# 7

# Genes and Disease: Defects, Quirks, and Compromises

The medical school lecture hall was surprisingly full for a Monday at eight A.M. The lecture dealt with nearsightedness. As the room darkened, the overhead spotlights glinted off the eyeglasses worn by nearly half the students. "So that's why so many showed up," murmured the professor.

"The facts are clear," he summarized an hour later. "Myopia is caused by excessive growth of the eye. When it gets too long from lens to retina, the focal point remains above the surface of the retina, so that the image is blurred. Refractive lenses, in the form of glasses or contact lenses, can refocus the image a bit further back so we can see clearly, overcoming nature's inexactitude."

Some hands began to wave. "But what causes the eye to grow too long?" asked one student.

"Genes," he said. "It's as simple as that. Some of us were just unlucky enough to get bad genes. If your identical twin is nearsighted, you will almost certainly be also. If your sibling is nearsighted, the likelihood is high, but not as high. Pulling all the figures together, myopia seems to be a genetic disease with a heritability of over eighty percent."

"But how could such genes survive before glasses were invented?" asked another student. "Without my glasses, I wouldn't last a day on the African plains." The class laughed uneasily.



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"Well, the genes might be recent mutations," said the professor. "Or perhaps Stone Age myopic people worked in camp sewing and weaving. In any case, the facts make it clear that myopia is a genetic disorder."

"But how could that be?" the student persisted. "The force of selection against it would be enormous. If such a severe defect can persist, then why aren't our bodies riddled with defects?"

"In fact, our bodies don't work very well," the professor said pointedly. "As you have been learning, we are bundles of genetic flaws. The body is a fragile, jury-rigged device. Our job as physicians is to fix Mother Nature's oversights."

The medical students grumbled a bit more among themselves but did not persist further.

## What Genes Do

The instructions for making a human body are contained in molecules of DNA, twisted into our twenty-three pairs of chromosomes. We are still learning the details, wonderful almost beyond belief, of how DNA stores and uses information to build a body. Each DNA molecule is like a ladder, with sides made up of alternating units of phosphate and a sugar called deoxyribose. The information is in the rungs, which are composed of pairs of four molecular components with names abbreviated *A*, *C*, *G*, and *T*. It is hard to comprehend the amount of information in the genetic code. The DNA in a single cell contains a sequence of twelve billion of the A-C-G-T symbols, the amount of information in a small library. If the DNA in a single human cell were untwisted and the molecules put end to end, it would stretch about two meters. If this were multiplied by the ten trillion cells in the body, it would stretch twenty billion kilometers, about the distance to the planet Pluto!

About 95 percent of human DNA is never translated into proteins. The rest can be divided into somewhere in the neighborhood of one hundred thousand functional subunits called genes. Each gene codes for a single protein. How this DNA chain of As, Cs, Gs, and Ts is translated into a protein is the realm of molecular biology, the fast-growing field that may make more changes in our lives than even the discovery of electricity. There are lonely voices crying for attention



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to the ethical and political implications of these changes, but the message has not yet gotten through to the general public. Soon it will. Already we have drugs made by DNA cloning. Food plants containing bacterial genes are in production. Pioneering experiments are now relieving previously hopeless diseases by inserting replacement genes into human cells. A less welcome possibility is that an insurance company might, as part of a routine blood test, read samples of DNA and thus learn a client's risks for a variety of diseases. Screening for some genetic disorders in the early stages of pregnancy is already routine, giving a mother of an abnormal fetus the option of terminating the pregnancy.

It is 2010, and Mary, a woman who was in elementary school in 1995, has just found out she is pregnant. "Well, you are pregnant, all right, Mary. Congratulations! The nurse will be here in a minute to explain the normal procedures, but I do need to find out if you want the standard gene screen. I presume so."

"Well, what does it involve?"

"The risks are nonexistent these days, but it is expensive unless you have executive-level health benefits."

"We do have the high-benefits package, but what will the tests tell me?"

"The basic screen identifies forty serious genetic diseases, and then you can get the supplement to look for things like nearsightedness and attention deficit disorder and susceptibility to alcoholism. Most people think it's worth it."

