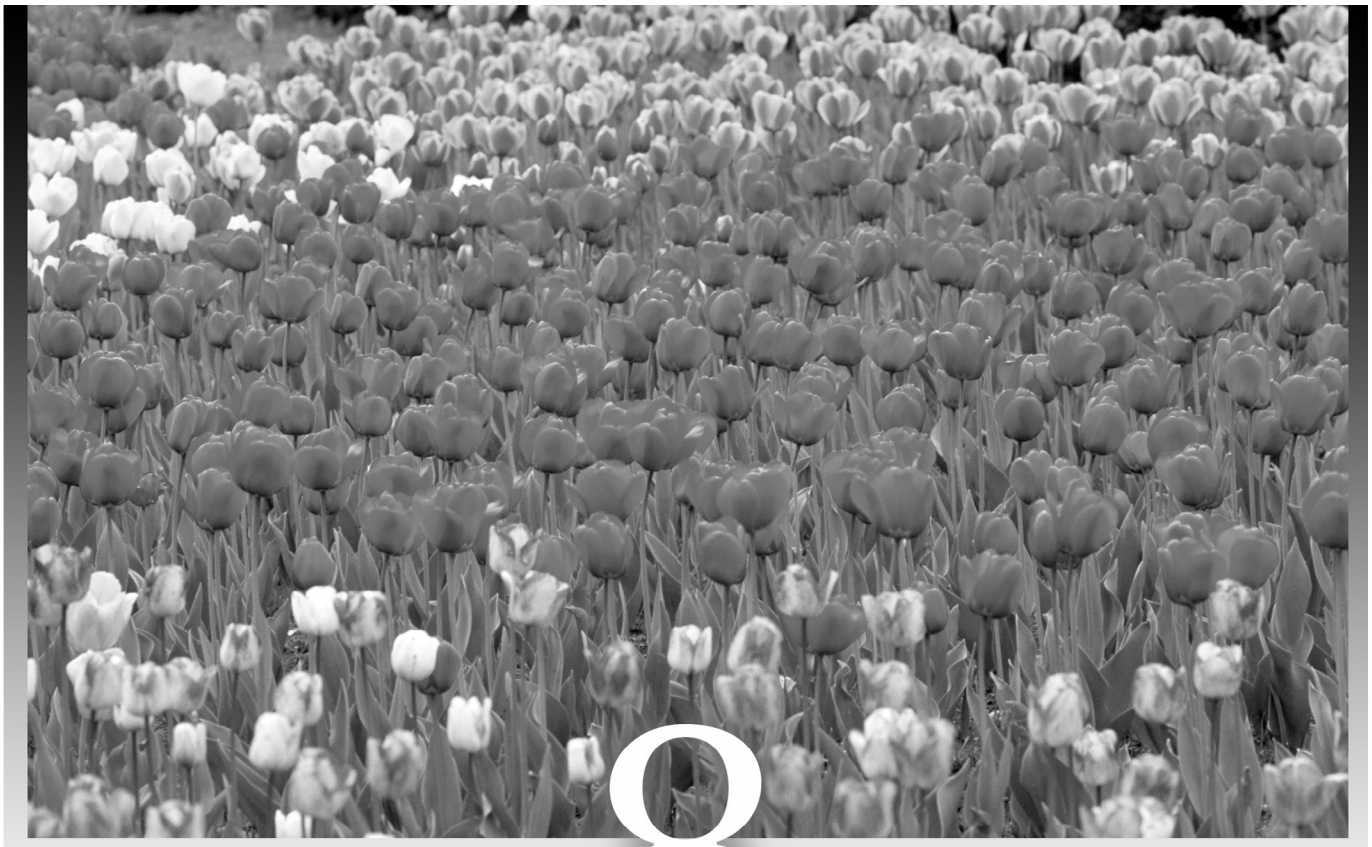


8

"Name the greatest of all the inventors. Accident."

Mark Twain, humorist

"Evolution is not 'of a very mystical nature.' It depends on accidents."

J. B. S. Haldane, geneticist

Variation: Spice of Life

outline

INTRODUCTION

Henry Ford, the automobile tycoon of the early twentieth century, devised and perfected a way to produce cars cheaply so they were affordable to more than just the wealthy. The car has been a common contrivance in our culture ever since. His first Model T was affordable, dependable (for the day), and in great demand. He brought the car to the people. But there was a hitch: Henry Ford, with tongue in cheek, boasted that you could buy his inexpensive Model T in any color you wished—just so long as it was black. At the time, black was the only color available, a carryover from the horse-and-buggy days. Later the color choices would increase, become two-tone, and even striped. But when they were first produced, Model T's were only black. But of course one color is no choice at all.

Variety is also the spice of life. If all organisms within a species were identical, similar to all-black cars, there would be no "choice." Survivors of a later generation would be identical to their ancestors of an earlier generation. Species would be fixed; evolutionary change would not occur. No difference, no evolution. Differential survival depends on differential features. As Darwin saw, evolution needs choices, but where does variation come from?

