Hox and related genes do not code directly for structural elements; rather, they encode proteins regulating other genes that, in turn, influence processes – such as cell proliferation, differentiation, adhesion, movement, and cell death – that result in the formation of structures (Fig. 10.5). *Hox* genes act like switches that control whether or not structures are formed and where in the body they are expressed. For example, the wild-type *Antennapedia* gene is normally expressed in the second thoracic segment, where it is thought to repress the development of head structures. In the classical *Antennapedia* mutant, the gene is expressed in the head, causing a pair of thoracic legs, rather than antennae, to develop. This change in the function of the gene is caused by a shift in its position on the chromosome, so that its expression is controlled by a promoter that influences the head rather than the thorax (Gilbert 1994).

Mutations of *Hox* genes do not result in the sudden initiation of new structures, as argued by Goldschmidt, but instead alter the expression of structures that were already present and whose origin resulted from changes in other, still not fully understood, genes. However, since the position and expression of limbs and other major body structures are regulated by *Hox* genes, knowledge of their area of expression and mode of activation provides a readily identifiable starting point for determining the character of other developmental processes that more directly regulate the nature and localization of the cells and tissues that form the structures.

The current, explosive growth of knowledge of the function and phylogenetic distribution of *Hox* genes results from the ease of recognizing the highly conservative homeobox region. This makes it practical to screen genomes of many different organisms and so locate all genes in which this particular base sequence is present. Krumlauf (1994) points out that progress in identifying and establishing the specific functions of genes more directly responsible for the formation of structures, but whose activities are regulated by the homeobox genes, has been much slower.

In nearly all invertebrate groups that have been studied, most *Hox* genes are arranged in a continuous linear sequence on a single chromosome. This is called the ***Hox* cluster**. The close similarity of each of the sequential genes suggests that they evolved from a single ancestral gene that underwent *tandem duplication,* which may be attributed to unequal crossing-over during meiosis. In the fruit fly, the eight genes can be differentiated into three series, anterior, medial, and posterior (or head, thorax, and abdomen), which correspond to the position along the body where they are expressed.

Vertebrates differ in having not just one but as many as four homeobox or *Hox* clusters, designated by the letters *A, B, C,* and *D* (or *a, b, c,* and *d*), each occupying a different chromosome. Each cluster has a different number of *Hox* genes, but all can be compared with those present in *Drosophila*. Thirteen positions along the four chromosomes are occupied by different **gene groups**, although not all positions are occupied on particular chromosomes. Clusters *A, C,* and *D* have four to five genes in the posterior series, all of which resemble a single gene, *Abdominal-B,* in *Drosophila,* suggesting that they resulted from tandem duplication. The genes in groups 2 and 3 are comparable to a single gene in the anterior series of *Drosophila*. Since these duplicated genes occur in more than one cluster in vertebrates, it is almost certain that they initially arose within a single cluster, followed by two du-