"But what if it shows a problem?"

"Yes . . . well . . . then we will have to talk about what to do. Probably you wouldn't want to terminate just for an increased likelihood of alcoholism or something like that, but it is better to know early. At any rate, it is better to find out now rather than after the problem arises, don't you think?"

"Well, I suppose so, but what am I supposed to do if, say, my baby is going to be nearsighted?"

"Well . . ."

It will be a few years before the comprehensive testing imagined above is available, but we already know the chromosomal locations of many genes and the code sequences of some. The goal of the controversial Human Genome Project is to unravel the



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entire code, to find the order of As, Cs, Gs, and Ts that make up the hundred thousand or so genes. When we have the code in hand, we will be able to compare the genes of any individual to those in the standard sequence, thus making it much easier to find abnormal genes.

But is there a "normal" human genetic makeup, as our term *standard sequence* might imply? We are not, of course, all identical. About 7 percent of human genes can differ from individual to individual. For most proteins the variation is low, about 2 percent, while for certain groups of enzymes and blood proteins, 28 percent of genes may have multiple versions. Often, as far as we can tell, different versions of the gene function identically. In other cases, one version (one *allele*) is normal, while the other is defective. In many cases the defective allele is *recessive*, meaning that it has no noticeable effect if paired with the normal allele. If the defective allele is *dominant*, however, even one copy will cause disease.

The problem for an evolutionist is to explain why there is genetic disease at all. Was the professor who gave the myopia lecture right? Are our bodies "bundles of genetic flaws" with legions of disease-causing genes that have not been eliminated by natural selection? Not exactly. There are many genetic defects that are so rare that natural selection has not been able to eliminate them, but they cause relatively little disease compared to more common genes that are, paradoxically, selected for even though they cause disease. We will soon explain how genes that cause disease can be selected for, but first we need to consider how genes work and the rare genetic abnormalities.

All it takes is a single error in the DNA of a sperm or an egg, a C instead of an A, or perhaps a single missing T, to cause a fatal genetic disease. Such errors arise from copying mistakes, from chemical damage, or from ionizing radiation. The wonder is that such errors are not more common. It is estimated that the likelihood of any given gene being altered is one in a million per generation. This means that, on average, about 5 percent of us start life with at least one brand-new mutation found in neither parent. In most cases such mutations have no detectable effects; in others they cause minor effects; in a few they are fatal.

As the individual develops from a single cell to an adult with about ten trillion cells, many more mistakes will creep in. Those that occur after most of the cells in the body have formed are likely to



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have little effect. Many mutations code for a protein that works about as well as the original or for a protein that is not even expressed in the kind of cell that has the mutation. If the mutation is fatal to the cell, even that will likely be of no consequence since there are usually plenty of other cells available to do the same job. A mutation in a single cell can, however, cause major problems if it knocks out some crucial part of the machinery that regulates cell growth and division. It takes only a single cell multiplying out of control to create a tumor that jeopardizes the whole organism. This hazard is countered by the multiple mechanisms discussed in Chapter 12.

Apart from the difficulties arising from an occasional mutation, how can even an enormously long sequence of only four chemical symbols manage to code for a complete human being? We know quite a bit about how DNA reproduces itself, how it produces RNA, how RNA produces protein molecules, and how these molecules combine to produce microscopic chains or two-dimensional sheets. Beyond that is a vast sea of ignorance in which there are scattered islands of understanding. For instance, we know about some cause-effect relationships and even some details of the machinery of hormonal regulation of tissue development. These isolated points of enlightenment, however, are only the beginnings of a general understanding of animal and plant development.

Even though developmental genetics is still largely mysterious, patterns of genetic transmission are well worked out. At conception, each of us got a copy of each gene at each locus on each chromosome from each parent. A single complete complement of genes (collectively a *genome*) is a random sample of a gene from each locus of the two complete genomes of each parent. So each of us, having two parents, must have two copies of each gene, two complete genomes that together constitute the *genotype*. What we observe in organisms is the *phenotype*, the expression of the genotype as influenced in the course of individual development by many subtle environmental factors. Sexual reproduction is a random shuffling of the genotypes of parents to provide the unique genotype of each offspring. If the shuffling, at a particular locus, gives identical copies of the same gene from both parents, the offspring is *homozygous* at that locus. If it gets a different contribution from each parent, it is *heterozygous*.

