5·9–5·10 Damage to the genetic code has a variety of causes and effects.

Damage to the genetic code can interfere with normal development.

5·9 What causes a mutation, and what are its effects?

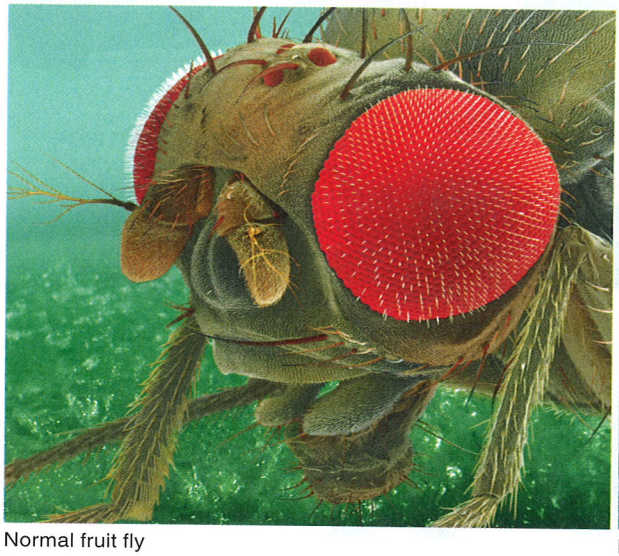
hrough the two-step process of transcription and translation, n organism converts the information held in its genes into he proteins necessary for life. But the process is only as good s the organism's underlying genetic information. Sometimes omething occurs to alter the sequence of bases in an rganism's DNA. Such an alteration is called a **mutation,** and can lead to changes in the structure and function of the roteins produced. Mutations can have a range of effects. ometimes they result in a serious, even deadly, problem for n organism. Sometimes they have little or no detrimental ffect. And occasionally—but very rarely—they may even urn out to be beneficial to the organism.

As an example of how mutations can affect organisms, onsider the case of breast cancer in humans. When two uman genes, called BRCA1 and BRCA2, are functioning roperly, they help to prevent breast cancer by helping to epair DNA damage, preventing cells from accumulating the hanges that lead to cancer. If the DNA sequence of either of hese genes is altered through mutation and the gene's normal unction is lost, the person carrying the gene has a ignificantly increased risk of developing breast cancer. Because a variety of other factors, including environmental ariables, are involved in development of cancer, it's mpossible to know for certain whether these individuals will develop breast cancer.) Currently, more than 200 different hanges in the DNA sequences of these genes have been detected, each of which results in an increased risk of developing breast cancer.

Given the havoc they can cause for an organism, it's not surprising that mutations have a bad reputation. After all, because they can change the protein produced, they can disrupt normal processes and harm the individual (**FIGURE 5-20**). But there are a couple of reasons why mutations' bad reputation may not be fully deserved. First, it turns out that many—perhaps even *most*—mutations are neutral, having neither a positive nor a negative effect on an organism's phenotype. This may be the case when a mutation occurs in a non-coding region of DNA. It can also occur when a change in DNA within a gene doesn't alter the function of the protein produced. Based on a recent study, researchers estimate that the rate of germ line mutations is approximately 10^{-8} per base pair per generation.

A second reason that mutations' bad reputation may be undeserved is the paradoxical fact that mutations are essential to evolution. Those mutations that don't kill an organism, or reduce its ability to survive and reproduce, can be beneficial. Every genetic feature in every organism was, initially, the result of a mutation. (In Chapter 8, we explore the relationship between mutation and evolution.) Ultimately, most mutations you inherit from your parents will have no effect. And all of you are carrying mutations that you will never know about!

It's important to note that mutations can occur in an organism's gamete-producing cells (that is, cells that produce sperm or eggs) as well as in its non-sex cells (such as skin cells



Normal fruit fly

Mutant fruit fly

FIGURE 5-20 Wreaking havoc. Mutations can change the protein produced by the altered gene, with disastrous consequences.

or cells in the lungs). Mutations in non-sex cells can have bad health consequences for the person carrying them. Many forms of cancer, such as lung cancer and skin cancer, result from such mutations. On the upside, non-sex-cell mutations are not passed on to your children. Mutations in the sex cells (gametes), on the other hand, do not have any adverse health effects on the person carrying them, but these mutations can be passed on to offspring, with terrible effects such as the induction of a miscarriage or the occurrence of birth defects. Individuals inheriting certain mutations from a parent—because the mutation occurred in the parent's sex cells or because the parent inherited the mutation from his or her parent—can be at increased risk for certain diseases such as breast cancer or cardiovascular disease.

