer from rickets, but it results from inherited disorders affecting their mineral metabolism rather than from a dietary deficiency. There are several different genetic causes of rickets; for each one, the specific metabolic problem must be identified and the treatment tailored appropriately.

Box 8
Cystic Fibrosis: An Example of the Costs of a Genetic Disease

Cystic fibrosis (CF) is enormously costly. Not all the costs are financial. The emotional and psychological impact of the disease is largely confined to those individuals who have CF themselves, and their immediate families. The financial burdens of CF are also extensive, and these are borne not only by the families directly affected, but also by the Canadian public at large.

Hospitalization
On average, people with CF are hospitalized for 10 days each year.
Cost: $20 million per year

Outpatient care
All CF patients attend outpatient clinics on a regular basis, where they are cared for by a multidisciplinary team of health professionals, including nurses, physicians, physiotherapists, and dieticians. Providing the necessary care costs approximately $4000 per patient annually.
Cost: $10 million per year

(continued on page 30)

Mapping and Sequencing

Work is under way, both in Canada and internationally, on mapping and sequencing of the human genome. The objectives are to provide a more detailed picture of DNA, and to investigate the role and function of genes and the DNA segments between genes. The resulting knowledge will also help to identify mutations associated with disease and susceptibility to disease.

Work is currently under way to map and sequence the human genome.

The purpose of mapping the human genome is to establish the precise position of the genes along the DNA molecule in relation to one another.[53] Physical maps show the geographic location of specific genes along the chromosomes. Linkage maps are based on correlating the relative positions of specific genes with the probability that they will be inherited together. It is reasonable to assume that the genes for traits that are almost always inherited together are located near each other and hence are likely to remain together during the natural process of DNA recombination.

Gene mapping establishes the precise position of genes along the DNA molecule.

Scientists hope to compile successively higher-resolution genetic linkage maps and complementary physical maps. Knowing the precise location of the genes along the DNA molecule is widely regarded as essential for modern medicine as we look toward the 21st century.[54]

On the other hand, there is considerable controversy over the relevance of sequencing the human genome. Sequencing establishes the precise order of base pairs and provides a far more detailed picture of the genome than mapping. Knowing the nucleotide sequences provides the needed reference to identify and understand variation in genes and the effects of that variation on health and disease. But the task of sequencing the estimated three billion base pairs that make up human DNA is formidable. It is expected that complete sequencing will require international cooperation and $200 million a year for at least 15 years.[55]

Sequencing establishes the precise order of base pairs.

Sequencing the entire genome is a lengthy and expensive process, but will help us understand the effects of genetic variation on health and disease.

A major point of debate is whether big sequencing projects should be delayed until improved sequencing and data-processing technology are available. A second issue is whether it is worthwhile to sequence the entire genome, or whether attention should focus first on stretches of DNA associated with protein production and stretches showing extensive variation associated with health and disease.[56]

Status of Knowledge

Our knowledge of genes, although increasing rapidly, is still limited. At present we do not know the exact number of genes in human DNA. Information is also incomplete on the precise role of specific genes and their products, the degree of genetic variability that exists in the population for each gene, specific mutations and their related disorders, and the factors that can trigger disease in genetically susceptible individuals. Of the estimated 50 000 to 100 000 human genes, only approximately 1600 have had their chromosomal location identified. Fewer than a quarter of these have had portions of their DNA sequenced, and the complete nucleotide sequence is known for fewer still.

Our knowledge of genes is still very limited.

Nevertheless, the information available on the genes that have been mapped and characterized, and on the distinctive DNA sequences (called markers) that

Box 8 (continued)

Drugs
The most commonly used drugs include antibiotics which combat or prevent lung infections, and aerosol solutions which thin and loosen mucus. The cost of all the drugs used to treat the disease averages $5000 per patient per year, but may reach as high as $10 000.
Cost: $12.5 million-$15 million per year

Equipment and nutritional support
Individuals with CF require regular home physiotherapy sessions involving equipment for percussion and postural drainage, and for inhalation therapy. The digestive dysfunction associated with the disease means that they also need vitamins and diet supplements.
Cost: $6 million per year

Lung transplantation
Transplantation is a comparatively new form of treatment for CF patients who are gravely ill. The number of procedures performed in Canada each year is expected to reach 30 or more in the near future. Each operation costs $150 000.
Cost: $4.5 million per year

Personal burdens
Individuals with CF and their families must cope, every day, with chronic illness and the prospect of early death. The disease may also compound the normal problems associated with adolescence, such as establishing independence and satisfying social relations. Although improved treatment of cystic fibrosis has resulted in a dramatic increase in life expectancy, people with CF face loss of personal and family income, loss of opportunity, and loss of a substantial portion of potential working life.
Cost: inestimable

Box 9
Frequencies of Genetic Disorders in Children and Young Adults in British Columbia (1952-83)

Category of Genetic Disorder*	Rate per Million Live Births	% of Total Births
Dominant	1395.4	0.14
Recessive	1665.3	0.17
X-linked	532.4	0.05
Chromosomal	1845.4	0.18
Multifactorial	46 426.2	4.64
Genetic, but unknown mode of inheritance	1164.2	1.16
TOTAL	53 018.9	5.3**

* For an explanation of the categories of genetic disorder, see Box 10.
** Figures do not sum due to rounding.

also allow genes to be traced in families, is a powerful tool with applications in the identification, counselling, and treatment of individuals at risk for specific genetic diseases.