MIXING IT UP

As it turns out, much genetic variation arises during normal sexual reproduction. For example, opportunities for new genetic variation occur during meiosis, when chromosomes are being prepared for packaging into gametes, and later during fertilization when egg and sperm fuse.

Recombination

Chromosomes come paired, one from the female and the other from the male. These chromosome pairs are homologous chromosomes, and they carry similar genes. During meiosis, homologous chromosomes pair up (synapse), and matched sections often exchange between the paired chromosomes. Genes reside on

comparable sites—loci—on homologous chromosomes. This allele exchange between homologous chromosomes is termed **crossing-over**. When crossing over occurs (figure 8.1), matched segments of homologous genes are exchanged. However, the particular alleles present at these loci of exchange may differ. Thus, the exchange mixes up combinations of alleles on sections of the chromosome. This makes for new allele combinations, thus for new variation in gametes, and thus for the expression of new variations of traits in offspring.

Sex

In diploid organisms, sexual reproduction is a roll of the genetic dice, resulting in offspring that are a mix of paternal and maternal genomes, about half from each. Offspring are not exact genetic copies of their father or mother, but a combination of both. Closely related, certainly, to their parents, but offspring are different, in possession of their own genetic identity.

Even bacteria find a way to mix new DNA into their genomes. Recall that bacteria increase in number by simple division—mitotic division. No sex. Resulting "progeny" are essentially exact copies of the original bacterium, forming clones or populations of identical progeny. But some genes jump directly from one bacterium to another as transmissible, short segments of DNA called **plasmids**. Plasmids can be one to many genes in length and even move between different species of bacteria. They leave the main DNA as little circles of genes and pass into suitable adjacent bacteria where they are incorporated into the DNA of the host bacterium. By such means, new genes are integrated into the DNA of bacteria, adding variety to clones. Medically, this method of gene transmission is important because by plasmid transfer, virulence and even resistance to antibiotics spreads through pathogenic bacteria.

MUTATIONS

Early Work

Early in the twentieth century, the rediscovery of Mendel and the added discoveries of chromosomes clarified the basis of heredity. But for all the clarity brought to the mechanism of inheritance, the new science of genetics did not speak to the question of where genetic variation came from in the first place. Mendel's genetics solved one conceptual obstacle for natural selection: the mechanism of inheritance, the basis for transmission generation-to-generation of favorable traits—no blending of traits, but instead particulate inheritance. However, it did not identify the source of new traits. That concept came from a happy accident turned into a useful idea by an observant Dutch botanist, Hugo DeVries, late in the nineteenth century.

DeVries worked with plant species, typically with the evening primrose. One day, when passing by an abandoned field, he noticed, growing wild, a form of the primrose unknown to him before. In follow-up experiments, both in the primrose and other plant species,

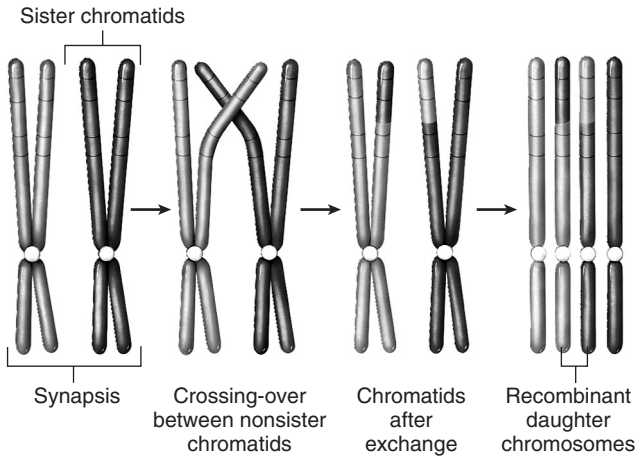


FIGURE 8.1 Crossing-Over During meiosis, chromosomes duplicate and homologous pairs synapse. Chromatids exchange homologous sections carrying alleles, producing recombinant daughter chromosomes with a different combination of alleles.

he noted that varieties occasionally occurred suddenly within a new generation of plants. These new characters appeared with no history in any previous generation. He called these abrupt hereditary changes **mutations**, and the organisms carrying them *mutants*.

Over the years 1901–1903, DeVries expounded the "Mutation Theory," the view that new species arose suddenly because of the abrupt appearance of distinct, large variations (mutations). The mutation theory drew many scientific disciples early in the twentieth century and was seen by some as an alternative to Darwin's ideas. Unfortunately, some zealots pushed this idea too far. They stood evolution on its head, arguing that abrupt, inheritable changes in an organism (mutations) were solely responsible for the appearance of new species (see chapter 9, polyploidy). In essence, gene changes drove evolution (DeVries), rather than simply producing variety upon which natural selection operated (Darwin).

Follow-up genetic research in the twentieth century confirmed the presence of mutations in the genetic material, although most of DeVries's supposed examples in the primrose turned out not to be alterations in individual genes. Instead, most of his examples resulted from new combinations of existing genes, such as those created by crossing-over. Nevertheless, the idea of gene mutations stuck and was later firmly established by careful genetic research. Mutations in the genome are now the recognized ultimate source of new genetic variation, the raw material upon which natural selection works.