A gene will have some average effect over the large number of individuals in which it finds itself over the course of generations, but its



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effect in any given individual may be quite different from the average. Genes interact with one another and with the environment in determining the features of a phenotype. So a sexually produced individual is unique in many ways and may differ strikingly from either parent. The development of one fertilized egg into two offspring (identical twins) is an asexual reproductive process that produces two individuals with the same genotype.

## RARE GENES THAT CAUSE DISEASE

Of the thousands of serious genetic diseases, the vast majority are rare, affecting fewer than one in ten thousand people. Most of these diseases result from recessives, genes that don't cause any trouble except in individuals unlucky enough to get two copies, so there is no normal allele at that locus. This misfortune becomes more likely if you marry a relative, who will have more genes identical to yours than a nonrelative will. This is why marriages between close relatives are more likely to produce abnormal babies.

It is hard for natural selection to eliminate a deleterious recessive gene. If, as is likely, people heterozygous for a rare recessive have no disadvantage, the rate of adverse selection may be so small that natural selection cannot depress the gene frequency further. If a gene is present in one in a thousand individuals and people normally marry nonrelatives, then on average only one in a million will be homozygous. Even if all of these unfortunate people die early in life, the effect of selection is weak. In this situation, new mutations can often create the defective gene as fast as natural selection eliminates it, because as the gene frequency decreases, the prevalence of homozygous individuals decreases even faster. A lethal recessive gene that is created by mutation in one out of a million pregnancies will stabilize in frequency at about one in a thousand individuals. This is indeed a situation in which the power of natural selection is limited.

Dominant genes are another matter. If you have even one copy of a dominant gene that causes a disease, you get the disease and, on average, so will half your children. One of the best known such genes causes Huntington's disease. Most people with this disease have no



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symptoms until their forties, when their memory fades and their muscles begin to twitch. Some of their nerve cells steadily degenerate until these people cannot walk, remember their own names, or care for themselves. This disease is a particularly vivid example because of its devastating effects and because all known cases can be traced to a small number of European families in the 1600s. One of the men migrated to Nova Scotia. The gene and the disease have been passed on to hundreds of his descendants, including the folk singer Woody Guthrie. In the 1860s a Spanish sailor from Germany, Antonio Justo Doria, settled on the western shores of Lake Maracaibo in Venezuela. His descendants now form the greatest concentration of people with Huntington's disease. Steady detective work and fabulous luck have enabled geneticists to pinpoint the Huntington's gene on the short arm of chromosome 4.

This brings us back to the mystery: Why hasn't this devastating gene been eliminated? The answer is that it usually causes little harm before age forty and thus cannot substantially decrease the number of children born to someone who later develops Huntington's disease. In fact, some studies have suggested that women who later develop Huntington's disease may have more than the average number of children. The reproductive rate of men is somewhat decreased, but net selection against the gene in modern societies must be very slight. Studies estimate that one out of twenty thousand people in the United States have the gene for Huntington's disease.

This disease again illustrates a principle emphasized in Chapter 2: natural selection does not select for health, but only for reproductive success. If a gene does not reduce the average number of surviving offspring, it may remain common even if it also causes a devastating illness. There are genes that cause disease but may possibly increase reproductive success (at least in modern societies)—notably the genes that cause manic-depressive illness. During mania some patients become sexually aggressive, while others accomplish feats that make them successful and thus attractive. If a gene increases the rate of successful reproduction—by whatever mechanism—it will spread.

Table 7-1 offers a classification, based on the beneficiary, of genes that cause disease. While there are many diseases that result from mutation and the limitations of natural selection, they account for relatively little sickness. In most cases the story is more complicated and interesting.