Mutations generally fall into two types: point mutations and chromosomal aberrations (**FIGURE 5-21**). In point mutations, one base pair is changed. In chromosomal aberrations, entire sections of a chromosome are altered.

Point mutations occur when one base pair in the DNA is substituted for another, or when a base pair is inserted or deleted. Insertions and deletions can be much more harmful than substitutions, because the amino acid sequence of a protein is thrown off. If a single base is added or removed, the three-base groupings in an mRNA get thrown off, and the entire sequence of amino acids stipulated "downstream" from that point will be wrong—the reading frame is shifted. It's almost like putting your hands on a computer keyboard, but offset by one key to the left or right, and then typing what should be a normal sentence. It comes out as gibberish.

Chromosomal aberrations are changes to the overall organization of the genes on a chromosome. Chromosomal aberrations are like the manipulation of large chunks of text when you are editing a term paper. The aberrations can involve the complete deletion of an entire section of DNA, the relocation of a gene from one part of a chromosome to elsewhere on the same chromosome or even to a different chromosome, or the duplication of a gene, with the new copy inserted elsewhere on the chromosome or on a different chromosome. Whatever the type of aberration, a gene's expression—the production of the protein that its sequence codes for—can be altered, as well as the expression of the genes around it.

Given the potentially hazardous health consequences of mutations, it is advisable to minimize their occurrence. Can this be done? Yes and no. There are three chief causes of mutation and, although one of them is beyond our control, the risk of occurrence of the other two can be significantly reduced (**FIGURE 5-22**).

1. Spontaneous mutations. Some mutations arise by accident as long strands of DNA are duplicating themselves—at the rate of more than a thousand bases a minute in humans—when cells are dividing (you'll read more details on this process in Chapter 6). Most errors are corrected by DNA repair enzymes, but some still slip through and there's not much we can do about them.

Q

Why do dentists put a heavy apron over you when they X-ray your teeth?

2. Radiation-induced mutations. Ionizing radiation, such as X rays, is radiation with enough energy to disrupt atomic structure—even break apart chromosomes—by removing tightly bound electrons. But even non-ionizing lower-energy radiation (which is not able to remove electrons) can damage