Mistakes Happen

When cells divide, DNA is duplicated; repeated cell division leads to repeated duplication of DNA. A human being might have more than 40,000 useful genes, many more than this in some plants. During DNA duplication, mistakes happen, producing gene mutations. Mutation rates differ considerably from gene to gene, but generally only about one mutation occurs in a gene per 100,000 cell divisions. The gametes—eggs and sperm—hold genetic material that passes to future generations. The DNA in a single human gamete, if laid out end to end, would reach up to 6 feet in length. To fit into the gamete, the DNA is coiled, condensed, and packaged into the individual chromosomes.

The gametes, and their genomes, are the *germ cell* line. A mutation here is passed from generation to generation through the gametes. On average, about four such mutations occur per person, per generation. One in a million gametes may carry a mutation. All other cells of the organism, other than the gametes, are the *somatic cells* (*soma*, Gr., body)—up to 100 trillion in the human body. A mutation here stays within the particular individual, but may be deadly for the individual. Some types of cancers result from such somatic mutations, wherein mutations disrupt normal, controlled somatic cell division. The cell goes on a dividing rampage, dividing repeatedly without restraint. These cells pile up, forming a tumor.

Mutations affecting the germ cells are varied. Some act on single genes, others act on gene complexes, and some affect whole sets of chromosomes. Most are spontaneous errors in DNA synthesis and division, spoken of as "random" errors. Occasionally, radiation or chemicals act as **mutagens** that directly damage DNA and produce mutations.

Point Mutations

Point mutations in a gene result from one or a few alterations in the base-pair coding sequence of the gene's DNA, thus producing a new allele of the gene. At their simplest, genes are functionally integrated sections of DNA related to a particular trait. Recall from chapter 4 that the coding language of DNA involves codons—repeating triplets of bases within the long string of bases that make up the DNA. Three chemical bases code for one amino acid; amino acids chained together form proteins. By changing one or several of the bases, the affected codon changes; thereby, the particular amino acid specified by that codon may change; and therefore the sequence of amino acids assembled into a protein may change. Changing one of its bases can produce a new gene. This occurs most commonly by insertion, deletion, or substitution of bases (figure 8.2). Like crowding in line, *insertion* adds a nucleotide base into the normal row, bumping up all of the following bases in sequence by one. Because the decoding of DNA starts at one end and progresses sequentially in steps, three by three, to the other end, insertion can change not only its codon, but also all downline from it. *Deletion* does the opposite—it eliminates a base, but has the same effect of changing the reading of downline bases. *Substitution* results in just that—replacement of one nucleotide base by another, changing only one codon.

Sickle-cell anemia, a heritable blood disease, is an example of substitution. A defective hemoglobin

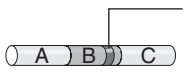
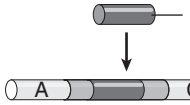
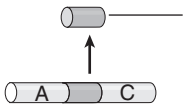
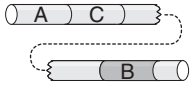
MUTATION	EXAMPLE RESULT
No Mutation 	Normal B protein is produced by the *B* gene.
Point Mutation Base substitution 	B protein is inactive because changed amino acid disrupts function.
Insertion 	B protein is inactive because inserted material disrupts proper shape.
Deletion 	B protein is inactive because portion of protein is missing.
Changes in Gene Position Transposition 	*B* gene or B protein may be regulated differently because of change in gene position.
Chromosomal rearrangement 	*B* gene may be inactivated or regulated differently in its new location on chromosome.

FIGURE 8.2 Mutations in the Genome Point mutations can occur through substitutions (change in bases), insertion (introduction of bases), or deletion (loss of bases) within the DNA. Major transposition of DNA segments can produce chromosomal inversion. Segments of DNA can be rearranged to new locations and even to other chromosomes, producing chromosomal translocation.

molecule is the result. Hemoglobin, contained in red blood cells, transports oxygen to active tissues. The large, defective hemoglobin molecule causes red blood cells to crumple—become sickle-shaped, making it difficult for them to speed through blood vessels. The misshapen red blood cells collect at critical spots, forming clots and causing pain; the warped cells have a shortened life span, which depletes their numbers and produces anemia (low numbers of red blood cells). The defective hemoglobin molecule is made up of 574 amino acids, only one of which is improperly coded—valine in place of glutamic acid (figure 8.3). This error, in turn, can be traced back to a single base substitution in DNA. Such a single point mutation produces a new allele that manufactures a defective hemoglobin molecule, with a cascade of unfortunate consequences.