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TABLE 7-1 BENEFICIARIES OF GENES THAT CAUSE DISEASE

The individual with the gene:

- Costs and benefits at different stages of the life cycle (Chapter 8); DR3 gene causes diabetes but gives an advantage in utero
- Benefits only in certain environments (e.g., G6PD deficiency is beneficial in areas with malaria; certain HLA haplotypes increase susceptibility to some diseases but protect against others)
- Quirks: Benefits (or at least no costs) in the ancestral environment, costs only in a modern environment (this chapter)

Other individuals:

- Heterozygote advantage to individuals with one copy of a gene, costs to individuals with two copies or none (e.g., the sickle-cell gene)
- The fetus at the expense of the mother (e.g., hPL, see Chapter 13)
- The father at the expense of the mother (or vice versa) (e.g., IGF-II, IGF-II receptor; see Chapter 13)
- Sexually antagonistic selection (e.g., hemochromatosis)

The gene at the expense of the individual:

- Outlaw genes that are perpetuated by meiotic drive (e.g. T-locus in mice)

No one:

- Mutations that occur at a rate equal to the selection rate (equilibrium)
- Some genes are especially vulnerable to mutation because they are very large (e.g., muscular dystrophy). Recessive genes are especially difficult to eliminate because as the frequency of the gene decreases, the force of selection decreases even faster
- Genes present in spite of adverse selection (genetic drift or founder effects)

## COMMON GENES THAT CAUSE DISEASE

Sickle-cell anemia is the classic example of a disease caused by a gene that is also useful. The gene that causes sickle-cell disease occurs mostly in people from parts of Africa where malaria has been prevalent. A person who is heterozygous for this gene gets substantial protection from malaria because the gene changes the hemoglobin structure in a way that speeds the removal of infected cells from the circulation. Homozygotes, how-



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ever, get sickle-cell disease. Their red blood cells twist into a crescent or sickle shape that cannot circulate normally, thus causing bleeding, shortness of breath, and pain in bones, muscles, and the abdomen. People with this disease suffer terribly in childhood, and until recently all of them died before reproducing. An individual homozygous for the normal allele has perfectly good red blood corpuscles but lacks the special resistance to malaria. The sickle-cell gene thus illustrates *heterozygote advantage.* Because of their resistance to malaria, heterozygotes are favored over both kinds of homozygotes: Homozygotes for the sickle-cell allele have low fitness resulting from sickle-cell disease, while homozygotes for the normal allele have low fitness resulting from their vulnerability to malaria. The relative strength of these two selective forces determines the allelic frequencies. Thus, a gene that causes a lethal childhood illness and a gene that makes one susceptible to malaria can both be maintained at high frequencies in the population.

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While the sickle-cell allele is the most frequently cited example of a gene that is selected for even though it causes disease, it is unusual for three reasons. First, it is not widely distributed, being originally found almost exclusively in people of tropical African descent. Second, the hemoglobin alteration is a simple sort of adaptation. Most adaptations, such as color vision or the capacity for fever, are complex, closely regulated systems whose assembly requires many genes. By contrast, the sickle-cell allele differs from that for normal hemoglobin only by a single T substituted for a single A. When this genetic code is translated into the protein hemoglobin, the amino acid valine ends up where glutamic acid should be. It is this molecular change that gives the blood cell its abnormal shape and other properties. Third, there is extraordinarily strong selection acting on one gene locus. It may well be that heterozygote advantage is common in human populations, but when selection against homozygotes is weak, the effect is hard to demonstrate.

In areas where malaria is rare, you would expect the sickle-cell allele to decrease in frequency. Indeed, African Americans, many of whom have lived in malaria-free regions for ten generations, show a lower sickle-cell frequency than Africans, lower than any admixture with Caucasian genes would explain. It appears that selection has been decreasing the frequency of the sickle-cell gene in regions where malaria is unimportant, as would be expected from evolutionary theory.



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Several other inherited blood abnormalities also protect against malaria, the most dramatic being a deficiency of the enzyme glucose-6-phosphate-dehydrogenase (G6PD). Patients with this abnormality get very sick when exposed to oxidizing medications such as quinine, the original and still effective antimalarial drug. When a malarial parasite uses oxygen in a red blood cell, a lack of G6PD causes the cell to burst, thus interfering with the reproduction of the malarial organism. The ability of some malarial parasites to make their own G6PD illustrates the prevalence of the host-parasite arms race.