Limitations in Canadian Health Data

Determining the role of genetics in the health of Canadians will require better methods of classifying disease and processing health data.

Canadian health data cannot be used to document reliably the contribution of genetic disease to death and disability, because the existing statistics do not allow for identification of the particular cause of the disease. To determine the role of genetics in the health and diseases of Canadians will require better knowledge of the causes of disease, more emphasis on genetic epidemiology, and better methods of classifying disease and processing health data.

The system currently used in Canada for classifying disease is the internationally accepted International Classification of Disease, Ninth Version (ICD-9).[57] The ICD-9 is generally not useful for indicating cause of disease. The Canadian representatives to the international committee responsible for amending the ICD system have called for modifications, including specification of cause of disease. In the interim, development and use of common, cause-related subcodes by Canadian genetic centres would expand the pool of comparable data.

Health record linkage clarifies distribution, cause, and progression of disease; most provinces are working on ways to link health records.

The linking of health records — bringing together health data for individuals and families to form a composite record — can clarify the distribution of disease within the population and the cause and progression of disease. Most provinces are now moving toward health record linkage because it provides better health statistics and related health care benefits. Unique identifier numbers are the most efficient way of achieving record linkage, but they have raised concerns regarding confidentiality and use of the data.[58] Nevertheless, protocols to protect confidentiality have been developed.

In establishing record linkage systems it is important that:

- different provincial systems be compatible, to accommodate movement of individuals between provinces and record linkage for family members in different provinces;
- appropriate guidelines and protocol to ensure confidentiality accompany the use of record linkage and unique identifier numbers;
- individuals be made aware of the benefits of unique identifiers, and of how confidentiality can be maintained.

Disease surveillance registries contribute to health care delivery and planning; more registries are needed.

There is also a strong need for additional disease surveillance registries, similar to the British Columbia Health Surveillance Registry, to provide information on the nature, frequency, and cause of handicapping conditions. When registries are part of the health care delivery and planning system, they should incorporate protocols to protect the confidentiality of the individuals registered.

The B.C. Registry is an excellent model. It has been tracking health problems since 1952 and has evolved a simple system for coding diseases by cause, making it an especially useful database for genetic epidemiology.[59] The Registry has been used to improve the delivery of services to people with genetically influenced disease, to plan for disabled populations, as well as for

Box 10
Major Mechanisms for Genetic Diseases

Single-Gene Disorders

In single-gene disorders the presence of one specific gene variant can result in the disease. Single-gene disorders that are *autosomal dominant* require only one of the pair of genes to be affected for the disorder to be manifested; the other gene can be normal. (Examples: Huntington disease, Marfan syndrome.)

In single-gene disorders that are *autosomal recessive* both genes of the pair must be affected for the disorder to occur. If one gene is variant and one gene is normal the individual is not subject to the disease but as a carrier can pass the gene for the disorder on to subsequent generations. (Examples: cystic fibrosis, thalassaemia, sickle cell anaemia.) Possessing a single affected gene can confer health advantages or disadvantages. A single gene for sickle cell anaemia confers a resistance to falciparum malaria. A single gene for ataxia telangiectasia is associated with increased incidence of breast cancer.

In *sex-linked single-gene disorders* the occurrence and effects of the disorder differ between males and females. In females the sex chromosome pair consists of two similar chromosomes (XX), and the above rules for recessive and dominant expression of disease hold true. In males the sex chromosomes are not similar (XY), and as a consequence a normally recessive gene on the X or Y chromosome will not be balanced by another, possibly normal, gene. (Examples: Duchenne muscular dystrophy, haemophilia A.)

Multifactorial Disorders

A variety of factors are implicated in the expression of a *multifactorial disorder.* The requirements can include specific variations of a number of different genes occurring in conjunction, or exposure to specific environmental conditions such as radiation, diet, infectious disease, or social environment, or both. (Examples: congenital heart defects, cleft lip and palate.)

Chromosomal Disorders

Several disorders are due to *chromosomal* abnormalities. These disorders are generally not hereditary. (Example: Down syndrome.)

research purposes. As the population ages, the Registry will help identify the genetic components of the chronic diseases of middle age.