Gene Duplication

New alleles provide new ways to express old genes. Some mutations lead to new genes with new possibilities. One such method is gene duplication, which results from a mistake. As homologous chromosomes pair up during meiosis, crossing-over begins, but an

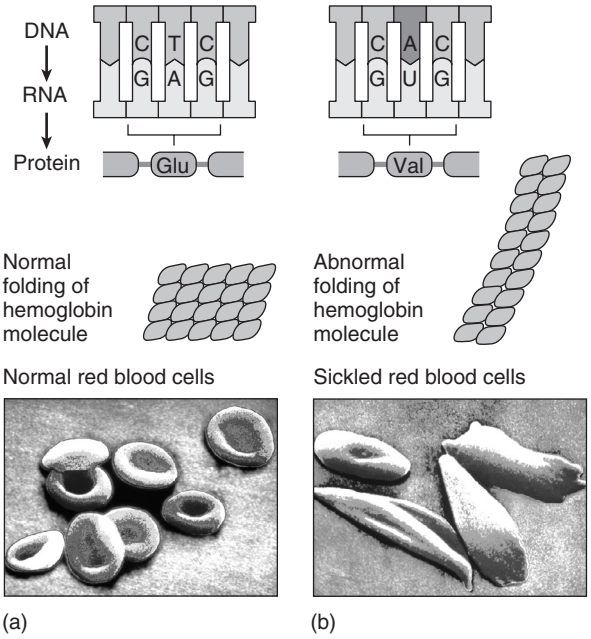


FIGURE 8.3 Sickle-Cell Disease A single base change in DNA results in a change in one RNA codon, producing a protein with one substituted amino acid. But this single change is enough to disrupt the normal action of hemoglobin and, hence, of the red blood cells. (a) Normal. DNA codes via RNA for the amino acid, glutamic acid, one of many proteins in the hemoglobin molecule. (b) Sickle-cell disease. A single base change in DNA codes via RNA for a different amino acid, valine. But this replaces a critical amino acid that is important in proper folding of the hemoglobin molecule; the resultant defective hemoglobin molecule produces sickled red blood cells.

Consider This—

Sickle-Cell Anemia: Disease against Disease

In many ways, sickle-cell anemia is a very curious condition. The malformed red blood cells and anemia are most severe in individuals homozygous for the recessive mutant allele. What is curious is that even heterozygous people also get some sickling. Such an adverse allele clearly has an adverse effect on fitness and should have been eliminated. Yet it is the most common inherited blood disorder in the United States, affecting about 70,000 Americans annually; most are African Americans, where it strikes 1 in 500. This rate is unexpectedly high. Usually, the overwhelming majority of substitution changes create alleles with little advantageous effect. Amino acid sequences have been under selection for millions of years, so it is no surprise that a substitution today brings no new benefit. There must be some counterbalancing benefit to the sickle-cell disease that accounts for its relatively high retention rate in humans.

As it turns out, people heterozygous for the gene—one copy of the normal allele and one copy of the mutant allele—enjoy some resistance to malaria. Apparently the infecting malaria parasite promotes sickling, prompting early elimination by the liver of the misshapen red blood cell and its resident parasite within. Where malaria is an environmental risk, the mutant allele is beneficial, partially balancing the disadvantages of the disease in oxygen transport. In such environments, the heterozygote enjoys benefits over both homozygote conditions: homozygous dominant (susceptible to malaria) or homozygous recessive (severe sickle-cell anemia). This is unusual, but the benefits of the heterozygote over homozygotes account for the unusually high incidence of the mutant.

error occurs wherein unequal crossover produces redundant sections of DNA on chromosomes (figure 8.4). The chromosome with the duplicated section of DNA now includes repeated copies of the gene (or genes) transferred during unequal crossover. Either gene can accumulate mutational changes without impairing normal function, because its twin gene is present to function normally. This seems to have occurred in normal human hemoglobin. The hemoglobin molecule is made up of six subunits, but only four are present at any particular stage in the life cycle of the individual. The four particular subgroups participating at any one time change during pregnancy, at birth, and within the young infant. The changing assortments of subunits reflect hemoglobin adjustments to different physiological demands of oxygen transport at these different ages. During vertebrate evolution, the gene presiding over hemoglobin manufacture apparently duplicated, and then duplicated again, giving us the six subgroups. The six are almost identical in their nucleotides, but provide differences in subunits that make up the hemoglobin molecule, and thereby fine-tune the ability of this composite molecule to carry oxygen under different demands at different ages in the life of the human.

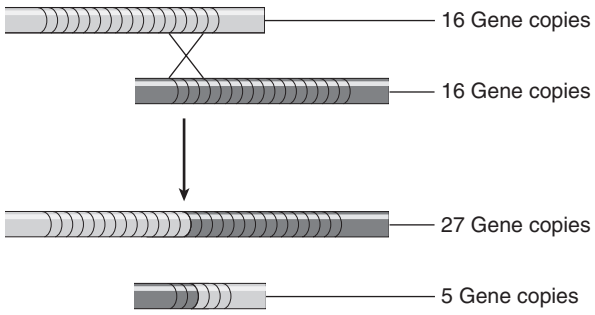


FIGURE 8.4 Unequal Crossing-Over During meiosis, synapsed chromosomes occasionally pair out of register with each other, and crossover then occurs between nonhomologous sections. As a result, genes are duplicated on one chromosome, and deleted on the other. Unequal crossover events are thought to produce gene duplication in eukaryotic evolution, providing new possibilities for gene function.