One in twenty-five northern Europeans has a copy of the recessive gene that causes cystic fibrosis, and 70 percent of cases are accounted for by a single mutant allele (ΔF508). According to Francis Collins, director of the Human Genome Project, this "suggests that there may have been some heterozygote selection or a very strong founder effect for this particular mutation in the northern European population." Exactly what benefits might maintain the frequency for the gene for cystic fibrosis remain unknown, but decreased death from diarrhea has been suggested.

Tay-Sachs disease kills all homozygote individuals before they reproduce but the gene is present in 3 to 11 percent of Ashkenazic Jews. Maintenance of this high a frequency would require an overall reproductive advantage of 6 percent for heterozygotes compared to homozygotes for the normal gene. Data on infection rates and population distributions suggest that the benefit to heterozygotes may have been protection against tuberculosis, historically a major selective force in Ashkenazic Jews. Fragile-X syndrome is still another common genetic disease, which causes mental retardation in about one out of every two thousand males born. For this syndrome there is direct evidence of increased reproductive success of heterozygous women.

University of California physiologist Jared Diamond recently emphasized another mechanism that can explain the unexpectedly high frequency of some genes that cause disease. He says that as many as eight out of ten conceptions end in early abortion or later miscarriage. The majority are never noticed because they occur before or just after implantation of the embryo. If a gene were to decrease the chances of miscarriage even slightly, it could be selected for even if it also increased the risk of developing a disease. Diamond gives the example of childhood-onset diabetes, which can be caused by a gene called DR3. If one parent is heterozygous and the other is homo-



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zygous for the normal allele, 50 percent of the babies would be expected to have the DR3 gene, but the observed rate is 66 percent! It seems that the presence of the DR3 gene in a fetus greatly decreases the miscarriage rate and thus it perpetuates itself, despite causing diabetes.

Phenylketonuria (PKU) may be another example of disease caused by a gene maintained by frustrating the mother's uterine selectivity. When homozygous it causes mental retardation because the body cannot handle normal levels of phenylalanine, an amino acid found in many foods. The retardation can be prevented if the child is given a diet free of this common component. PKU is a fine example of a disease that is completely genetic yet whose effects are completely preventable by environmental manipulation. It is so common (one person in a hundred has the gene) that most states require screening at birth. Why is it so common? Like the diabetes-risk gene, the PKU gene seems to reduce the likelihood of miscarriage and thus to perpetuate itself despite causing disease.

## Outlaw Genes

Oxford biologist Richard Dawkins has viewed the body as the gene's way of making more genes. Genes cooperate to form cells, organs, and individuals only because that is the best way of making more copies of themselves. The body's cells are factories, each with specialized functions, that must cooperate in order for the individual to survive and reproduce. There isn't any way for genes to get into the next generation except by doing their part for the whole organism. Or is there? Given the stakes, one would expect that any gambit that would get a gene into the next generation would be used, even if it decreased the viability of the individual. Does this occur?

Certain genes do compete to get into a sperm or egg, even to the detriment of their carriers. There are several examples, the best known being the T-locus gene in mice. Two copies of the abnormal allele are lethal in males, but males with only one copy transmit it to more than 90 percent of their offspring, instead of the usual 50 percent. This is a fine example of an outlaw gene whose actions benefit itself but harm both the individual and the species. We know about



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it because it produces a striking effect and because we can do carefully controlled experiments on mice. Might there not be minor human defects that owe their existence to a biased transmission of genes from parent to offspring that balances the decrement of fitness from the defect?

One possibility is polycystic ovaries. This disorder, which accounts for 21 percent of all visits to infertility clinics, is characterized by menstrual irregularity, obesity, and signs of masculinization. A recent study found that 80.5 percent of sisters of women with polycystic ovaries were also affected, a number far too high to be explained by an autosomal dominant or an X-linked gene. Researcher William Hague and his colleagues in Adelaide, Australia, have considered the possibilities that the condition results from transmission of DNA in the cytoplasm of the ovum or from genes that distort the process of meiosis in ways that increase their own chances of getting into an egg, a phenomenon called meiotic drive.