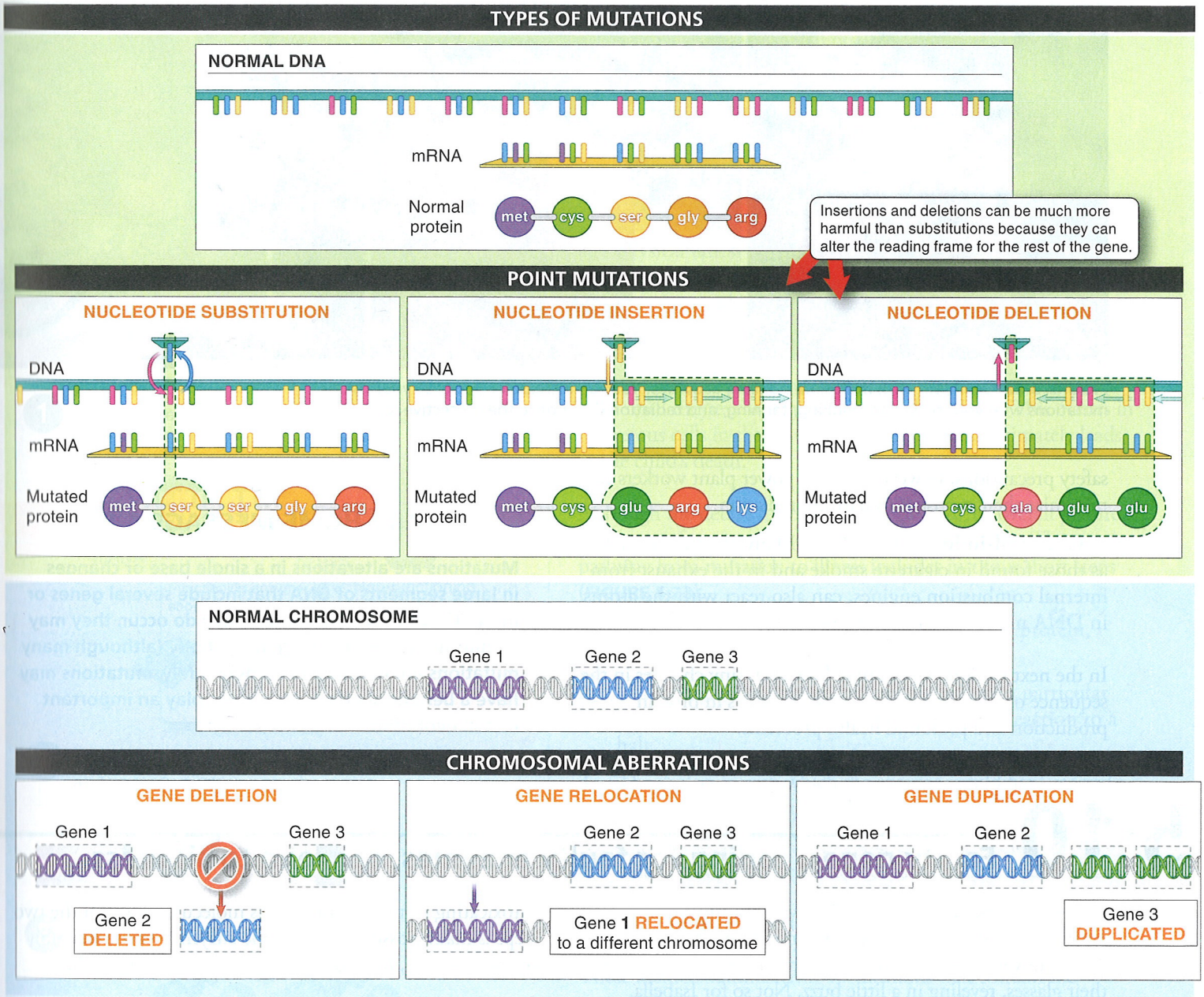


FIGURE 5-21 Point mutations and chromosomal aberrations.

In point mutations, one nucleotide is changed, whereas in chromosomal aberrations, entire sections of a chromosome are altered.

DNA. Ultraviolet (UV) rays from the sun, for example, can be absorbed by certain bases in DNA and cause them to rearrange bonds. This can prevent them from pairing correctly with the complementary DNA strand and can transform a cell into a cancer cell. This is why long-term sun exposure can contribute to the development of skin cancer. Because ionizing rays cannot pass through lead, the lead apron a doctor or dentist puts over you when you get an X ray protects your body from the ionizing radiation.

Another source of dangerous radiation is found in the core of nuclear power plants, where radioactive atoms are used and produced in energy-generating reactions. The high energy of the radioactivity that fuels the production of usable energy can pass through your body and disrupt your DNA, causing point mutations and chromosomal aberrations. With the proper

Q Why is it dangerous to be near the core of a nuclear power plant?

FIGURE 5-22 Gambling with mutation-inducing activities. You can increase or decrease your risk of mutations with your behavior: smoking, tanning, and radiation (but notice the protective lead apron).

safety precautions, however, nuclear power plant workers can minimize their exposure to harmful radiation.

3. Chemical-induced mutations. Many chemicals, such as those found in cigarette smoke and in the exhaust from internal combustion engines, can also react with the atoms in DNA molecules and induce mutations.

In the next section, we examine how even tiny changes in the sequence of bases in DNA can lead to errors in protein production and profound health problems.

TAKE-HOME MESSAGE 5·9

Mutations are alterations in a single base or changes in large segments of DNA that include several genes or more. They are rare, but when they do occur, they may disrupt normal functioning of the body (although many mutations are neutral). Extremely rarely, mutations may have a beneficial effect. Mutations play an important role in evolution.

5·10 Faulty genes, coding for faulty enzymes, can lead to sickness.

Isabella joins her friends in sipping wine during a dinner party. As the meal progresses, her companions become tipsy. Their conversations turn racy, their moods relaxed. They refill their glasses, reveling in a little buzz. Not so for Isabella. Before her first glass is empty, she experiences a "fast-flush" response: her face turns crimson, her heart begins to race, and her head starts to pound. Worse still, she soon feels the need to vomit.