Chromosomal Mutations

Large chunks of DNA can become flipped around within their chromosomes, reversing the sequence of genes within; this is *chromosomal inversion*. Sometimes pieces of chromosomes get transplanted to other chromosomes, a result known as *chromosomal translocation*. Both are quite disruptive, in particular because of the resultant difficulty in pairing homologous chromosomes during meiosis. But clumps of genes within an inversion sometimes act as a "supergene" and are inherited as a unit. Occasionally, such supergenes can bring major benefits. Within fruit flies, some inversions become more common in colder climates, and less so in warm climates, forming a gradient within populations from cold to warm regions. The fruit fly inversions contain specific combinations of alleles that function especially well in cold, wet weather, apparently favoring larger body size and acclimation to the temperature.

Another type of chromosomal mutation is **polyploidy**, wherein whole sets of chromosomes may be added. Commonly, the diploid ($2n$) number may double, forming a tetraploid ($4n$), and all double again forming an octoploid ($8n$). This is rare in animals, but common in plants. Polyploidy addresses a problem arising when part of a chromosome duplicates. Partial chromosomal duplications may survive in the individual plant where they first occur, but when gametes are formed, the duplicated chromosomal segment may lack a partner section of chromosome with which to pair during meiosis. This partner mismatch in turn produces defective gametes with an odd number or arrangement of chromosomes. Upon fertilization, this incomplete chromosome will not entirely restore the normal diploid number in the offspring, and consequently offspring are usually sterile. But by duplicating chromosomal number, polyploidy solves this problem of finding matching, homologous chromosomes. By first doubling, each chromosome automatically gains a homologous partner with which to pair during meiosis. For example, one of the most frequent errors leading to polyploidy occurs during meiosis where diploid ($2n$) gametes are formed. If the plant contains both male and female reproductive structures and self-fertilizes, then tetraploid ($4n$) offspring result. In turn, these new offspring ($4n$) form "haploid" gametes—now the norm for them, $2n$. When they mature, if they self-fertilize or cross with a similar tetraploid sibling, then the chromosomal number is restored in their offspring—the new tetraploid number, $4n$. A breeding population of tetraploids is established. Polyploidy is a significant factor in plant evolution, especially in ferns and flowering plants wherein the majority of species are polyploid, evidence of past speciation via polyploid duplication of chromosomes.

It is not known why polyploidy should be so prevalent in plants generally, and in ferns and flowering plants in particular. New varieties and even species may form quickly, but of course each must meet the discipline of natural selection and find adaptive favor. From the introduction of this chapter, recall Hugo DeVries and the flower that inspired him, the evening primrose. The variety of primrose that he noticed in the abandoned field turns out to be a polyploid, or partial polyploid, of the primrose. Of course, he guessed or knew nothing of the sort at the time. It was a variety that appeared suddenly. A contemporary of his, William Bateson, would be first to notice another type of mutation, even more bizarre.

Hox Genes and Their Kingdoms

We owe the term *homeotic* to William Bateson (1861–1926) and to his interest in biological variation. He noted that normal body parts of animals and plants are often switched, transforming a part into the likeness of another, producing odd varieties. For example, he observed that, on occasion, the stamens of a flower transformed into petals. In 1894, he called such varieties *homeotic* (*homeo-*, same; *-otic*, condition) *mutants*. A more recent example comes from fruit flies. The repeating body segments of a normal fly are clumped into three body regions—head, thorax, and abdomen. The *head* includes eyes, mouth parts, and sensory antennae; the *thorax* has wings, legs, and haltere (balancing organ); the *abdomen* holds most of the body organs but lacks legs, wings, antennae or other appendages. Occasionally, in one generation, an abrupt, transforming mutation occurs. Close up, the homeotic mutant looks like it stepped out of a science fiction movie. A leg replaces the antennae on the head, or a second wing-bearing segment is added to the thorax, giving the mutant two pairs of wings. One body part is replaced by another.

Today we know that such major changes are due to **homeotic genes**—master gene switches that bring under their command legions of secondary genes responsible,

in turn, for the formation of body parts. Although first worked out in arthropods (fruit flies in particular), similar homeotic genes have been found throughout the animal kingdom and even in plants and fungi (yeast). Although sometimes restricted to vertebrates, the term ***Hox* genes** is now more commonly used to embrace all these homeotic genes, wherever they occur. I will do so here. Before looking at the details of *Hox* gene action, we first need to understand the context in which they act.

Egg to Adult

The egg is one cell, the adult is billions of cells. To get from egg to adult, repeated cell division must occur, beginning with fertilization. Initially, division is restricted to cleaving the egg, but eventually proliferation of dividing cells contributes as well to growth in size of the embryo (figure 8.5). Each somatic cell formed by division contains an equivalent and full complement of DNA.