## Genetic Quirks: Myopia and Many Others

The above diseases result from the specific effects of one gene, but susceptibility to many diseases is determined by the complex effects of many genes. Hardly a week goes by without a newspaper report on the genetics of heart disease, breast cancer, or drug abuse. In most of these polygenic diseases we don't know how many genes are responsible or what chromosomes they are on. We know only that the risk increases if close relatives have the disease. Such associations become especially convincing when people who were adopted as infants show closer resemblances to their biological families than to those in which they grew up, thus reducing the likelihood that the similarity is due to environmental factors.

Susceptibility to coronary artery disease is a good example. The risk of having a heart attack depends considerably on genes. A man whose father had a heart attack before the age of fifty-five has a risk of early death from heart attack five times that of other men. Twins



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with identical genes have heart-attack rates more similar than those of nonidentical twins, even when all the twin pairs share the same environment. Does this mean that heart attacks are caused by a genetic defect? In some cases, yes. Several abnormalities of cholesterol metabolism have been discovered, one of which is an early candidate for treatment by genetic engineering in which a new gene is inserted into the cells of blood vessel walls. But we also know that heart disease results from eating a high-fat diet. Japanese immigrants to the United States who adopt the high-fat diets of this country have heart attacks more than twice as often as their relatives back home. The rate of premature death from heart disease is high enough that natural selection must be steadily weeding out any genes that contribute to the risk. People often want to know what proportion of heart disease results from genes and what proportion from the environment, but this is not the way the question should be asked. To find out why, let's return to the mystery of myopia.

As the professor said, myopia is a genetic disease. If one identical twin has myopia, the other will almost certainly have it. We have also argued that such a harmful genetic defect would not be expected to persist. Yet about 25 percent of Americans have myopia, often so severe that they would have a hard time in a hunter-gatherer society. How well could they avoid predators, fight in a battle, or recognize a face at fifty paces? Recall poor Piggy, the castaway in *Lord of the Flies*, who without his glasses was trapped "behind the luminous wall of his myopia." Given the disadvantage, it is perhaps no surprise that present-day hunter-gatherer populations have a low incidence of myopia. So why is it so common in modern populations?

When we look carefully at the transition from hunter-gatherer to industrial societies, we see that myopia does not result from a new gene. Native people in the Arctic were seldom nearsighted when they were first contacted by Europeans, but when their children began attending school, 25 percent of them became myopic. It would seem that learning to read and prolonged confinement to classrooms may permanently impair the vision of a substantial proportion of children. Why should this be?

Imagine, for a moment, the difficulty of accurately growing an eye. The cornea and the lens have to focus an image exactly on the retina, even as the eyeball grows steadily during childhood. How exact does the length of the eyeball have to be? The leeway is 1 percent of the



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length of the eyeball, about the thickness of a fingernail. Is it possible to program the growth of the cornea, the lens, and the eyeball so that the image stays exactly in focus? Unlikely. Yet somehow, even as it grows, the eye keeps images in focus. How?

In a series of experiments, scientists at several laboratories are trying to work out the mechanisms that lead to nearsightedness. First, they noted that an eye with a clouded view grows longer than a normal eye, whether the clouding results from inherited disease, from injury, or from wearing foggy glasses. This is the case for chickens, rabbits, some monkeys, and some other animals, as well as humans. Next, they cut the nerve that carries information from the eye to the brain and found that in some species this stopped the excessive growth of the eye. They began to suspect that whenever a blurred image falls onto the retina, the brain sends back a message, in the form of a growth factor, that induces expansion of the eyeball. The clincher: when only one part of the visual field is blurry, only that part of the eye grows. This kind of asymmetrical growth results in astigmatism.

This mechanism is as necessary as it is elegant. In order to ensure coordinated development of the parts of the eye, the brain processes a signal from the retina, detects blurring, and sends back a signal to increase growth at the particular spot where it is needed. When growth is sufficient, the stimulus stops, and growth does too—except in some people. For 25 percent of us, there is something about reading or other close work that causes the eye to keep growing. Perhaps it is the blurred edges of letters or the plane of focus on a book held close with distant objects all around. It seems possible that printing children's books with especially large, sharply defined letters on oversized pages could prevent some nearsightedness.