How can people respond so differently to alcohol? It comes down to a difference in a single base pair in their DNA, a single difference that can influence dramatically a person's behavior, digestion, respiration, and general ability to function. The base-pair change leads to the production of a non-functional enzyme, and the lack of a functional version of this enzyme leads to physical illness. Let's look at the details.

When we consume alcohol, our bodies start a two-step process to convert the alcohol molecules from their intoxicating form into innocuous molecules. Each of the two steps is made possible by a specific enzyme, whose assembly instructions are, for most people, coded in their DNA.

"Fast-flushers" such as Isabella complete the first step of breaking down alcohol, but cannot fully complete the breakdown because they carry defective genetic instructions for making aldehyde dehydrogenase, the enzyme that makes possible the second step of the process. A poisonous substance subsequently accumulates, and the symptoms of the fast-flush reaction are due to this substance's toxic effects in the body.

Approximately half of the people living in Asia carry a non-functional form of the gene for aldehyde dehydrogenase, a mutation that may confer a greater benefit than harm. In

Q Why do many Asians have unpleasant experiences associated with alcohol consumption?

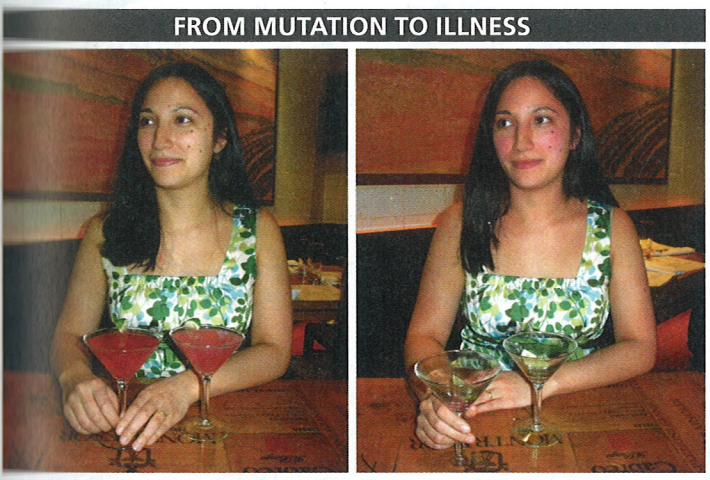


FIGURE 5-23 **Faulty enzymes can interfere with metabolism.**

a study of 1,300 alcoholics in Japan, not a single one was a fast-flusher, even though half of all Japanese people are fast-flushers. The minor change in the genetic code that makes alcohol consumption an unpleasant experience may be responsible for the lower incidence of alcoholism among Japanese and other Asian people.

In many other cases—perhaps in the majority of genetic diseases—the link between a particular defective DNA sequence and physical illness is equally direct. Recall from Chapter 3 the case of Tay-Sachs disease. In Tay-Sachs disease, an individual inherits genes with a mutation that causes an inability to produce a critical lipid-digesting enzyme in their lysosomes, the cellular garbage disposals. Because these organelles cannot digest certain lipids, the lipids accumulate, undigested. The lysosomes swell until they eventually choke the cell to death. This occurs in numerous cells in the first few years of life, and ultimately leads to the child's death.

Although the details differ from case to case, the overall picture is the same for many, if not most, inherited diseases. The pathway from mutation to illness includes just four short steps (**FIGURE 5-23**).

1. A mutated gene codes for a non-functioning protein, commonly an enzyme.
2. The non-functioning enzyme can't catalyze a particular reaction as it normally would, bringing the reaction to a halt.
3. The molecule with which the enzyme would have reacted (to convert it to another substance) accumulates, just as half-made products would pile up on a blocked assembly line.
4. The accumulating chemical causes sickness and/or death.

The fact that many genetic diseases involve illnesses brought about by faulty enzymes suggests some strategies for treatment. These include administering medications that contain the normal-functioning version of the enzyme. For instance, lactose-intolerant individuals can consume the enzyme lactase, which for a short while gives them the ability to digest lactose. Alternatively, lactose-intolerant individuals can reduce their consumption of lactose-containing foods to keep the chemical from accumulating, thus reducing the problems that come from lactose overabundance.

TAKE-HOME MESSAGE 5·10

Most genetic diseases result from mutations that cause a gene to produce a non-functioning enzyme, which in turn blocks the functioning of a metabolic pathway.