Because all cells have the same set of DNA instructions, any particular cell anywhere in the embryo could form muscle or nerve, or contribute to an arm or leg. But these cells and parts cannot appear randomly, or the embryo will be a scramble of bits and pieces in odd places. Arms must develop in the front, hindlimbs at the back; eyes must be on the head, and in fact the head must be on the front end, and so on. Placement and appearance of body parts must sprout in the embryo in the right positions. Organization is required. This organization begins by establishing basic body symmetry—front to back, top to bottom. Formally, a **polarity** is established in the young embryo wherein anterior and posterior ends (front and back) and dorsal and ventral (top and bottom) regions are delineated. Usually this is done through chemical gradients, where distinct chemicals are concentrated at one region and decrease toward the other, as for example, from front to back. Such chemical gradients, along with other chemical information, provide *positional information* within the embryo. The chemicals act as guideposts directing the subsequent positioning and placement of parts. By setting up this axis early, it is in place as a blueprint or chemical scaffolding to guide ensuing placement and building of body parts. In some animals, *Hox* genes actually turn on to set up body polarity; in others, polarity is established in the unfertilized egg. By whichever means, positional information is set up early, ready to direct placement of subsequent embryonic body parts and events.

Shaping Up: Positions and Parts

With the body polarity in place, the embryo can now be built, and most of the *Hox* genes work in this embryonic environment. Positional information within the embryo and environmental cues working through chemical intermediaries activate *Hox* genes, which in turn activate large banks of structural genes. *Hox* genes are *regulatory genes* that manage parts of the genetic program controlling structural genes; *structural genes* actually make products involved in building the phenotype. Particular *Hox* genes determine where paired wings form, where legs develop, or how a flower's parts are arranged. *Hox* genes are called master control genes because they may regulate 100 or more structural genes. Consequently, even a small change in one *Hox* gene can magnify into huge effects through the downstream structural genes over which it presides. There is amazing molecular similarity in *Hox* genes throughout the animal kingdom, further testimony here at the molecular level to the underlying evolutionary continuity between groups.

Hox genes are found in clusters with their loci lined up on chromosomes. The *Hox* genes in the cluster are in the same front-to-back order as the body part they affect (figure 8.6). A small change in one *Hox* gene in a cluster can produce large changes in the body region over which it presides, adding segments, or legs, or wings, or removing them.

Evolutionary Changes

Research continues. Many answers await research outcomes. But some promising correlations between *Hox* gene changes and major evolutionary events are apparent (figure 8.7). Major changes between major animal phyla are correlated with duplications in *Hox* genes or an increase in the number of *Hox* genes (figure 8.7a). The number of body regions over which a *Hox* gene presides may expand, thereby adding segments, or change the character of typical segments (figure 8.7 b, c). Through mutations that change downstream gene action, parts on segments are added or eliminated (figure 8.7 d).

Hox genes are elegant and complex. They are highly conserved anatomically (nucleotide sequences) and uniform in their expression (regulatory genes). What seems to have evolved is how they are activated and how downstream target genes respond. Research is turning up a more complex story. Apparently, some