Myopia is a classic illustration of a disease whose cause is simultaneously strongly genetic and strongly environmental. To become myopic, a person must have both the myopia genotype and exposure to early reading or other close work. Many other diseases also result from complex gene-environment interactions. For instance, some people eat all the fat they want and never get heart disease, while others eat the same amount of fat and drop dead at age forty. Similarly, some people go through all kinds of losses and never become seriously depressed. For others, the loss of a pet can set off a severe episode of melancholia. Remember also the gene-environment inter-



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action in PKU. For such diseases, it is a mistake to ask what proportion of the cause is genetic and what proportion is environmental. They are both completely genetic and completely environmental.

Can conditions such as myopia and clogged arteries be blamed on defective genes? In our current environment the genes that cause these conditions can certainly create a disadvantage, but in the ancestral human environment many of them might have caused no trouble at all or might even have conferred some real benefits. Perhaps hunter-gatherers with the myopia gene have better vision during childhood. A craving for fatty foods might have been thoroughly adaptive in an environment where such foods were scarce. For this reason we prefer to call such genes not defects, but *quirks*. They have no deleterious effects except in people who are exposed to novel environmental influences. Dyslexia may be another example, difficulty in reading not being a problem for hunter-gatherers.

Susceptibility to drug or alcohol addiction likewise depends on historically abnormal conditions. There are strong genetic influences on susceptibility to alcoholism, but they were a relatively modest problem before the reliable availability of beverages with at least several percent alcohol. Before the rise of agriculture and the vintners' and brewers' development of yeast strains tolerant of high alcohol concentrations, these genes probably were no problem at all. It may prove fruitless to search for a "gene for alcoholism." There may be many such genes on different chromosomes that can make a person susceptible to alcoholism. Many of these genes probably have some positive effects—for instance, a tendency to continue pursuing sources of reward despite difficulties, or a tendency to experience strong reinforcement in response to stimulation of certain brain areas. While it may be tempting to postulate genetic defects in people who abuse drugs, we think it is more likely that the genetic factors that influence drug use will turn out to be a diversity of genetic quirks.

Is there even such a thing as a normal human genome? Certainly no one string of DNA code is ideal, with all deviations to be stigmatized as abnormal. While we humans have much in common, our genes are diverse. There is no one ideal type but only the many varied phenotypes that express the diversity of human genes, all competing in varying environments to get copies of themselves into the next generation.



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## Don't Let Genes Scare You

There are widespread but totally unjustified fears and pessimism about genetic influences on human disease and behavior. There is an associated pervasive distrust of scientists who recognize and study these influences. To some extent these anti-gene sentiments reflect a more general antagonism to biological and especially evolutionary explanations among social scientists, the general public, and even some medical professionals. Many people suppose that human behavior and any aspects of human disease that arise from human nature are matters to be dealt with entirely by religion or sociopolitical action, not by seeking biological causes and remedies. When they get cancer or heart disease, however, most people become less concerned about such abstractions.

Is it pointless to try to alter biologically inherited conditions? For some reason, this seems to be a widespread assumption. A recent discussion of myopia contrasted a "use-abuse theory," said to imply that the condition was preventable, with a "genetically determined" theory, said to imply the impossibility of prevention. Fortunately, the subsequent discussion supported the idea expressed in this chapter that myopia is indeed genetically determined and also undoubtedly preventable. In fact, the finding that a medical condition is inherited should generally be considered good news. Genetically programmed development is very much a material process and susceptible to material manipulation. It was the study of the genetic cause of PKU that led to the discovery that its effects could be prevented by a diet free of phenylalanine. Studies of the actions of genes, and of their occasional failure to act, are already preventing and curing many diseases. As Melvin Konner observed in 1983, "The discovery of a genetic determination for a disorder may provide the best hope for an environmental treatment of it." Many others have since made the same point.

Studies of the genetic bases of disease deserve every encouragement, and clinical medicine makes good use of information provided by such studies. When a gene acts against the interests of the patient, the physician should act against the gene. As Oxford biologist Richard Dawkins puts it, we should "rebel against the tyranny of the selfish replicators."



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