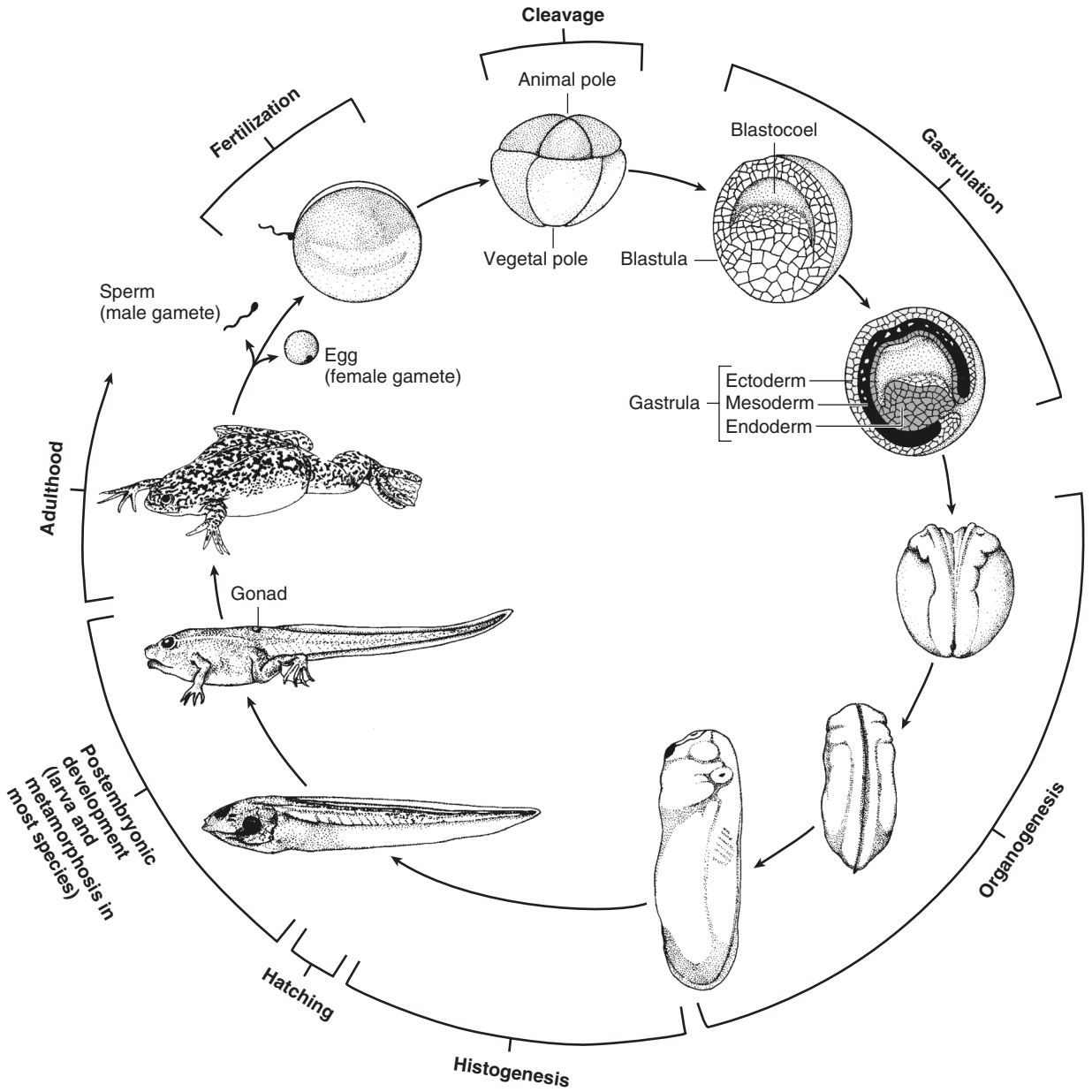


FIGURE 8.5 From Single Cell to Millions of Cells—Life Cycle of a Frog A sperm fertilizes the single-celled egg, and cell division (cleavage) begins, leading to a multicellular blastula with a fluid-filled core (blastocoel). Major rearrangements (gastrulation) of formative cellular layers (ectoderm, mesoderm, endoderm) lead next to an embryonic stage wherein these formative embryonic cells become arranged into organs (organogenesis) and specific tissues (histogenesis). Upon hatching, the larva feeds and grows further, eventually undergoing a major anatomical change (metamorphosis), becoming a juvenile and then an adult frog, which reproduces to repeat the cycle.

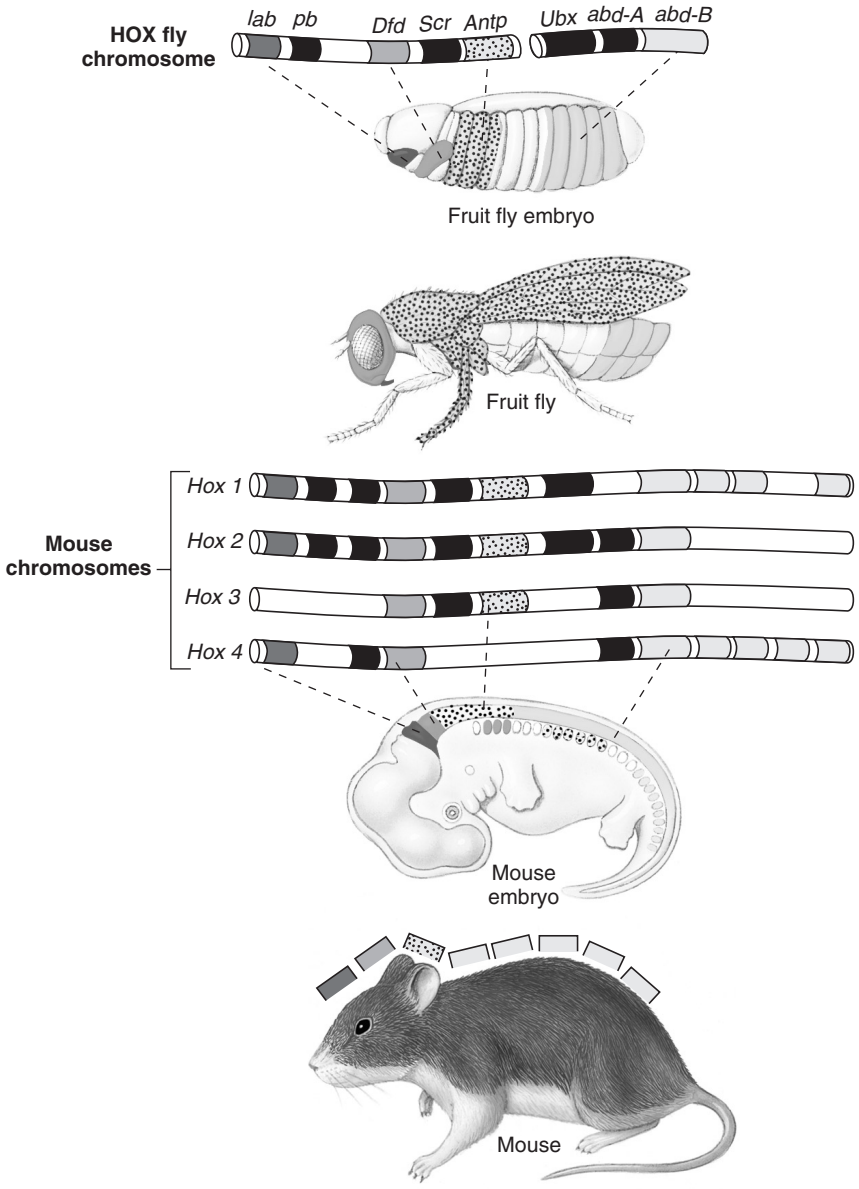


FIGURE 8.6 *Hox* Genes In the fruit fly *(Drosophila melanogaster), Hox* genes are located in clusters on a single chromosome, the HOX fly chromosome. In the mouse *(Mus musculus),* similar genes are located on four chromosomes. In the fly and mouse, these genes control the development of front-to-back parts of the body.

Hox genes are turned on and off repeatedly during embryonic development, responding to the changing chemical and anatomical conditions within the developing embryo. Not only do *Hox* genes simultaneously turn on legions of structural genes, but some can directly and selectively control single, individual downstream genes as well. *Hox* genes turned on at one stage in embryonic development may be turned on again later but produce a different effect. *Hox* genes and their triggers may remain more or less the same, but

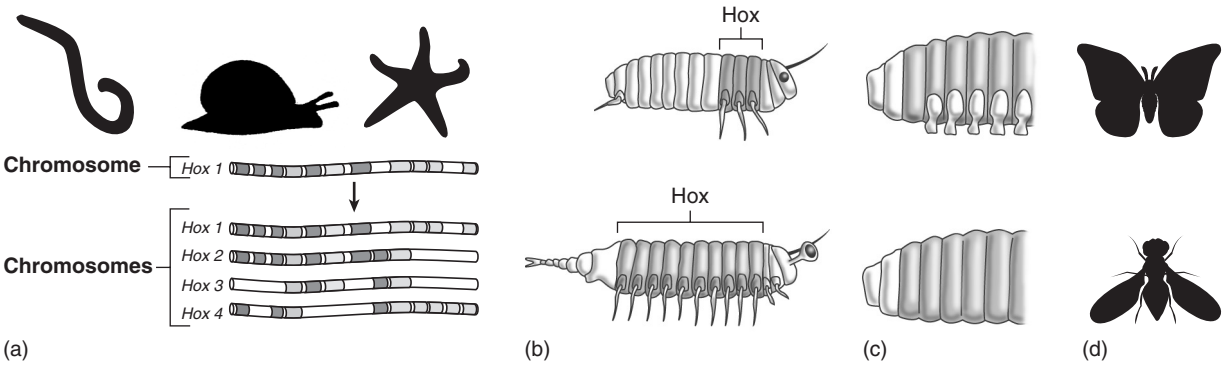


FIGURE 8.7 Evolutionary Changes Via *Hox* Genes Several major changes are thought to be based on changes in *Hox* genes and in their pathways of control of structural genes. These include changes in the number of *Hox* genes producing phyla-level changes (a), broad changes of *Hox* expression over body regions (b), local changes of *Hox* expression (c), and changes in regulation of downstream genes or in function, here changing the second-segment wings of a moth or butterfly into the haltere of flies (d). (After Gellon and McGinnis, 1998)

downstream tissues respond differently. Within flies, the pair of halteres, riding on the thoracic segment behind the single pair of wings, is apparently a modification of the wings that occupied that position in ancestors (figure 8.7 d).

OVERVIEW

Even if big mutations occur, the discipline of natural selection still rules. Gene mutations set the boundaries of variation, but natural selection culls out the unworkable, the maladaptive, the disadvantageous. Variation and selection are partners producing descent with adaptive modifications. Variation produces novelties that must meet the demands of the environment. A mutation producing featherless, or nearly featherless, birds may or may not be advantageous. If occurring in a bird that depends on flight to escape predators, then the featherless trait is highly disadvantageous and individuals carrying the mutation are likely lost from the population. On the other hand, if the featherless trait occurs in a bird on a remote island that is predator-free, then it may be advantageous and spread within the population. Variation arises from the basics of normal meiosis, and from the variation that comes from mixing of new combinations within the process of sexual reproduction.

Variation also arises from mutations within the genome. With millions of years to experiment, to shape, and to refine organisms, it is not surprising that new mutations usually are deleterious. They disrupt a fine-tuned and harmonious working system. But if large-scale morphological changes are to occur, then major gene changes occur from time to time. The different groups of animals are quite diverse. Yet underlying the diversity is a shared, ancient structural blueprint based on genetic modifications at points, in chromosomes, and within master genes. The great structural similarity, at the level of the genes, testifies again to the solid evolutionary relationship among all animals. But this common genetic blueprint also suggests the genetic basis of major adaptive changes. Both large and small, variation produces the opportunity for evolutionary descent with modification. Phenotypic changes, based on underlying heritable genetic variation, may collect within a population and lead to divergence of groups and formation of new species. This is the process of speciation, which we will turn to in chapter 9.

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